NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Committee Papers

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Merck Sharp & Dohme
2. **Clarification questions and company responses**
3. **Public Health England Evidence Report**
4. **Patient group, professional group and NHS organisation submission** from:
   a. Action Bladder Cancer UK- *endorsed by patient expert Allen Knight*
   b. Fight Bladder Cancer- *endorsed by patient expert Lydia Makaroff*
5. **Expert submission from Dr Simon Crabb**, clinical expert nominated by Merck Sharp & Dohme
6. **Evidence Review Group documents** prepared by Warwick Evidence
   a. ERG report
   b. Factual accuracy check
   c. Erratum
7. **Technical engagement response** from Merck Sharp & Dohme
8. **Technical engagement responses from experts:**
   a. Peter Clark, CDF Clinical lead
9. **Technical engagement response from consultees and commentators:**
   a. Action Bladder Cancer UK
   b. Joint response from the Royal College of Physicians
10. **Evidence Review Group critique of company response to technical engagement** prepared by Warwick Evidence
11. **Final Technical Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA519

Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF guidance review

[ID1536]

Company evidence submission for committee

24th July 2019

File name	Version	Contains confidential information	Date
MSD Submission Pembrolizumab CDF review [ID1536]	**1.0**	**Yes**	**24th July 2019**

Contents

Tables and figures

Cancer Drugs Fund review submission

A.1 Background

As per the Terms of Engagement (ToE) document [1]:

- Pembrolizumab is recommended for use within the Cancer Drugs Fund (CDF) [2] as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:
    - pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression, and
    - the conditions in the managed access agreement for pembrolizumab are followed.

- The committee acknowledged that the pivotal trial, KEYNOTE-045 [3, 4], demonstrated an improvement in the overall survival (OS) compared with docetaxel, paclitaxel or vinflunine. However, the survival data used in the modelling were immature. (FAD, section 3.7 and 3.26) [2].

- There was some uncertainty around the estimations of long-term survival. The choice when to start the extrapolation and the curves used had a significant impact on the cost effectiveness estimates.

- Based on the company's commercial offer as part of the managed access agreement proposal, and the preferred assumptions and extrapolations, the cost-effectiveness estimates using either the ERG's or company's preferred overall survival extrapolation were between £44,504 and £46,447 per quality-adjusted life year (QALY) gained although other plausible estimates were higher. However, the cost-effectiveness estimates assumed that, despite a 2-year stopping rule, the effect of pembrolizumab continued for the duration of the model which the committee considered to be implausible.

- The committee considered that pembrolizumab has plausible potential to be cost effective and that further data collection would reduce the uncertainty around OS and continued treatment effect.

A.2 Key committee assumptions

Table 1. Key committee assumption as per ToE document [1]

Area	Committee preferred assumptions
Population	• Adults with locally advanced or metastatic urothelial carcinoma who have had platinum-containing chemotherapy • The remainder of the urothelial carcinoma population covered by the marketing authorisation (for whom cisplatin is unsuitable) will be addressed in a subsequent appraisal when the relevant clinical evidence is available.
Comparators	Paclitaxel, docetaxel and best supportive care are relevant comparators for people who have had platinum-containing chemotherapy
Model structure	The company's model structure is appropriate for decision making
Stopping rule	2 year stopping rule is appropriate given current available evidence but should be reviewed in light of any new evidence
Extrapolation of overall survival	• A piecewise model is appropriate, but the best time to switch to a parametric curve is uncertain - Company method: Start extrapolation at 40 weeks using a log-normal curve - ERG method: Start extrapolation at 24 weeks using a log-logistic curve • There are several plausible OS extrapolation curves • Extrapolation of OS is unclear and require further data collection
5-year survival rate	A 5-year survival rate of 5% to 11% for standard of care (SoC) is reasonable for decision-making
Utilities	• Utilities should be based on progression state, and the current age-related disutility algorithm should be used. • Utility estimates should exclude the vinflunine data • Utility estimates should be pooled across treatment arms
Duration of treatment effect	• A lifetime treatment effect considered by the committee to be implausible • Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment
PDL1 expression	• Pembrolizumab appears more clinically effective in people whose disease is PD-L1 positive
End of life	• Life expectancy for people with urothelial carcinoma is less than 24 months, and pembrolizumab extends life by at least 3 months • Pembrolizumab meets the criteria for end-of-life treatments
ERG's model corrections	Committee agree with the following correction from the ERG's model: • excluded the vinflunine data from the utilities • pooled utilities across treatment arms by progression state • used an updated algorithm to calculate age-related disutility • changed the proportion of people having docetaxel and paclitaxel to UK market share • used a Weibull parametric curve to extrapolate progression-free survival • extrapolated the overall survival trial data at 24 weeks • used a log-logistic parametric curve to extrapolate OS

Abbreviations: ToE, terms of engagement; ERG, evidence review group; OS overall survival; PD-L1, program death ligand 1.

A.3 Other agreed changes

As per the ToE document [1], MSD has not made any changes to the decision-problem, and no additional evidence is submitted beyond the agreed further data collection from KEYNOTE-045 [3, 4] to address the key uncertainties that the committee are seeking to resolve.

A.4 The technology

Table 2. Table 2 Technology being reviewed

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging with its ligands PD-L1 and PD-L2 [5] .
Marketing authorisation/CE mark status	The indication to which this submission relates to is as follows: **KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.** The above indication was approved as a Type II variation via the EMA's Centralised Procedure. The date of the Commission Decision was 20 July 2017 [6].
Indications and any restriction(s) as described in the summary of product characteristics	The marketing authorisation for Pembrolizumab also currently covers the following indications [7]: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. • KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults. • KEYTRUDA as monotherapy is indicated for the 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 KEYTRUDA. • KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

	• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. • KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.
Method of administration and dosage	The recommended dose of KEYTRUDA as monotherapy is either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) administered as an intravenous infusion over 30 minutes.
Additional tests or investigations	For the indication under consideration, no diagnostic test is required to identify the population for whom pembrolizumab is indicated
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100mg vial. The mean treatment duration per patient including the CDF follow up period was 6.84 months or 10.46 administrations. Based on 200mg every 3 weeks, this equates to an average cost of a course of treatment at list price of £55,019.60 (no. of administrations x cost per administration, 10.46 x £2,630 x 2) The maximum treatment duration would be 2 years.
Commercial arrangement (if applicable)	Currently a simple discount patient access scheme (PAS) is operational for all pembrolizumab indications approved through baseline commissioning. The Providers will purchase pembrolizumab from MSD and MSD will supply the same at its confidential NHS net discount price for all indications, i.e. at a [redacted] discount on MSD's list price, plus VAT, where applicable. This discount would apply to the indication covered by this submission upon successful exit from the CDF into routine commissioning.
Date technology was recommended for use in the CDF	25 April, 2018
Data collection end date	The Managed Access Agreement (Appendix H) specified that the data collection period was anticipated to conclude in December 2018 when enough evidence was anticipated to exist to confirm the long-term efficacy of pembrolizumab. In this submission to inform the CDF guidance review of TA519 [2, 8], follow-up data is provided from KEYNOTE-045 with a data cut-off date of 30 November 2018 [9-11].

A.5 Clinical effectiveness evidence

Table 3. Primary source of clinical effectiveness evidence

Study title	KEYNOTE-045 [3, 4]
Study design	KEYNOTE-045 [3, 4] was a randomised, active-controlled, multi-site, open-label phase III trial of intravenous (IV) pembrolizumab monotherapy versus investigator's choice of either paclitaxel, docetaxel or vinflunine, in patients with metastatic or locally advanced/unresectable urothelial cancer that had recurred or progressed following platinum-containing chemotherapy
Population	• Histologically or cytologically-confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. • Experienced progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin) • Received no more than two prior lines of systemic chemotherapy for metastatic urothelial cancer.

	• Measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. • ECOG Performance status of 0, 1 or 2
Intervention(s)	Pembrolizumab, 200 mg IV Q3W
Comparator(s)	SoC (comprised of one of the following): • Paclitaxel 175 mg/m2 Q3W • Docetaxel 75 mg/m2 Q3W • Vinflunine 320 mg/m2 Q3W NB: For the purpose of the analyses presented in this submission, a comparison of pembrolizumab versus only those comparators of relevance from a UK perspective are presented, herefater referred to as UK SoC (paclitaxel or docetaxel)
Outcomes collected that address committee's key uncertainties	• **OS** • **PFS** • **Time on Treatment** *Bold outcomes are included in the economic model*
Reference to section in appendix	Appendix D. - Section A.6 (page 9 to 13) Appendix D – Section A.8 (page 13 to 18); A.9 (page 20)

A.6 Key results of the data collection

Results are presented below based on a data cut-off date of 30 November 2018 [9-11] (database lock date of 13 March 2019), which occurred post final analysis of the KEYNOTE-045 study [3, 4], to support this submission to NICE for the CDF guidance review of TA519 [2] [8].

A.6.1 *OS*

OS - ITT population – KEYNOTE-045

OS was defined as time from randomisation to death due to any cause, expressed in days. Subjects without documented death were considered right censored at the day of last contact. Subjects who had survival update after the data cut-off date of 30 November 2018 [9-11] were censored at the cut-off date. OS data were analysed using the ITT approach. OS results in the ITT population of KEYNOTE-045 [3, 4], before adjusting for treatment switching, are presented in Appendix E (Table 1 and Figure 1).

OS – ITT population - analysis after adjusting for treatment switching

The KEYNOTE-045 study protocol [12] did not state that patients randomised to the SoC arm were expressly allowed to receive anti-PD-L1 or anti-PD-1 treatment after documented disease progression, but neither was it prohibited within the protocol. As the survival benefit associated with pembrolizumab is diluted due to switching, conventional survival analysis will underestimate the survival benefit associated with pembrolizumab. Therefore, for the estimation of the OS in the control arm, OS was adjusted, using the simplified 2-stage method [13] (in line with Committee preferences as per the ToE document [1]), to reflect the actual benefit of patients receiving the regimens in the control arm in the absence of treatment switching to alternative therapies, as it is reflective of clinical practice. The breakdown of the disposition of the control group is depicted in Figure 2, Appendix E. Details on the modelling approach are described in Appendix E. Results are presented in Table 2 and Figure 3, Appendix E.

OS -– Subgroup analysis (pembrolizumab versus UK SOC) - analysis after adjusting for treatment switching

For the UK base case, additional subgroup analyses were conducted (as listed below), to provide analyses of relevance for the comparison of pembrolizumab versus SoC comparators available in UK clinical practice (i.e. only docetaxel or paclitaxel, excluding vinflunine; hereafter referred to as UK SoC). The focus is on estimation with uncertainty quantified by the 95% confidence interval (CI). The sub-populations were defined as follows:

- Subjects pre-assigned by investigator, prior to randomisation, to receive either paclitaxel or docetaxel should they subsequently be randomised to the SoC arm, are included in the analyses according to the treatment group they were randomised to.
- Subjects pre-assigned by investigator, prior to randomisation, to receive paclitaxel should they subsequently be randomised to the SoC arm, are included in the analyses according to the treatment group they were randomised to.
- Subjects pre-assigned by investigator, prior to randomisation, to receive docetaxel should they subsequently be randomised to the SoC arm, are included in the analyses according to the treatment group they were randomised to.

Details on the subject disposition and baseline characteristics for these subgroups are provided in Appendix E (Tables 3 - 4 and Figure 4). Results are presented below in Table 4 and

Figure 1 for the subgroup of subjects pre-assigned to UK SoC.

Subjects Pre-Assigned to UK SoC (Paclitaxel or Docetaxel)

Table 4. Analysis of OS | No re-censoring - Subjects pre-assigned to UK SoC - ITT - Comparison pembrolizumab versus UK SoC - adjusting for treatment switch to anti-PDL1 treatment in SoC arm using 2-stage analysis

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‖
Control	182	147 (80.8)	2026.2	7.3	7.0 (5.5, 8.7)	32.2 (25.2, 39.4)	---	---
Control, Adjusted ¶	182	147 (80.8)	1559.6	9.4	6.2 (5.2, 7.4)	25.0 (18.6, 31.9)	---	---
Pembrolizumab	188	144 (76.6)	2923.5	4.9	10.1 (7.6, 12.9)	43.5 (36.3, 50.6)	0.64 (0.49, 0.81)	0.0139

Stage 1 model††	Acceleration factor‡‡
§ Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy	5.370 (3.231,10.094)

¶ Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and haemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.

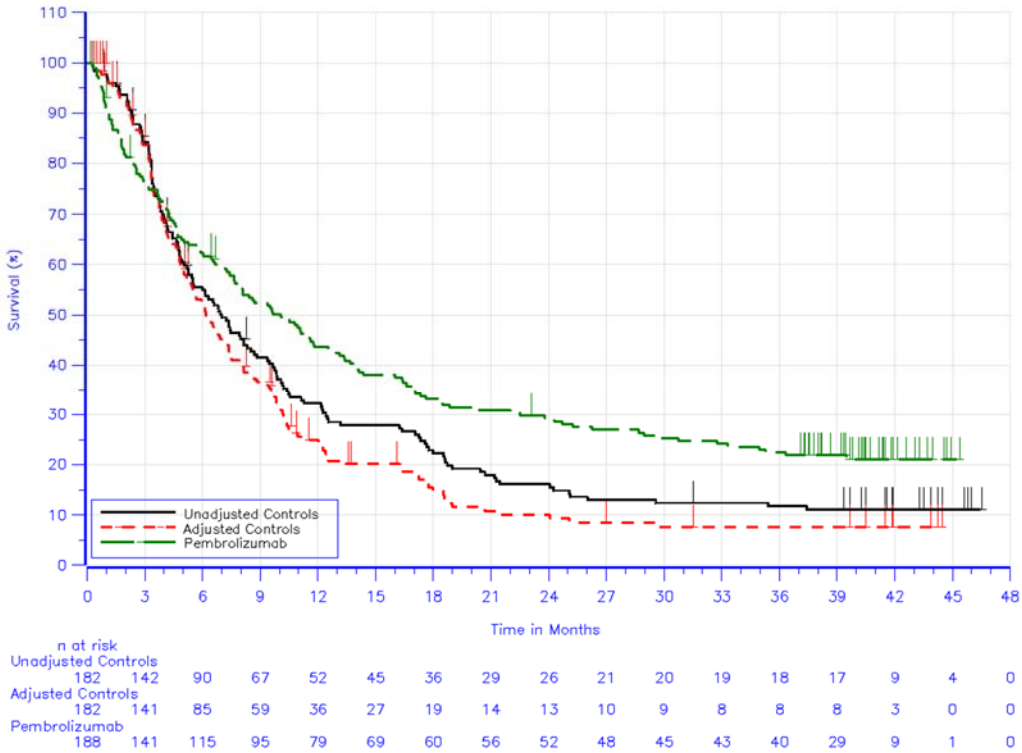
‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.

†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumour (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and haemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression.

§ Patients were eligible to receive subsequent therapy if they had documented progression.

‡‡ Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy. The 95% CI is based on the same bootstrap samples as for the Cox regression model

Figure 1. Kaplan-Meier (KM) Curves of OS Adjusting for Treatment Switch using 2-stage analysis - No re-censoring - Subjects Pre-Assigned to UK SoC - ITT



Similar results were seen in the analyses based on the two other above mentioned subgroups (subjects pre-assigned to paclitaxel and subjects pre-assigned to docetaxel), with the results for these subgroups presented in Appendix E (Tables 5 - 6 and Figures 5 - 6).

A.6.2 *PFS*

PFS - ITT population

PFS was defined as time from randomisation to the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' review or death due to any cause, whichever occurs first, expressed in days. Subjects without an event (progression or death) at the time of last tumour assessment were considered right censored at the last disease assessment date. PFS data were analysed using the ITT approach. PFS results in the ITT population of KEYNOTE-045, are presented in Appendix E (Table 7 and Figure 7)

PFS - Subgroup analysis (pembrolizumab versus – UK SoC)

Additional subgroup analysis for PFS outcome was conducted to provide analyses of relevance for the comparison of pembrolizumab versus UK SoC. The focus is on estimation with uncertainty quantified by the 95% CI.

PFS results are presented below (Table 5 and

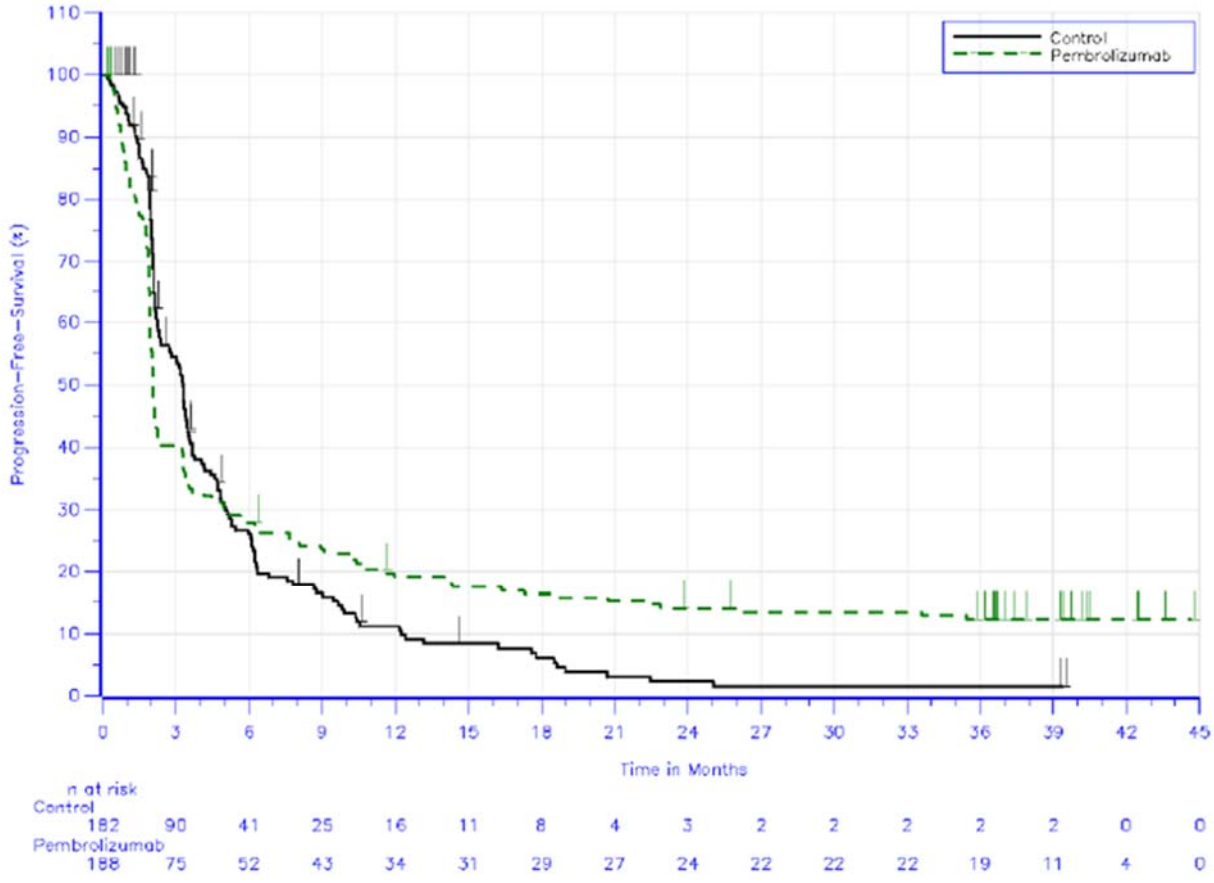
Figure *2*) for the subgroup of subjects pre-assigned to UK SoC

Table 5. Analysis of PFS Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) Subjects Pre-assigned to UK SOC ITT

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Control	182	159 (87.4)	859.7	18.5	3.3 (2.3, 3.5)	11.2 (6.8, 16.7)	---	---
Pembrolizumab	188	162 (86.2)	1512.8	10.7	2.1 (2.0, 2.2)	19.2 (13.8, 25.1)	0.95 (0.76, 1.19)	0.6183

Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (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).
‡‡ Two-sided p-value based on log-rank test.

Figure 2: KM of PFS Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) Subjects Pre-assigned to UK SoC (ITT)



A.6.3 *Time-on-treatment (ToT) – ITT population*

Results of ToT from KEYNOTE-045 from the November 2018 data cut [10] is presented in Table 6; results are presented with a breakdown by control group. Please note that only UK SoC are relevant for this submission, therefore vinflunine results have been shadowed. This data was used to inform the model as described in Section A.8.4.

Table 6. Summary of drug exposure

	Paclitaxel N=84	Docetaxel N=84	Vinflunine N=87	Pembrolizumab N=266
Time on Therapy (months)				
Mean	2.96	2.12	3.19	6.84
Median	1.45	1.43	2.10	3.45
SD	3.17	2.02	2.93	7.62
Range	0.03 to 14.19	0.03 to 10.48	0.03 to 13.50	0.03 to 24.28
Number of Administrations				
Mean	5.05	3.90	5.32	10.46
Median	3.00	3.00	4.00	6.00
SD	4.29	2.75	4.03	10.62
Range	1.00 to 21.00	1.00 to 14.00	1.00 to 19.00	1.00 to 36.00

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 30NOV2018

A.7 Evidence synthesis

Not applicable.

A.8 Incorporating collected data into the model

A.8.1 *Overall Method of Modelling Effectiveness*

The model effectiveness parameters were estimated from the KEYNOTE-045 patient-level data for OS, PFS and ToT [9-11]. Parametric models were fitted to the KM data and the survival curve fitting was carried out in line with the NICE Decision Support Unit (DSU) guidelines [14]. The proportional hazard (PH) assumption was verified to assess whether independent survival models needed to be explored in each treatment arm (i.e. independent separate survival models were explored when the PH assumption did not hold). Furthermore, the cumulative hazard plot and the log cumulative hazard plot were assessed. The parametric models fitted were the Weibull, exponential, log-normal, log-logistic, Gompertz and generalized gamma distributions. Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection (comparing fitted distribution to study KM plots), were used to select the best-fitted parametric distributions for the base case. Finally, the clinical plausibility of the extrapolated results was considered in selecting the final distribution functions for the model.

During the teleconference with NICE and the ERG on 14 June 2019 in preparation for the CDF review of TA519 [2] [8], the ERG requested that the CDF guidance review submission should include information on graphical outputs for models fitted to the data for PFS and OS, which fit a time-varying hazard ratio. Please refer to Appendix G ("ERG request") for results of these analyses.

A.8.2 *Selection of OS extrapolations:*

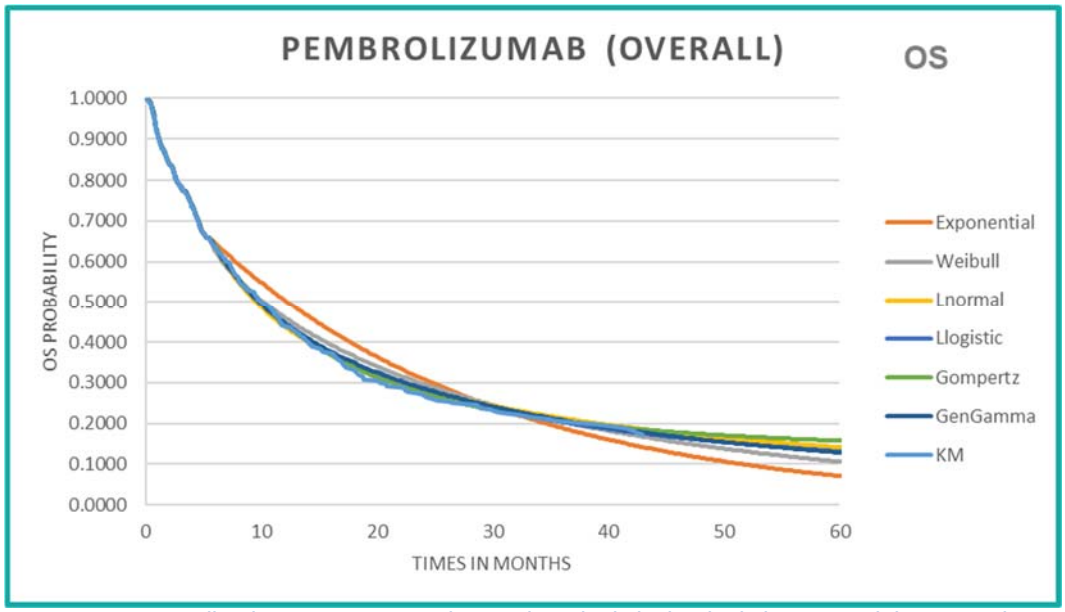
As described in Section A.6.1, a simplified 2-stage approach [13, 15] was used as the most appropriate method to adjust for the effects of switching to anti-PD-L1 or anti-PD-1 treatments from the UK SoC arm within KEYNOTE-045 [11].

The crossing of log-cumulative hazard plots of pembrolizumab and UK SoC (Appendix F, Figure 1) did not support the proportional hazard assumption. In addition, the Schoenfeld residuals plot (Appendix F, Figure 2) deviates from the y=0 horizontal line for most of the time period, which is a further indication of a violation of the proportional hazard assumption. The Schoenfeld residual test showed that there is enough evidence against the assumption of proportional hazards (p=0.011). Therefore, separate model fittings for pembrolizumab and UK SoC arm were undertaken for the projection of OS.

The cumulative hazard plot (Appendix F, Figure 3) demonstrates that the change in hazard is not constant over time in the pembrolizumab arm as well as in the UK SoC arm. Thus a 2-phase piecewise modelling approach (KM + parametric approach) was considered more appropriate than the use of single parametric model. The cumulative hazard curves start separating from week 24, while there is a clearer change in the slope after around 40 weeks. To remain consistent with the ToE document, the ERG method to start extrapolation at 24 weeks has been chosen as the base case and extrapolation at 40 weeks is presented as a scenario analysis (see Table 13).

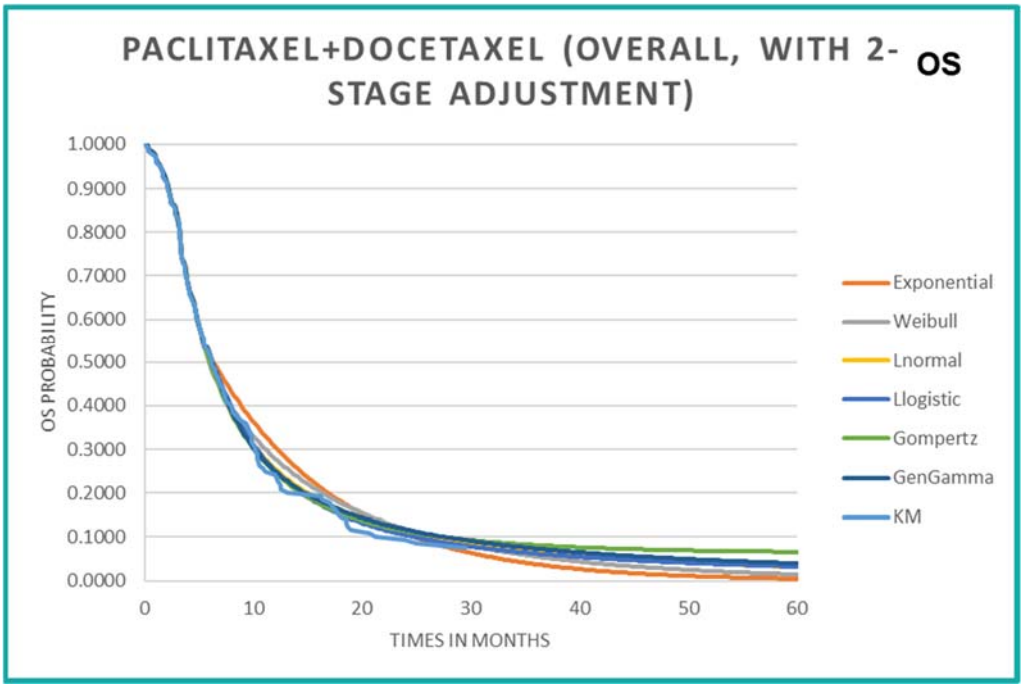
To fit and extrapolate OS after 24 weeks, a log-logistic distribution was selected for both the pembrolizumab and UK SoC arms, based on AIC/BIC criteria and visual fit of the data from the updated data-cut which informs this submission (November 2018 data-cut; see Figure 3 and Figure 4 and Appendix F, Table 1). Additionally, the log-logistic distribution yields 3.2% for 5-year survival rate for UK SoC arm which is consistent with 2-3% suggested by expert clinical opinion engaged by the ERG (FAD, section 3.15) [2]. The log-logistic distribution is also in line with the ERG preference during the original appraisal of TA519 [8], and the committee was in agreement, as confirmed in the ToE document [1] (see section A.2)

Figure 3: OS Parametric Function Fitting in the Pembrolizumab Arm



Key: GenGamma, generalized gamma; KM, Kaplan–Meier; Llogistic, log-logistic; Lnormal, log-normal; OS, overall survival.

Figure 4: OS Parametric Function Fitting in the UK SoC (Paclitaxel or Docetaxel) Arm With 2-Stage Adjustment



Key: GenGamma, generalized gamma; KM, Kaplan–Meier; Llogistic, log-logistic; Lnormal, log-normal; OS, overall survival.

A.8.3 *Selection of PFS extrapolations:*

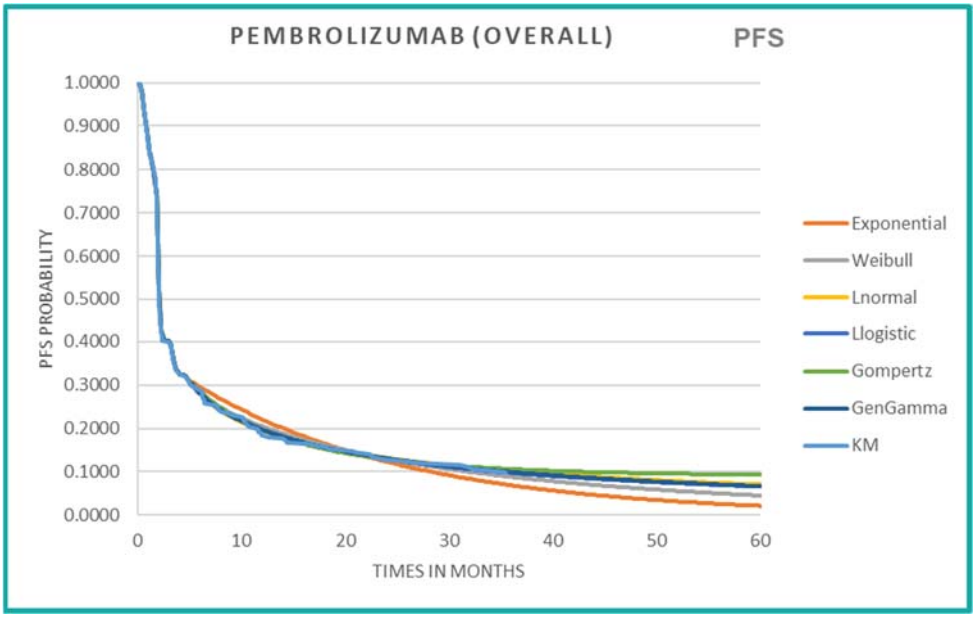
The log-cumulative hazard plot shows the plots of the two treatment arms are not parallel and cross, which signalled a violation of the proportional hazards assumption (Appendix F, Figures 4). Additionally, the Schoenfeld residuals plot (Appendix F, Figure 5) deviating from the y=0, together with the Schoenfeld residual test results ($p<0.05$), rejected the assumption of proportional hazards. Therefore, separate models were used based upon the pembrolizumab and UK SoC data separately for the projection of PFS.

A protocol-driven drop of PFS curves between weeks 0 and 9 did not allow a good visual fit with single parametric curves. Therefore, a 2-phase piecewise approach was used to fit PFS. The first point at which a clear separation occurs between the curves of the cumulative hazard plot (Appendix F, Figures 6) is at Week 21. As a result, Week 21 was used for the base case analysis, where KM data were used directly for the first 21 weeks of model time horizon, and parametric functions were fitted from then onwards.

Based on the AIC and BIC statistics and visual inspection of the data from the updated data - cut which informs this submission (November 2018 data-cut [9-11]), the log-normal parametric function was selected as the base case for the pembrolizumab arm (

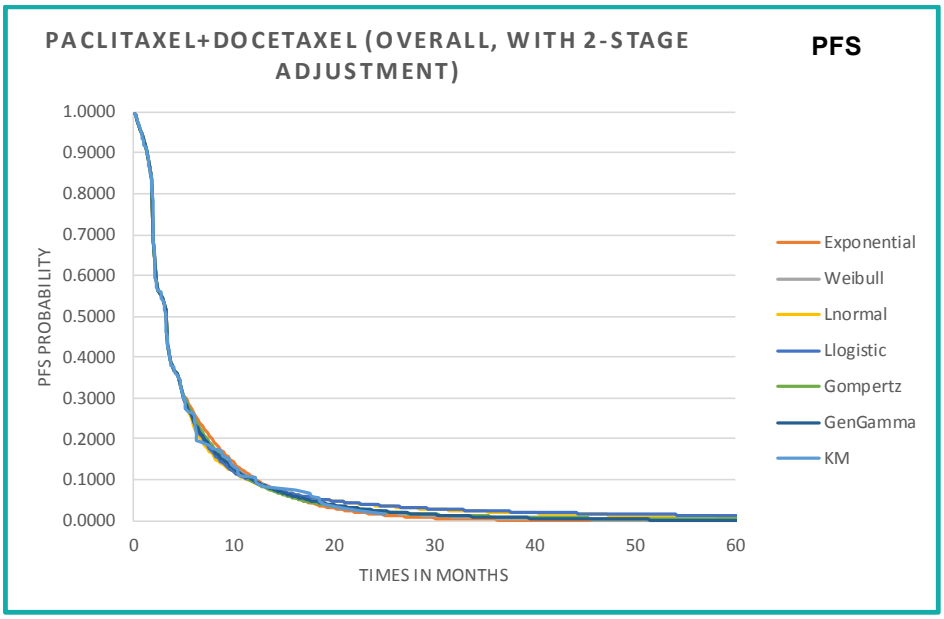
Figure 5 below and Appendix F, Table 2). For the UK SoC arm, statistical analysis was inconclusive with the Weibull function having the lowest AIC and the exponential function the lowest BIC. Given that all the functions had very similar visual fits of PFS curve, the log-normal curve was selected for the SoC arm to be consistent with the extrapolation of the pembrolizumab arm (Figure 6). Weibull was recommended by the ERG and NICE for TA519 [2] [8] based on the earlier data-cut available at the time of the original submission, and thus has been explored here through scenario analysis (see Table 13).

Figure 5: PFS KM Data with Standard Parametric Curve Fitting from 21 Weeks Onwards in the Pembrolizumab Arm



Key: GenGamma, generalized gamma; KM, Kaplan–Meier; Llogistic, log-logistic; Lnormal, log-normal; PFS, progression-free survival.

Figure 6: PFS KM Data with Standard Parametric Curve Fitting from 21 Weeks Onwards in the UK SoC (Paclitaxel or Docetaxel) Arm



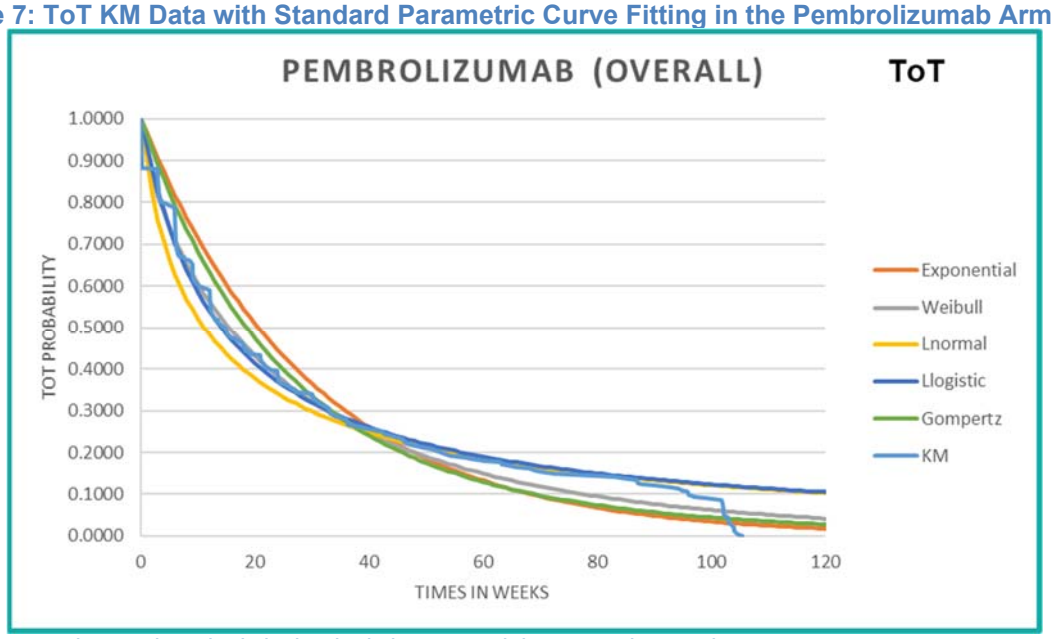
Key: GenGamma, generalized gamma; KM, Kaplan–Meier; Llogistic, log-logistic; Lnormal, log-normal; PFS, progression-free survival

A.8.4 *Time on treatment (ToT):*

As per the KEYNOTE-045 trial [10], patients were treated until RECIST-defined disease progression [16], development of unacceptable toxicity, withdrawal of consent, decision by the investigator to discontinue therapy, or the completion of 2 years of pembrolizumab therapy. For pembrolizumab, parametric functions were fitted to the ToT KM data from the updated data-cut which informs this submission (November 2018 data-cut) to estimate treatment duration (Figure 7). The generalized gamma function had the closest statistical fit based on AIC and BIC; however, it did not converge. Thus, the next closest fit, Weibull, was selected.

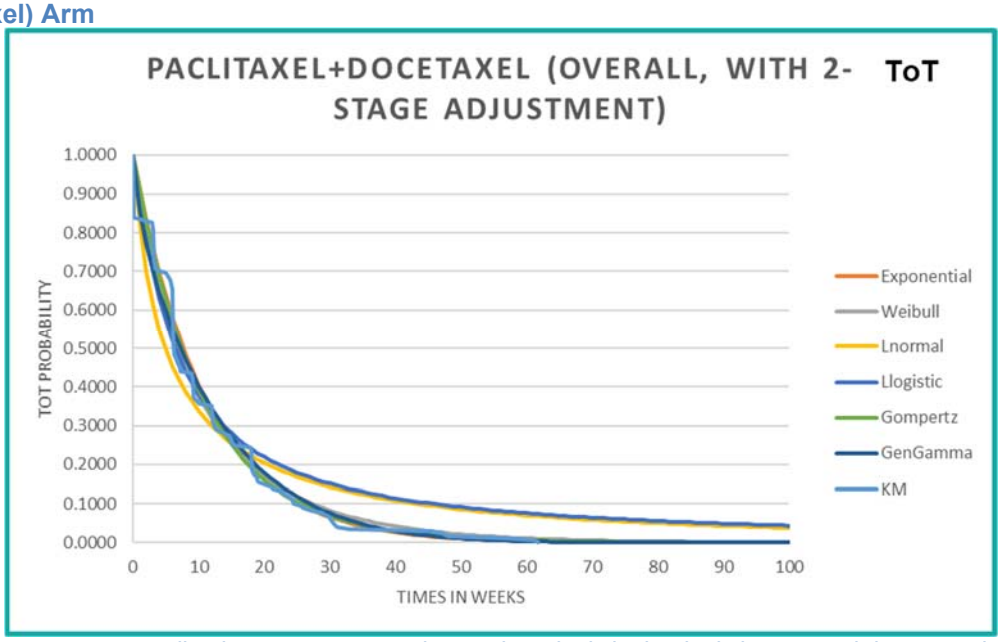
For UK SoC, the AIC and BIC combined with visual inspection of the data from the updated data-cut which informs this submission were used to select the generalized gamma distribution for the base case (Figure 8). These distributions are also in line with the original appraisal of TA519 [2] [8].

Figure 7: ToT KM Data with Standard Parametric Curve Fitting in the Pembrolizumab Arm



Key: *KM, Kaplan–Meier; Llogistic, log-logistic; Lnormal, log-normal; ToT, time on treatment.*

Figure 8: ToT KM Data with Standard Parametric Curve Fitting in the UK SoC (Paclitaxel or Docetaxel) Arm



Key: GenGamma, generalized gamma; KM, Kaplan–Meier; Llogistic, log-logistic; Lnormal, log-normal; ToT, time on treatment.

A.8.5 *Duration of treatment effect:*

A 5-year treatment effect duration (from the start of treatment) has been chosen in the company base case, which is line with committee preferred assumptions, as stated in the ToE document for CDF review [1]. The choice of at least a 5-year treatment effect is also supported by recently published 5-year data from the advanced non-small-cell-lung cancer (NSCLC) cohort in the pivotal KEYNOTE-001 trial [17], which estimates a 15.5% increased OS with pembrolizumab in previously treated patients, and provides evidence that patients treated with pembrolizumab for 2 years or more, continue to respond with the 5-year survival at 75%. The longest follow-up for pembrolizumab in any tumour type comes from the melanoma cohort of KEYNOTE-001 [18] (median follow-up 55 months), which demonstrates continued robust and durable responses in advanced melanoma; the 5-year survival rates in patients with advanced melanoma receiving pembrolizumab were 34% overall with 73% responses ongoing. These data, despite being from different tumour types, add to the body of evidence on the long-term treatment effect of pembrolizumab.

Scenario analyses have been provided which cap the duration of treatment effect of pembrolizumab at both 3 years and 10 years following the start of treatment (see Table 13).

A.9 Key model assumptions and inputs

New company base-case:

Please refer to section **Error! Reference source not found.**for details of the key committee assumptions outlined in the ToE for CDF review [1], received by MSD on 16 April 2019. With this submission, updated OS, PFS and ToT data is presented and incorporated into the economic model from a new data-cut from the KEYNOTE-045 study, dated 30 November 2018 [9-11].

The new company base case reflects the key Committee assumptions, which incorporates the ERG model corrections that were accepted by the Committee (as per the ToE document; section A.2, Table 1 [1]). Please refer to Table 7 for a summary of the company model inputs and rationale for inclusion.

Table 7: Key model assumptions and inputs

Model input and cross reference	Company's original parameter /assumption	Company's updated parameter /assumption	Source/Justification
OS data input. Company submission section B.5.3, page 175	Evidence from KEYNOTE-045 study, data cut-off September 2016 [19] and follow up data cut-off January 2017 [20]	Evidence from KEYNOTE-045 study, further data collection during CDF period – data cut-off November 2018 [9-11]	As part of the managed access agreement, further follow-up data from the pivotal trial KEYNOTE-045 has been collected beyond the pre-specified final analysis. Data from this latest data cut, dated 30 November 2018, has subsequently been incorporated into the cost-effectiveness model [9-11].
PFS data input. Company submission section B.5.3 page 182	Evidence from KEYNOTE-045 study, data cut-off September 2016 [19] and follow up data cut-off January 2017 [20]	Evidence from KEYNOTE-045 study, further data collection during CDF period – data cut-off November 2018 [9-11]	As part of the managed access agreement, further follow-up data from the pivotal trial KEYNOTE-045 has been collected beyond the pre-specified final analysis. Data from this latest data cut, dated 30 November 2018, has subsequently been incorporated into the cost-effectiveness model [9-11].
ToT data input. Company submission section B.5.5, page 202	Evidence from KEYNOTE-045 study, data cut-off September 2016 [19] and follow up data cut-off January 2017 [20]	Evidence from KEYNOTE-045 study, further data collection during CDF period – data cut-off November 2018 [9-11]	As part of the managed access agreement, further follow-up data from the pivotal trial KEYNOTE-045 has been collected beyond the pre-specified final analysis. Data from this latest data cut, dated 30 November 2018, has subsequently been incorporated into the cost-effectiveness model [9-11].
Modelling PFS. Company submission section B.5.3.3 page 182	Weibull curve to extrapolate PFS	Log normal parametric curve to extrapolate PFS	Goodness of fit statistics and visual inspection shows that log normal is the best fitting extrapolation for the updated clinical data (see section **Error! Reference source not found.**)

Modelling OS. Company submission section B.5.3.2 page 176	Log normal parametric curve to extrapolate OS	Log logistic parametric curve to extrapolate OS.	Goodness of fit statistics and visual inspection shows that the Log logistic is the best fitting extrapolation for the updated clinical data. Additionally, extrapolation with this choice of curve provides results that are consistent with the Expert clinical opinion concerning 5-year OS in the SoC arm, as preferred by the ERG and accepted by the committee (see section **Error! Reference source not found.**)
Time point at which to extrapolate OS trial data using a piecewise model. Company submission section B.5.3.2 page 202	40 weeks cut-off point	24-week cut-off point	Preferred by ERG at the time of the original submission (and reflected in the ToE document) based on crossover of cumulative hazards and consistent start of separation of KM OS curves. These assumptions still hold for the new data cut-off of November 2018 [9-11] (see section **Error! Reference source not found.**).
Duration of continued treatment effect. Final appraisal determination section 3.16, page 14	Lifetime continued treatment effect	Continued treatment effect capped at 5 years after starting pembrolizumab treatment	The committee was aware that the duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty for new immunotherapies. Therefore, the Committee preference was to cap at 3 years and 5 years following the start of treatment. A 3-year and 10-year cap is presented as scenario analyses, see section A.12 and Table 13.
Utility estimates. Company submission section B.5.4.1, page 186	Utilities based on time to death	Utilities based on progression state	Utilities based on progression state, and current age-related disutility have been applied in this submission, as preferred by the ERG and specified in the ToE document [1].
Utility estimates Company submission section B.5.4.1	Vinflunine data included and pooled across treatment arms	Vinflunine data should be excluded and pooled across treatment arms	As specified in the ToE document, the committee concluded that vinflunine is not used in clinical practice and should therefore be excluded. This approach has been followed in this submission
Posology. SmPC sections 4.2 and 5.1 [7]	The recommended dose of KEYTRUDA as monotherapy is 200mg every 3 weeks (Q3W) administered as an intravenous infusion over 30 minutes.	The recommended dose of KEYTRUDA as monotherapy is either 200 mg Q3W or 400 mg every 6 weeks (Q6W) administered as an intravenous infusion over 30 minutes. The latter dosing regimen (400mg Q6W) is an additional dosing regimen which was not licensed at the time of the original	On 28 March 2019, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for a new extended dosing schedule applicable to all monotherapy indications of Keytruda (pembrolizumab) in the European Union [7] [21]. 100% of patients treated with the new extended schedule is presented as a scenario (see Table 13)

		submission. However, for the base case we continue to assume the old dosage being used for consistency with the previous submission.	
Patient Access Scheme (PAS) Contract variation agreement no. [redacted]	The economic analyses undertaken included a PAS discount of the cost of pembrolizumab	The economic analyses undertaken includes a new PAS discount of the cost of pembrolizumab	Updated to reflect the PAS discount that is now applied to the supply of pembrolizumab through routine commissioning for indications approved by NICE, as the PAS discount [redacted] since the time of the original submission.

A.10 Cost-effectiveness results (deterministic)

A.10.1 *Replication of the key cost-effectiveness result(s) considered by committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF*

The results of the economic model that reflect the data-cuts provided during the original appraisal (September 2016 [19] and January 2017 data-cuts [20]), are presented in Table 8 below. NICE TA519 [2, 8] stated that pembrolizumab has plausible potential to be cost effective. When applying the key committee assumptions, committee agreed corrections from the ERG's model and a 5-year continued treatment effect, this resulted in the plausible ICER at CDF entry of £59,729.

Table 8: Cost effectiveness results at CDF entry: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
UK SoC	[redacted]	1.20	0.80	-	-	-	-	-
Pembrolizumab	[redacted]	2.25	1.50	£41,607	1.05	0.70		£59,729

Incorporating committee preferred assumptions, committee agreed corrections from the ERG's model and a 5-year duration of treatment effect - (discounted with original PAS)

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

A.10.2 *Cost-effectiveness results that incorporate the data collected during the CDF data collection period, with all model inputs and parameters unchanged from cost-effectiveness analysis provided in the above section A.10.1*

Compared to Table 8 above, the cost effectiveness results provided in Table 9 below incorporates the data collected during the CDF collection period (data cut-off 30 November

2018 [9-11]), but with all model inputs and parameters unchanged from the Committee and ERG preferences at the time of the original appraisal. This generates an ICER of £54,743 (see Table 9).

Table 9: Cost effectiveness results with CDF data collection and model input and parameters unchanged from the cost effectiveness analysis at CDF entry

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
UK SoC	[redacted]	1.06	0.71	-	-	-	-	-
Pembrolizumab	[redacted]	2.14	1.43	£39,215	1.09	0.72		£54,743
Incorporating committee preferred assumptions, committee agreed corrections from the ERG's model and a 5-year duration of treatment effect - (discounted with original PAS)								
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

A.10.3 *Cost-effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions*

Compared to Table 9 above, the cost-effectiveness results shown in Table 10 below, not only incorporate data collected during the CDF data collection period, but also reflect a change to the committee and ERG preferred assumptions, justifiable based on the new data. This change made by MSD, is the choice of a Log normal rather than a Weibull PFS curve (please see section A.8.3 for the PFS curve selection). Additionally, the results incorporate a revised PAS which is detailed in Table 7. The updated model shows that patients treated with pembrolizumab accrued 1.46 QALYs compared to 0.72 among patients in the UK SoC cohort. The corresponding ICER when pembrolizumab is compared to UK SoC was £47,123. These results demonstrate pembrolizumab to be cost-effective compared to UK SoC when considering a willingness to pay threshold of £50,000 per QALY.

Table 10 Cost-effectiveness results with CDF data collection plus any associated changes: New company base-case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
UK SOC	[redacted]	1.06	0.72	-	-	-	-	-
Pembrolizumab	[redacted]	2.14	1.46	£35,035	1.09	0.74		£47,123
Incorporating committee preferred assumptions and ERG's model corrections as outlined in the ToE for CDF review (discounted with new PAS and Log normal PFS extrapolations)								
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

A.11 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The incremental cost-effectiveness results obtained from the PSA are presented in Table 11. The results show that the PSA results are very similar to the deterministic results.

Table 11 Updated base-case results (probabilistic) – B.5.8.1 (page 218)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
UK SOC	[redacted]	1.06	0.72					
Pembrolizumab	[redacted]	2.15	1.46	£35,184	1.08	0.74		£47,734

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

The corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 9 and

Figure *10*. The cost-effectiveness acceptability curve shows that there is approximately a 63% probability of pembrolizumab being cost-effective when compared to UK SoC at the £50,000 per QALY threshold applicable to end-of-life technologies.

Figure 9 Scatterplot of probabilistic results (1,000 simulations; results discounted, with PAS) – B.5.8.1 (page 219)

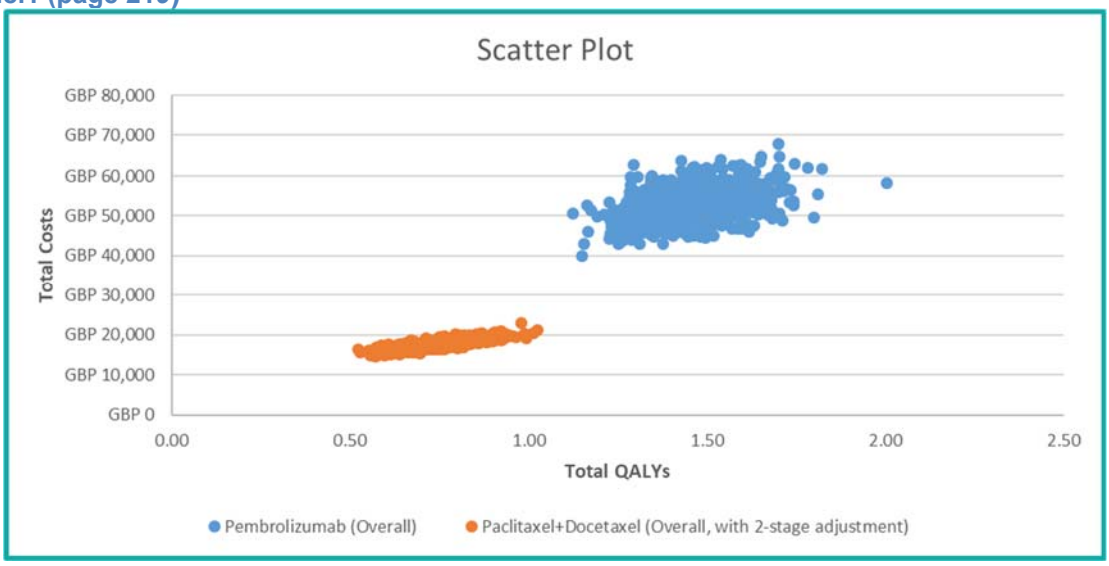
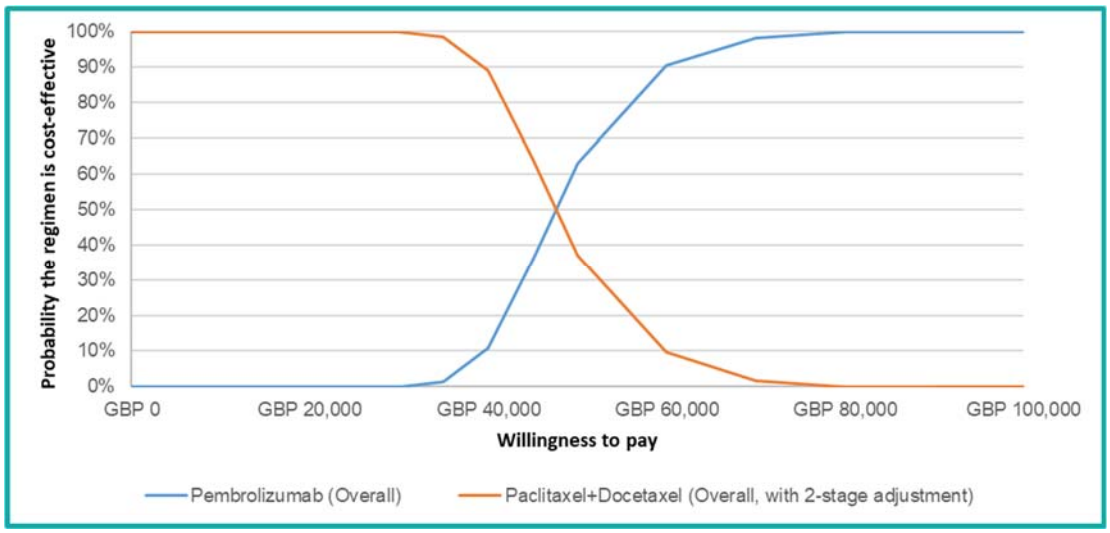


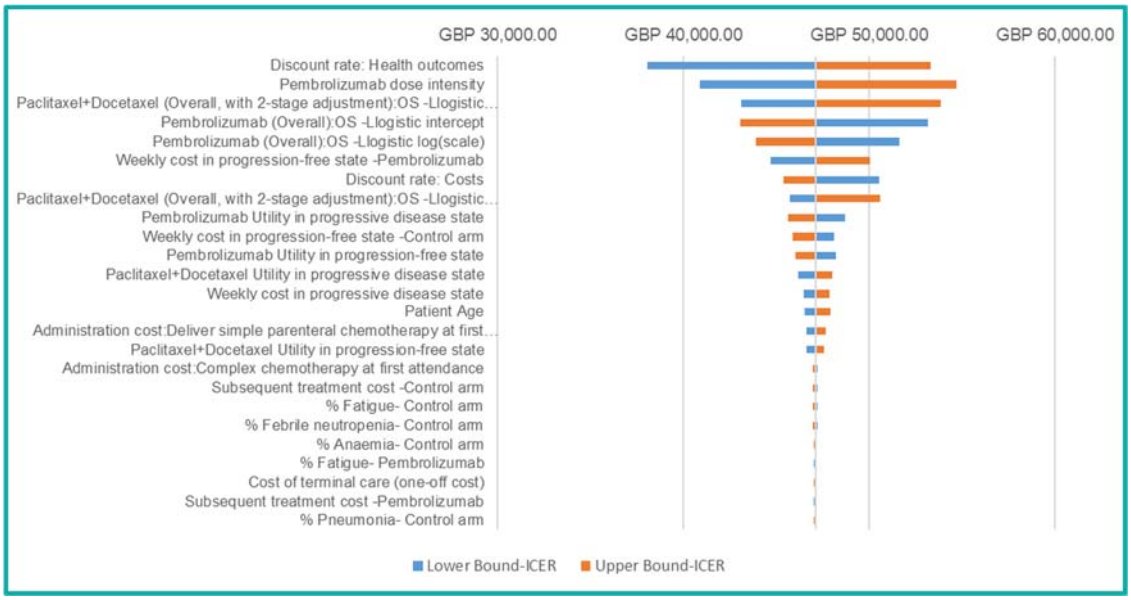
Figure 10: Cost-effectiveness acceptability curve (results discounted, with PAS)



A.12 Key sensitivity and scenario analyses

The tornado diagram depicted in Figure 11 shows the impact of parameter variation on the ICER as derived from the one-way sensitivity analysis (OWSA) for pembrolizumab versus UK SoC. The variations that had the most impact on the ICER for both pembrolizumab versus UK SoC were the discount rate for health outcomes, dosing intensity of pembrolizumab, and the extrapolation of OS.

Figure 11: Tornado Diagram for the Incremental Cost-Effectiveness Ratio of Pembrolizumab versus UK SoC (Discounted) - B.5.8.2 (page 221)



Detailed results of the OWSA are presented in Table 12. The ICER ranged from £38,073/QALY to £54,710/QALY for pembrolizumab versus UK SoC.

Table 12: One-Way Sensitivity Analysis Results (Discounted - Pembrolizumab versus UK SoC (Paclitaxel or Docetaxel)

Parameter	Lower bound-ICER	Upper bound-ICER
Discount rate: Health outcomes	38073	53337
Pembrolizumab dose intensity	40883	54710
Pembrolizumab (Overall):OS -Llogistic intercept	53199	43062
Paclitaxel+Docetaxel (Overall, with 2-stage adjustment):OS -Llogistic intercept	43141	53880
Pembrolizumab (Overall):OS -Llogistic log(scale)	51650	43938
Weekly cost in progression-free state -Pembrolizumab	44712	50054
Discount rate: Costs	50581	45399
Paclitaxel+Docetaxel (Overall, with 2-stage adjustment):OS -Llogistic log(scale)	45739	50620
Pembrolizumab Utility in progressive disease state	48740	45635
Pembrolizumab Utility in progression-free state	48246	46068
Key: ICER, incremental cost-effectiveness ratio; Llogistic, log-logistic; OS, overall survival; PF, progression free; PP, post-progression; PFS, progression-free survival.		

Scenarios were conducted to test the uncertainty within the model and parameter uncertainty.

The scenarios tested include:

- Alternative week cut-off for OS extrapolation
- Alternative treatment effect cap for OS
- Alternative pembrolizumab dosing schedule
- Alternative parametric function for PFS

For each scenario, the resulting ICERs are described in Table 13.

Table 13 Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			**£47,123**
1. Cut-off point from which to start extrapolation of OS using the log-logistic curve in the second phase of the piecewise approach. A 24-week cut-off was chosen in the base-case to be in line with committee accepted assumptions as stated in the ToE [1] (section A.2.Table 1, extrapolation of OS).	40-week cut-off point for OS extrapolation	A longer cut-off point (40 weeks) from which to start extrapolation allows for the full use of the OS KM curve and therefore maximises the use of the trial data. Additionally, a clear change in slope of the KM curve occurs later at week 40.	£45,877 (-£1,246)
2. Long term treatment effect. 5-year cap on the benefits of pembrolizumab from the start of treatment	3-year cap on benefits of pembrolizumab from the start of	3 years chosen as a scenario based on committee accepted assumption of 3 or 5 years.	£51,970 (+4,847)

was used in the base case to be consistent with the Committee accepted assumption as stated in the ToE [1] (section A.2.Table 1, Duration of treatment effect).	treatment and a longer 10-year cap on the benefits	10 years chosen in view of clinical trial data and clinical expert opinion, which suggests that longer term duration of treatment effect is associated with immunotherapies due to their distinct mechanism of action [17, 18].	£44,173 (-£2,950)
3. Dosing schedule. The base case includes 100% of patients on the dosing schedule used in the original submission (200 mg Q3W), which was the only licensed dosing scheduled at that time (original company submission section 1.2, table 2, mode of administration and dosage).	100% of patients on the new extended dosing schedule of 400 mg every 6 weeks (Q6W) administered as an intravenous infusion.	On 28 March 2019, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for a new extended dosing schedule for pembrolizumab for all the monotherapy indications in the European Union [7] [21].	£47,652 (+£529)
4. Choice of PFS extrapolation curve for both pembrolizumab arm and control arm. The log-normal was used to extrapolate PFS in the base case (see section A.8.3 for explanation of PFS curve selection).	Weibull function to extrapolate PFS	Weibull was recommended by the ERG and NICE for TA519 [22], and thus was explored here through scenario analysis.	£48,518 (+1,395)

A.13 Key issues and conclusions based on the data collected during the CDF review period

Pembrolizumab for previously treated advanced or metastatic urothelial cancer meets NICE's criteria to be considered as a life extending treatment at the end of life. During the original appraisal (TA519 [2, 8, 22]), the Committee considered that pembrolizumab has plausible potential to be cost-effective, and that further data collection would reduce the uncertainty around OS and continued treatment effect; therefore, a recommendation was made as an option for use in the CDF. To adhere to the commitment made in the Data Collection Agreement which formed part of the Managed Access Agreement for TA519 [8] (Appendix H), an additional data-cut, dated November 2018, has been conducted from the KEYNOTE-045 trial data [9-11], which is beyond the pre-specified final analysis. As agreed with NICE, only OS, PFS and ToT data has been updated – all other data variables remain as per the original submission (e.g. AEs and utilities) [23]. This data, which forms the basis of this CDF guidance review, provides an additional ~23 months of follow-up data beyond the latest available data-cut (January 2017 [20]) provided during the original appraisal (clarification questions stage).

The results from the November 2018 data-cut [9-11] provide unequivocal evidence that treatment with pembrolizumab is superior to the UK SoC. The adjusted OS analysis using a 2-stage model for the November 2018 data shows that pembrolizumab substantially reduces the risk of death by 36% compared with UK SoC in patients with previously treated advanced or metastatic urothelial cancer (Table 4). The results are not only consistent with previous data-cuts, which used the same analysis approach (January 2017 data-cut HR = 0.72 [20]), but also demonstrates a continued improvement in OS over the time with pembrolizumab when compared to UK SoC.

The cost-effectiveness of pembrolizumab has again been evaluated through a three-state (PFS, post-progression and death) partitioned survival model, which projected health outcomes (i.e. OS and PFS) to estimate patients' HRQoL and costs. QALYs were estimated by considering progression-based utilities derived from EQ-5D data collected in KEYNOTE-045 trial [4, 9-11]. Clinical and economic outcomes were projected over a 35-year time horizon to cover the anticipated lifetime of the population initiating second-line therapy and assessed as part of this submission.

A 2-phase piecewise approach was used based on KEYNOTE-045 data [4, 9-11], following NICE DSU guidance [13-15]. With the incorporation of the updated OS, PFS and ToT data from the November 2018 data-cut [9-11], the model estimates that patients treated with pembrolizumab gain 0.74 additional QALYS compared to UK SoC. The ICER when comparing pembrolizumab to UK SoC is [redacted] at NHS list prices. A patient access scheme comprising of a simple discount to the list price of pembrolizumab has been agreed with NHS England (last revised 09 November 2018) and when this is applied to the drug acquisition cost of pembrolizumab, the ICER is reduced to £47,123. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per QALY gained is 63%. The results demonstrate that pembrolizumab, as an end of life therapy, meets the NICE criteria to be considered a cost-effective use of NHS resources. The improved ICER is within the threshold of £50,000 per QALY for 'end-of-life' technologies which the committee has previously agreed applies to pembrolizumab for the treatment of advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

Results from multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY (discounted, with the PAS). The inputs that mostly effect the cost-effectiveness analyses results were the discount rates for health outcomes, the dose intensity, and extrapolation of OS. The sensitivity analyses conducted demonstrated that the cost-effectiveness of pembrolizumab is resilient to the different sources of uncertainty assessed.

The base-case analyses cover the all-comers population, given that KEYNOTE-045 [4, 9-11] demonstrated efficacy in patients regardless of PD-L1 subgroup, and the current NICE guidance (TA519 [8]) is reflective of an all-comers population. In conclusion, pembrolizumab offers a cost-effective option, representing value for money for the NHS, with an innovative mode of action and demonstrable survival benefit in patients with previously treated advanced or metastatic urothelial cancer.

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14 August 2019

Dear Linda,

Re. ID1536: CDF guidance review – Pembrolizumab for previously treated advanced or metastatic urothelial cancer (TA519)

Please find enclosed MSD's responses to the clarification questions from the ERG, concerning the clinical and cost effectiveness data for the above-mentioned CDF guidance review submission.

We believe that we have addressed all of the questions but should you or the ERG require any further clarification, please do not hesitate to contact us.

Best regards,

Kalpana D'Oca
Team Lead – HTA & OR

Section A: Clarification on effectiveness data

Question A1. Priority question:

Please can you provide the following:

a) For pembrolizumab vs. standard of care (SoC) including vinflunine:
   - Overall survival (OS) hazard ratio with 95% confidence interval (CI) for the intention to treat (ITT) population, PD-L1 ≥1% and PD-L1≥ 10% subgroups.
   - Progression-free survival (PFS) hazard ratio with 95% CI for the ITT population, PD-L1 ≥1% and PD-L1≥ 10% subgroups.

   Please ensure these are all without adjustment for treatment switching.

b) For pembrolizumab vs. UK SoC (excluding vinflunine):
   - OS hazard ratio with 95% CI for the ITT population, PD-L1 ≥1% and PD-L1≥ 10% subgroups.
   - PFS hazard ratio with 95% CI for the ITT population, PD-L1 ≥1% and PD-L1≥ 10% subgroups.

   Please ensure these are all without adjustment for treatment switching.

Company response A1. a)

For pembrolizumab vs. SoC (including vinflunine) please find in Table 1 the OS hazard ratio (HR) with 95% CI for the ITT population, as well as the PD-L1 ≥1% and PD-L1≥ 10% subgroups. Please note that the OS HR and related 95% CI for the ITT population had already been provided in the CDF guidance review submission (Appendix E [Table 1 and Figure 1]). As requested, these results are without adjustment for treatment switching.

Table 1. OS for ITT population and by PD-L1 status (≥1% and ≥ 10% cut-off) point estimate and 95% CI (ITT Population)

	Control		Pembrolizumab		Pembrolizumab vs. control HR (95% CI) †
	N	N. of events (%)	N	N. of events (%)	
Overall (ITT)	272	224 (82.4)	270	213 (78.9)	0.72(0.59,0.87)
PD-L1 ≥ 1%	120	99 (82.5)	110	82 (74.5)	0.59(0.43,0.80)
PD-L1 ≥ 10%	90	73 (81.1)	74	55 (74.3)	0.56(0.38,0.82)

† Based on Cox regression model with treatment as covariates and stratified by ECOG Performance Scale (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
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine

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For pembrolizumab vs. SoC (including vinflunine) please refer to Table 2 which shows the PFS HR with 95% CI for the ITT population, as well as the PD-L1 ≥1% and PD-L1≥ 10% subgroups. Please note that the PFS HR and related 95% CI for the ITT population had already been provided in the CDF guidance review submission (Appendix E [Table 7 and Figure 7]).

As requested, these results are without adjustment for treatment switching.

Table 2. PFS based on RECIST 1.1 per Central Radiology Assessment (Primary Censoring Rule) for ITT population and by PD-L1 status (≥1% and ≥ 10% cut-off) point estimate and 95% CI (ITT Population)

	Control		Pembrolizumab		Pembrolizumab vs. control HR (95% CI)
	N	N. of events (%)	N	N. of events (%)	
Overall (ITT)	272	238 (87.5)	270	239 (88.5)	0.96(0.80,1.16)
PD-L1 ≥ 1%	120	105 (87.5)	110	93 (84.5)	0.92(0.69,1.24)
PD-L1 ≥ 10%	90	78 (86.7)	74	64 (86.5)	0.94(0.66,1.34)

† Based on Cox regression model with treatment as covariates and stratified by ECOG Performance Scale (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
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Company response A1. b)

For pembrolizumab vs. UK SoC (excluding vinflunine) please find in Table 3 the OS HR with 95% CI for the ITT population. Table 4 and 5 present the OS HR with 95% CI for PD-L1 ≥1% and PD-L1≥ 10% subgroups respectively. As requested, these results are without adjustment for treatment switching.

Table 3. Analysis of OS - Subjects Pre-assigned to UK SoC (paclitaxel or docetaxel) ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Control	182	147 (80.8)	2026.2	7.3	7.0 (5.5, 8.7)	32.2 (25.2, 39.4)	---	---
Pembrolizumab	188	144 (76.6)	2923.5	4.9	10.1 (7.6, 12.9)	43.5 (36.3, 50.6)	0.74 (0.59, 0.94)	0.0139

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (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).
‡‡ Two-sided p-value based on log-rank test.

Table 4. Analysis of OS Subjects Pre-assigned to UK SoC (paclitaxel or docetaxel) (PD-L1 ≥ 1% population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Control
							Hazard Ratio‡ (95% CI)‡
Control	87	70 (80.5)	934.3	7.5	7.0 (4.8, 9.5)	31.5 (21.5, 41.9)	---
Pembrolizumab	86	63 (73.3)	1437.9	4.4	11.6 (7.7, 16.4)	48.6 (37.6, 58.8)	0.58 (0.40, 0.84)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by ECOG Performance Scale (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).

Table 5. Analysis of OS Subjects Pre-assigned to UK SoC (paclitaxel or docetaxel) (PD-L1 ≥ 10% population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Control
							Hazard Ratio‡ (95% CI)‡
Control	69	54 (78.3)	714.4	7.6	5.2 (4.1, 8.7)	28.9 (18.1, 40.5)	---
Pembrolizumab	58	42 (72.4)	895.0	4.7	8.1 (5.0, 14.1)	42.5 (29.4, 55.0)	0.51 (0.32, 0.81)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified ECOG Performance Scale (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).

For pembrolizumab vs. UK SoC (excluding vinflunine) please refer to Table 6 and 7 which show the PFS HR with 95% CI for the PD-L1 ≥1% and PD-L1≥ 10% subgroups respectively. As requested, these results are without adjustment for treatment switching. The PFS HR and related 95% CI for the UK SoC (excluding vinflunine) ITT population, unadjusted for treatment switching, were already provided in the CDF guidance review submission (company submission [Table 5 and Figure 2]).

Table 6. Analysis of PFS Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) Subjects Pre-assigned to UK SoC (paclitaxel or docetaxel) (PD-L1 ≥ 1%) - ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Control Hazard Ratio‡ (95% CI)‡
Control	87	75 (86.2)	421.9	17.8	3.3 (2.4, 3.5)	10.7 (5.0, 18.8)	---
Pembrolizumab	86	71 (82.6)	764.1	9.3	2.1 (2.0, 3.4)	21.1 (13.2, 30.3)	0.88 (0.63, 1.25)

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by ECOG Performance Scale (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).

Table 7. Analysis of PFS Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) Subjects Pre-assigned to UK SoC (paclitaxel or docetaxel) (PD-L1 ≥ 10%) - ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. Control Hazard Ratio‡ (95% CI)‡
Control	69	59 (85.5)	296.7	19.9	3.3 (2.3, 3.5)	8.7 (3.2, 17.6)	---
Pembrolizumab	58	49 (84.5)	469.2	10.4	2.1 (1.9, 3.4)	17.4 (8.9, 28.2)	0.86 (0.57, 1.29)

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by ECOG Performance Scale (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).

Question A2:

Figure 2 of Appendix E of the company submission appendices appears to show that some patients who were eligible for switching to anti-PD-L1 treatment did not crossover, and that some patients who were ineligible for switching did receive anti-PD-L1 treatment. Please provide further explanation of this.

Company response A2:

In the context of the 2-stage method of analysis that aims to adjust for subjects receiving subsequent therapy, subjects who experienced documented disease progression (PD) (per RECIST 1.1) were defined as being eligible to receive subsequent anti-PD-1/PD-L1 therapy. This definition was separate and unrelated to the contents of the protocol amendment (MK-

3475-045-15; finalised on 14-Dec-2016, Appendix 1) that provided details around eligibility of subjects on the control arm who stop receiving investigator's choice of paclitaxel, docetaxel or vinflunine, and developed PD per RECIST 1.1 to enter the Crossover Phase for treatment with pembrolizumab (refer to Section 7.1.5.2.2 of the protocol for eligibility criteria).

It is at the investigator's and subject's discretion as to how to treat following discontinuation from study treatment. As a result, eligibility for subsequent therapy, outside of subjects that qualified for the Crossover Phase, is not defined in the protocol. There might be multiple reasons why a subject in the control arm, that did not discontinue study treatment due to confirmed PD (per RECIST 1.1), may have switched to a subsequent anti-PD-1/PD-L1 therapy. The specific reasons are not available but could include subjects that discontinued study treatment for progression not supported by RECIST 1.1 (i.e., clinical progression) and adverse events (AE).

Conversely, not all subjects in the control arm who experienced documented PD received subsequent anti-PD-1/PD-L1 therapy. The specific reasons are not available but could include subjects that discontinued study treatment due to fatal PD, as well as subjects that died prior to having the opportunity to receive an anti-PD-1/PD-L1 therapy. Additionally, it could include subjects that discontinued due to PD, but then withdrew consent from further participation in the study and subsequent therapy was not obtained.

Section B: Clarification on cost-effectiveness data

Survival data

Question B1. Priority question:

Please provide figures equivalent to Figure 3 and Figure 4 in the company submission, but on the cumulative hazard scale (i.e. one treatment and one time-to-event outcome per figure, combining observed data with all fitted parametric models). Please produce a separate pair of figures for models fitted at each cut-point included in the economic model (PFS: 9, 15, 21 and 27 weeks; OS: 16, 24, 32 and 40 weeks). Please also provide additional figures on OS and PFS scales at the other cut-points that are not already provided (PFS: 9, 15 and 27 weeks; OS: 16, 32 and 40 weeks).

Company response B1:

The requested analyses are provided below. However as stated during the teleconference arranged with NICE/ERG on 08 August 2019 to discuss the clarification questions, MSD would like to reiterate that the rationale for this request seems unclear; from MSD's perspective, the appropriate cut-point for the OS model was a subject discussed at length during the original

appraisal of TA519, as described below. MSD believes that the approach taken in our CDF guidance review submission dated 24 July 2019 appropriately addresses the consensus reached during the original appraisal.

- During the original appraisal of TA519, MSD provided additional analysis in response to clarification questions. A full sensitivity analysis of the week 16 cut-point was provided at this time, along with an updated cost-effectiveness model including this cut point in order to allow the ERG the opportunity to explore this further. Addendum 2 of the ERG report dated 06 October 2017 stated, "*The ERG believes that the 24-week cut-off for OS should be used as it is from this point that the hazard has stabilised and demonstrates behaviour that is representative of the hazard moving forward in time….*".
    - We note that during the teleconference with NICE/ERG on 08 August 2019, when MSD queried the rationale for this request, the ERG stated they wish to explore the same rationale that was used for choosing the PFS cut-point for the 2-piece model (i.e. curves crossing), as the basis for further investigating the cut-points for the OS model; in particular, the earlier week 16 cut-point when the cumulative hazard curves demonstrate that the pembrolizumab and UK SoC arms first cross.
    - While MSD acknowledges that the cumulative OS curves do indeed cross at week 16, the plot below in Figure 1 (replicated from Figure 3 in Appendix F of the CDF guidance review submission) shows the curves converge again and only start to consistently move apart after week 24, which is consistent with the above-mentioned ERG position at the time of the original appraisal of TA519. This is more clearly depicted in Figure 2 (replicated from Figure 1 in Appendix F of the CDF guidance review submission) which depicts the log scale (log-CH plot, converge at 3.2, and exp(3.2)=24).

Figure 1. Cumulative hazard plot of OS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and UK SoC based on KEYNOTE-045 (November 2018 data-cut, with adjustment for control)

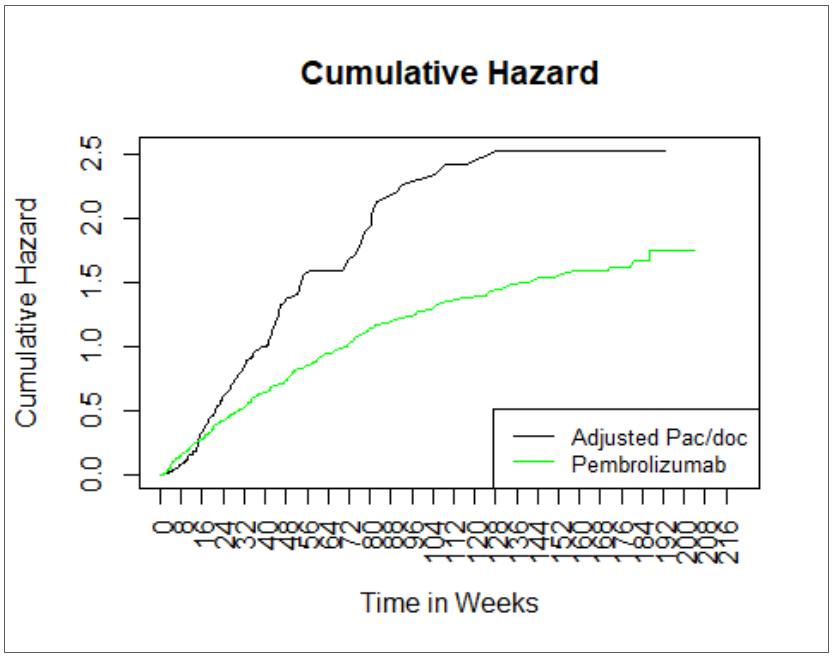
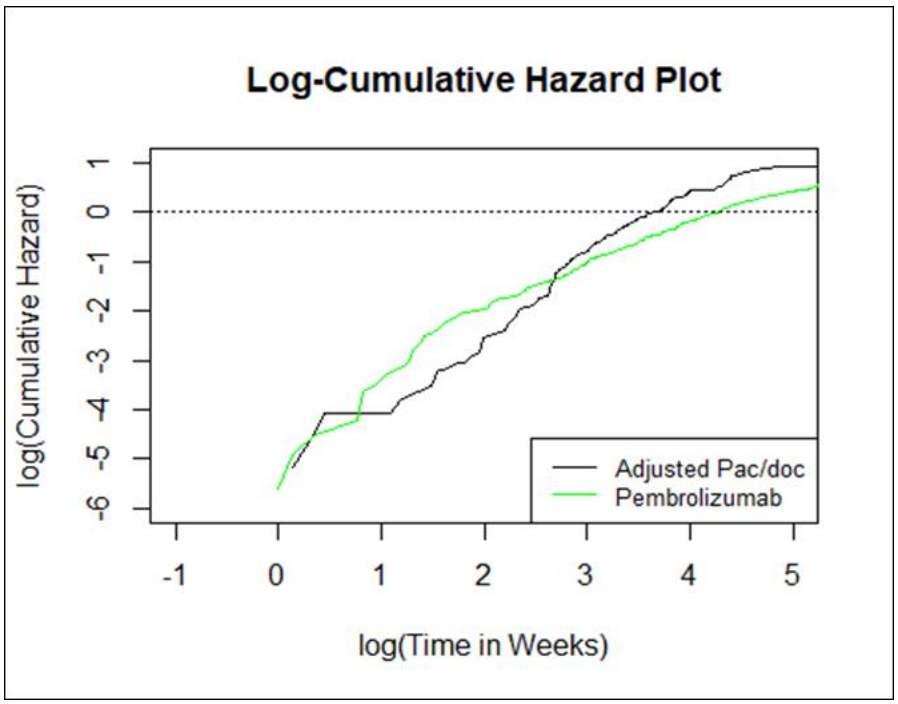


Figure 2. Log-cumulative hazard plot for OS from KEYNOTE-045 (two-stage adjustment for control) (November 2018 data-cut)



- In TA519 published on 25 April 2018, section 3.14 states that the Committee concluded that using either time point (week 24 or week 40) to extrapolate the trial data could be plausible and it was unable to judge the most appropriate time point for decision-making. The committee therefore considered both time points in its decision-making.

- The Terms of Engagement (ToE) for CDF review of TA519 very clearly tabulates the key committee assumptions, and under the section 'ERG model corrections', states that the committee agree with the ERG in extrapolating the overall survival trial data at 24 weeks. Consequently, in our base case presented in the CDF guidance review submission dated 24 July 2019, MSD had included the ERG preferred week 24 cut-point. Sensitivity analysis was presented which reflected the 40-week cut point from which to extrapolate overall survival.
- MSD would like to emphasise that the additional data collected during the CDF collection period provides further data to extend the KM curve. The first 40-week period in which the appropriate cut-point is being explored for OS extrapolation does not change; therefore the cumulative survival curves which are used to explore the appropriate position of the cut-point remains unchanged from those reviewed at the time of the original appraisal of TA519.

To answer the request in Question B1, the following is provided below:

- Figure 3 to Figure 6: OS and PFS parametric function fitting in the pembrolizumab and UK SoC arms on the cumulative hazard scale, for the base-case cut-point (OS: 24 weeks; PFS: 21 weeks).
- Figure 7 to Figure 18: OS and PFS parametric function fitting in the pembrolizumab and UK SoC arms on the cumulative hazard scale, fitted at other cut-points (OS: 16, 32 and 40 weeks; PFS: 9, 15 and 27 weeks).
- Figure 19 to Figure 30: Additional figures on OS and PFS scales depicting the parametric function fitting in the pembrolizumab and UK SoC arms at the other cut-points (OS: 16, 32 and 40 weeks; PFS: 9, 15 and 27 weeks).

Figure 3. OS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 24 Weeks)

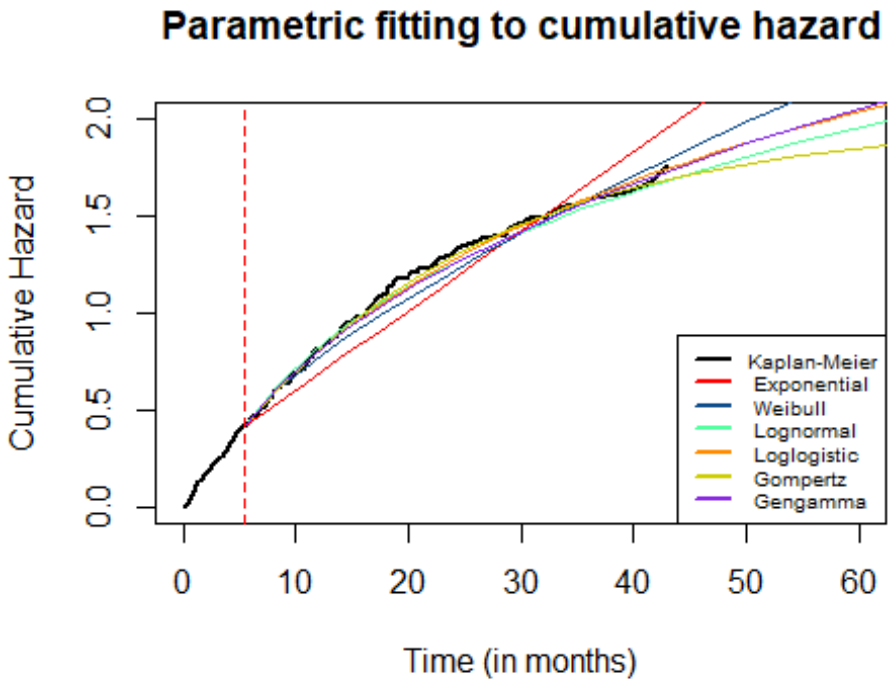


Figure 4. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment - Cumulative Hazard Scale (Cut-point of 24 Weeks)

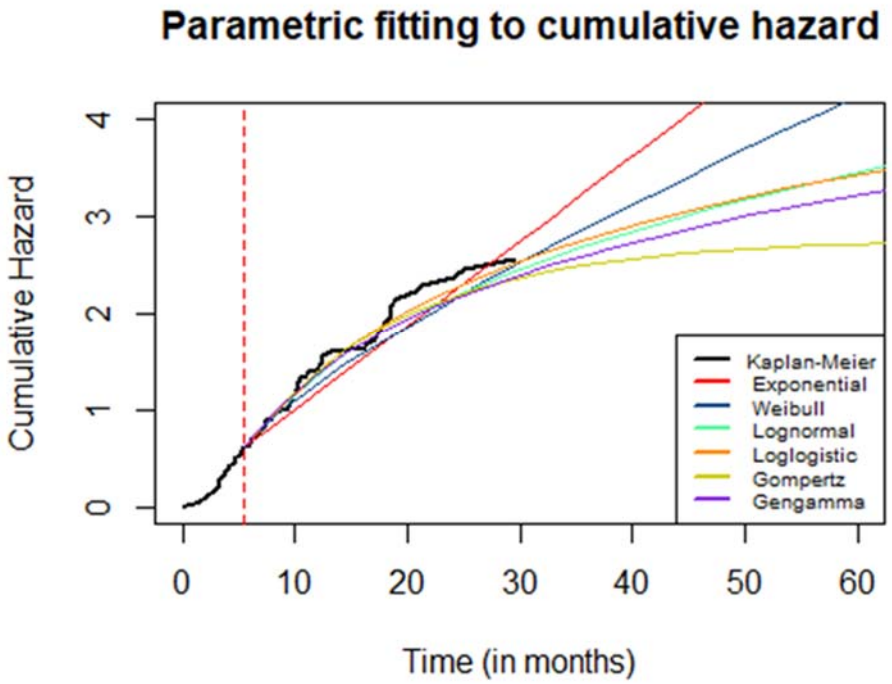


Figure 5. PFS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 21 Weeks)

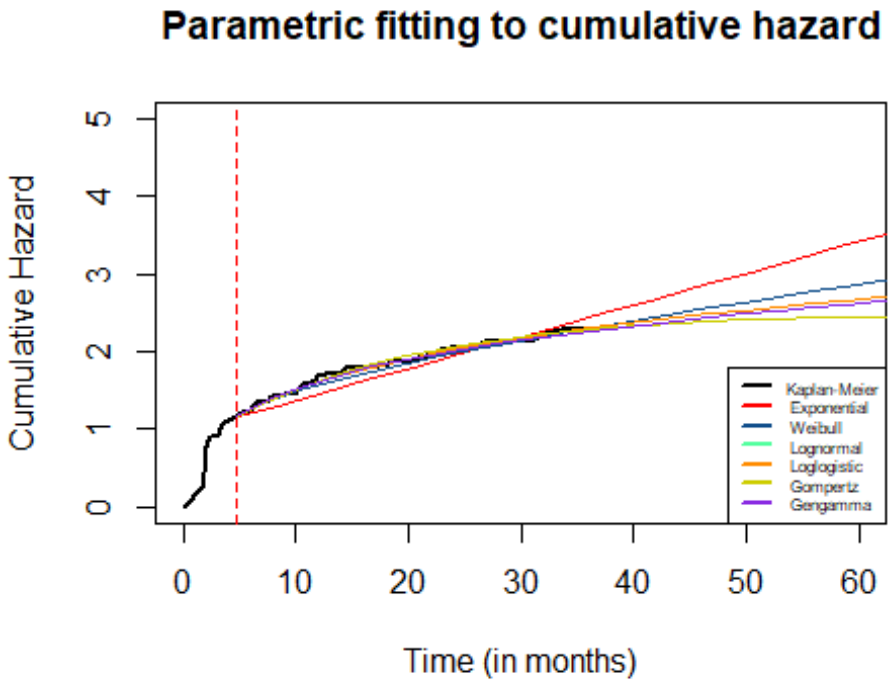


Figure 6. PFS Parametric Function Fitting in the UK SoC Arm - Cumulative Hazard Scale (Cut-point of 21 Weeks)

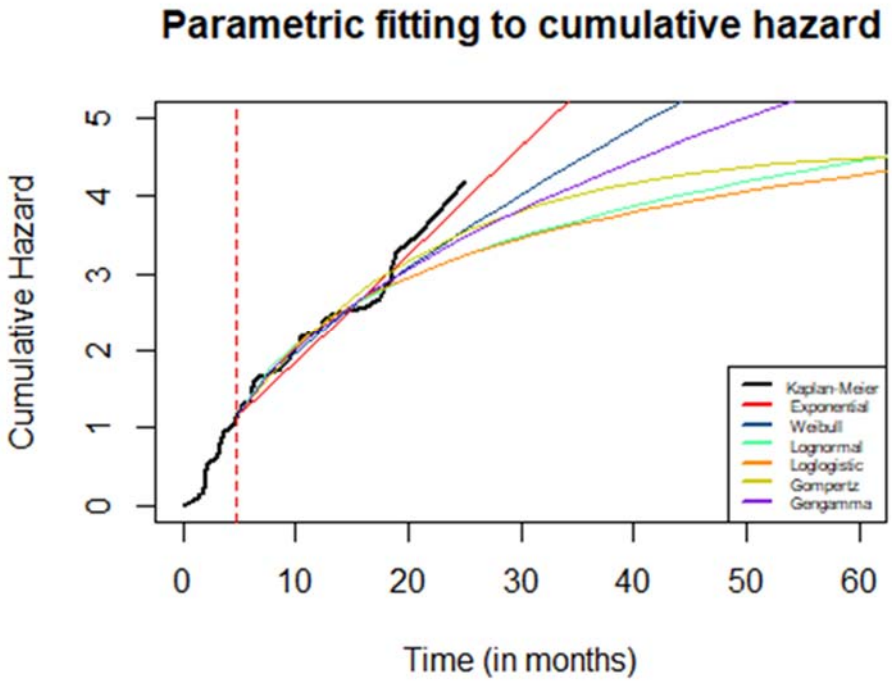


Figure 7. OS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 16 Weeks)

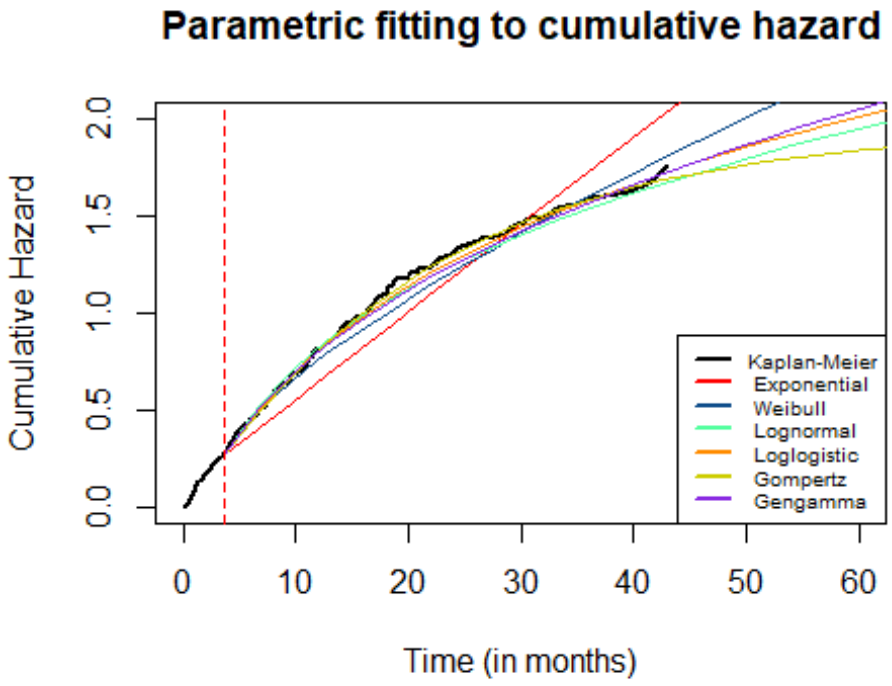


Figure 8. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment - Cumulative Hazard Scale (Cut-point of 16 Weeks)

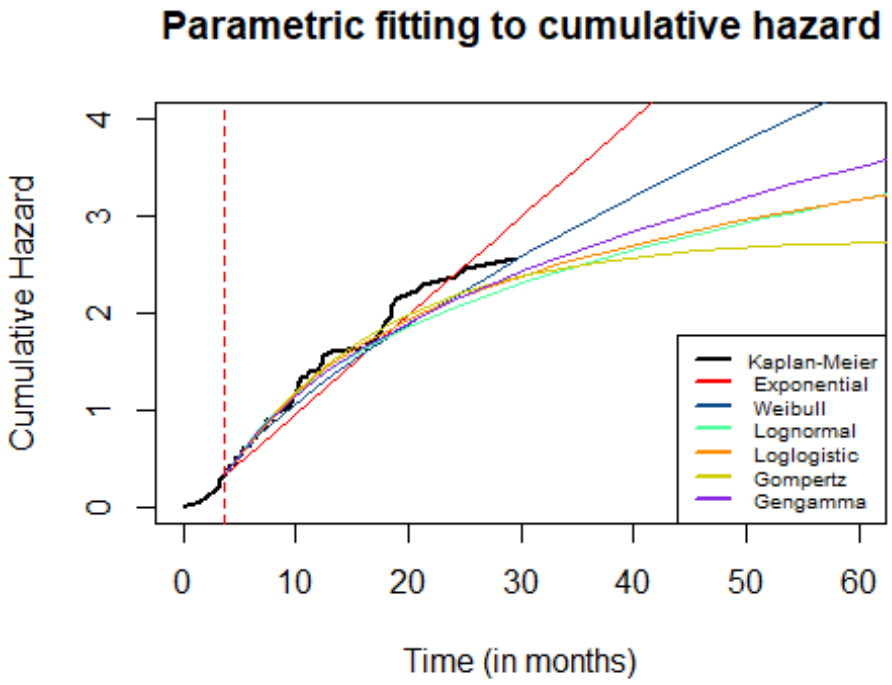


Figure 9. OS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 32 Weeks)

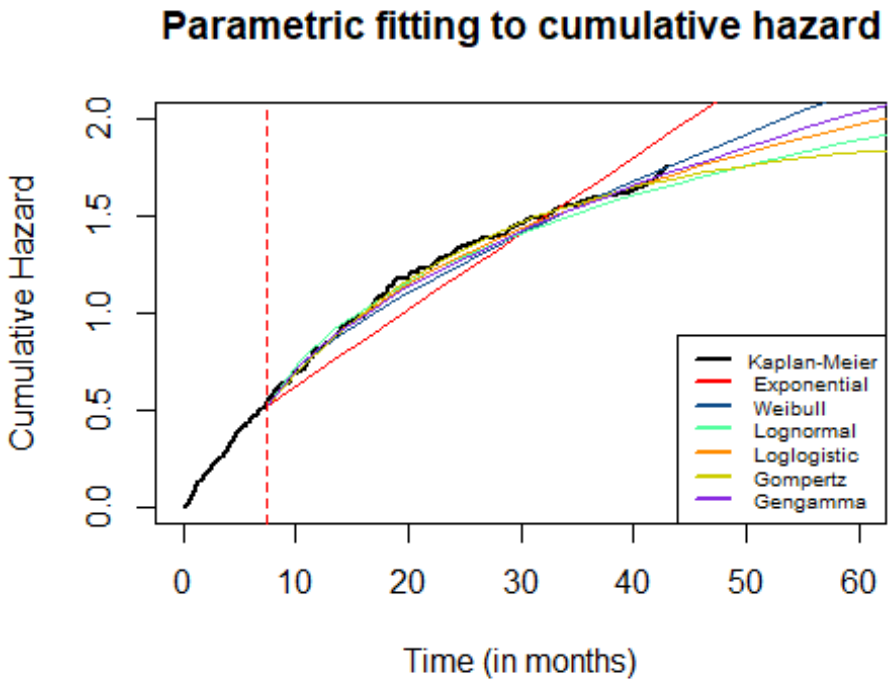


Figure 10. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment - Cumulative Hazard Scale (Cut-point of 32 Weeks)

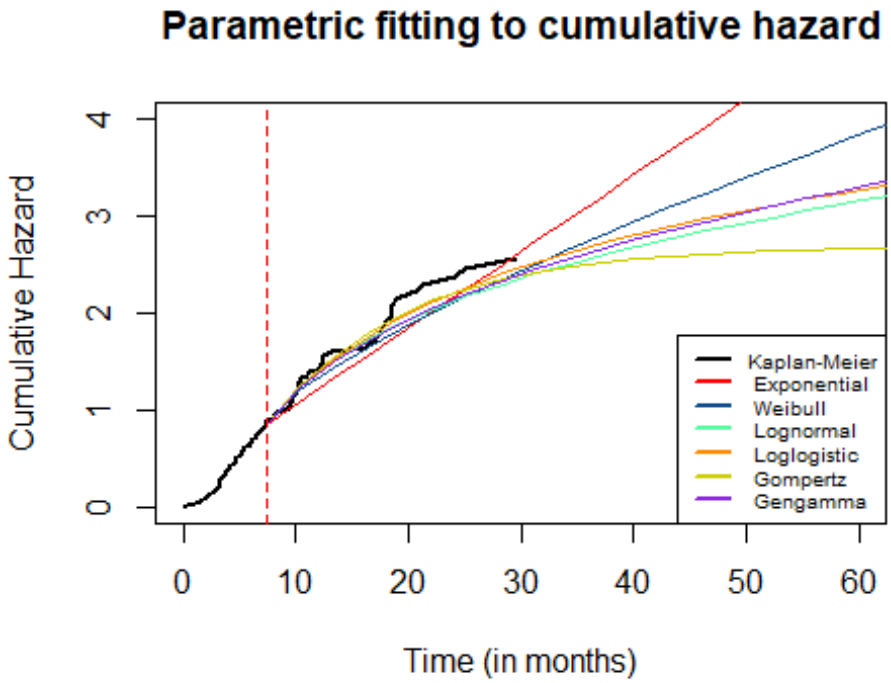


Figure 11. OS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 40 Weeks)

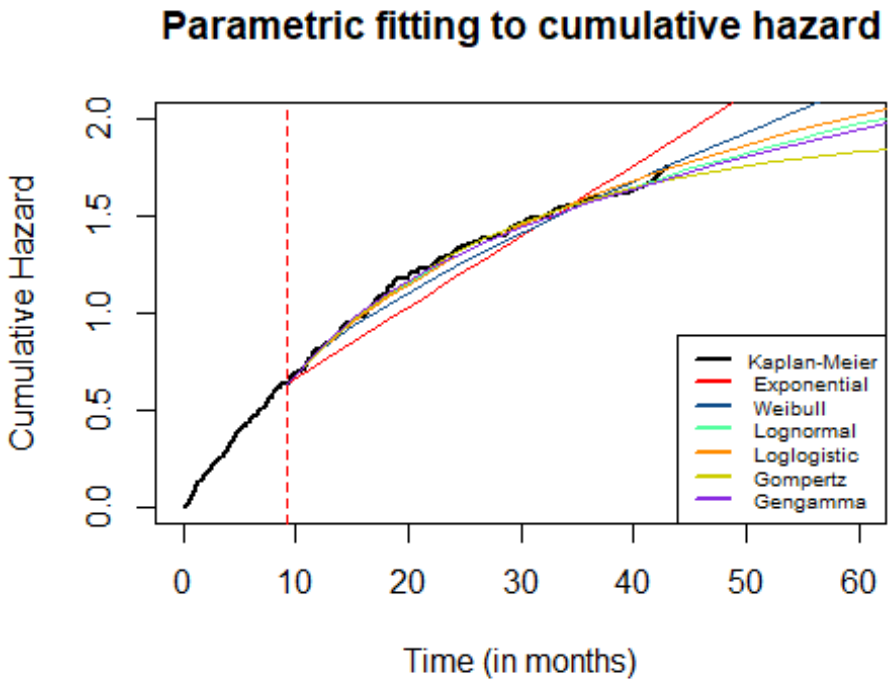


Figure 12. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment - Cumulative Hazard Scale (Cut-point of 40 Weeks)

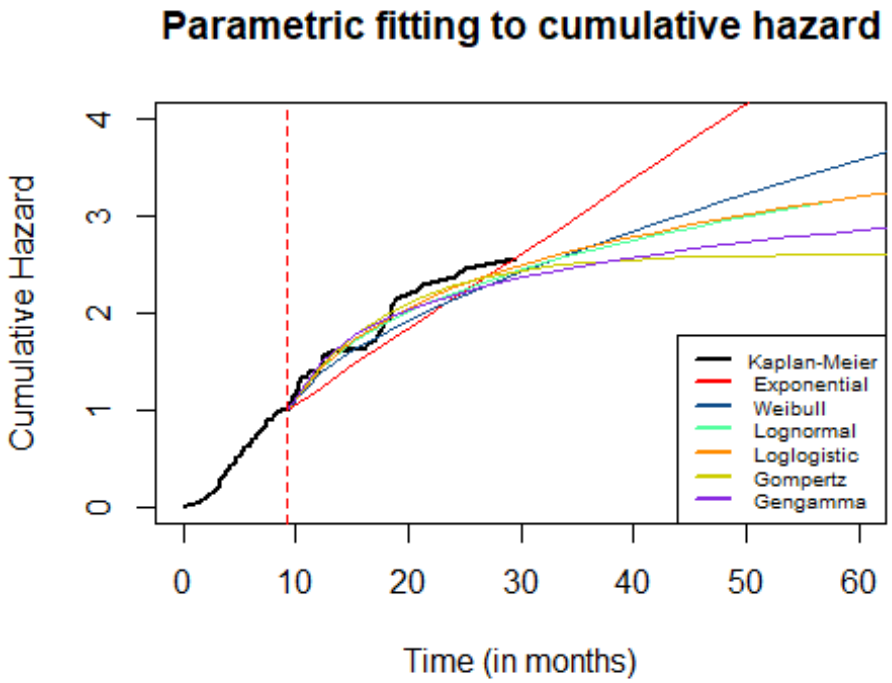


Figure 13. PFS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 9 Weeks)

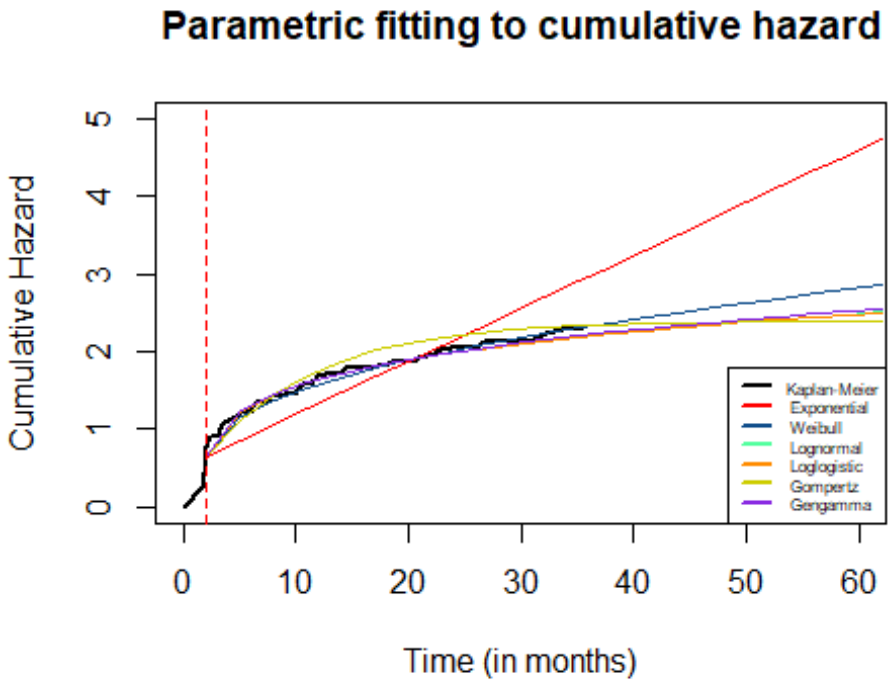


Figure 14. PFS Parametric Function Fitting in the UK SoC Arm - Cumulative Hazard Scale (Cut-point of 9 Weeks)

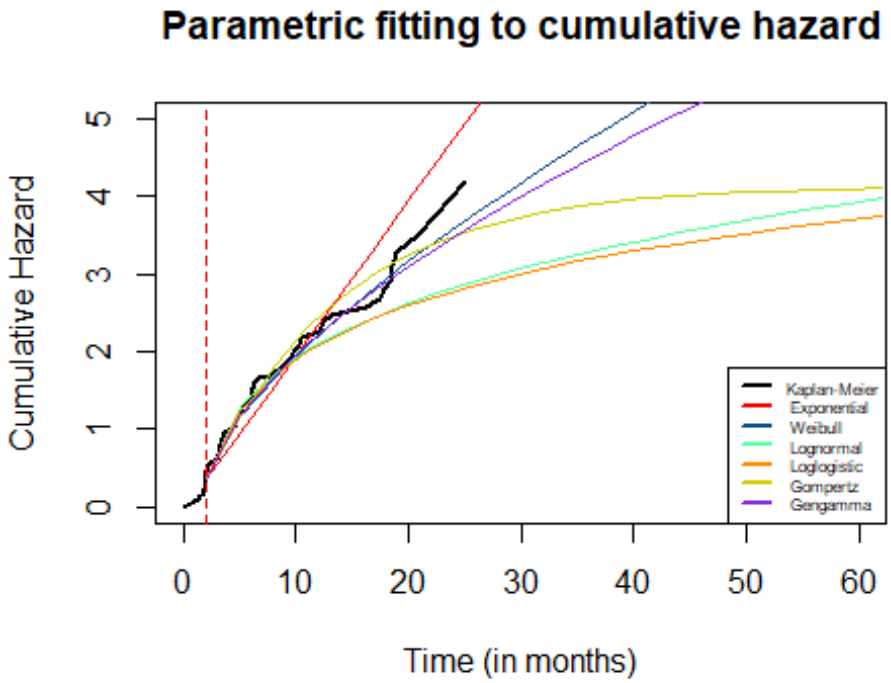


Figure 15. PFS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 15 Weeks)

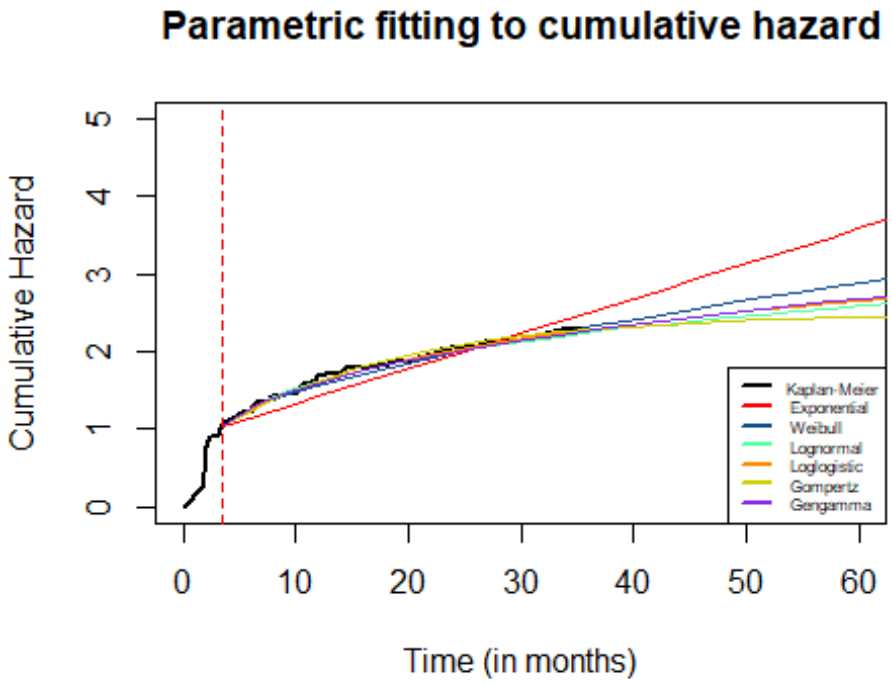


Figure 16. PFS Parametric Function Fitting in the UK SoC Arm - Cumulative Hazard Scale (Cut-point of 15 Weeks)

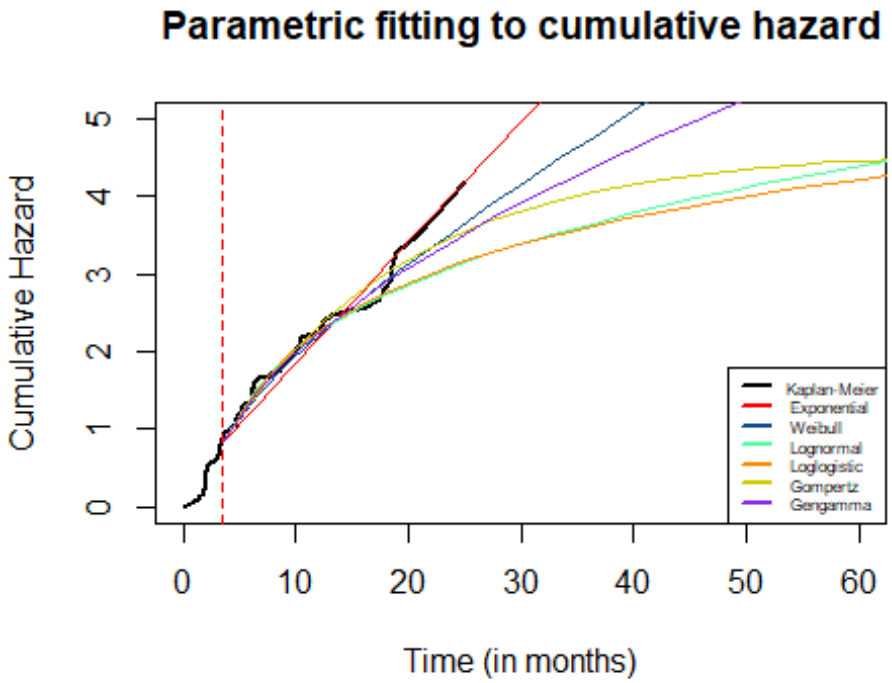


Figure 17. PFS Parametric Function Fitting in the Pembrolizumab Arm - Cumulative Hazard Scale (Cut-point of 27 Weeks)

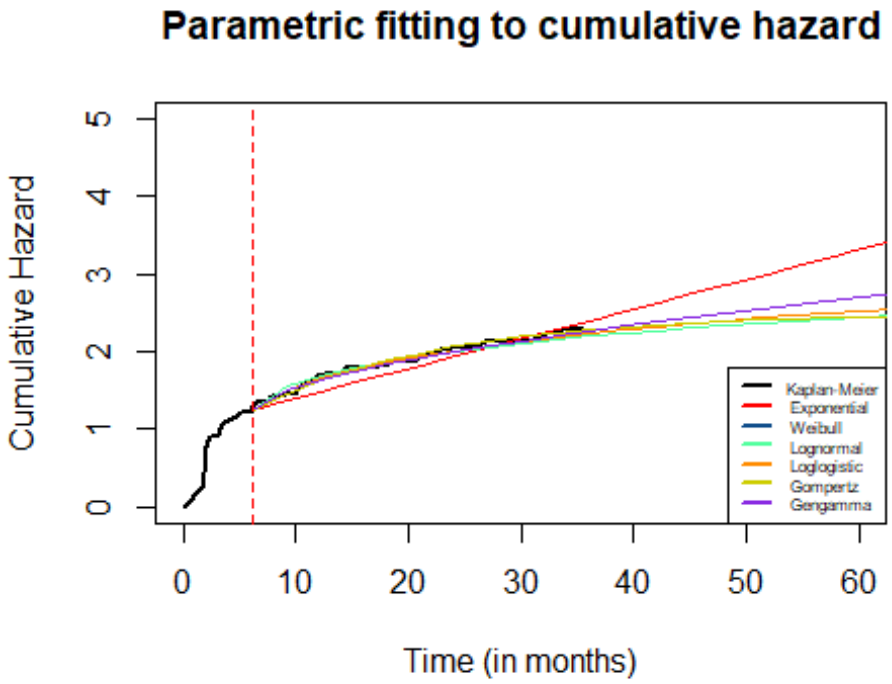


Figure 18. PFS Parametric Function Fitting in the UK SoC Arm - Cumulative Hazard Scale (Cut-point of 27 Weeks)

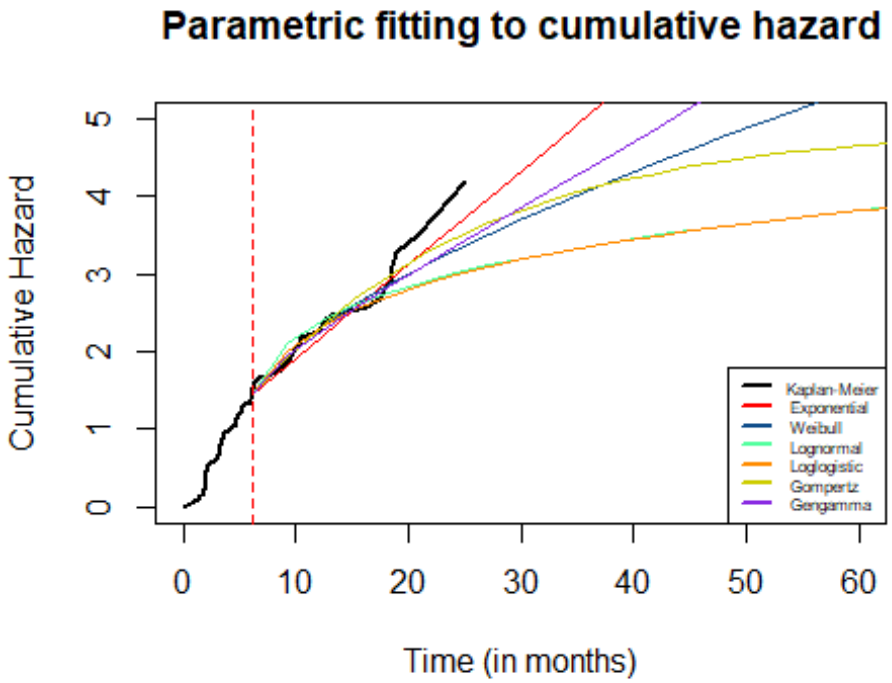


Figure 19. OS Parametric Function Fitting in the Pembrolizumab Arm (Cut-point of 16 Weeks)

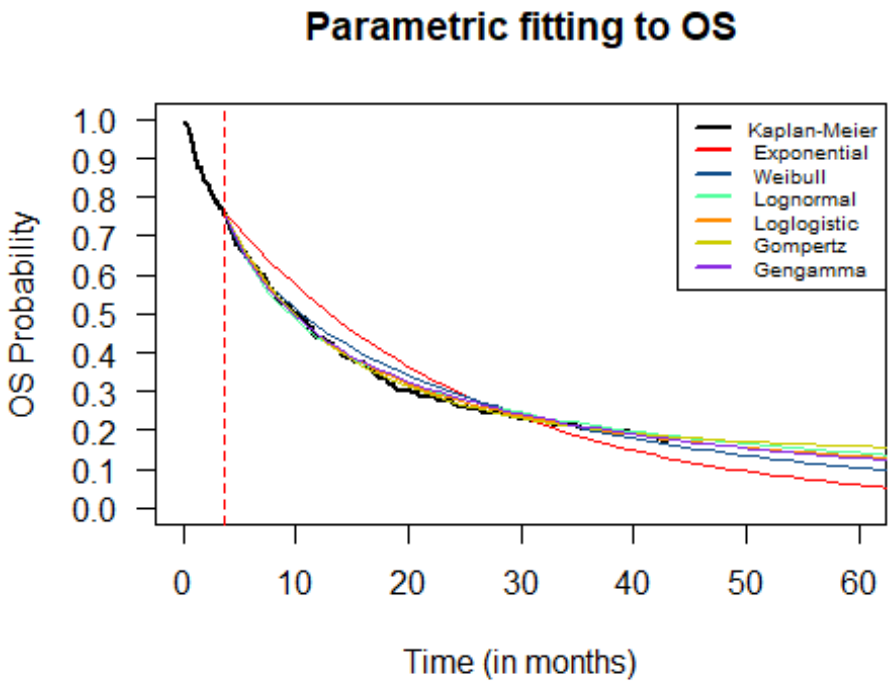


Figure 20. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment (Cut-point of 16 Weeks)

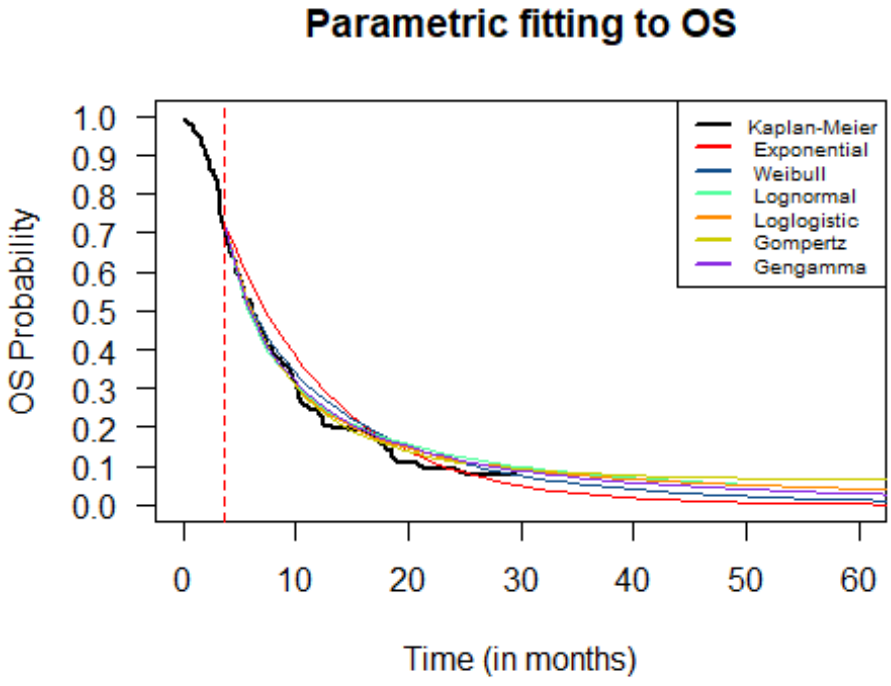


Figure 21. OS Parametric Function Fitting in the Pembrolizumab Arm (Cut-point of 32 Weeks)

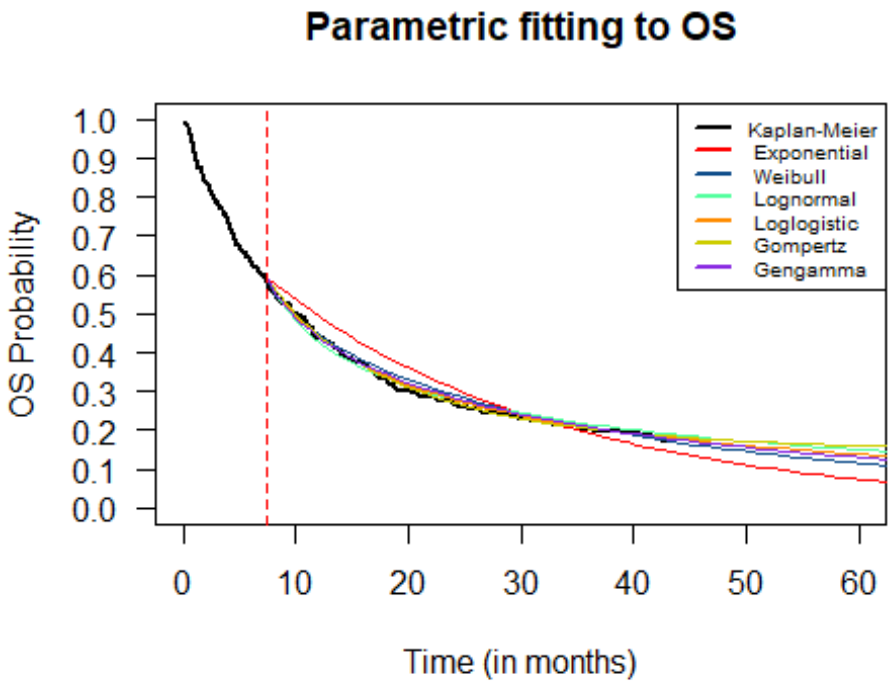


Figure 22. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment (Cut-point of 32 Weeks)

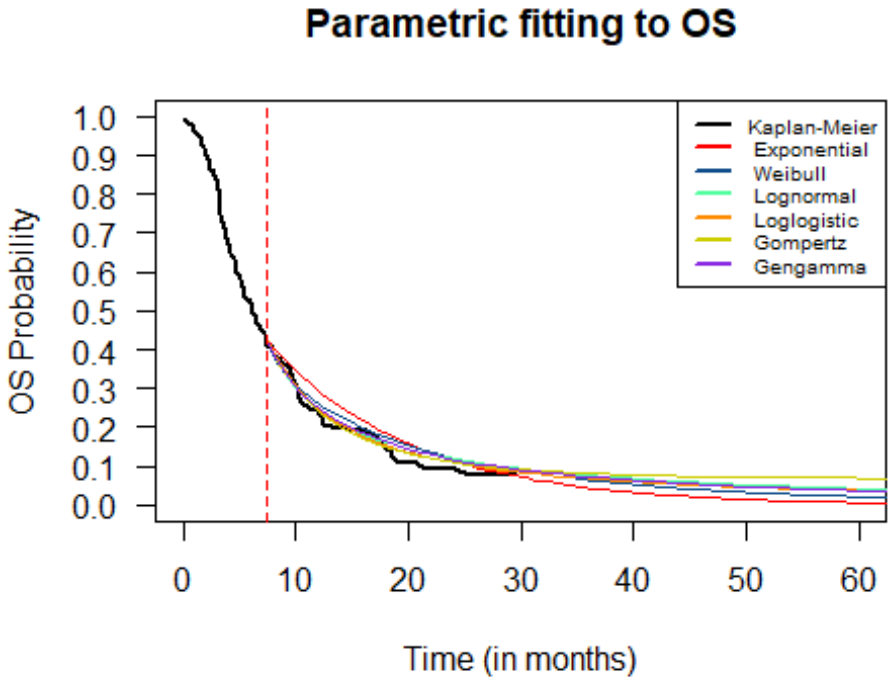


Figure 23. OS Parametric Function Fitting in the Pembrolizumab Arm (Cut-point of 40 Weeks)

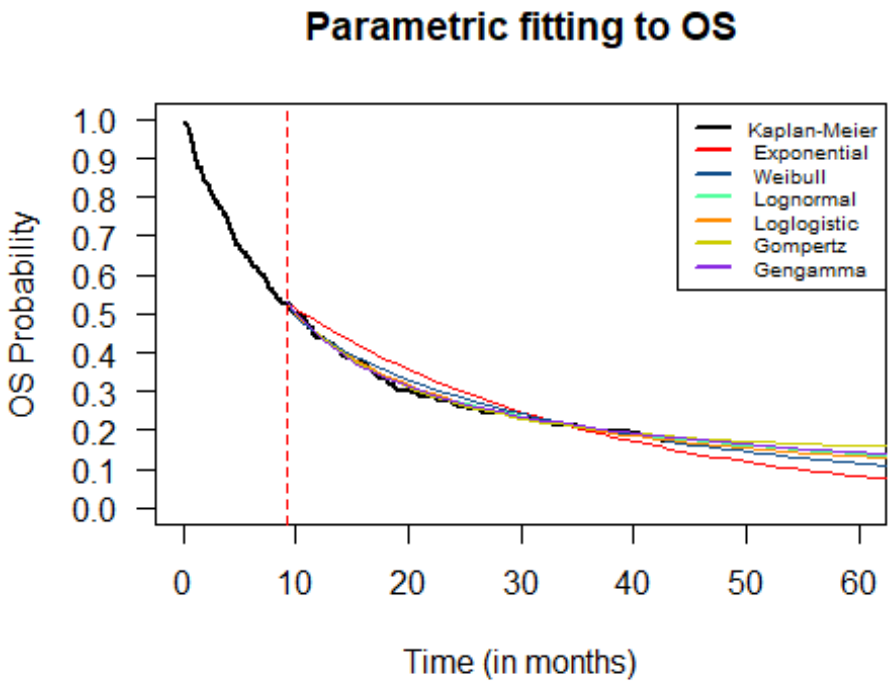


Figure 24. OS Parametric Function Fitting in the UK SoC Arm With 2-Stage Adjustment (Cut-point of 40 Weeks)

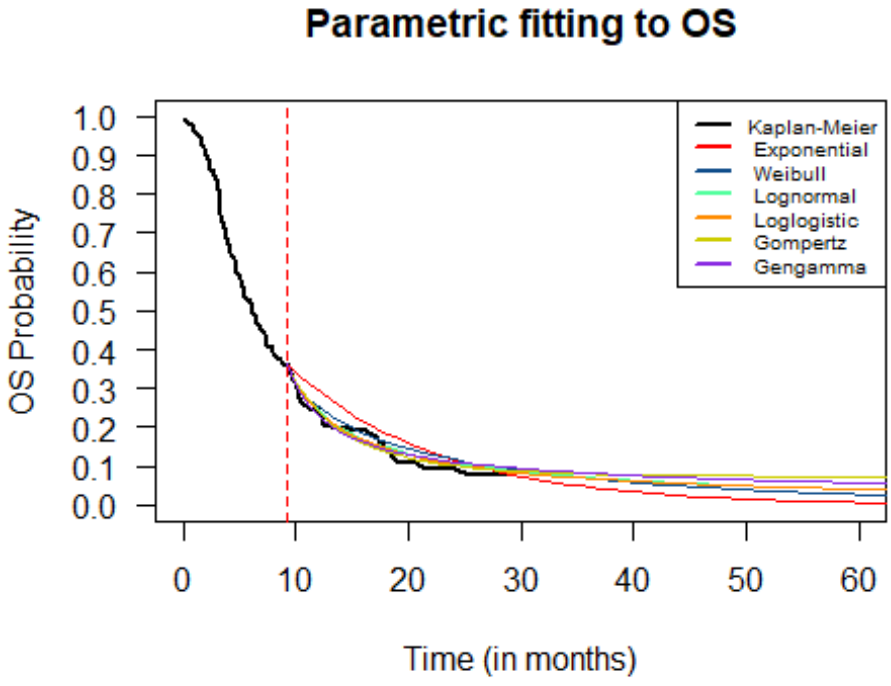


Figure 25. PFS Parametric Function Fitting in the Pembrolizumab Arm (Cut-point of 9 Weeks)

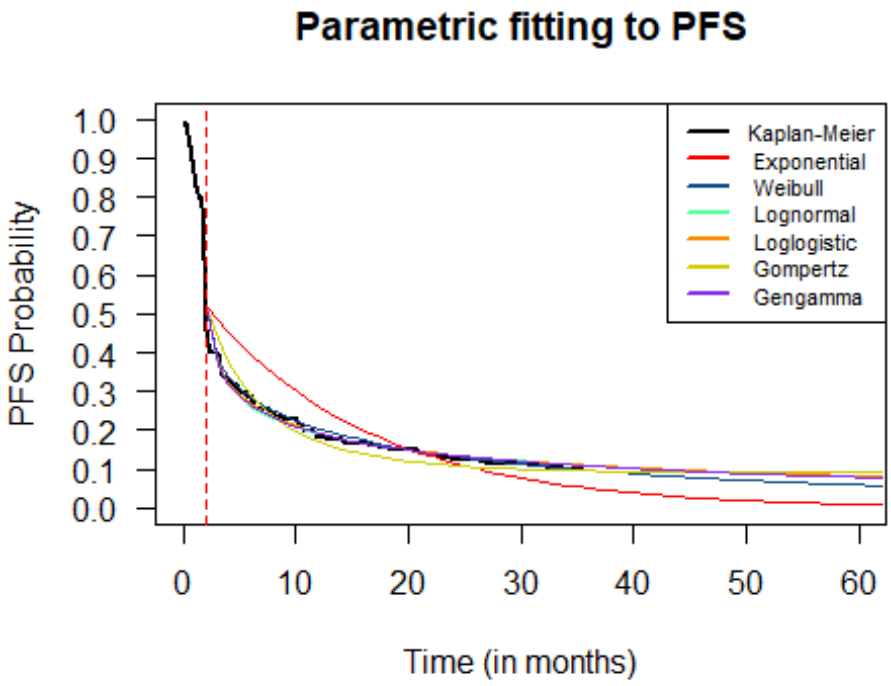


Figure 26. PFS Parametric Function Fitting in the UK SoC Arm (Cut-point of 9 Weeks)

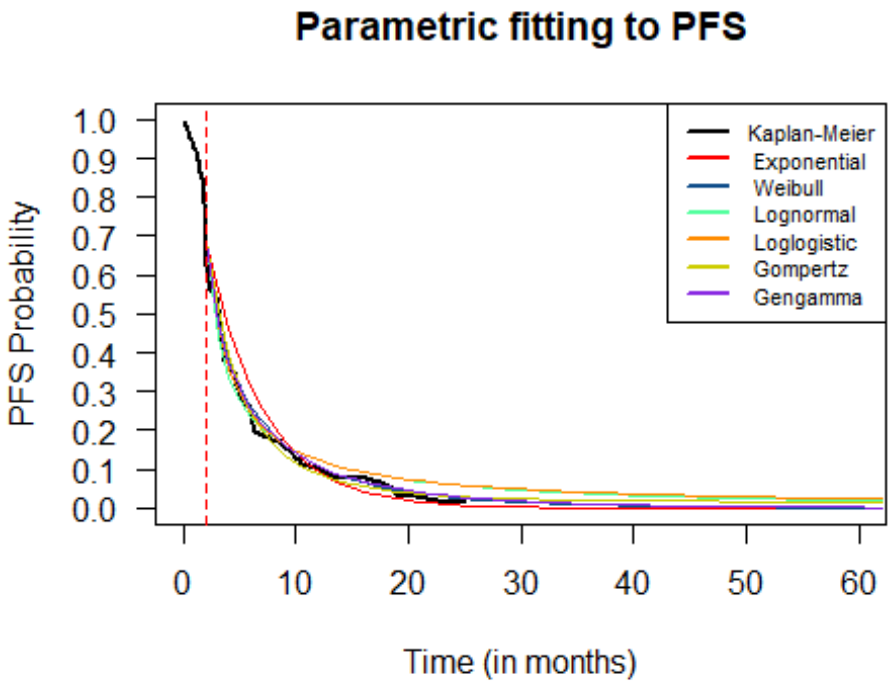


Figure 27. PFS Parametric Function Fitting in the Pembrolizumab Arm (Cut-point of 15 Weeks)

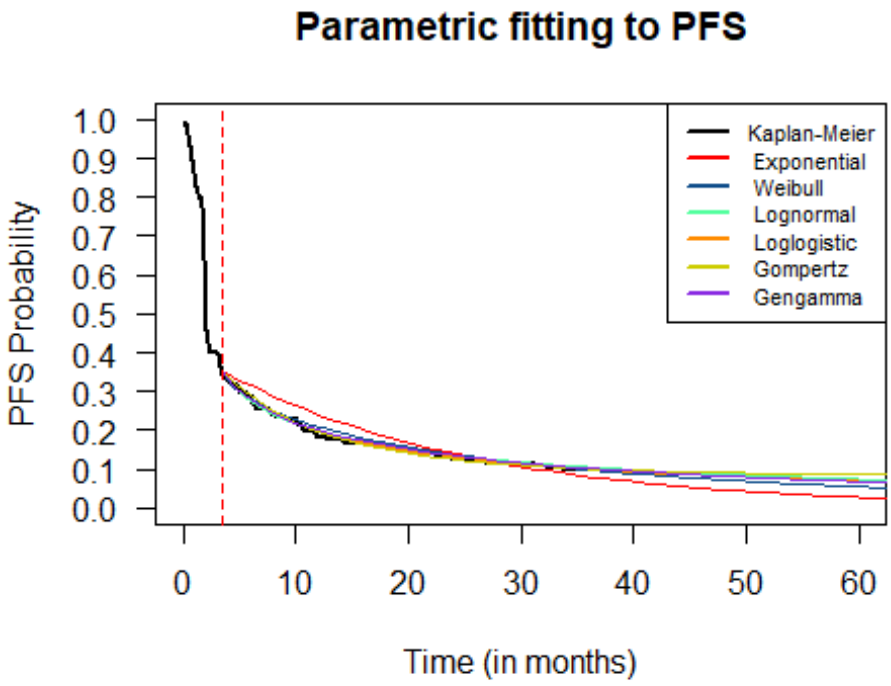


Figure 28. PFS Parametric Function Fitting in the UK SoC Arm (Cut-point of 15 Weeks)

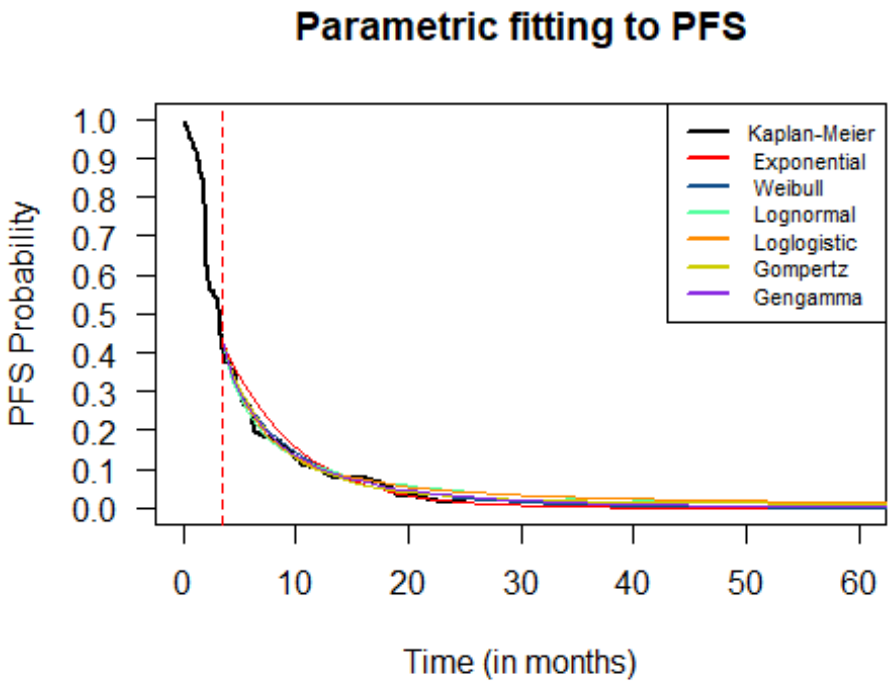


Figure 29. PFS Parametric Function Fitting in the Pembrolizumab Arm (Cut-point of 27 Weeks)

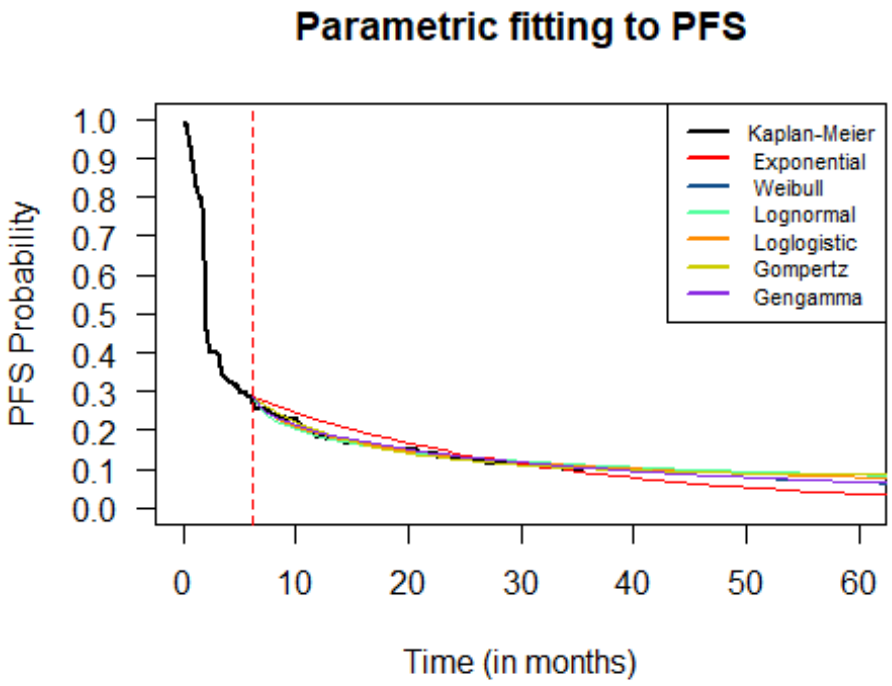
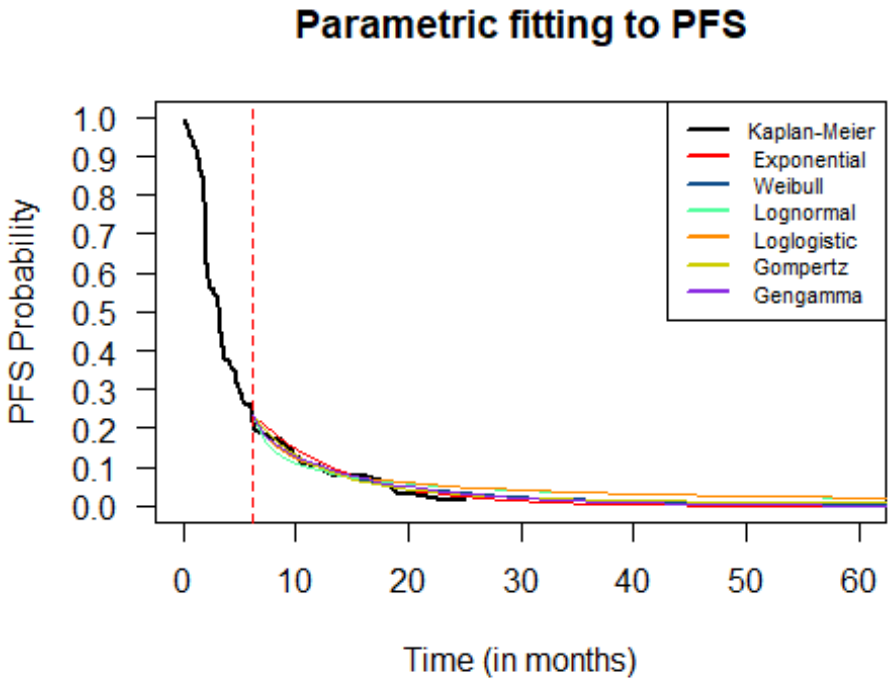


Figure 30. PFS Parametric Function Fitting in the UK SoC Arm (Cut-point of 27 Weeks)



Question B2. Priority question:

Please confirm whether the OS analysis in Appendix G of the company submission appendices accounts for treatment switching (2 stage) or uses ITT event times. Please provide the analysis for both scenarios.

Company response B2:

We confirm that the OS analysis in Appendix G of the company submission appendices accounts for the treatment switching with 2-stage approach, in the UK SoC population. The analyses for the scenario with no treatment switching in the UK SoC population are provided below.

Figure 31. Graphical output for OS model fitted with time varying hazard ratio for UK SoC (paclitaxel or docetaxel) without treatment switch adjustment

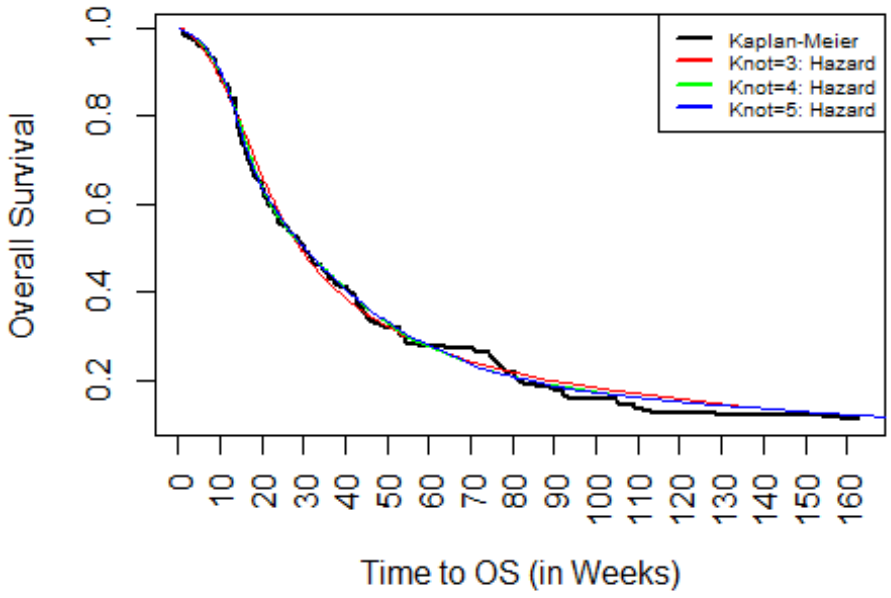
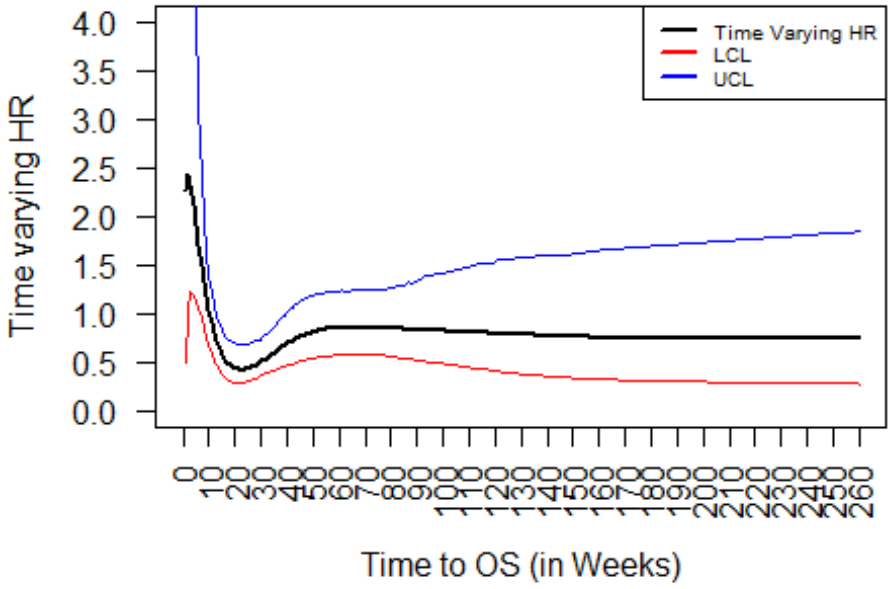
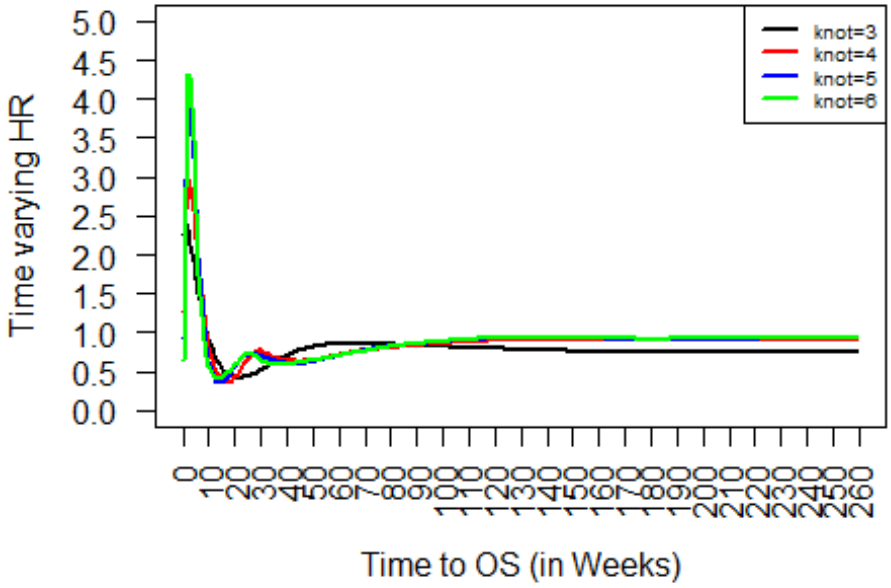


Figure 32. Time varying hazard ratio of OS for Pembrolizumab vs UK SoC (paclitaxel or docetaxel) without treatment switch adjustment



Note: The maximum follow-up for OS was 204 weeks and 202 weeks for pembrolizumab and paclitaxel/docetaxel respectively; the last event recorded in OS for were at 187 week and 163 weeks respectively

Figure 33. Time varying hazard ratio of OS for Pembrolizumab vs UK SoC (paclitaxel or docetaxel) without treatment switch adjustment: sensitivity analyses



Note: The maximum follow-up for OS was 204 weeks and 202 weeks for pembrolizumab and paclitaxel/docetaxel respectively; the last event recorded in OS for were at 187 week and 163 weeks respectively

Question B3. Priority question:

Please provide data to allow ERG to both easily reproduce the analysis presented in Appendix G of the company submission appendices, as well as allow the ERG to carry out sensitivity analysis. Please provide the survival time data (both ITT and 2 stage adjusted) from KEYNOTE-045, as well as the code, so the analysis can be easily reproduced.

Company response B3:

The summary data (both ITT and 2 stage adjusted) from KEYNOTE-045, including KM data, and the number of patients at risk, were already provided in the tab "KN045_1" in the submitted model. This level of summary data will allow the ERG to reconstruct the IPD, using the published statistical approaches (e.g. Guyot et al. 2012). The reconstructed IPD won't be identical to the original data but close enough to fit the survival curves since it contains all the events information with only censoring information missing. The code for the analysis presented in Appendix G is provided as a separate file labelled Appendix 2.

An updated model is provided with this clarification response letter; please use the tab KN045_1 to carry out sensitivity analysis.

Question B4:

Please can you confirm that PFS for the ITT analysis is not adjusted for treatment switching (company submission, section A.6.2)?

Company response B4:

MSD confirms that none of the analyses for PFS within KEYNOTE-045 were adjusted for treatment switching.

Question B5:

Page 7 of the company submission states "The mean treatment duration per patient including the CDF follow up period was 6.84 months or 10.46 administrations."
Page 18 of the company submission states "As per the KEYNOTE-045 trial [10], patients were treated until RECIST-defined disease progression [16], development of unacceptable toxicity, withdrawal of consent, decision by the investigator to discontinue therapy, or the completion of 2 years of pembrolizumab therapy."

a) Please provide a breakdown of the number of patients who discontinued pembrolizumab treatment for each of the above reasons within the KEYNOTE-045 trial.

b) Data presented for this CDF review is solely based on the trial data cut-off date of 30 November 2018. If possible, please provide any further data on mean treatment duration for pembrolizumab for this treatment indication from the UK population since the start of the CDF period.

Company response B5. a)

Please refer to Table 8 for the breakdown of patients who discontinued pembrolizumab (based on disease progression, adverse events, withdrawal of consent, investigator decision or complete response), based on the APaT population in KEYNOTE-045. Please note that the corresponding table specifically for the subgroup of patients pre-assigned to paclitaxel or docetaxel (i.e. pembrolizumab vs. UK SoC) was already presented in Table 3 of the Appendices to the Company's CDF guidance review submission dated 24 July 2019.

Table 8. Subject Disposition All Subjects (APaT Population)

	Control	Pembrolizumab
	n (%)	n (%)
Subjects in population	255	266
Status for Trial		
Discontinued	230 (90.2)	218 (82.0)
Adverse Event	9 (3.5)	14 (5.3)
Death	204 (80.0)	195 (73.3)
Lost To Follow-Up	1 (0.4)	1 (0.4)
Physician Decision	1 (0.4)	0 (0.0)
Withdrawal By Subject	15 (5.9)	8 (3.0)
Ongoing in Trial	25 (9.8)	48 (18.0)
Status for Study Medication in Trial Segment Treatment		
Started	255	266
Completed	0 (0.0)	24 (9.0)
Discontinued	255 (100.0)	241 (90.6)
Adverse Event	36 (14.1)	29 (10.9)
Clinical Progression	29 (11.4)	26 (9.8)
Complete Response	1 (0.4)	11 (4.1)
Excluded Medication	2 (0.8)	0 (0.0)
Physician Decision	28 (11.0)	6 (2.3)
Progressive Disease	130 (51.0)	165 (62.0)
Protocol Violation	0 (0.0)	1 (0.4)
Withdrawal By Subject	29 (11.4)	3 (1.1)
Treatment Ongoing	0 (0.0)	1 (0.4)

Each subject is counted once for Trial Status based on the latest Survival Follow-up record.

Each subject is counted once for Study Medication Status based on the latest corresponding disposition record.
Unknown: A disposition record did not exist at the time of reporting.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Company response B5.b)

MSD does not hold any further data on mean treatment duration for pembrolizumab for this treatment indication from the UK population. KEYNOTE-045, with a data cut-off date of November 2018, is the only MSD sponsored study which provides data to inform the CDF guidance review of TA519. We are not aware of any further studies that could provide additional evidence on the mean treatment duration of pembrolizumab for this treatment indication.

Question B6

Please provide the code and data to allow simple recalculation of the acceleration factor (mentioned in the notes from Table 4 in the company submission). Please also reproduce analysis using UK SoC patients only (excluding vinflunine).

Company response B6

To address the query raised during the clarification question TC with the ERG and NICE on 8 August 2019, MSD confirms that the acceleration factor reported in Table 4 of the company submission for the CDF guidance review (reproduced below as Table 9 for ease of reference) was calculated based on the UK SoC patients only (i.e. subjects pre-assigned to paclitaxel and docetaxel only, prior to randomisation). Along with the response to Question A1 of this clarification letter, both unadjusted and adjusted estimates of HR (95% CI) have now been provided for UK SoC patients.

As requested, please find below the code that was used to provide the acceleration factor for the 2-stage methodology, as presented in Table 4 of the company submission.

```
proc lifereg data= input_data order=internal;
   class crosstrt categorical_covariates;
  model time_variable*censor(1) = crosstrt continuous_covariates
categorical_covariates /distribution=distribution_of_interest;
run;
```

Regarding the accompanying documentation of the variables used, please see below:

Crosstrt is a treatment indicator variable taking values (Crossover anti-PDL1 treatment, No Crossover).

Continuous variables

- Age (years)
- Time to disease progression (days)
- Haemoglobin (g/dl) at secondary baseline
- Tumour size at secondary baseline

Categorical variables

- Gender (male/female)
- ECOG status at secondary baseline (0, >= 1)
- Liver metastates at randomization (present, absent)
- Time since last prior chemotherapy at randomization (< 3 months, >= 3 months)
- Site of primary tumour (upper tract, lower tract)

Below, we have also reproduced Table 2 from the Appendices to the company submission for the CDF guidance review (reproduced below as Table 10 for ease of reference), which includes the acceleration factor for adjusted ITT population (including vinflunine). When comparing the acceleration factor between the adjusted ITT population (including vinflunine; Table 10 below) and adjusted UK SoC population (subjects pre-assigned to paclitaxel or docetaxel, prior to randomisation; Table 9), it is noted that the uncertainty in the acceleration factor for the UK SoC population is greater than that for the whole ITT population. The approach taken by MSD is to calculate the acceleration factor for the same population being analysed, rather than calculate it for a defined population and analyse it for another. MSD does not believe it would be appropriate to change the covariates in the model as the same pre-specified model approach has been kept throughout the study, and for all data-cuts. In general, across the many 2-stage models that have been run, the uncertainty in acceleration factors increases as the sample size (and numbers of subjects receiving subsequent therapy) decreases.

Table 9: Acceleration factor calculated for adjusted UK SoC population: Analysis of OS | No re-censoring - Subjects pre-assigned to UK SoC - ITT - Comparison pembrolizumab versus UK SoC - adjusting for treatment switch to anti-PDL1 treatment in SoC arm using 2-stage analysis

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Treatment vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]
Control	182	147 (80.8)	2026.2	7.3	7.0 (5.5, 8.7)	32.2 (25.2, 39.4)	---	---
Control, Adjusted [¶]	182	147 (80.8)	1559.6	9.4	6.2 (5.2, 7.4)	25.0 (18.6, 31.9)	---	---
Pembrolizumab	188	144 (76.6)	2923.5	4.9	10.1 (7.6, 12.9)	43.5 (36.3, 50.6)	0.64 (0.49, 0.81)	0.0139

Stage 1 model[††]	**Acceleration factor[‡‡]**
[§] Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy	5.370 (3.231,10.094)

[¶] Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and haemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.

[‖] Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumour (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and haemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression.

[§] Patients were eligible to receive subsequent therapy if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy. The 95% CI is based on the same bootstrap samples as for the Cox regression model

Table 10: Acceleration factor calculated for adjusted ITT population (including vinflunine: Analysis of OS | No Recensoring - ITT - Comparison Pembrolizumab versus SoC - Adjusting for Treatment Switch to anti-PDL1 treatment in SoC arm using 2-stage analysis

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Treatment vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]
Control	272	224 (82.4)	2923.9	7.7	7.2 (6.1, 8.0)	29.7 (24.1, 35.4)	---	---
Control, Adjusted [¶]	272	224 (82.4)	2357.2	9.5	6.5 (5.3, 7.4)	23.1 (18.0, 28.6)	---	---
Pembrolizumab	270	213 (78.9)	4173.5	5.1	10.1 (8.0, 12.3)	44.2 (38.2, 50.1)	0.62 (0.50, 0.76)	0.0006

Stage 1 model[††]	**Acceleration factor[‡‡]**
[§] Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy	5.320 (3.443,8.446)

[¶] Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and hemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.

‖ *Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.*

†† *Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumor (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and hemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression.*

§ *Patients were eligible to receive subsequent therapy if they had documented progression.*

‡‡ *Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy. The 95% CI is based on the same bootstrap samples as for the Cox regression model*

(Database Cutoff Date: 30NOV2018).

Question B7.

Please provide justification on the use of bootstrapping to calculate the 95% CI of the hazard ratio in Table 4 in the company submission, given that the proportional hazards assumption was violated.

Company response B7:

Generally, the proportional hazards (PH) approach is used for consistency with approaches used for the Clinical Study Reports (CSRs) and manuscripts. In addition, it is known that the Cox proportional hazards model is rather robust to deviations from proportional hazards, so the estimated hazard ratio (HR) from a Cox model gives an acceptable estimate of the averaged treatment effect over time, although not quantitatively correct over the entire follow-up period. An alternative approach would be to allow for non-PH and let the HR vary over time, i.e. estimate HRs per time intervals. However, this will be very difficult to interpret.

The issue of bootstrapping does not seem to be related to that of PH. The bootstrapping is done to account for the uncertainty in the estimate of the acceleration factor obtained in stage 1 and should be carried through to the estimation of the confidence interval of the 2-stage adjusted hazard ratio (HR).

Section C: Textual clarification and additional points

Additional question received from the ERG after the clarification questions teleconference which took place on 08 August 2019: Relating to the current economic model (25/07/2019 version), on the KN045_1 sheet, in scenario 8.

- In cells CN7 and CN8, there is no change in the numbers at risk, despite there being a change in the proportion alive in cells CM7 and CM8.
- The value of CN7 in this version of the model is 175. However, in a previous version of the economic model (24/08/2017) CN8 has value 174. In another version (28/03/2017) CN8 has value 175.
- The value of CN7 is not 182 at time 0

The ERG would appreciate if you could look into this and provide an explanation for these aspects of the model.

Company response:

Please accept MSD's apologies for the errors. MSD confirms the following:

- The value of CN7 in this version of the model should be corrected to 182 at time 0. The value of CN6 (# at risk in time 0, instead of CN8 as mentioned in ERG's question) in previous versions of the economic model (24/08/2017, 28/03/2017) should be corrected to 182 as well.
- An updated model, with the corrections to the relevant cells, is provided with this response to the list of clarification questions.

References

1. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012 Dec;12(1):9.

Public Health England

Protecting and improving the nation's health

Pembrolizumab for treating previously treated advanced or metastatic urothelial cancer review

Report for the NICE Appraisal Committee review of TA519

Patients receiving pembrolizumab for previously treated advanced or metastatic urothelial cancer

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Contents

Background

The Public Health England and NHS England partnership on cancer data – using routinely collected data to support patient care

High quality and timely cancer data underpin NHS England (NHSE) and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHSE partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHSE commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[1]. From the 29th July 2016 NHSE, in partnership with the National Institute for Health and Care Excellence (NICE) implemented a new approach to the appraisal and funding of cancer drugs. The CDF operates as a managed access scheme, providing patients with earlier access to new and promising treatments where there is significant uncertainty as to their clinical and cost effectiveness. During the period of managed access, data is collected to address the uncertainties identified by the NICE appraisal committee: a report on this data is produced for the review of each topic at the end of the CDF managed access period[2].

PHE analyse data derived from patient-level information collected within the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

Pembrolizumab and urothelial cancer

Pembrolizumab was recommended for use in the CDF as an option for treating adults with locally advanced or metastatic urothelial cancer who have received prior platinum-containing chemotherapy. The standard of care (SOC) for patients with locally advanced or metastatic urothelial is docetaxel or paclitaxel.

NICE Appraisal Committee review of pembrolizumab in treating previously treated advanced or metastatic urothelial cancer [TA519]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of pembrolizumab in treating previously treated advanced or metastatic urothelial cancer [TA519] and published guidance for this indication in April 2018[3].

Due to the clinical uncertainties outlined below, the committee recommended that the drug should be considered for funding through the CDF for a period of 9 months, from March 2018 to December 2018, whilst data was collected.

Results from an ongoing clinical trial evaluating pembrolizumab in the licensed indication are likely to answer many of clinical uncertainties raised by the NICE committee and are expected to become available during the CDF funding period. The ongoing trial that will support the evaluation of pembrolizumab is the KEYNOTE-045 trial.

This report provides 'real world' information on the use of pembrolizumab in England in this indication, outside of the clinical trial setting and acts as a secondary source of information alongside the results of the KEYNOTE-045 clinical trial[4]. The key area of interest is long-term overall survival (OS). As a result of the short data collection period, OS will not be calculated by PHE, instead, the KEYNOTE-045 trial will publish OS.

Areas of clinical uncertainty

Overall survival: long-term OS of pembrolizumab compared to UK SOC (docetaxel and paclitaxel).

OS of pembrolizumab and the comparator cohort (docetaxel and paclitaxel) will be reported in the KEYNOTE-045 trial.

Approach

Representatives from NHSE, NICE, PHE and the company, Merck Sharp & Dohme Ltd (MSD) formed a working group to agree a Data Collection Agreement (DCA). This agreement set out the real-world data to be collected and analysed to support the re-appraisal of pembrolizumab whilst in the CDF. It also detailed the treatment criteria for patient access to pembrolizumab through the CDF and CDF entry and exit dates.

This report includes patients with CDF prior approval applications (via Blueteq®) for pembrolizumab, followed-up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohorts of interest

NHSE collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form can capture any essential baseline demographic and clinical characteristics of patients, needed for CDF evaluation purposes.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all treatment criteria to commence treatment. NHSE pass information to PHE on all patients with an approved CDF application (which therefore met the treatment criteria).

NHSE shares an extract from the Blueteq database with PHE monthly. This extract contains NHS numbers, primary diagnosis and drug information. The data exchange is governed by a data sharing agreement between both organisations.

PHE collates data on all SACT prescribed by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Pembrolizumab treatment criteria

For pembrolizumab there are 13 treatment criteria that must be met which are that:

- the patient has histologically or cytologically documented transitional cell carcinoma of the urothelial tract
- the patient's disease is either locally advanced (that is T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)
- there has been disease progression during or following previous platinum-based chemotherapy for inoperable locally advanced or metastatic urothelial cancer
- the patient has either not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy or has been treated with adjuvant chemotherapy or neoadjuvant chemotherapy or with chemo-radiotherapy AND has relapsed 12 or less months since completing platinum-based chemotherapy
  - patients meeting this criterion are eligible to be considered as previously treated for locally advanced/metastatic disease in this indication but must satisfy all other criteria
- the patient has an ECOG performance status (PS) score of 0 or 1 or 2

- the patient has not received prior treatment with any anti-PD-1, anti-PDL1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTL-4) antibody unless it was received as part of the pembrolizumab compassionate access scheme for this indication and the patient meets all other criteria listed here
- the patient has no symptomatically active brain metastases or leptomeningeal metastases
- pembrolizumab is being given as monotherapy and will commence at a fixed dose of 200mg per infusion
- a formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
- the patient is to be treated until disease progression and loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner
- the patient will receive a maximum treatment duration of 2 years
- treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle
- pembrolizumab is to be otherwise used as set out in its Summary of Product Characteristics

CDF applications – de-duplication criteria

Before conducting any analysis on CDF treatments, the CDF database is examined to identify duplicate applications. The following de-duplication rules are applied:

- if 2 trusts apply for pembrolizumab for the treatment of advanced or metastatic urothelial cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF Trust (the Trust applying for CDF treatment) matches the SACT treating Trust is selected
- if 2 trusts apply for pembrolizumab for the treatment of advanced or metastatic urothelial cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF Trust did not match the SACT treating Trust
- if 2 applications are submitted for pembrolizumab for the treatment of advanced or metastatic urothelial cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected

Initial CDF cohorts

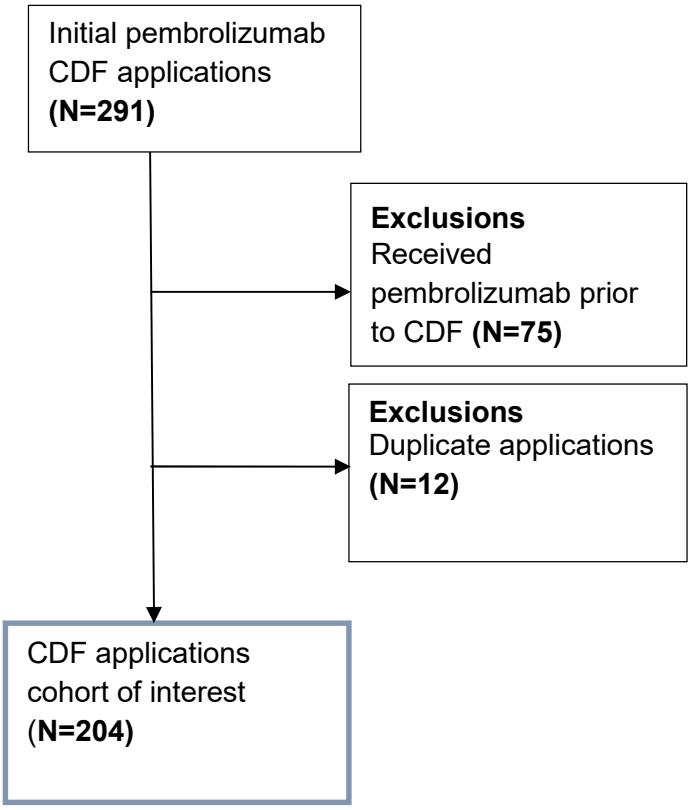
Analysis is limited to applications made from the date pembrolizumab for the treatment of advanced or metastatic urothelial cancer entered the CDF onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an EAMS programme or a compassionate access scheme run by the company and may have different eligibility criteria compared to the treatment criteria detailed in the managed access agreement for this indication.

The CDF applications, included in these analyses, have been limited to 16 March 2018 to 16 August 2018, to allow subsequent follow up in the SACT dataset. A snapshot of SACT data was taken on 5 January 2019 and made available for analysis on the 11 January 2019. The snapshot includes SACT activity up to the 30 September 2018. Tracing the patients' vital status was carried out on 22 January 2019 using the Personal Demographics Service (PDS)[5].

There were 291 Blueteq applications for CDF funding for pembrolizumab for treating advanced or metastatic urothelial cancer between 16 March 2018 and 16 August 2018. This relates to 279 unique patients.

An additional 75 patients were excluded from these analyses as they appeared to have received pembrolizumab for the treatment of advanced or metastatic urothelial cancer prior to the drug being available through the CDF, and, as such, are outside the cohort of interest.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for pembrolizumab for advanced or metastatic urothelial cancer between 16 March 2018 and 16 August 2018



Linking CDF cohort to SACT

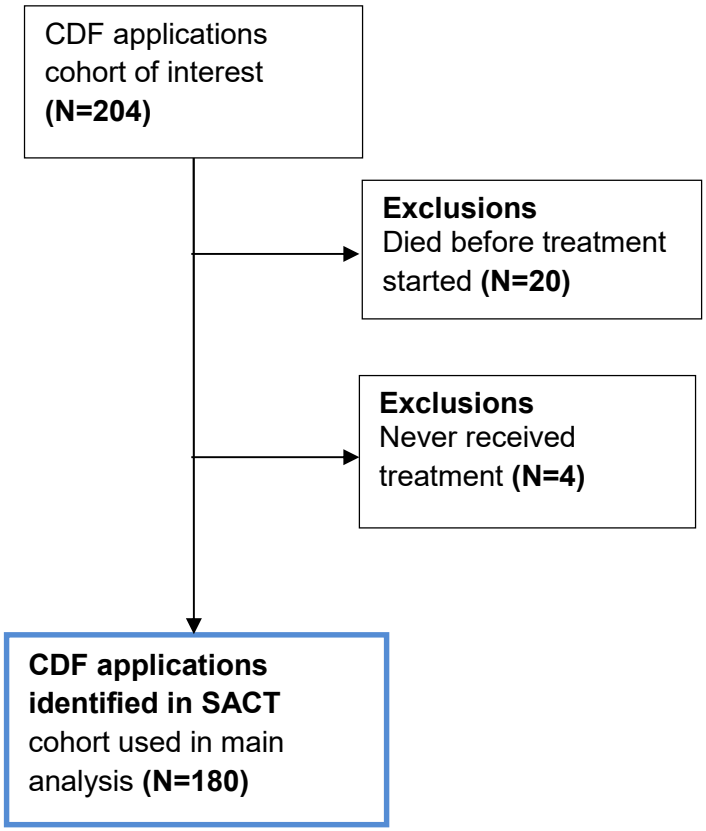
We used NHS numbers to link SACT records to the CDF cohort in NHSE's Blueteq system (as identified in figure 1). Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application, this included information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes.

Results

Cohort of interest

Of the 204 new applications for CDF funding for pembrolizumab for locally advanced or metastatic urothelial cancer who have received prior platinum-containing chemotherapy, 24 did not have a treatment record in SACT, 20 died before treatment started and 4 never received treatment for other reasons (see figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq) applications for pembrolizumab for treating previously treated advanced or metastatic urothelial cancer between 16 March 2018 and 16 August 2018



A maximum of 180 pembrolizumab records are expected in SACT for patients who were still alive and eligible to commence treatment (Figure 2).100% (180/180) of these applicants for CDF funding had a treatment record in SACT.

The SACT data liaison officers[1] follow-up patients that have a CDF application for pembrolizumab for the treatment of advanced or metastatic urothelial cancer and no treatment data in SACT on an ongoing basis, throughout the CDF managed access period. This information is captured locally within PHE and used to monitor ascertainment of treatment information in SACT. The data liaison team follow up on missing patients with the Trust responsible for the CDF application. In cases where a patient has not gone on to receive treatment, this is recorded.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is >90% for all key items and 100% for gender, primary diagnosis and date of birth.

Table 1: Completeness of key SACT data items for the pembrolizumab cohort (N=180)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Performance status at start of regimen	91%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. The percentage completeness provided for outcome summary is for records with an expected outcome. Outcomes are expected if a patient has an outcome summary recorded in the SACT dataset, a patient has died or has not received treatment in at least 3 months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes were expected for 102 patients. Of these, 102 have an outcome summary recorded in the SACT dataset, 100% (102/102).

[1] The SACT data liaison team at PHE, work directly with NHS trusts to support routine submission of SACT data; answering trust questions; providing practical support both remotely and in person; and identifying and resolving data quality issues. The team are also responsible for following up CDF patients with missing and incomplete data. They identify, contact and work with the NHS trust making the Blueteq application to fill key data gaps.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=102)

Variable	Completeness (%)
Regimen outcome summary	100%

Patient characteristics

The median age of the 180 patients receiving pembrolizumab was 70 years and was consistent for both genders.

Table 3: Patient characteristics

Patient characteristics				
			n	%
Sex	Male		135	75%
	Female		45	25%
Age	40-49		5	3%
	50-59		21	12%
	60-69		60	33%
	70-79		79	44%
	80+		15	8%
Performance status		0	44	24%
		1	97	54%
		2	21	12%
		3	1	1%
		4	0	0%
	Unknown		17	9%

Outcome summary

Table 4 provides a breakdown of the treatment outcome recorded in SACT when a patient's treatment has come to an end. 43% (N=78) patients were still on treatment at the latest SACT data follow-up (30 September 2018).

Table 4: Treatment outcomes (N=180)

Outcome	**Frequency**	**%**
Stopped treatment – progression of disease	56	55%
Stopped treatment – acute chemotherapy toxicity	7	7%
Stopped treatment – patient choice	7	7%
Stopped treatment – died	32	31%
Total number of patients that have ended treatment	**102**	**57%**
Patients still on treatment	78	43%
Total	**180**	

Conclusions

As a result of the short data collection period, OS and treatment duration were not calculated. Analyses in this report are based on patients with a CDF application for pembrolizumab for treating previously treated advanced or metastatic urothelial cancer between 16 March 2018 and 16 August 2018, where a treatment record was captured in SACT. Patients were followed until 30 September 2018.

SACT ascertainment was 100%. All unique CDF applications for pembrolizumab for the treatment of advanced or metastatic urothelial cancer were either reported to SACT or the trust responsible for the CDF application confirmed that the patient did not receive treatment.

Patient characteristics from the SACT dataset show that proportionally more men received pembrolizumab as a treatment option for urothelial cancer when compared to females (75% male, 25% female). Most of the cohort were patients between 60 and 79 years (77%) and 90% of patients had a performance status between 0 and 2 at the start of their regimen; this is in line with the treatment criteria stated in the managed access agreement.

At the end of the data collection period, 102 patients were identified as no longer receiving treatment; of these, 100% (N=102) patients had an outcome submitted by the treating Trust confirming the reason why each patient had ended their treatment. Fifty-five per cent (N=56) patients had stopped treatment due to disease progression and 31% (N=32) had died.

References

1. Cancer Drugs Fund. [Internet]. NHS England: 2017 [cited 2019 Jan]. Available from: www.england.nhs.uk/cancer/cdf/

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3. National Institute for Health and Care Excellence: 2018 [cited 2019 Feb]. Available from: www.nice.org.uk/guidance/ta519/resources/managed-access-agreement-april-2018-pdf-4840935805

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5. The Personal Demographics Service (PDS) [Internet]. NHS Digital: 2018 [cited 2019 Jan]. Available from: https://digital.nhs.uk/Demographics

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Action Bladder Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Action Bladder Cancer UK is a registered charity providing support to those affected by bladder cancer. We have three main strands to our work: • Raising awareness • Supporting patients • Improving outcomes, including research We are working to raise awareness for bladder cancer by: • Raising awareness of the signs and symptoms among the public so they seek advice sooner • Improving awareness and investigation techniques among health professionals to improve early diagnosis • Publicising our work, including funded research, for instance in May Awareness Month We are working to improve patient support through: • Our high quality information materials and resources library • Actively increasing the number of bladder cancer patient support groups across the UK • Providing advice and support to both new and existing groups and helping to bring groups together • Helping to give bladder cancer patients a voice We are working to improve outcomes and research into bladder cancer by: • Identifying the key research priorities • Encouraging, contributing to and funding research • Improving research data and statistics • Improving the treatment and management of bladder cancer to increase patient survival rates in line with that achieved for other common cancers

	We are funded by donations, legacies, fundraising events and by corporate donations. Our corporate donors are bound by our corporate statement as follows: CORPORATE STATEMENT Action Bladder Cancer UK is a charity working to support those with bladder cancer and to improve outcomes for patients. We are committed to working in ethical collaboration with commercial and corporate partners in the interest of people affected by bladder cancer. We will accept funding from appropriate corporate and industry supporters. Neither our work, our campaigning nor our information materials will be influenced by accepting any corporate donations or sponsorship. We feel it is important to work with companies that manufacture drugs, treatments or devices which will treat or support bladder cancer patients. We will work in a transparent partnership with appropriate pharmaceutical companies and the medical device industry where these relationships will help promote and improve the interests of bladder cancer patients and fit within the objectives of our charity. We would not accept support from any pharmaceutical or medical industry company for work that we consider to that lie outside the agreed objectives of our charity. We are happy to accept funding, or support in kind, from appropriate corporate supporters outside the health or pharmaceutical sectors. Each corporate collaboration will be assessed and agreed on an individual basis by the charity executive. We are grateful for the support shown by our existing corporate supporters which help us in our work.

	ABC UK has 9 Trustees including a healthy mix of clinicians, urology consultants, oncologists, cancer nurse specialist, GP with interest in bladder cancer, researchers and patients. We have three employees and outsourced secretariat.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Action Bladder Cancer UK is a national charity which is supported by a diverse and comprehensive array of health professionals and patients. We have established over 25 bladder cancer support groups over the past two years and continually speak to patients, CNSs, researchers and consultants. We also provide direct support to patients and carers who contact us by email or telephone.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Awareness is so poor that initial diagnosis is invariably a shock and Bladder Cancer (BCa) remains a difficult disease to talk about due to general lack of awareness. The fact that recurrence is so high and progression is so common, it makes it a difficult condition to live with, despite treatment for NMIBC being relatively straightforward and effective. The particular condition of locally advanced or metastatic BCa for this consultation where platinum chemotherapy has already been given and where survival rates are known to be poor. Therefore, the specific condition is very difficult for both patient and carer, being characterised by: chronic fatigue, pain, nausea, high dependence and difficulty voiding urine, leading to a

	low and deteriorating QoL..
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients tell us that they receive markedly different levels and quality of treatment from different hospitals, and from different parts of the country – the 'postcode lottery' (NB one of the four key findings of the May 2019 published, 'Geographic patterns in cancer survival in England', shows that BCa survival is actually deteriorating in some areas). This is particularly so where they are transferred from a district hospital to a BCa centre of excellence. The annual National Cancer Experience Survey routinely reports a very low level of patient satisfaction for urological cancers. All other common cancers have enjoyed significant improvements in survival and new tretaments. This is not the case for BCa. **Pembrolizumab represents an innovative treatment and lifeline for many patients.**
8. Is there an unmet need for patients with this condition?	There is a very high unmet need for this condition. The specific indication is for patients who have failed to respond to platinum based chemotherapy – the previous best standard of care. A very high proportion of locally advanced or metastatic BCa patients will not survive 5 years. These patients will endure a painful and debilitating decline which is also very difficult, both physically and emotionally, for carers and family. Pembrolizumab (and other new immunotherapy treatments) offers a lifeline to such patients. However, we understand that only about 15 – 20% will enjoy a lasting improvement to their QoL, and even then, we understand that the CDF provides for only 2 years of Pembrolizumab, whereas patients that show a complete response need it for much longer. So there remains a massive and urgent unmet need, especially when one considers the advances that have been made in the treatment of other common cancers.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	In its simplest form the treatment represents hope to many for whom other treatment options have been exhausted. Therefore the main benefits include: - complete response - prolonging life - improved quality of life for patient, carer, family, friends. The mental health benefits that go hand in hand with the treatment are significant for patient and family/carer. The treatment is typically better tolerated than chemotherapy and is relatively easy to administer.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	For the specific condition, locally advanced or metastatic BCa that has failed platinum based chemotherapy, the patient is terminally ill. Within this context there are few if any significant disadvantages. There are side effects, and whilst these are typically less than for chemotherapy, some patients may not tolerate them.

	The other main 'disadvantage' is that the treatment is known to be effective for a minority (15 – 20%). So patients know that this is their last chance of returning to a good QoL, and that the chance is a small one. It would be good for all concerned if a prognostic test or biomarker could be found that would determine the drug's effectiveness for an individual patient.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not known, although we would strongly assert that any and all patients with this condition that have failed chemotherapy would benefit from the opportunity to have this treatment. This is a relatively small population which is more prevalent among the elderly. Significant co-morbidities will affect treatment options and suitability. Many patients with metastatic cancer have poor renal function and cannot be given platinum based chemotherapy (cisplatin), However it would be highly desirable to study patient outcomes and to attempt to develop prognostic tests of suitability using, for instance, biomarkers and genomic sequencing, to enable the treatment to be used as precision medicine. It would also be useful for patients to contribute to the 'Life and Bladder Cancer' PROMS (Patient Reported Outcome Measures Study), being run by Leeds/Sheffield.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None known. Although women tend to be diagnosed at a later stage than men, meaning that their survival is lower.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Bladder Cancer has had relatively little research and new treatment development in recent decades. Despite it being one of the 10 most prevalent cancers, and very expensive for the NHS to treat, mortality rates of c50% have shown NO improvement in the past 30 years. The mechanism of this new drug is different from anything available to treat BC today, hence the treatment is highly innovative. ABC UK supports the licencing and use of the treatment within the NHS. Ideally more research could be commissioned to optimise the treatment regimen and to better understand the mechanism of treatment, ultimately leading to biomarkers to identify patients for whom the treatment would be effective/ineffective.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • ABC UK supports the licencing and use of the treatment within the NHS	

- The treatment is highly innovative
- The treatment gives hope to many for whom other treatment options have been exhausted
- Further research/trials to optimise the treatment and develop biomarkers would be highly desirable
- Consideration should be given for research/trails for use of the treatment earlier in the disease progress and/or as a primary treatment

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Fight Bladder Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight Bladder Cancer is a patient advocacy group and charity for bladder cancer, based in the UK. We run a 24/7 confidential online support group that has approx. 4,000 users at any one-time, local support groups around the country and a national 1 to 1 bladder buddy services. As patients and carers ourselves, our knowledge of the patient experience with bladder cancer is second to none in the UK. The charity is funded by individual donations, grants, and financial support from Roche, MSD, BMS, and Janssen.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have a confidential online forum of 3000+ patients and carers, offer telephone and email support, a 1 to 1 peer support service and conduct regular surveys. We collaborated with bladder cancer charities in Canada and USA to understand patient experience of pembrolizumab for previously treated advanced or metastatic urothelial cancer in North America.
Living with the condition	
6. What is it like to live with the condition? What do carers	

experience when caring for someone with the condition?	Metastatic or advanced urothelial cancer has a very poor prognosis. The current treatments can often have quite serious side effects that significantly reduce the quality of life for the final months. For carers, it is a period of ultimate worry and exhaustion as you care for your loved one as the patient and their medical team fight to preserve life for as long as possible. At this point in the pathway there is currently very limited choice on treatments. Most current treatments are also very invasive, have significant side effects and substantially affect the patient emotionally as well. With treatment, it is a constant battle to delay the further growth and spread of the cancer. Treatment that is invasive, has many side effects including ones that are potentially fatal in themselves. The condition is a physically and emotionally tough with a regime of chemotherapy, a known low prognosis, and the understanding that the battle is to "prolong life" rather than resulting in a cure. Everything is tinged with a sadness and a sorrow of "will this be the last time I do this?". The psychological effects of this disease are truly awful. For most patients, the diagnosis results in a constant stream of treatments and interventions to deal with the often-serious side effects. Normal life is suspended and even when you are not undergoing the treatment itself, the exhaustion and side effects dramatically reduce the ability to have a normal life. Most normal life activities have to be suspended whilst the clinicians battle the cancer and the side effects. Patients report that it has a substantial impact on their ability to work, ability to travel and ability to exercise For carers, the pressure is on them, from day one, to help support and care for their loved ones. Carers report that it has a substantial impact on their ability to work, ability to travel and ability to spend time with family and friends.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	For advanced/metastatic urothelial cancer, prognosis is very poor with very limited treatments being available. In addition to the chemotherapy treatments, the patients are likely to need other medical treatments such as radiotherapy to the part of the body where the cancer has spread, surgery to remove the cancer in the bladder, surgery to unblock the ureters or urethra and drugs to strengthen the bones. Urothelial cancer predominantly a cancer of older people with most patients being over 60 years of age. This often results in the patient being less able to tolerate the side effects of intensive chemotherapy. In addition, the patient is often unwell because of the cancer, other medical problems such as heart, lung and liver problems together with poor kidney function. All of which will restrict the effective use of the chemotherapy treatment. The Quality of Life of these patients with the existing models of care is very poor with very little opportunity to have quality time with their loved ones. "I know that it is unlikely to cure me, but why does it have to be so difficult to have time and the energy to make memories with my family?"
8. Is there an unmet need for patients with this condition?	Many of the existing treatments for urothelial cancer have limited effectiveness which results in the poor overall prognosis for this cancer and specifically very poor for those with advanced/metastatic cancer. There is a substantial unmet need for treatment options that can meaningfully improve survival and quality of life in patients with advanced bladder cancer following chemotherapy or who are not eligible for chemotherapy.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The new technology for the treatment of urothelial cancer offers hope for patients and carers for this much ignored cancer. The hope is that these possible new treatments will improve prognosis, reduce recurrence and reduce side effects. Ideally, we hope to see improvements against all of these factors but understand that not every patient will see benefits across them all. The prospect of some hope that their life expectancy can be improved can, at a minimum, give them that essential extra time to come to terms with the diagnosis, make memories, make plans for the short but valuable extra time that this treatment could give. Pembrolizumab is the first PD-1 inhibitor to show a significant overall survival benefit for bladder cancer in a phase 3 trial. Pembrolizumab has shown to significantly prolong the time to deterioration in health compared to chemotherapy. This is further demonstrated by the real-life stories of patients. Possibly the most dramatic result of this new treatment option is that certain people seem to do very well on it with significant extension of life. Whilst this is not seen in all patients, it certainly gives hope where is currently very little. Patients surveyed have indicated that based on their personal experiences with Pembrolizumab they ranked it extremely effective at controlling their bladder cancer. Quality of life indications from the trial data, together with the stories from patients, is that Pembrolizumab has reduced side effects when compared to platinum-based therapies. When comparing to side-effects from other therapies, patients have said it was much better than other therapies in terms of severity of side-effects. There is also an indication that the quantity of life-threatening adverse events is substantially reduced. Patients surveyed also indicated that Pembrolizumab had an overwhelmingly positive effect on their quality of life. Patients generally feel that Pembrolizumab does not interfere with everyday activities.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Currently we do not know enough details about the effectiveness or the quality of life issues surrounding the new technology to pass judgement at this stage. Patients would always want to balance effectiveness on recurrence and progression against the quality of life during and after treatment. Concerns would be any problems with toxicity and side-effects, but limited details known at the present. Patients surveyed have reported fatigue, skin rash, low platelet counts, decreased thyroid function, decreased appetite, itchiness, and diarrhoea while one other had moderate diarrhoea only. Treatment time is also an issue, as often the day of treatment can be an all-day event for some patients.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is possible that the use of this technology might benefit specific sections of the patient population according to how their immune system reacts to the treatment and it might be possible to identify these patients with the use of biomarkers or the like. The patients who would benefit most would likely be those whose current first line treatment has failed but it is possible that this technology could become an effective first line treatments across the pathway Current trials are mainly in the use for metastatic patients but there is a potential for use at other points in the pathway.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None known**
Other issues	
13. Are there any other issues that you would like the committee to consider?	Urothelial cancer has come at the bottom of the annual NHS cancer patient experience survey since its launch. The new technology offers a ray of hope for a step change in treatment for this much ignored cancer. The high risk of recurrence and progression has led to this cancer seeing one of the highest associated suicide rates for cancer patients due to the emotional strains of the treatment and quality of life issues.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • No new treatments for urothelial cancer for over 35 years • Urothelial cancer has the highest recurrence rate of any cancer due to existing treatments being relatively ineffective • Existing treatments are invasive and have significant side effects and resultant Quality of Life issues • The new immunotherapy treatments could see a step change in treating this much ignored cancer where we have not seen any real improvements in decades.	

- They will possible offer hope to many, extra time to many and possibly be curative for some.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Simon Crabb**
2. Name of organisation	**University of Southampton**

3. Job title or position	**Associate Professor in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	There are two main aims, which are to extend survival and to optimise quality of life. In these circumstances pembrolizumab, on average, achieves both of these aims compared to chemotherapy. Data suggest also that other secondary endpoints are improved compared to chemotherapy including the toxicity profile of treatment, the objective tumour response rate and the median duration of response.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	My view is that I would prioritise the combination of disease control (so stable or shrunk) with the duration of these responses. In most patients, in my experience of either pembrolizumab or other treatment options, this is what primarily drives quality of life. The key benefit for immunotherapy over chemotherapy seems to be in the 'tail of the curve' where some patients will derive a prolonged period of disease control. Although it is also true to say that the objective response rate (the percentage with tumour shrinkage) is higher based on RECIST based measurements compared to chemotherapy.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The median overall survival in the chemotherapy control arm of the KEYNOTE-045 trial (in the original publication) was 7.4 months (95% CI, 6.1 to 8.3) and effectively all patients die of their cancer. Moreover, this was only for those patients deemed to be fit enough to actually receive chemotherapy. Therefore, a less toxic treatment that can be shown to extend survival using a novel therapeutic approach, as KEYNOTE-045 showed for pembrolizumab for the first time in this disease, was clearly meeting an unmet need.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The European Association of Urology guideline on bladder cancer (https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/#7_8) recommends specifically to use pembrolizumab in this setting. They give this a 'Strong' rating strength (see section 7.8.9). NICE guidelines on urothelial cancer (https://www.nice.org.uk/guidance/ng2) are out of date as they were written before the advent of immunotherapy for this disease. They recommended the chemotherapy that pembrolizumab has since been shown to be superior to in the KEYNOTE-045 trial.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	This is well defined with strong consistency across the country. First line treatment of advanced incurable disease is treated with cisplatin based chemotherapy if a patient is fit enough to receive it (roughly half of UK patients are fit enough). Those that are 'cisplatin ineligible' would be offered carboplatin based chemotherapy or, if they have a cancer that has high PD-L1 expression, the alternative option of immunotherapy with pembrolizumab or atezolizumab. The standard of care option for second line treatment after either cisplatin or carboplatin based chemotherapy (the setting for this appraisal) is then with immunotherapy with either pembrolizumab or atezolizumab. In the UK most clinicians would tend to choose pembrolizumab over atezolizumab as the KEYNOTE-045 trial demonstrated a positive survival advantage for the former over chemotherapy. For patients with an incurable recurrence within 12 months after the receipt of platinum-based adjuvant or neoadjuvant therapy for localized muscle-invasive disease, the consensus would be to use immunotherapy with pembrolizumab as a 'second line' treatment as outlined above (i.e. not to repeat chemotherapy first).
• What impact would the technology have on the current pathway of care?	Pembrolizumab used as a post chemotherapy second line treatment, in the manner under consideration here, and described above, is available currently through the Cancer Drugs Fund (CDF) and has been

	widely adopted. We would therefore continue its use, which remains the appropriate standard of care treatment at this point.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	As described above pembrolizumab is available through the CDF and so is being used routinely and it is the internationally accepted standard of care treatment option currently. If it (and atezolizumab) were removed we would revert back to chemotherapy which is more toxic and has less favourable outcomes. Both these immunotherapy and chemotherapy options are outpatient intravenous treatments and so the resource use in general terms is similar.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This is already established. It is being used by oncologists with a specialist interest in bladder cancer in tertiary referral cancer units and centres. The move from chemotherapy to immunotherapy that KEYNOTE-045 has caused has not altered how and where treatment is being done.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. As described above it is the same teams that were previously giving chemotherapy and it is already well established through CDF access to pembrolizumab. The need for training on the differences in side effect profile (less toxicity but a difference in patterns of what can happen) is now fully established across the country as we have been using these drugs for a few years now for this and other cancers.
12. Do you expect the technology to provide clinically	

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Pembrolizumab has been shown, in a well conducted phase III trial (KEYNOTE-045), to improve median overall survival, and other secondary endpoints, with a favourable toxicity profile to chemotherapy. So yes, there is a clinically meaningful benefit from pembrolizumab over the prior option of chemotherapy.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes (see above).
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not that we can identify to date, assuming that pateints meet the current CDF criteria which reflect the KEYNOTE-045 eligibility criteria. Work on predictive biomarkers for who would benefit from pembrolizumab has not been successful in identifying anything that can yet be utilised in this setting (this is distinct from the first line setting).
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	Less difficult in the sense that it is less toxic. We are already using pembrolizumab routinely through the CDF and the teams and back up systems for toxicity are the same as for our prior use of chemotherapy. The period of time a few years ago when these were new drugs has passed and we can now say that the

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	distinct patterns of side effect management are fully established in routine care in the centres that will give this.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting will be by detection of clinical progression of the cancer (or relapse if within 12 months of prior adjuvant/neoadjuvant chemotherapy) by CT scanning. Stopping will be on the development of unacceptable toxicity (not very common) or disease progression (more common) detected usually by CT scanning. This are not really different from prior treatment with chemotherapy.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes in the sense that we had been using chemotherapy for a few decades with no new options for treatment or improvement in outcomes and KEYNOTE-045 introduced the use of an entirely different therapeutic approach with pembrolizumab.
• Does the use of the technology address any particular unmet need of the patient population?	As described above, outcomes are poor and pembrolizumab extends survival with less toxicity from treatment.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicity can occur with pembrolizumab. The patterns are distinct but overall less severe than with the prior standard of chemotherapy. In general, most side effects are straight forward to manage with dose delay and use of corticosteroids.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The KEYNOTE-045 trial control arm was a good reflection of the prior standard of care with chemotherapy that was used in the UK. So the trial is a clear advance on our prior standard (chemotherapy).
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival is the most important outcome, which was the primary endpoint of KEYNOTE-045. The trial also included a number of important secondary endpoints and treatment related toxicity. These favour pembrolizumab.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. Routine use of pembrolizumab is closely matched to the outcomes, both efficacy and toxicity, that were described in KEYNOTE-045.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA519]? Please note, the original scope from [TA519] is being used in this review, therefore no additional comparators will be considered.	Not for second line use after prior chemotherapy. There are some changes to how we use first line immunotherapy in cisplatin ineligible patients relating to PD-L1 expression (described above under 10) but this group of patients are distinct from those that would receive pembrolizumab in the setting under consideration here. What this means is that you might expect a higher number of patients to receive pembrolizumab in the second line setting than the first line setting (and the same for atezoliazumab).

22. How do data on real-world experience compare with the trial data?	Remarkably similar in everything that I have seen to date. The trial is a good reflection of the 'real world' experience.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
23b. Consider whether these issues are different from issues with current care and why.	They are not.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Pembrolizumab extends median survival compared to the prior standard of care of chemotherapy
- It also improves a number of other important secondary efficacy endpoints
- It does this with a different pattern of, but overall less difficult, toxicity profile
- It is already firmly adopted by the UK community and is regarded internationally as the standard of care treatment option
- Patients, in my experience, want to receive immunotherapy

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519 [ID1536]

Produced by Warwick Evidence

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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

Daniel Gallacher (Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses; Mary Jordan (Research Fellow) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Xavier Armoiry (Honorary Clinical Research Fellow) conducted, reviewed and critiqued the clinical effectiveness evidence; Mubarak Patel (Research Associate) conducted, reviewed and critiqued the survival analysis; Pam Royle (Information Specialist) checked the company searches and undertook any additional searching; Hema Mistry (Associate Professor) co-ordinated the project and the report, and provided comments on the report.

Contents

List of Tables

List of Figures

Definition of terms and list of abbreviations

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CDF	Cancer Drugs Fund
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CPS	Combined Positive Score
CS	Company Submission
ECOG	Eastern Cooperative Oncology Group
ERG	Evidence Review Group
HR	Hazard Ratio
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention-To-Treat
KM	Kaplan Meier
NHS	National Health Service
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PAS	Patient Access Scheme
PD-L1	Programmed Death ligand 1
PFS	Progression-Free Survival
PHE	Public Health England
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
SoC	Standard of Care
ToE	Terms of Engagement
UK	United Kingdom

Executive Summary

1.1. Critique of the adherence to Committees preferred assumptions from the Terms of Engagement in the company's submission

The Company have adhered to the majority of the Committee's preferred assumptions from the Terms of Engagement (ToE); the key deviations are:

- The company prefer a log normal curve for extrapolation of progression-free survival (PFS).
- The Committee suggested 3 and 5 year durations of treatment effect. The company preferred 5 years, but this is not supported by strong evidence.

1.2. Summary of the key issues in the clinical effectiveness evidence

Pembrolizumab used as single agent was evaluated against standard of care (SoC) - either paclitaxel, docetaxel or vinflunine in the KEYNOTE-045 trial. The trial had PFS and overall survival (OS) as co-primary endpoints.

Pembrolizumab does not significantly reduce the risk of a PFS event as measured by the hazard ratio compared to either SoC or United Kingdom (UK) SoC.

Pembrolizumab, when compared to UK SoC (excluding vinflunine), reduces the risk of death by 26% in the entire population, by 42% in patients with PD-L1 CPS≥1%, and by 49% in patients strongly positive for PD-L1 CPS≥10%.

As the optimal approach of treatment switching is unclear the Evidence Review Group (ERG) maintains the 2-stage approach in their base-case, but present intention-to-treat (ITT) analysis of the UK SoC arm as scenario analysis that should also be carefully considered.

1.3. Summary of the key issues in the cost-effectiveness evidence

The ERG consider 4 main issues which impact the cost-effectiveness evidence.

1) PFS extrapolation (Section 4.2.1)

The ERG agree on the 21 week cut off point used by the company. The company prefer a log normal curve for extrapolation of PFS. The ERG's preference is a Weibull curve as it remains the best fitting to the control arm according to Akaike Information Criterion (AIC), is

among one of the best fitting to the pembrolizumab arm and is consistent with the observed data. It was the ERG's original choice and the Committee's preferred assumption.

2) Treatment Switching (Section 3.2.1)

This refers to the decision to use 2-stage adjusted OS data or ITT OS data for the UK SoC arm for model fitting. The company prefer the 2-stage adjustment method. The ERG are concerned about the assumptions this method makes: (1) a uniform treatment effect and (2) wide confidence intervals. Additionally, the new data has increased the magnitude of the acceleration factor applied during 2-stage adjustment, making the choice between methods a more critical factor due to its influence on cost-effectiveness outcomes. Therefore, the ERG reconsiders this parameter in the report.

A comparsion to the external study of vinflunine patients by Bellmunt et al.[1], suggests the acceleration factor is too harsh in its penalty to the UK SoC arm (i.e. the benefit assumed from treatment switching is too optimistic, so when removed from UK SoC patients their OS appears shorter than expected). The ERG acknowledges that ITT analysis will likely be biased in the other direction so have elected to stay with the 2-stage adjustment method. However, it is believed that the true effect of treatment switching on OS lies somewhere in between the two and they could be considered slightly unrealistic best and worst case scenarios.

3) OS extrapolation (Section 4.2.2)

The ERG are content to use a 24 week cut-off. The 40 week cut-off is not believed to be a feasible option given the behaviour of the data at this point, but other cut-offs may be plausible. The choice of curve remains unclear, with the biggest distinction between their outputs being their long-term predictions for pembrolizumab. If the Committee accepts that a handful of patients will remain alive for 10 years, a log-curve or generalised-gamma is appropriate. If not, a Weibull may be more suitable. Ultimately, the long-term efficacy is unknown. Generalised-gamma provides an optimistic extrapolation for both arms whereas Weibull is pessimistic for both. Log logistic and log normal curves are both optimistic for pembrolizumab but pessimistic for UK SoC.

4) Treatment Effect Duration (Section 4.2.5)

The focus here is the duration of the relative effect of pembrolizumab compared to patients on docetaxel/paclitaxel. Options suggested by the Committee and implemented by the company were 3 and 5 year durations. These durations appear arbitrary, but are in line with other appraisals. The company preferred 5 years, but this is not supported by strong

evidence. The ERG considers that as most patients stopped initial treatment in the first [redacted], it may be very plausible that the hazard rates for people who survive for 3 years are equal beyond this point. Evidence for an effect duration of at least 5 years provided by the company was weak and came from a single arm study in melanoma, and included response data, whereas the company did not provide any data on response from KEYNOTE-045 in this CS. The beginnings of a waning effect is clearly observed within KEYNOTE-045 and due to switching adjustment and there being only a small number of people at risk in the tail of the control arm, the ERG conclude there is no meaningful data to provide clear evidence of any effect beyond 2 years.

1.4. Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions based on the new data are summarised in Table 1:

- Weibull extrapolation of PFS initiated at 21 weeks
- Log logistic extrapolation of OS initiated at 24 weeks
- 3-year cap on treatment effect
- 2-stage adjustment for treatment switching

Implementation of the ERG's preferred assumptions surrounding these parameters increases the company's submitted incremental cost-effectiveness ratio (ICER) by £6,555, from £47,123 to £53,678 per QALY.

Table 1: ICER resulting from ERGs preferred assumptions

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
UK SoC	[redacted]	0.71	-	-	-
Pembrolizumab	[redacted]	1.34	£33,757	0.63	£53,678

1.5. Summary of exploratory and sensitivity analyses undertaken by the ERG

Additional analyses were undertaken by the ERG around uncertain parameters. Alternative plausible extrapolations for OS (Section 4.2.2), analyses using ITT approach rather than the 2-stage adjustment method (Section 3.2.1), varying the duration of treatment effect (Section 4.2.5) and the most optimistic and pessimistic outcome parameters for duration of treatment effect and OS combined are presented in Table 2. These produce a range of plausible ICER values between £42,643 and £87,208.

Table 2: Exploratory analyses undertaken by ERG

Scenario	UK SoC Costs	UK SoC QALYs	Pembrolizumab Costs	Pembrolizumab QALYs	ICER £/QALY
1. OS extrapolation using log normal changed from log logistic used in both company and ERG base-cases	[redacted]	0.70	[redacted]	1.26	£58,705
2. OS extrapolation using generalised gamma curve from log logistic used in both company and ERG base-cases	[redacted]	0.75	[redacted]	1.35	£55,202
3. ITT analysis of ERG base-case replacing 2-stage adjustment for treatment switching	[redacted]	0.93	[redacted]	1.39	£65,469
4. Duration of treatment effect capped at 5-years as used in company's base-case	[redacted]	0.71	[redacted]	1.43	£48,518
5. Duration of treatment effect capped at 10-years	[redacted]	0.71	[redacted]	1.49	£45,377
6. Duration of treatment effect lifetime	[redacted]	0.71	[redacted]	1.52	£44,473
7. Duration of treatment effect capped at 2-years	[redacted]	0.71	[redacted]	1.24	£61,315
8. OS extrapolation using log normal with lifetime treatment effect	[redacted]	0.70	[redacted]	1.55	£42,643
9. OS extrapolation using generalised gamma curve with 3-year treatment effect and ITT analysis	[redacted]	1.07	[redacted]	1.56	£61,653
10. OS extrapolation using Weibull curve with 2-year treatment effect	[redacted]	0.64	[redacted]	0.99	£87,208

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

Pembrolizumab (KEYTRUDA®) has been available in England since April 2018 through the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing therapy only if:

- Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression and
- The conditions in the managed access agreement for pembrolizumab are followed.

The Committee in its recommendations noted that in the KEYNOTE-045 trial, pembrolizumab improved overall survival and has the potential to be cost-effective. However, there was significant uncertainty in the extrapolation of overall survival and in turn, in the incremental cost-effectiveness ratios (cost-per quality-adjusted life years gained) obtained from the economic modelling.

2.2. Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

The key Committee preferred assumptions from the terms of engagement (ToE) are summarised in Table 1 in the company submission (CS), only the key changes are listed in Table 3 below.

Table 3: Preferred assumption from Terms of Engagement

Assumption	Terms of engagement	Addressed to by the company submission	Rationale if different	ERG comment
Extrapolation of overall survival (OS) and progression-free survival (PFS)	• A piecewise model is appropriate, but the best time to switch to a parametric curve is uncertain - Company method: Start extrapolation at 40 weeks using a log normal curve - Evidence Review Group (ERG) method: Start extrapolation at 24 weeks using a log logistic curve • There are several plausible OS extrapolation curves - Extrapolation of OS is unclear and require further data collection • Used a Weibull parametric curve to extrapolate PFS	OS - yes The company have started their OS extrapolation at 24 weeks in their base-case using a log logistic curve and explored 40 weeks in scenario analysis. PFS – partially The choice of curve for PFS remains different.	The company justify use of log normal curve for PFS as goodness of fit statistics and visual inspection suggest best fit to pembrolizumab arm trial-data	OS: The ERG maintains 24 weeks is one of the more plausible time points to commence OS extrapolation and 40 weeks cannot be supported due to the behaviour of the UK SoC data at that time-point. PFS: The ERG maintains its preference for the Weibull curve. It is the best fit to the control arm, among the best fitting to the pembrolizumab arm and is consistent with the most current observable data.
Duration of treatment effect	• A lifetime treatment effect considered by the Committee to be implausible • Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment	Yes The company used a 5 year cap on treatment benefit in their base-case analysis and 3 year cap on treatment benefit in their scenario analysis	The company relied on evidence from the KEYNOTE-001 trial, a single arm study of melanoma patients treated with pembrolizumab, to justify assumption of 5 year treatment benefit.	The ERG did not find KEYNOTE-001 provided sufficient evidence of sustained treatment benefit in this population. Both the 3 and 5 year cap on treatment benefit were equally advocated in the ToE and the ERG found little evidence to support treatment benefit from 2 years onward.
ERG's model corrections	Committee agree with the following correction from the ERG's model: • excluded the vinflunine data from the utilities • pooled utilities across treatment arms by progression state • used an updated algorithm to calculate	Partially The company have adhered to all ERG corrections made to their previous model except they have used a log normal curve to extrapolate PFS instead of a Weibull	See rationale above	See comment above

	age-related disutility • changed the proportion of people having docetaxel and paclitaxel to UK market share • used a Weibull parametric curve to extrapolate PFS • extrapolated the overall survival trial data at 24 weeks • used a log logistic parametric curve to extrapolate OS	curve in this submission.		

3. CLINICAL EFFECTIVENESS

3.1. Summary of new clinical evidence

- As in the original appraisal, the source of evidence to support the clinical effectiveness and safety of pembrolizumab for previously treated advanced or metastatic urothelial cancer comes from one single phase 3 randomised controlled trial (RCT) named KEYNOTE-045.

- This RCT compared pembrolizumab with standard of care (SoC) which comprised of docetaxel, paclitaxel or vinflunine, the latter not being available in the United Kingdom (UK).

- The KEYNOTE-045 trial had progression-free survival (PFS) and overall survival (OS) as co-primary endpoints which were both evaluated in the total population, and in the following subgroups: patients positive for Programmed cell Death 1 Ligand 1 (PD-L1) (combined positive score (CPS) ≥1%), and patients strongly positive for PD-L1 (CPS≥10%), this means KEYNOTE-045 had six primary objectives.

- Patient recruitment occurred from November 2014 to November 2015 with data cut-off on September 2016 at the time of original CS and January 2017 on later analyses submitted by the Company.

- In the Cancer Drugs Fund Review of TA519, the latest data cut-off from KEYNOTE-045 is 30 November 2018, this means almost two years (22 months) of additional data have been provided. This data cut-off date occurred post final analysis of KEYNOTE-045.

- Although pembrolizumab has been made available within the National Health Service (NHS) through the CDF since April 2018, no clinical effectiveness and safety data based on the UK clinical practice have been provided in this submission.

- Results from the latest survival analyses in accordance with original study design (randomisation between pembrolizumab and SoC without adjustment for treatment switching) were briefly stated in the main CS and numerically reported only in the appendices, with restriction to the entire population of KEYNOTE-045; results in the patient subgroups (PD-L1 (CPS≥1%) and PD-L1 (CPS≥10%)) were not reported. This was obtained from the Company after request by the ERG at clarification stage.

- In Table 4, the ERG have reported the main findings of survival analyses (both PFS and OS) from the most recent follow-up of patients from KEYNOTE-045 with reference to the previous analyses with less mature follow-up. Of note, the survival data presented by the Company in the present submission are more mature compared to those published in May 2019 by Fradet et al.[2] in their report of long-term efficacy outcomes of KEYNOTE-045 (data cut-off date was October 2017).

- Results reported in Table 4 suggest similar survival outcomes with the most updated follow-up data compared to the original CS:
    - Pembrolizumab does not significantly reduce the risk of a PFS event as measured by the hazard ratio compared to either SoC or UK SoC.
    - Pembrolizumab, when compared to SoC (including vinflunine), reduces the risk of death by 28% in the entire population, by 41% in patients with PD-L1 CPS≥1%, and by 44% in patients strongly positive for PD-L1 CPS≥10%.
    - Pembrolizumab, when compared to UK SoC (excluding vinflunine), reduces the risk of death by 26% in the entire population, by 42% in patients with PD-L1 CPS≥1%, and by 49% in patients strongly positive for PD-L1 CPS≥10%. This suggests that pembrolizumab has a better effect in patients with high CPS.
    - Similar trends were observed in the 2019 paper by Fradet et al.[2] which reported survival outcomes after earlier data cut-off date (results not reported in the ERG report).

- While OS results also suggest the hazard ratio (HR) is stable with more mature follow-up, the claim made by the Company that a waning effect should not be considered before five years is deemed speculative given the current evidence available. The ERG believes this statement should be viewed cautiously, more as an optimistic scenario. This will be further discussed by the ERG in the cost-effectiveness Section 4.2.

Table 4: Main survival outcomes from KEYNOTE-045

Survival outcome	**PFS (HR with 95% Confidence Interval)**		**OS (HR with 95% Confidence Interval)**	
Data cut-off date	**September 2016**	**November 2018**	**September 2016**	**November 2018**
Comparison: Pembrolizumab vs SoC				
Entire population	0.98 (0.81, 1.19)	0.96 (0.80,1.16)	0.73 (0.59, 0.91)	0.72 (0.59, 0.87)
PD-L1 (CPS≥1%)	0.91 (0.68, 1.24)	0.92 (0.69,1.24)	0.61 (0.43, 0.86)	0.59 (0.43, 0.80)
PD-L1 (CPS≥10%)	0.89 (0.61, 1.28)	0.94 (0.66,1.34)	0.57 (0.37, 0.88)	0.56 (0.38, 0.82)
Comparison: Pembrolizumab vs UK SoC				
Entire population	NA*	0.95 (0.76, 1.19)	[redacted]	0.74 (0.59, 0.94)
PD-L1 (CPS≥1%)	NA*	0.88 (0.63, 1.25)	[redacted]	0.58 (0.40, 0.84)
PD-L1 (CPS≥10%)	NA*	0.86 (0.57, 1.29)	[redacted]	0.51 (0.32, 0.81)

NA* - Figures are not available to report

3.2. Critique of new clinical evidence

3.2.1. Treatment Switching

As 40 patients who received UK SoC in the control arm of the KEYNOTE-045 trial also received anti-PD1/PDL1 treatment, the company chose to implement a technique which attempts to remove any additional benefit these patients may have received from change in treatment, in terms of overall survival. Some of these patients switched upon disease progression, whilst some did not.

The 2-stage technique involves calculating an acceleration factor from an analysis of the survival times of the 25 patients who did switch upon disease progression, compared to those who did not switch upon disease progression, adjusting for covariate differences. It is unclear how the 15 patients who switched at a different stage are included in this analysis. This acceleration factor is applied to the survival/censoring times of those who switched to estimate an event time for each patient had they not received anti-PD1/PDL1 therapy. The ERG has some concerns with this approach, which should be considered carefully due to the impact on the following survival extrapolations for the UK SoC arm (see CS Figure 1). These concerns were briefly mentioned by the ERG in the previous appraisal for this indication, and are raised here again due to the increased magnitude of the acceleration factor, and the increased number of patients whose event times change. The previous estimate of the acceleration factor was 3.86 based on 14 patients, whereas the current estimate of 5.37 is based on 25 patients.

The main concern relates to how the acceleration factor is calculated and applied to all patients who switched following disease progression. The ERG accept that it is likely that some patients did benefit from switching treatment. However, it is unlikely that all patients who did switch benefitted from their anti-PD1/PDL1 treatment. Evidence to support this is shown in the early stages of KEYNOTE-045 where pembrolizumab appears inferior to UK SoC for the first 3 months of follow-up. Additionally, immunotherapies have not demonstrated universal effectiveness.[3] Yet the acceleration factor is calculated and applied as an average effect in the 2-stage approach, despite the fact that it is unlikely that a uniform effect was achieved by treatment switching among the patient group. For example, those patients who switched but died soon after progressing may not have experienced the same time ratio of benefit as those who may have gone on to receive anti-PD1/PDL1 treatment for 6 months or more. The company were unable to provide any clarification about why certain patients switched when others did not. If it was not at random, then the acceleration factor

may be capturing the effect of an unmeasured prognostic factor, rather than the effect of switching treatments.

Importantly, the 95% confidence interval (CI) around the acceleration factor estimate is quite large (Estimate: 5.370; 95% CI: 3.231, 10.094). This demonstrates considerable uncertainty around this influential parameter. The ERG requested that the company estimate the acceleration factor including vinflunine patients, in an attempt to reduce the uncertainty. The estimate from this analysis was consistent, but did little to reduce the uncertainty (Estimate: 5.320; 95% CI: 3.443, 8.446).

The 2-stage approach also fails to consider patients from the survival analysis who switched at a time other than at disease progression, which may introduce bias into the analysis if there is some underlying pattern among these patients.

The final concern is the company opted to use the 2-stage approach without re-censoring. This means that shrunken censoring times are dependent on prognostic factors and may introduce bias to the analysis. It must be noted that re-censoring can lead to a loss of information and may not always be beneficial to the analysis.

Alternative methods of adjusting for treatment switching were not beneficial, and were discussed in the previous review of this indication. The other approach is to not adjust for treatment switching and proceed with the intention-to-treat (ITT) analysis. The ERG acknowledge there are concerns with this approach as it is likely that some patients in the control arm did receive some benefit from a treatment they switched to later in the trial. Failing to adjust for this introduces bias favouring the control arm, which may be stronger than the potential biases when the 2-stage method is used.

When comparing both the ITT and 2-stage data from the KEYNOTE-045 trial with the vinflunine arm of the trial by Bellmunt et al.[1], the ERG's clinical advisor stated they would expect patients in the UK SoC arm of the KEYNOTE-045 to have similar or slightly superior overall survival compared to the vinflunine patients. Comparison of the observed data demonstrates 2-stage adjustment may penalise the survival times too severely, whilst the ITT may be too optimistic (see Table 5). As the optimal approach is unclear, the ERG maintains the 2-stage approach in their base-case, but present ITT analysis of the UK SoC arm as scenario analysis that should also be carefully considered.

Table 5: Comparison of Observed Overall Survival

OS comparison to observed studies	Bellmunt 2013[1]	KEYNOTE-045 UK SoC arm ITT	KEYNOTE-045 UK SoC arm 2 stage adjustment
Median OS	6.9 months	7.0 months	6.2 months
12 month OS	27%	32%	25%
24 month OS	11%	16%	10%
30 month OS	5.5%	12%	7.7%

3.3. Additional work on clinical effectiveness undertaken by the ERG

3.3.1. Data from Public Health England

The Public Health England (PHE) report[4] on pembrolizumab due to the short-time frame (i.e. 9 months) for data collection did not collect any information on OS and treatment duration of pembrolizumab. However, information on patient baseline characteristics during the CDF data collection were provided and were similar to the KEYNOTE-045 trial. Approximately three-quarters were male patients; the median age was 70 (PHE report) and 67 (KEYNOTE-045) years; and the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) score of 1 was 53.9% (PHE report) and 55.5% (KEYNOTE-045) at the start of their regimen. PHE report noted that 43% of patients were still on treatment, 18% had died and 31% had disease progression and treatment stopped (in KEYNOTE-045 according to corresponding Kaplan-Meier (KM) the respective figures were 43% (at 10 weeks), 18% (at 12 weeks) and 31% (at 9 weeks). Overall, the ERG has no concerns with the data collected via CDF and those presented in the CS.

3.4. Conclusions of the clinical effectiveness section

Pembrolizumab used as single agent was evaluated against SOC (either paclitaxel, docetaxel, or vinflunine) in the KEYNOTE-045 trial. The trial had PFS and OS as co-primary endpoints.

Pembrolizumab does not significantly reduce the risk of a PFS event as measured by the hazard ratio compared to either SoC or UK SoC.

Pembrolizumab, when compared to UK SoC (excluding vinflunine), reduces the risk of death by 26% in the entire population, by 42% in patients with PD-L1 CPS≥1%, and by 49% in patients strongly positive for PD-L1 CPS≥10%.

As the optimal approach of treatment switching is unclear the ERG maintains the 2-stage approach in their base-case, but present ITT analysis of the UK SoC arm as scenario analysis that should also be carefully considered.

4. COST-EFFECTIVENESS

4.1. Summary of the company's submitted economic evaluation by the ERG

4.1.1. Model structure, population, intervention and comparators, perspective, time horizon and discounting

There have been no changes to the model structure, population, intervention and comparators, perspective, time horizon or discounting of the model submitted by the company, which was accepted previously by the Committee.

4.1.2. Treatment effectiveness and extrapolation

Duration of treatment effect has been capped at 5 years after starting pembrolizumab to reflect Committee preference to limit to 3 and 5 years rather than lifetime continued treatment effect as previously presented. Weibull curve extrapolation of PFS at 21 weeks was preferred by the ERG and Committee, however the company used a log normal extrapolation in their new base-case. This has been inadequately justified by reference to goodness of fit statistics and on the basis of visual inspection. Extrapolation of OS has been updated from a log normal parametric curve at a 40-week cut-off point, to a log logistic parametric curve at a 24-week cut-off as per ERG and Committee preferred approach.

4.1.3. Health-related quality of life

Utility estimates have been updated from the original CS which used utility values based on time to death. They are now in line with the ERG and Committee preferred approach using utility values based on progression state with current age-related disutility applied (see ToE document). Similarly, to follow Committee and ERGs preferences, utility estimates have excluded vinflunine data and have been pooled across treatment arms.

4.1.4. Resource use and costs

Resource use and costs were unchanged from the original CS except for acquisition cost of pembrolizumab where a new patient access scheme (PAS) discount was included. This reflected an increased discount from [redacted] to [redacted].

4.2. Critique of the company's submitted economic evaluation by the ERG

The company have largely adhered to the ToE for the purposes of the CDF review with exception of PFS extrapolation, using log normal rather than log logistic and changing the duration of treatment effect from lifetime to a 5-year cap. The ERG agree with the majority of the company's revised base-case, as they have now addressed previous concerns. However, the ERG has further concerns regarding the extrapolation curve chosen for both PFS and OS, the duration of treatment effect selected and method used to adjust for treatment switching (as highlighted in Section 3.2.1 of the clinical effectiveness critique).

4.2.1. PFS critique

As maintained from the previous review of pembrolizumab for this indication, the assumption of proportional hazards was still violated and so the company chose to fit parametric curves to the two arms of the KEYNOTE-045 trial independently, an approach accepted by the ERG.

Due to the unusual behaviour of the PFS KM curves in the beginning of the trial, the company preferred to fit the parametric curves to data generated later in the trial, where the extrapolations were found to be more plausible. The ERG also accept this approach and rationale.

Previously, the 21-week cut-off was preferred by both the company and the ERG, and this is maintained in this current CS.

In their selection of which parametric curve to extrapolate PFS from 21 weeks, the company considered Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and the visual fits for the curves to both arms of KEYNOTE-045. They report that the log normal was the best fitting to the pembrolizumab arm, and was also chosen for the UK SoC arm in the absence of a clear optimal fit here.

The ERG accept that the log normal does have the lowest AIC and BIC value for the pembrolizumab arm, however the values are not lower than those of log logistic, Weibull and Gompertz distributions by enough to be considered a significantly better fit. As the difference is less than 2 (Table 6), each of these four curves could be considered on equal merit under the standard interpretation of AIC and BIC. It is unclear why the company chose to prioritise

the fit to the pembrolizumab arm rather than the UK SoC arm of the trial. It is the ERGs preference to use the Weibull model, as it is the best fitting model to the control arm according to AIC, and the second best fitting according to BIC, where its difference from the model with the lowest BIC is less than 2 units. Meanwhile, for the control arm, the log normal AIC has a difference of 3 from the lowest AIC, and a difference of 4.2 from the lowest BIC, which suggests there is not substantial support for the log normal curve for this arm.
The choice of the Weibull curve is consistent with the ERGs previous preferred PFS curve, and which was also accepted by the Committee. It is also the most consistent with the observed data at 2 and 3 years in both arms of the KEYNOTE-045 trial (see Table 7 and Table 8). The ERG also verified the visual fit of the Weibull curve using the cumulative hazard plots provided by the company in their clarification response.

Table 6: AIC and BIC values for PFS extrapolations from 21 weeks (CS Table 2 from Appendix F)

	Model for pembrolizumab for week 21+ in overall population		**Model for control for week 21+ in overall population**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	529.4	531.8	383.5	385.4
Weibull	525.4	530.2	382.8	386.6
Gompertz	524.2	529.0	383.9	387.7
Llogistic	523.9	528.7	385.5	389.3
Lnormal	523.5	528.3	385.8	389.6
GenGamma	525.5	532.7	384.7	390.3

Table 7: Comparison of 21 Week PFS Extrapolations for UK SoC with observed data from KEYNOTE-045

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gamma	Observed in KN045
1 year	0.1017	0.0979	0.0919	0.0927	0.0930	0.0954	[redacted]
2 year	0.0160	0.0233	0.0375	0.0382	0.0235	0.0252	[redacted]
3 yea	0.0025	0.0065	0.0213	0.0232	0.0099	0.0084	[redacted]

r							
5 year	0.0001	0.0006	0.0098	0.0125	0.0041	0.0013	[redacted]
10 year	0.0000	0.0000	0.0030	0.0055	0.0025	0.0000	[redacted]

Table 8: Comparison of 21 Week PFS Extrapolations for Pembrolizumab with observed data from KEYNOTE-045

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gamma	Observed in KN045
1 year	0.2191	0.2033	0.1939	0.1968	0.1948	0.1952	[redacted]
2 year	0.1225	0.1290	0.1313	0.1287	0.1283	0.1306	[redacted]
3 year	0.0685	0.0879	0.1015	0.0970	0.1059	0.0992	[redacted]
5 year	0.0214	0.0450	0.0706	0.0659	0.0932	0.0667	[redacted]
10 year	0.0012	0.0109	0.0398	0.0375	0.0901	0.0349	[redacted]

4.2.2. OS critique

Before extrapolating the OS data, the company investigated whether the proportional hazards assumption held in the observed data. As it did not hold, the company fitted separate parametric curves to each arm of the trial data. The ERG agree with this approach.

The company state that because the change in hazard is not constant over time in both arms, it was more appropriate to use a piecewise modelling approach (i.e. to use Kaplan-

Meier data followed by a parametric fit). The ERG do not agree with this rationale alone, as many of the parametric curves assume a hazard profile that change at different rates over time. However, the behaviour of the cumulative hazard in the early follow-up stages is different to the longer-term follow-up, specifically in the UK SoC population. Thus, the ERG support the decision to use a piecewise approach.

The company previously stated a preference to use a 40 week cut-point from which to begin the parametric extrapolation, however the ERG stated a preference to extrapolate from 24 weeks. The company have now used 24 weeks as their base-case in the current CS.

The ERG has reviewed the available evidence to select the optimal cut-point based on the new data cut included in the company submission; however, there is no clear best choice. Possible options were 16, 24, 32 and 40 weeks. The ERG remains against using 40 weeks as immediate behaviour after this point on the UK SoC arm is not reflective of the long-term behaviour.

As there is little to distinguish between the remaining options, the ERG are happy to remain with the 24 week cut point, as put forward by the company. A comparison of the extrapolations showed that the choice did not have a large impact on the long-term extrapolation.

From 24 weeks the company chose a log logistic extrapolation. Whilst the Gompertz curve had the lowest AIC and BIC, the underlying shape of the Gompertz hazard resulted in long-term extrapolations were clearly implausible. The log logistic was the next best fitting model according to both AIC and BIC, whilst also providing plausible long term estimates (see Table 14 in the Appendix).

The OS data from KEYNOTE-045 is less mature than the PFS data, with fewer events having occurred. Whilst reliance on goodness-of-fit statistics alone should always be avoided, it is particularly true for immature data. Both AIC and BIC only inform on the fit to the observed data, and not on the accuracy of any extrapolation. When the data are very mature, AIC and BIC can be leaned on more heavily.

Whilst both the log normal and log logistic models have the lowest AIC and BIC, one should also consider their behaviour in the tail of their extrapolations. Both of the log models have a sharply decreasing hazard over time, which means a small number of patients will live for a long time. This can be contrasted with the Weibull model for example, which in this instance

also has a decreasing hazard rate over time, however its hazard rate remains higher than that of the two log models. This can be seen through a comparison of the extrapolations in Table 9 and Table 10 (see Appendix Table 15 to Table 18 for extrapolations using alternative treatment durations). Whilst these three curves produce similar predictions for the first few years of the trial follow-up, there are clear differences in their longer-term predictions, especially in the pembrolizumab arm. The ERG believe that the choice of extrapolation curve should be dictated by the plausibility of the extrapolations. However, the predictions for the UK SoC patients are similar across almost all parametric curves. When combined with the fact that there is no evidence for the long-term efficacy of pembrolizumab for these patients, it remains difficult to select the optimal curve for extrapolation. The ERG consider that four curves could be plausible for the OS extrapolation: Weibull, log normal, log logistic and generalised gamma.

The ERG's clinical advisor suggested that some sustained long-term benefit could be plausible for patients receiving pembrolizumab, supporting the selection of the log-curves. Hence, the ERG will maintain the selection of the log logistic curve in their base-case, and consider the other three potential curves in scenario analyses. An inspection of the cumulative hazard plot for each of the four models, provided by the company in their clarification response, maintained the plausibility of each of the four curves.

Table 9: Overall survival predictions from extrapolation of UK SoC from 24 weeks with a 2-stage adjustment

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.3012	0.2752	0.2517	0.2464	0.2427	0.2463	[redacted]
2 year	0.1066	0.1168	0.1131	0.1041	0.1134	0.1167	[redacted]
3 year	0.0377	0.0554	0.0667	0.0621	0.0815	0.0736	-
5 year	0.0047	0.0145	0.0317	0.0325	0.0662	0.0397	-
10 year	0.0000	0.0008	0.0099	0.0136	0.0632	0.0160	-
20 year	0.0000	0.0000	0.0026	0.0057	0.0631	0.0060	-
30 year	0.0000	0.0000	0.0010	0.0035	0.0631	0.0032	-
35 year	0.0000	0.0000	0.0007	0.0029	0.0631	0.0025	-

Table 10: Overall survival predictions from extrapolation of pembrolizumab from 24 weeks assuming a three year duration of treatment effect

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045

1 year	0.5013	0.4578	0.4351	0.4446	0.4417	0.4434	[redacted]
2 year	0.3070	0.2955	0.2834	0.2789	0.2733	0.2850	[redacted]
3 year	0.1861	0.2024	0.2117	0.2022	0.2057	0.2069	[redacted]
5 year	0.0233	0.0529	0.1007	0.1057	0.1673	0.1118	-
10 year	0.0001	0.0028	0.0314	0.0441	0.1595	0.0451	-
20 year	0.0000	0.0000	0.0081	0.0186	0.1594	0.0168	-
30 year	0.0000	0.0000	0.0033	0.0113	0.1594	0.0090	-
35 year	0.0000	0.0000	0.0023	0.0093	0.1594	0.0071	-

4.2.3. Time-on-treatment critique

For time-on-treatment, the company fitted separate parametric curves to the data for each arm of KEYNOTE-045. This approach is consistent with the previous review of this appraisal.

The company used the statistical goodness of fit criteria, AIC and BIC, to select the best fitting curve. The generalised gamma reportedly had the lowest scores for both arms, but failed to converge for the pembrolizumab arm, so was only used for the UK SoC arm. The Weibull was chosen for the pembrolizumab arm extrapolation, as it was the second best fitting to the data.

The ERG have minor concerns that curves of different forms were used for each arm, however, switching both arms to Weibull had a negligible impact on the analysis, and so the ERG are content to accept the company's assumptions surrounding time-on-treatment.

4.2.4. Treatment switching critique

The ERG has multiple concerns regarding the calculation and application of the acceleration factor used by the company to account for treatment switching effects. For a detailed discussion please refer to Section 3.2.1.

4.2.5. Treatment Effect Duration

Previously the company assumed a lifetime benefit of pembrolizumab in its economic analysis. They also provided alternative scenarios assuming the treatment effect would last for 3, 5 or 10 years – that is to say that the hazard rate for OS for patients receiving pembrolizumab reverts to the hazard rate for the control arm after each period of time in the

economic model. On the level of evidence currently available, these three effect durations appear to be chosen arbitrarily, but are consistent with other appraisals in this area. In this CS, the company has included the 5-year cap into their base-case analysis, stating that this is in-line with the ToE document. The ERG note that the 3-year cap was also presented in the ToE, with equal weighting to the 5-year cap.

Unfortunately, the availability of additional follow-up data sheds little light on the true treatment duration. The ERG requested that the company perform an analysis allowing a flexible time varying hazard ratio to capture any changes in the hazard ratio that were observed in the trial, given that the proportional hazards was clearly violated. In response (see CS Appendix G), the company used OS data incorporating the 2-stage switching adjustment. This adjustment is discussed in detail in Section 3.2.1, but is important here as it influences the length of follow-up of UK SoC patients. Without adjustment, there are [redacted] patients at risk of an event after 2 years of follow-up, but under the 2-stage adjustment there are just [redacted] patients at risk. But even in the unadjusted UK SoC arm, there are just [redacted] OS events that occur after 2 years. The ERG requested that the company reproduce the analysis without the 2-stage adjustment, though it is likely that, either with or without the adjustment, that there are too few data to draw any conclusion about a treatment effect beyond 2 years.

In the company's initial analysis, using the 2-stage adjustment, it is clear that the relative efficacy of the two arms in the early stages of follow-up are well captured, with pembrolizumab appearing inferior for the first 8 weeks of follow-up. Pembrolizumab then appears most effective at between 20 and 30 weeks with a hazard ratio of 0.39, where the effect appears to begin to wane slightly, up to a hazard ratio of 0.72 before reaching a plateau from 170 weeks with a hazard ratio of 0.62. The mean estimate of the hazard ratio does not cross above one again after the first 8 weeks, so there is no clear evidence that the treatment effect fully wanes within the observed follow-up period. The upper 95% CI around the estimate does cross one at roughly 63 weeks, suggesting there is no longer a significant difference between the two arms from this point, though this is undoubtedly linked with the small number of patients remaining at risk, and is not strong evidence of a loss of treatment effect.

In the analysis without any adjustment for treatment switching, a similar trend is observed with the hazard ratio reaching a lowest point between weeks 20 and 30 with a value of 0.43. The hazard ratio ascends to 0.89 at 60 weeks of follow-up, before plateauing at roughly 0.77 from around 3 years. The upper 95% CI crosses one at 39 weeks. The ERG interpret that

there is strong evidence of some degree of waning effect within the observed follow-up. However, there is insufficient evidence to conclude whether the waning continues, or whether a treatment effect is sustained beyond 2 years of follow-up, due to the small number of patients and lack of events in the UK SoC arm. The company could present evidence including vinflunine patients, which may provide useful information for the estimation of a relative treatment effect.

The company's sole source of evidence for a treatment effect beyond 3 years comes from the single arm KEYNOTE-001 study of pembrolizumab for patients with advanced melanoma or non-small cell lung cancer (NSCLC). The ERG has a number of concerns with this comparison. Firstly, these are different diseases and it is unclear whether it is right to make any generalisations between the trials. Also, for KEYNOTE-001 melanoma patients, and possible NSCLC patients, there was no limit on the length of the course of pembrolizumab, and patients could also begin a second course under certain criteria, whereas patients in KEYNOTE-045 were restricted to two years treatment. In KEYNOTE-001 melanoma patients, a response was sustained at 5 years of follow-up in 89% of complete-responders, and 63% of partial-responders.[5] For NSCLC patients, the median duration of response was 16.8 months for treatment naïve patients, and 38.9 months for previously treated patients.[6] However, as there was no comparator, it is not possible to gauge how this compares relative to other interventions at this point of follow-up. It is this relative effect that is of particular interest in this decision making process, due to the nature of how the hazard ratio applied in the economic model.

Whilst information on both the number of responders and duration of response in KEYNOTE-045 could influence the preferred duration of treatment effect, the company have not presented this evidence from the latest data cut. The ERG note that Fradet et al[2], which is based on a October 2017 data cut, report a maximum observed response of 30.0+ months for pembrolizumab, and 29.9+ months for the control arm. In the absence of further data it is the ERG's preference to choose the three-year treatment effect. It is also in-line with what has been observed for NSCLC patients in KEYNOTE-001.

The ERG will also consider a scenario based on 2-year treatment effect since no meaningful data are available from the 2-stage adjustment beyond this point, and that the upper confidence interval crosses one before this point. It is also when all patients are no longer receiving pembrolizumab, though most discontinued much earlier (mean = 6.84 months). Five and ten year effect durations will also be explored in scenario analyses. The Committee should note that the choice of the treatment effect duration only alters the hazard rate for the

pembrolizumab arm to become equal to that of the UK SoC arm, and it is plausible that these rates are very similar in patients who survive beyond 3 years. This does not affect the modelling of the benefit of pembrolizumab observed in the first 3 years of KEYNOTE-045.

The ERG also requested additional analyses varying the knot locations in the spline models to investigate where this would reveal any more information on the duration of treatment effect. The ERG recreated the patient level data from the information contained in the economic model. The ERG fitted their own spline models which captured the same waning of the treatment effect in the observed follow-up, despite failing to converge.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The updated CS base-case model produces an incremental cost-effectiveness ratio (ICER) of £47,123 when pembrolizumab is compared to UK SoC. This is achieved when the model is updated to incorporate the Committee and ERG preferred assumptions (summarised in Table 3 of this report) and by changing the extrapolation curve used for PFS from a Weibull to a log normal parametric curve. Additionally, a change in PAS since the original submission from [redacted] to [redacted] is applied. Table 11 below summarises the total costs, total quality-adjusted life years (QALYs) and associated ICERs when the model is updated for all the ERG and Committee preferred assumptions as per ToE (CS Table 7).

Table 11: Summary of cost-effectiveness results incorporating data from CDF collection period

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Cost-effectiveness results at CDF entry (CS Table 8)					
UK SoC	[redacted]	0.80	-	-	-
Pembrolizumab	[redacted]	1.50	£41,607	0.70	£59,729*#
Cost-effectiveness results with CDF data collection and model input and parameters unchanged (CS Table 9)					
UK SoC	[redacted]	0.71	-	-	-
Pembrolizumab	[redacted]	1.43	£39,215	0.72	£54,743*
Cost-effectiveness results with CDF data collection plus any associated changes (CS Table 10)					
UK SoC	[redacted]	0.72	-	-	-
Pembrolizumab	[redacted]	1.46	£35,035	0.74	£47,123**

#Figures from original appraisal (data-cuts September 2016 and January 2017)

**Incorporating Committee preferred assumptions, Committee agreed corrections from the ERG's model and a 5-year duration of treatment effect - (discounted with original PAS of [redacted])*

***Committee preferred assumptions and ERG's model corrections, but log normal PFS extrapolation used and discounted with new PAS of [redacted]*

5.2. Company's sensitivity analyses

The company's probabilistic sensitivity analysis (PSA) produced an ICER of £47,734, which is similar to the deterministic ICER of £47,135. The scatterplot and cost-effectiveness acceptability curve (CEAC) generated by these results are shown is CS Figures 9 and 10, (the CEAC is reproduced below). Using a cost per QALY threshold of £50,000, the CEAC suggests approximately a 63% probability of pembrolizumab being cost-effective.

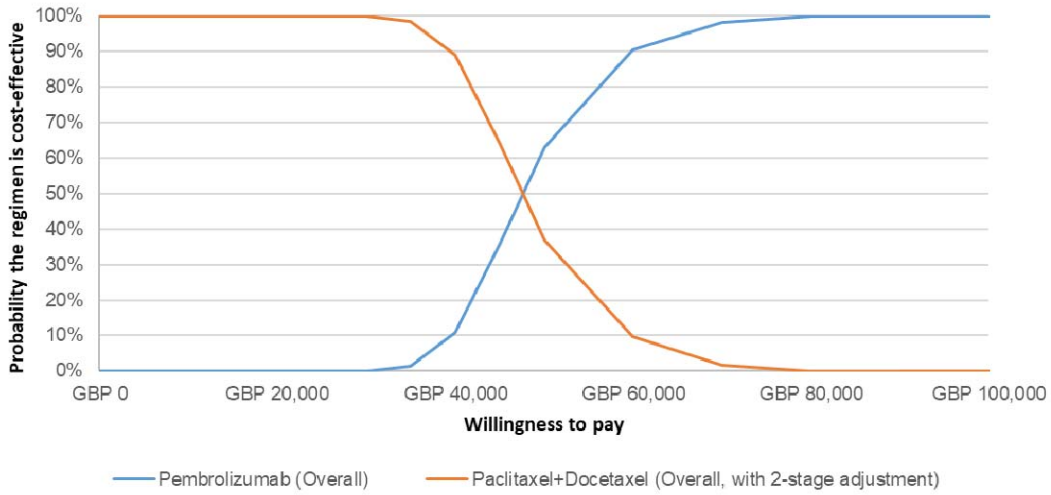

Figure 1: Cost-effectiveness acceptability curve (results discounted, with PAS) - CS Figure 10

One-way sensitivity analyses were conducted to explore the impact of parameter variation on the ICER. Results ranged from £38,073 per QALY to £54,710 per QALY for pembrolizumab versus UK SoC (See CS table 12 for detailed results). The major drivers of variation were discount rate for health outcomes, dosing intensity of pembrolizumab, and the extrapolation of OS.

5.3. Company's scenario analyses

The scenarios tested by the company include (see CS Table 13 for further information):

- Alternative week cut-off for OS extrapolation – 40 weeks
- Alternative treatment effect cap for OS – 3 years and 10 years
- Alternative pembrolizumab dosing schedule – extended dosing schedule 400mg every 6 weeks (representing a change from 200mg every 3 weeks as endorsed by European Medicines Agency's Committee for Medicinal Products for Human Use in March 2019.
- Alternative parametric function for PFS – Weibull function.

Reducing the treatment effect to 3-years had the greatest impact, increasing the ICER by £4,847 to £51,970. Similarly, the extended dosing schedule and Weibull extrapolation of PFS increased the ICER by £529 and £1,395 respectively, but neither was sufficient to raise the ICER above £50,000 per QALY. The 40-week cut-off for OS extrapolation and 10-year treatment effect in turn reduced the ICER by £1,246 and £2,950 per QALY.

5.4. ERG's preferred assumptions and additional analyses

The ERGs preferred assumptions are to fit a Weibull curve for the extrapolation of PFS data and to cap the duration of treatment effect at 3-years. These changes increase the company ICER by £6,555 to an ERG preferred deterministic ICER of £53,678 (see Table 12).

Table 12: ERG's preferred model assumptions

ERG preferred assumption	Scenario detail	Brief rationale and section in ERG report	Impact on base-case ICER
Company base-case			£47,123
1. PFS extrapolation Weibull	PFS extrapolation changed from Log normal curve in new company base-case to Weibull curve	The Weibull curve is best fitting to the control arm of the model, consistent with the ERGs previously accepted PFS and most consistent with the observed data at 2 and 3 years in both arms of the KEYNOTE-045 trial.	£48,518 (+£1,395)
2. 3-year duration of treatment effect	Duration of treatment effect reduced from 5 year cap in company base-case to a maximum 3-year effect	As there is insufficient evidence to conclude whether waning continues, or a treatment effect is sustained beyond 2 years of follow-up. The ERG have chosen a 3 year duration of treatment effect, this is highlighted in ToE and is preferred alongside 5 year cap.	£51,970 (+£4,847)
3. PFS extrapolation Weibull and 3-year duration of treatment effect	PFS extrapolation and 3-year duration of treatment effect applied to company base-case	Combining change in PFS extrapolation and duration of treatment effect encompass all ERGs preferred assumptions to form new ERG base-case.	£53,678 (+£6,555)

5.5. Exploratory and sensitivity analyses undertaken by the ERG

Additional analyses were undertaken by the ERG surrounding parameters of main uncertainty. Alternative plausible extrapolations for OS (Section 4.2.2) are explored in scenarios 1 and 2. Analyses using an ITT approach rather than the 2-stage adjustment method (Section 3.2.1) are applied in scenarios 3 and 9. Variation of anticipated duration of treatment effect (Section 4.2.5) are analysed in scenarios 4-7 and most optimistic and pessimistic outcome parameters for duration of treatment effect (Section 4.2.5) and OS (Section 4.2.2) combined are presented in scenarios 8 and 10 respectively. These produce a range of ICER values between £42,643 and £87,208 (see Table 13).

Table 13: Impact on the ICER of additional analyses undertaken by the ERG

Scenario	UK SoC Costs	UK SoC QALYs	Pembrolizumab Costs	Pembrolizumab QALYs	ICER £/QALY
ERGs new preferred base-case	[redacted]	0.71	[redacted]	1.34	£53,678
1. OS extrapolation using log normal changed from log logistic used in both company and ERG base-cases	[redacted]	0.70	[redacted]	1.26	£58,705 (+£5,027)
2. OS extrapolation using generalised gamma curve from log logistic used in both company and ERG base-cases	[redacted]	0.75	[redacted]	1.35	£55,202 (+£1,524)
3. ITT analysis of ERG base-case replacing 2-stage adjustment for treatment switching	[redacted]	0.93	[redacted]	1.39	£65,469 (+£11,791)
4. Duration of treatment effect capped at 5-years as used in company's base-case	[redacted]	0.71	[redacted]	1.43	£48,518 (-£5,160)
5. Duration of treatment effect capped at 10-years	[redacted]	0.71	[redacted]	1.49	£45,377 (-£8,301)
6. Duration of treatment effect lifetime	[redacted]	0.71	[redacted]	1.52	£44,473 (-£9,205)
7. Duration of treatment effect capped at 2-years	[redacted]	0.71	[redacted]	1.24	£61,315 (+£7,637)
8. OS extrapolation using log normal with lifetime treatment effect	[redacted]	0.70	[redacted]	1.55	£42,643 (-£11,035)
9. OS extrapolation using generalised gamma curve with 3-year treatment effect and ITT analysis	[redacted]	1.07	[redacted]	1.56	£61,653 (+£7,975)
10. OS extrapolation using Weibull curve with 2-year treatment effect	[redacted]	0.64	[redacted]	0.99	£87,208 (+£33,530)

The two factors exerting the greatest influence on ICER values are the adjustment for treatment switching and the duration of treatment effect. ITT analysis (i.e. with no adjustment for treatment switching) increases the ERG base-case ICER by £11,791 to £65,469 per QALY. When duration of treatment effect is extended from 3 years, in the ERG base-case, to 10 years the ICER is reduced by £9,205 to £45,377 per QALY. However, when the treatment effect is capped at 2 years, the ICER increases by £7,637 to £61,315. Of the 10 scenario analyses conducted, only 3 scenarios produced an ICER under £50,000 per QALY, all of which assumed a treatment effect lasting 5 years or more (see Table 13).

Equivalent additional analyses were performed on the company base-case, applying their preferred assumptions to all parameters except the ones specifically changed in the scenario. Results are shown in Table 19 in the Appendix. Similarly, all additional analyses summarised in Table 13 were repeated using ITT analysis instead of the 2-stage adjustment method. See Table 20 in the Appendix for results.

5.6. Conclusions of the cost effectiveness section

Adhering to the ToE, the company have presented the most recent data from the 30 November 2018 data cut of the KEYNOTE-045 trial. The company confirmed during clarification that they had no more recent data from either the trial or knowledge of other published literature, and nothing was identified separately by the ERG. The ERG gained access to CDF data through PHE, but this only provided details of patient-baseline characteristics.

The company have made significant changes since their original CS by adopting the majority of the Committee's key assumptions as outlined in the ToE. Where deviation from the Committee's preferred assumption was made with the choice of log normal curve for PFS extrapolation rather than Weibull, justification was made based on updated clinical data informing goodness of fit statistics and visual fit. However, the ERG found this unconvincing and maintains its preference for Weibull extrapolation of PFS.

Substantial uncertainty remains around the reliability of the cost-effectiveness evidence submitted. The clinical evidence for OS remain too immature to support a confident choice of curve for extrapolation. Similarly, there is inconclusive evidence to determine the duration of treatment effect owing to the small number of patients at risk in the tail of the trial. The ERG does not find the single arm KEYNOTE-001 study of pembrolizumab for patients with

advanced melanoma or NSCLC, relied upon by the company, sufficient evidence of a treatment effect beyond 3 years in this population.

Also of concern to the ERG is the methodology used by the company to account for treatment switching. The ERG concludes that as all available methods have issues, it would be sensible to consider ICERs generated when ITT analysis is performed (i.e. no adjustment), in addition to those when 2-stage analysis is implemented, as this significantly influences the ICER upwards (as highlighted in Table 20 in Appendix).

The company base case produces a total QALY gain of 1.46 with an ICER of £47,123 whereas the ERG base case produces a total QALY gain of 1.34 with an ICER of £53,678 per QALY. This difference is achieved through a change in two assumptions. Firstly, the choice of extrapolation for PFS is changed from a log normal curve in the company base-case to Weibull in the ERG base-case. Secondly, the duration of treatment effect is reduced from 5-years assumed by the company to 3-years considered more plausible by the ERG.

The company provided appropriate but limited scenario analyses. Of the 4 scenarios presented, only 2 explored these key areas of uncertainty. One extended the start point for OS extrapolation from 24-weeks to 40-weeks, with the other analysing the impact of a 3-year and 10-year cap on treatment effect (See CS Table 13).

The evidence submitted by the company directly addresses the decision problem defined in the final scope but despite the inclusion of the most current available data, the strength of evidence provided remains weak due to its immaturity and limited amount available.

In conclusion, the ERG base-case analysis has an ICER of £53,678, £6,555 more than the company's submitted ICER of £47,123. Scenario analyses performed by the ERG demonstrate that the considerable uncertainty in the efficacy of pembrolizumab directly translates into uncertainty into the incremental cost-effectiveness ratio.

6. References

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7. Appendix

Table 14: AIC and BIC for OS models fitted from 24 weeks

	Model for pembrolizumab in overall population		Model for control in overall population	
	AIC	BIC	AIC	BIC
Exponential	1384	1387.1	680	682.5
Weibull	1373.3	1379.6	676	680.9
Gompertz	1365.3	1371.7	663.4	668.3
Llogistic	1366.4	1372.7	664.1	669
Lnormal	1369	1375.3	664.3	669.2
GenGamma	1369.8	1379.3	665.7	673.1

Table 15: Overall survival predictions from extrapolation of pembrolizumab from 24 weeks assuming a lifetime duration of treatment effect

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.5013	0.4578	0.4351	0.4446	0.4417	0.4434	[redacted]
2 year	0.3070	0.2955	0.2834	0.2789	0.2733	0.2850	[redacted]
3 year	0.1880	0.2038	0.2125	0.2027	0.2057	0.2073	[redacted]
5 year	0.0705	0.1058	0.1411	0.1308	0.1575	0.1284	-
10 year	0.0060	0.0259	0.0736	0.0690	0.1378	0.0566	-
20 year	0.0000	0.0024	0.0340	0.0353	0.1364	0.0199	-
30 year	0.0000	0.0003	0.0204	0.0237	0.1364	0.0095	-
35 year	0.0000	0.0001	0.0166	0.0203	0.1364	0.0070	-

Table 16: Overall survival predictions from extrapolation of pembrolizumab from 24 weeks assuming a five year duration of treatment effect

	Expon	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.5013	0.4578	0.4351	0.4446	0.4417	0.4434	[redacted]
2 year	0.3070	0.2955	0.2834	0.2789	0.2733	0.2850	[redacted]
3 year	0.1880	0.2038	0.2125	0.2027	0.2057	0.2073	[redacted]
5 year	0.0698	0.1051	0.1408	0.1306	0.1576	0.1283	-
10 year	0.0004	0.0055	0.0439	0.0545	0.1502	0.0518	-
20 year	0.0000	0.0000	0.0113	0.0230	0.1501	0.0192	-
30 year	0.0000	0.0000	0.0047	0.0139	0.1501	0.0104	-
35 year	0.0000	0.0000	0.0033	0.0115	0.1501	0.0081	-

Table 17: Overall survival predictions from extrapolation of pembrolizumab from 24 weeks assuming a ten year duration of treatment effect

	Expon	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.5013	0.4578	0.4351	0.4446	0.4417	0.4434	[redacted]
2 year	0.3070	0.2955	0.2834	0.2789	0.2733	0.2850	[redacted]
3 year	0.1880	0.2038	0.2125	0.2027	0.2057	0.2073	[redacted]
5 year	0.0705	0.1058	0.1411	0.1308	0.1575	0.1284	-
10 year	0.0060	0.0258	0.0734	0.0689	0.1378	0.0566	-
20 year	0.0000	0.0002	0.0189	0.0290	0.1377	0.0210	-
30 year	0.0000	0.0000	0.0078	0.0176	0.1377	0.0114	-
35 year	0.0000	0.0000	0.0055	0.0145	0.1377	0.0089	-

Table 18: Overall survival predictions from extrapolation of pembrolizumab from 24 weeks assuming a two year duration of treatment effect

	Expon	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.5013	0.4578	0.4351	0.4446	0.4417	0.4434	[redacted]
2 year	0.3038	0.2933	0.2819	0.2775	0.2726	0.2839	[redacted]
3 year	0.1075	0.1391	0.1661	0.1657	0.1958	0.1790	[redacted]
5 year	0.0135	0.0364	0.0790	0.0867	0.1592	0.0967	-
10 year	0.0001	0.0019	0.0247	0.0362	0.1518	0.0390	-
20 year	0.0000	0.0000	0.0064	0.0152	0.1517	0.0145	-
30 year	0.0000	0.0000	0.0026	0.0092	0.1517	0.0078	-
35 year	0.0000	0.0000	0.0018	0.0076	0.1517	0.0061	-

Table 19: Using company base case as reference for all other parameters

Scenario	UK SoC Costs	UK SoC QALYs	Pembrolizumab Costs	Pembrolizumab QALYs	ICER £/QALY
1. OS extrapolation using log normal changed from log logistic used in both company and ERG base cases	[redacted]	0.71	[redacted]	1.40	£49,549 (+2,426)
2. OS extrapolation using generalised gamma curve from log logistic used in both company and ERG base cases	[redacted]	0.75	[redacted]	1.44	£49,894 (+2,771)
3. ITT analysis of company base case replacing 2-stage adjustment for treatment switching	[redacted]	0.93	[redacted]	1.48	£56,671 (+9,548)
4. Duration of treatment effect capped at 2-years	[redacted]	0.72	[redacted]	1.27	£59,288 (+12,165)
5. Duration of treatment effect capped at 3-years	[redacted]	0.72	[redacted]	1.37	£51,970 (+4,847)
6. Duration of treatment effect capped at 10-years	[redacted]	0.72	[redacted]	1.53	£44,173 (-2,950)
7. Duration of treatment effect lifetime	[redacted]	0.72	[redacted]	1.55	£43,317 (-3,806)
8. OS extrapolation using Weibull curve with 2-year treatment effect	[redacted]	0.64	[redacted]	0.99	£87,969 (+40,846)
9. OS extrapolation using generalised gamma curve with 3-year treatment effect and ITT analysis	[redacted]	1.07	[redacted]	1.60	£58,857 (+11,734)
10. OS extrapolation using log normal with lifetime treatment effect	[redacted]	0.71	[redacted]	1.59	£41,608 (-5,515)

Table 20: Replication of Table 13 in main report using ITT analysis for each scenario to show impact on the ERG's base-case ICER

Scenario	UK SoC Costs	UK SoC QALYs	Pembrolizumab Costs	Pembrolizumab QALYs	ICER £/QALY
ERGs new preferred base-case	[redacted]	0.71	[redacted]	1.34	£53,678
1. OS extrapolation using log normal changed from log logistic used in both company and ERG base-cases with ITT analysis	[redacted]	0.91	[redacted]	1.33	£70,520 (+£16,842)
2. OS extrapolation using generalised gamma curve from log logistic used in both company and ERG base-cases with ITT analysis	[redacted]	1.07	[redacted]	1.56	£61,653 (+£7,975)
3. ITT analysis of ERG base-case replacing 2-stage adjustment for treatment switching	[redacted]	0.93	[redacted]	1.39	£65,469 (+£11,791)
4. Duration of treatment effect capped at 5-years as used in company's base-case with ITT analysis	[redacted]	0.93	[redacted]	1.45	£58,850 (+£5,172)
5. Duration of treatment effect capped at 10-years	[redacted]	0.93	[redacted]	1.50	£54,722 (+£1,044)
6. Duration of treatment effect lifetime with ITT analysis	[redacted]	0.93	[redacted]	1.52	£53,532 (-£146)
7. Duration of treatment effect capped at 2-years with ITT analysis	[redacted]	0.93	[redacted]	1.32	£74,858 (+£21,180)
8. OS extrapolation using log normal with lifetime treatment effect with ITT analysis	[redacted]	0.91	[redacted]	1.55	£50,139 (-£3,539)
9. OS extrapolation using generalised gamma curve with 3-year treatment effect and ITT analysis	[redacted]	1.07	[redacted]	1.56	£61,653 (+£7,975)

10. OS extrapolation using Weibull curve with 2-year treatment effect with ITT analysis	[redacted]	0.82	[redacted]	1.09	£103,323 (+£49,645)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 29 August 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Treatment effect duaration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, paragraph1 states… 'Evidence for an effect duration of at least 5 years provided by the company was weak and came from a single arm study in melanoma….'	The wording should be changed to '… Evidence for an effect duration of at least 5 years provided by the company was *limited* and came from a single arm *study of pembrolizumab for patients with advanced melanoma or non-*	The change to wording is more objective and accurately reflects the evidence presented from a pivotal trial investigating the efficacy of pembrolizumab, which includes different tumour types and the longest follow-up for	We have updated the text to clarify the sentence.

	small cell lung cancer (NSCLC)…'	pembrolizumab in any tumour type; this being the melanoma cohort with a median follow-up of 55 months.	
Page 11, Table 3, preferred assumption on duration of treatment effect, states 'The company relied on evidence from the KEYNOTE-001 trial, a single arm study of melanoma patients treated with pembrolizumab…'	The wording should also include non-small cell lung cancer (NSCLC). 'The company relied on evidence from the KEYNOTE-001 trial, a single arm study of melanoma patients or *non-small cell lung cancer (NSCLC)* treated with pembrolizumab…'	The change accurately reflects the evidence presented from a pivotal trial investigating the efficacy of pembrolizumab in two separate cohorts of patients.	We have updated the text to clarify the sentence.
Page 26, section 4.2.5 states '…They also provided alternative scenarios assuming the treatment effect would last for 3, 5 or 10 years'	Addition of the wording 'from the start of treatment' 'They also provided alternative scenarios assuming the treatment effect would last for 3, 5 or 10 years *from the start of treatment*.'	Provides clarity to the scenarios investigated.	We have updated the text to clarify the sentence.
Page 27, final paragraph states '…Firstly, these are different diseases'	Change of wording from disease to tumour types 'Firstly, these are different *tumour types'*	Accurate reflection of evidence provided in the same disease area but different tumour types	This is not a factual error. No changes have been made.

Issue 2 Extrapolation of survival curves

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6, section 1.3 states…'The company prefer a log normal curve for extrapolation of PFS'	The wording should be changed to…' The company prefer a log normal curve for extrapolation of PFS, *as it is the best fitting to the pembrolizumab arm based on AIC/BIC statistics and visual inspection.'*	The change better reflects the justification of choice of PFS extrapolation by providing context to the choice of extrapolation curve.	We have updated the text to clarify the sentence.

Page 10 section 2.1 states…'However, there was significant uncertainty in the extrapolation of overall survival…'	Suggested removal of the wording 'significant'. New wording to read, 'However, there was uncertainty in the extrapolation of overall survival…'	The proposed wording does not overstate the uncertainty and reflects The Terms of Engagement of CDF Review; page 2 highlights that…'further data collection would reduce the uncertainty around overall survival…'. Furthermore, the technology appraisal guidance on page 4 states 'Pembrolizumab has plausible potential to be cost effective. Further data collection would reduce the uncertainty around overall survival and continued treatment effect.'	We have updated the text accordingly.
Page 20 section 4.1.2. regarding PFS extrapolation states '…This has been inadequately justified by reference to goodness of fit statistics and on the basis of visual inspection'.	Suggest removal of the wording 'inadequately' '…This has been justified by reference to goodness of fit statistics and on the basis of visual inspection'.	MSD does not agree that the justification provided was inadequate. NICE DSU technical support document 14 on survival analysis was followed to justify the selection of appropriate PFS model selection. The standard procedure of visual inspection, statistical fitting were conducted.	We have updated the text and removed this sentence.

Issue 3 Exploratory Analyses undertaken by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 table 2 and page 38 table 19 are labelled as '…Exploratory analyses undertaken by ERG'	Suggested additional wording added 'Exploratory analyses undertaken by ERG *to the ERG base case'*	Does not cause any confusion regarding which assumptions were used for the additional exploratory analysis.	We have updated the text to clarify the sentence.

Issue 4 Summary of key issues in cost effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 7 point 2) first paragraph states '…The company prefer the 2-stage adjustment method.'	Suggested additional wording added 'The company prefer the 2-stage adjustment method, *consistent with the original submission and the committee concluded as appropriate for decision making'*	Additional wording provides clarity and minimises uncertainty in the preferred approach for the analysis of overall survival. The technology appraisal guidance (TA519) section 3.6 confirms that the committee concluded that the 2-satge method is appropriate for decision making.	No change necessary, no factual error or inconsistency.
Page 7 point 2) second paragraph states… 'The ERG acknowledges that ITT analysis will likely be biased in the other direction so have elected to stay with the 2-stage adjustment method.'	Additional wording added specific to UK SoC patients: 'The ERG acknowledges that ITT analysis *(UK SoC)* will likely be biased in the other direction so have elected to stay with the 2-stage adjustment method.'	Additional wording provides clarity to the treatment arm being discussed.	We have updated the text to clarify the sentence.
Page 7 point 4) states…'Options suggested by the Committee and implemented by the company were 3 and 5 year durations.'	Change of wording from options suggested to preferred assumptions: …'*Preferred assumption* by the Committee and implemented by the company were 3 and 5 year durations.'	The Terms of Engagement for CDF Review states that the...'Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment.' MSD has followed NICE's expectation for the company submission for CDF review based on the terms of engagement document.	No change necessary, not a factual error.
Page 7 point 4) states… 'These durations appear arbitrary, but are in line with other appraisals.'	Proposed change of sentence to 'These durations are *consistent* with the *preferred committee assumptions and* are in	These durations are not arbitrary and were agreed as preferred assumptions by the committee as	No change necessary, not a factual error.

	line with other appraisals.'	detailed in The Terms of Engagement document for CDF review.	

Issue 5 Comparison of observed overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 5 page 18 of the ERG report present: - 6.2 months median OS for KEYNOTE-045 UK SoC arm ITT - 7.0 months for KEYNOTE-045 UK SoC arm 2-stage adjustment. - for the 12 months OS for KEYNOTE-045 UK SoC arm 2-stage adjustment a 24.5% is reported	The median OS for KEYNOTE-045 UK SoC arm ITT should be 7.0 months The median OS for KEYNOTE-045 UK SoC arm 2-stage adjustment should be 6.2 months The 12 months OS for KEYNOTE-045 UK SoC arm 2-stage adjustment should be 25.0%	Some of the figures and proportion within Table 5 of the ERG report have been inverted or incorrectly reported. Table 4 of MSD submission for the CDF review [ID1536] reports the correct figures and proportion for: - the median OS in KEYNOTE-045 UK SoC arm ITT (7.0 months) - the median OS in KEYNOTE-045 UK SoC arm 2-stage adjustment (6.2 months) - the 25.0% rate of OS at 12 months in KEYNOTE-045 UK SoC arm 2-stage adjustment	Thank you for identifying this inaccuracy. We have amended the table accordingly.

Erratum: Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519 [ID1536]

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Declared competing interests of the authors
None

ERG Report for CDF review

We are grateful to the company for their suggestions for improvements on our review of pembrolizumab for previously treated advanced or metastatic urothelial cancer. Please find below the corrected pages amended according to the company's feedback.

Executive Summary

Critique of the adherence to Committees preferred assumptions from the Terms of Engagement in the company's submission

The Company have adhered to the majority of the Committee's preferred assumptions from the Terms of Engagement (ToE); the key deviations are:

- The company prefer a log normal curve for extrapolation of progression-free survival (PFS).
- The Committee suggested 3 and 5 year durations of treatment effect. The company preferred 5 years, but this is not supported by strong evidence.

Summary of the key issues in the clinical effectiveness evidence

Pembrolizumab used as single agent was evaluated against standard of care (SoC) - either paclitaxel, docetaxel or vinflunine in the KEYNOTE-045 trial. The trial had PFS and overall survival (OS) as co-primary endpoints.

Pembrolizumab does not significantly reduce the risk of a PFS event as measured by the hazard ratio compared to either SoC or United Kingdom (UK) SoC.

Pembrolizumab, when compared to UK SoC (excluding vinflunine), reduces the risk of death by 26% in the entire population, by 42% in patients with PD-L1 CPS≥1%, and by 49% in patients strongly positive for PD-L1 CPS≥10%.

As the optimal approach of treatment switching is unclear the Evidence Review Group (ERG) maintains the 2-stage approach in their base-case, but present intention-to-treat (ITT) analysis of the UK SoC arm as scenario analysis that should also be carefully considered.

Summary of the key issues in the cost-effectiveness evidence

The ERG consider 4 main issues which impact the cost-effectiveness evidence.

1) PFS extrapolation (Section **Error! Reference source not found.**)

The ERG agree on the 21 week cut off point used by the company. The company prefer a log normal curve for extrapolation of PFS as it was the best fitting to the pembrolizumab arm according to Akaike Information Criterion (AIC) and BIC. The ERG's preference is a Weibull curve as it remains the best fitting to the control arm according to AIC, is

among one of the best fitting to the pembrolizumab arm and is consistent with the observed data. It was the ERG's original choice and the Committee's preferred assumption.

1) Treatment Switching (Section **Error! Reference source not found.**)

This refers to the decision to use 2-stage adjusted OS data or ITT OS data for the UK SoC arm for model fitting. The company prefer the 2-stage adjustment method. The ERG are concerned about the assumptions this method makes: (1) a uniform treatment effect and (2) wide confidence intervals. Additionally, the new data has increased the magnitude of the acceleration factor applied during 2-stage adjustment, making the choice between methods a more critical factor due to its influence on cost-effectiveness outcomes. Therefore, the ERG reconsiders this parameter in the report.

A comparison to the external study of vinflunine patients by Bellmunt et al.[1], suggests the acceleration factor is too harsh in its penalty to the UK SoC arm (i.e. the benefit assumed from treatment switching is too optimistic, so when removed from UK SoC patients their OS appears shorter than expected). The ERG acknowledges that ITT analysis (UK SoC) will likely be biased in the other direction so have elected to stay with the 2-stage adjustment method. However, it is believed that the true effect of treatment switching on OS lies somewhere in between the two and they could be considered slightly unrealistic best and worst case scenarios.

2) OS extrapolation (Section **Error! Reference source not found.**)

The ERG are content to use a 24 week cut-off. The 40 week cut-off is not believed to be a feasible option given the behaviour of the data at this point, but other cut-offs may be plausible. The choice of curve remains unclear, with the biggest distinction between their outputs being their long-term predictions for pembrolizumab. If the Committee accepts that a handful of patients will remain alive for 10 years, a log-curve or generalised-gamma is appropriate. If not, a Weibull may be more suitable. Ultimately, the long-term efficacy is unknown. Generalised-gamma provides an optimistic extrapolation for both arms whereas Weibull is pessimistic for both. Log logistic and log normal curves are both optimistic for pembrolizumab but pessimistic for UK SoC.

3) Treatment Effect Duration (Section 0.0.4.2.5)

The focus here is the duration of the relative effect of pembrolizumab compared to patients on docetaxel/paclitaxel. Options suggested by the Committee and implemented by the company were 3 and 5 year durations. These durations appear arbitrary, but are in line with other appraisals. The company preferred 5 years, but this is not supported by strong

evidence. The ERG considers that as most patients stopped initial treatment in the first [redacted], it may be very plausible that the hazard rates for people who survive for 3 years are equal beyond this point. Evidence for an effect duration of at least 5 years provided by the company was weak and came from melanoma patients in a single arm study (Keynote-001), and included response data, whereas the company did not provide any data on response from KEYNOTE-045 in this CS. The beginnings of a waning effect is clearly observed within KEYNOTE-045 and due to switching adjustment and there being only a small number of people at risk in the tail of the control arm, the ERG conclude there is no meaningful data to provide clear evidence of any effect beyond 2 years.

1.1. Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions based on the new data are summarised in Table 1:

- Weibull extrapolation of PFS initiated at 21 weeks
- Log logistic extrapolation of OS initiated at 24 weeks
- 3-year cap on treatment effect
- 2-stage adjustment for treatment switching

Implementation of the ERG's preferred assumptions surrounding these parameters increases the company's submitted incremental cost-effectiveness ratio (ICER) by £6,555, from £47,123 to £53,678 per QALY.

Table 1: ICER resulting from ERGs preferred assumptions

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
UK SoC	[redacted]	0.71	-	-	-
Pembrolizumab	[redacted]	1.34	£33,757	0.63	£53,678

1.1. Summary of exploratory and sensitivity analyses undertaken by the ERG

Additional analyses were undertaken by the ERG around uncertain parameters. Alternative plausible extrapolations for OS (Section **Error! Reference source not found.**), analyses using ITT approach rather than the 2-stage adjustment method (Section **Error! Reference source not found.**), varying the duration of treatment effect (Section 0.0.4.2.5) and the most optimistic and pessimistic outcome parameters for duration of treatment effect and OS

combined are presented in Table 2. These produce a range of plausible ICER values between £42,643 and £87,208.

Table 2: Exploratory analyses undertaken by ERG to the ERG base case

Scenario	UK SoC Costs	UK SoC QALYs	Pembrolizumab Costs	Pembrolizumab QALYs	ICER £/QALY
1. OS extrapolation using log normal changed from log logistic used in both company and ERG base-cases	[redacted]	0.70	[redacted]	1.26	£58,705
2. OS extrapolation using generalised gamma curve from log logistic used in both company and ERG base-cases	[redacted]	0.75	[redacted]	1.35	£55,202
3. ITT analysis of ERG base-case replacing 2-stage adjustment for treatment switching	[redacted]	0.93	[redacted]	1.39	£65,469
4. Duration of treatment effect capped at 5-years as used in company's base-case	[redacted]	0.71	[redacted]	1.43	£48,518
5. Duration of treatment effect capped at 10-years	[redacted]	0.71	[redacted]	1.49	£45,377
6. Duration of treatment effect lifetime	[redacted]	0.71	[redacted]	1.52	£44,473
7. Duration of treatment effect capped at 2-years	[redacted]	0.71	[redacted]	1.24	£61,315
8. OS extrapolation using log normal with lifetime treatment effect	[redacted]	0.70	[redacted]	1.55	£42,643
9. OS extrapolation using generalised gamma curve with 3-year treatment effect and ITT analysis	[redacted]	1.07	[redacted]	1.56	£61,653
10. OS extrapolation using Weibull curve with 2-year treatment effect	[redacted]	0.64	[redacted]	0.99	£87,208

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

Pembrolizumab (KEYTRUDA®) has been available in England since April 2018 through the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing therapy only if:

- Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression and
- The conditions in the managed access agreement for pembrolizumab are followed.

The Committee in its recommendations noted that in the KEYNOTE-045 trial, pembrolizumab improved overall survival and has the potential to be cost-effective. However, there was uncertainty in the extrapolation of overall survival and in turn, in the incremental cost-effectiveness ratios (cost-per quality-adjusted life years gained) obtained from the economic modelling.

2.2. Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

The key Committee preferred assumptions from the terms of engagement (ToE) are summarised in Table 1 in the company submission (CS), only the key changes are listed in Table 3 below.

Table 3: Preferred assumption from Terms of Engagement

Assumption	Terms of engagement	Addressed to by the company submission	Rationale if different	ERG comment
Extrapolation of overall survival (OS) and progression-free survival (PFS)	• A piecewise model is appropriate, but the best time to switch to a parametric curve is uncertain - Company method: Start extrapolation at 40 weeks using a log normal curve - Evidence Review Group (ERG) method: Start extrapolation at 24 weeks using a log logistic curve • There are several plausible OS extrapolation curves - Extrapolation of OS is unclear and require further data collection • Used a Weibull parametric curve to extrapolate PFS	OS - yes The company have started their OS extrapolation at 24 weeks in their base-case using a log logistic curve and explored 40 weeks in scenario analysis. PFS – partially The choice of curve for PFS remains different.	The company justify use of log normal curve for PFS as goodness of fit statistics and visual inspection suggest best fit to pembrolizumab arm trial-data	OS: The ERG maintains 24 weeks is one of the more plausible time points to commence OS extrapolation and 40 weeks cannot be supported due to the behaviour of the UK SoC data at that time-point. PFS: The ERG maintains its preference for the Weibull curve. It is the best fit to the control arm, among the best fitting to the pembrolizumab arm and is consistent with the most current observable data.
Duration of treatment effect	• A lifetime treatment effect considered by the Committee to be implausible • Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment	Yes The company used a 5 year cap on treatment benefit in their base-case analysis and 3 year cap on treatment benefit in their scenario analysis	The company relied on evidence from melanoma patients in KEYNOTE-001 trial, a single arm study of pembrolizumab, to justify assumption of 5 year treatment benefit.	The ERG did not find KEYNOTE-001 provided sufficient evidence of sustained treatment benefit in this population. Both the 3 and 5 year cap on treatment benefit were equally advocated in the ToE and the ERG found little evidence to support treatment benefit from 2 years onward.
ERG's model corrections	Committee agree with the following correction from the ERG's model: • excluded the vinflunine data from the utilities • pooled utilities across treatment arms by progression state • used an updated algorithm to calculate	Partially The company have adhered to all ERG corrections made to their previous model except they have used a log normal curve to extrapolate	See rationale above	See comment above

Table 4: Comparison of Observed Overall Survival

OS comparison to observed studies	Bellmunt 2013[1]	KEYNOTE-045 UK SoC arm ITT	KEYNOTE-045 UK SoC arm 2 stage adjustment
Median OS	6.9 months	7.0 months	6.2 months
12 month OS	27%	32%	25.0%
24 month OS	11%	16%	10%
30 month OS	5.5%	12%	7.7%

3.3. Additional work on clinical effectiveness undertaken by the ERG

3.3.1. Data from Public Health England

The Public Health England (PHE) report[4] on pembrolizumab due to the short-time frame (i.e. 9 months) for data collection did not collect any information on OS and treatment duration of pembrolizumab. However, information on patient baseline characteristics during the CDF data collection were provided and were similar to the KEYNOTE-045 trial. Approximately three-quarters were male patients; the median age was 70 (PHE report) and 67 (KEYNOTE-045) years; and the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) score of 1 was 53.9% (PHE report) and 55.5% (KEYNOTE-045) at the start of their regimen. PHE report noted that 43% of patients were still on treatment, 18% had died and 31% had disease progression and treatment stopped (in KEYNOTE-045 according to corresponding Kaplan-Meier (KM) the respective figures were 43% (at 10 weeks), 18% (at 12 weeks) and 31% (at 9 weeks). Overall, the ERG has no concerns with the data collected via CDF and those presented in the CS.

3.4. Conclusions of the clinical effectiveness section

Pembrolizumab used as single agent was evaluated against SOC (either paclitaxel, docetaxel, or vinflunine) in the KEYNOTE-045 trial. The trial had PFS and OS as co-primary endpoints.

Pembrolizumab does not significantly reduce the risk of a PFS event as measured by the hazard ratio compared to either SoC or UK SoC.

Pembrolizumab, when compared to UK SoC (excluding vinflunine), reduces the risk of death by 26% in the entire population, by 42% in patients with PD-L1 CPS≥1%, and by 49% in patients strongly positive for PD-L1 CPS≥10%.

4. COST-EFFECTIVENESS

4.1. Summary of the company's submitted economic evaluation by the ERG

4.1.1. Model structure, population, intervention and comparators, perspective, time horizon and discounting

There have been no changes to the model structure, population, intervention and comparators, perspective, time horizon or discounting of the model submitted by the company, which was accepted previously by the Committee.

4.1.2. Treatment effectiveness and extrapolation

Duration of treatment effect has been capped at 5 years after starting pembrolizumab to reflect Committee preference to limit to 3 and 5 years rather than lifetime continued treatment effect as previously presented. Weibull curve extrapolation of PFS at 21 weeks was preferred by the ERG and Committee, however the company used a log normal extrapolation in their new base-case. Extrapolation of OS has been updated from a log normal parametric curve at a 40-week cut-off point, to a log logistic parametric curve at a 24-week cut-off as per ERG and Committee preferred approach.

4.1.3. Health-related quality of life

Utility estimates have been updated from the original CS which used utility values based on time to death. They are now in line with the ERG and Committee preferred approach using utility values based on progression state with current age-related disutility applied (see ToE document). Similarly, to follow Committee and ERGs preferences, utility estimates have excluded vinflunine data and have been pooled across treatment arms.

4.1.4. Resource use and costs

Resource use and costs were unchanged from the original CS except for acquisition cost of pembrolizumab where a new patient access scheme (PAS) discount was included. This reflected an increased discount from [redacted] to [redacted].

The company used the statistical goodness of fit criteria, AIC and BIC, to select the best fitting curve. The generalised gamma reportedly had the lowest scores for both arms, but failed to converge for the pembrolizumab arm, so was only used for the UK SoC arm. The Weibull was chosen for the pembrolizumab arm extrapolation, as it was the second best fitting to the data.

The ERG have minor concerns that curves of different forms were used for each arm, however, switching both arms to Weibull had a negligible impact on the analysis, and so the ERG are content to accept the company's assumptions surrounding time-on-treatment.

4.2.4. Treatment switching critique

The ERG has multiple concerns regarding the calculation and application of the acceleration factor used by the company to account for treatment switching effects. For a detailed discussion please refer to Section **Error! Reference source not found.**.

4.2.5. Treatment Effect Duration

Previously the company assumed a lifetime benefit of pembrolizumab in its economic analysis. They also provided alternative scenarios assuming the treatment effect would last for 3, 5 or 10 years from the start of treatment – that is to say that the hazard rate for OS for patients receiving pembrolizumab reverts to the hazard rate for the control arm after each period of time in the economic model. On the level of evidence currently available, these three effect durations appear to be chosen arbitrarily, but are consistent with other appraisals in this area. In this CS, the company has included the 5-year cap into their base-case analysis, stating that this is in-line with the ToE document. The ERG note that the 3-year cap was also presented in the ToE, with equal weighting to the 5-year cap.

Unfortunately, the availability of additional follow-up data sheds little light on the true treatment duration. The ERG requested that the company perform an analysis allowing a flexible time varying hazard ratio to capture any changes in the hazard ratio that were observed in the trial, given that the proportional hazards was clearly violated. In response (see CS Appendix G), the company used OS data incorporating the 2-stage switching adjustment. This adjustment is discussed in detail in Section **Error! Reference source not found.**, but is important here as it influences the length of follow-up of UK SoC patients. Without adjustment, there are [redacted] patients at risk of an event after 2 years of follow-up, but

under the 2-stage adjustment there are just [redacted] patients at risk. But even in the unadjusted UK SoC arm, there are just [redacted] OS

Table 5: Exploratory analyses undertaken by ERG to the company base case

Scenario	UK SoC Costs	UK SoC QALYs	Pembrolizumab Costs	Pembrolizumab QALYs	ICER £/QALY
1. OS extrapolation using log normal changed from log logistic used in both company and ERG base cases	[redacted]	0.71	[redacted]	1.40	£49,549 (+2,426)
2. OS extrapolation using generalised gamma curve from log logistic used in both company and ERG base cases	[redacted]	0.75	[redacted]	1.44	£49,894 (+2,771)
3. ITT analysis of company base case replacing 2-stage adjustment for treatment switching	[redacted]	0.93	[redacted]	1.48	£56,671 (+9,548)
4. Duration of treatment effect capped at 2-years	[redacted]	0.72	[redacted]	1.27	£59,288 (+12,165)
5. Duration of treatment effect capped at 3-years	[redacted]	0.72	[redacted]	1.37	£51,970 (+4,847)
6. Duration of treatment effect capped at 10-years	[redacted]	0.72	[redacted]	1.53	£44,173 (-2,950)
7. Duration of treatment effect lifetime	[redacted]	0.72	[redacted]	1.55	£43,317 (-3,806)
8. OS extrapolation using Weibull curve with 2-year treatment effect	[redacted]	0.64	[redacted]	0.99	£87,969 (+40,846)
9. OS extrapolation using generalised gamma curve with 3-year treatment effect and ITT analysis	[redacted]	1.07	[redacted]	1.60	£58,857 (+11,734)
10. OS extrapolation using log normal with lifetime treatment effect	[redacted]	0.71	[redacted]	1.59	£41,608 (-5,515)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Tuesday 1 October 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second, fully redacted, version of your comments (AIC/CIC shown as [redacted]). See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Simona Boccaletti**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Merck Sharp & Dohme**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

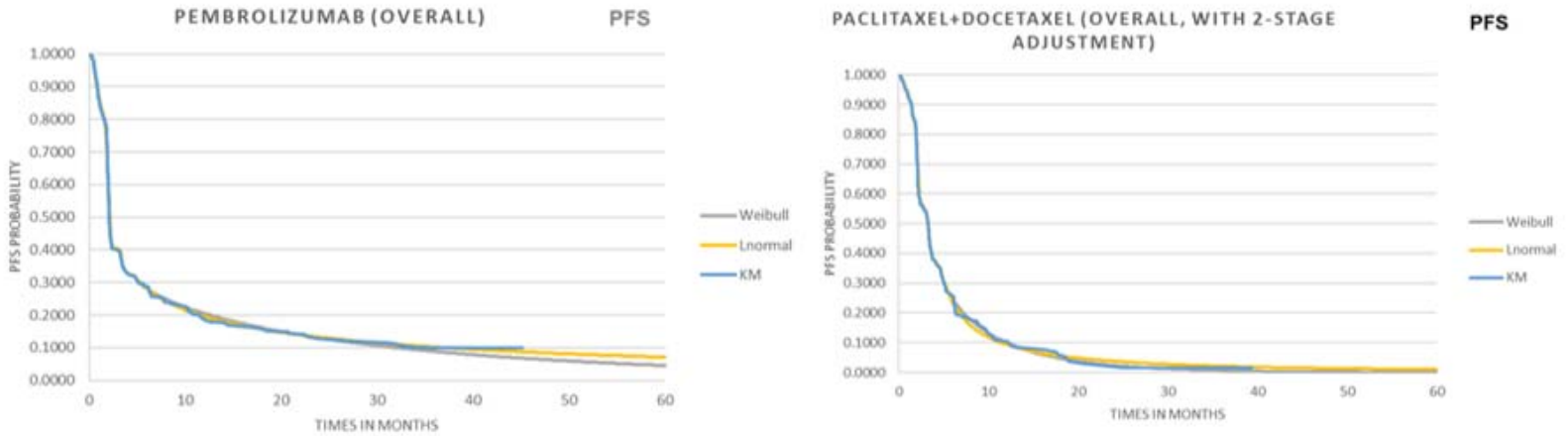
Issue 1: Choice of extrapolation for progression-free survival (PFS)	
Is the log-normal distribution or the Weibull distribution the most appropriate extrapolation of PFS, for both the pembrolizumab and UK standard of care (SoC) arms?	**MSD believes that the most appropriate extrapolation curve of PSF is the log-normal.** MSD's approach to parametric curve selection for the PFS extrapolation from week 21 was based on both AIC/BIC statistics and visual inspection, as presented in our submission. We considered the impact of each curve selection on both the within-trial observed period and on long-term predictions based on extrapolations. Although MSD acknowledges that for the UK SoC arm, the Weibull extrapolation is one of the best fitting curves based on AIC/BIC statistics and visual inspection within the observed trial period, this extrapolation is in fact the 4th best fitting to the observed data in the pembrolizumab arm based on the above-mentioned statistics criteria. MSD does not consider the ERG's justification for parametric curve selection based on the AIC/BIC in the UK SoC arm to be robust. The ERG has stated that as the difference in AIC/BIC is less than 2 for the various parametric curves when fitted to the pembrolizumab KM data, all curves should be considered under equal merit; however, MSD does not consider this to be a standard interpretation of AIC and BIC. It is important to note that the differences between the Weibull and log-normal curves when applied to the UK SoC arms are very modest, both within the observed trial period and in the longer-term prediction: the log-normal curve PFS predictions in the UK SoC arm are only 1% higher than the Weibull curve at year 2, 3, 4, and 5 and just 0.3% higher at 10 years (Table 1). In contrast, the choice of parametric curve selection has greater impact on the longer-term extrapolation in the pembrolizumab arm (Table 1).

Table 1. PFS – AIC/BIC statistics

	PFS - UK SOC			PFS - Pembrolizumab		
	Weibull	Log normal	Observed in KN045	Weibull	Log normal	Observed in KN045
1 year	0.0979	0.0919	0.11	0.2033	0.1939	0.188
2 year	0.0233	0.0375	0.02	0.1290	0.1313	0.13
3 year	0.0065	0.0213	Insufficient follow-up (but <0.015)	0.0879	0.1015	Insufficient follow-up (but <0.10)
5 year	0.0006	0.0098	-	0.0450	0.0706	-
10 year	0.0000	0.0030	-	0.0109	0.0398	-

When considering visual inspection, the log-normal curve is clearly a better fit to the pembrolizumab KM data (Figure 1). Weibull fitting overestimates the KM curve for pembrolizumab between months 10-17, but subsequently underestimates it towards the end of the observed period, from month 30 onwards (Figure 1). This results in a distinct difference in the longer-term predictions for pembrolizumab based on the choice of parametric curve selected for extrapolation, with Weibull seemingly penalizing the projected PFS in the pembrolizumab arm, being 3% lower than the log normal extrapolation

Figure 1. PFS extrapolation: MSD base-case with Log-normal curve and ERG base-case with Weibull

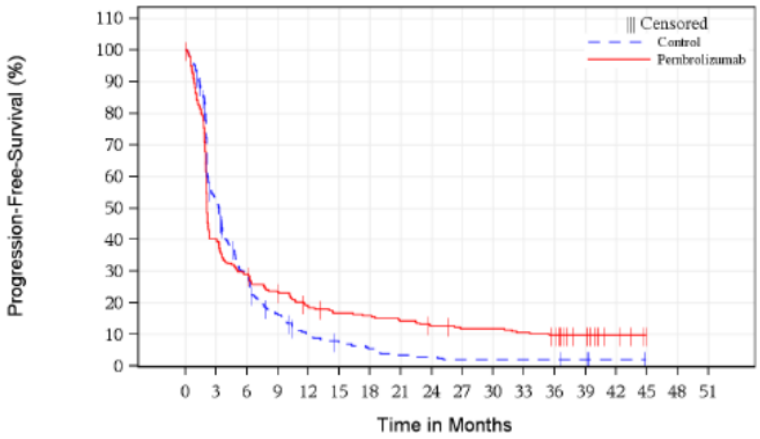


MSD has consulted with a clinical expert to validate our approach to parametric curve selection for PFS extrapolation. The clinical expert confirmed that MSD's approach, of selecting based on the best fit to the pembrolizumab KM data and then for consistency applying the selected parametric curve to the UK SoC arm, seems reasonable and appropriate, considering that the UK SoC curves overlap very closely. The clinical expert further endorsed the MSD approach to prioritising curve fitting to the pembrolizumab arm over the UK SoC arm, to allow emphasis on the understanding of the tail of the extrapolations of the pembrolizumab arm and therefore the longer-term expectations in PFS when using pembrolizumab. Based on the clinical expert feedback, when using immunotherapies such as pembrolizumab in this patient population, clinicians expect to see an extended tail on the PFS curve (rather than a drastic shift in the median PFS), which is aligned to what is seen in different tumour types treated with pembrolizumab. Consistent with this expectation, the flat, long tail of the PFS curve in the pembrolizumab arm from KEYNOTE-045 is already demonstrated based on the observed data from the November 2018 data-cut (see red KM curve in Figure 2). The clinical expert confirmed that in his opinion, the extrapolated

log-normal curve better reflects the handful of patients responding and remaining progression-free, leading to a longer tail in the survival curve.

MSD's opinion is that the that the log-normal fitting depicted in Figure 1 above not only represents the best fitting curve, but also results in an extrapolated curve that is more aligned to clinical expectation.

Figure 2. KM estimates of PFS based on RECIST 1.1. per Central radiology Assessment (Primary Censoring rule) – ITT population



The clinical expert consulted also provided insights on the immunologic effect and plausibility of the longer-term effect on PFS at 5 years based on the log-normal vs. Weibull extrapolation. Clinical experience confirmed that the 5-year PFS based on log-normal extrapolation from 21 weeks (7% with pembrolizumab, vs 1% with UK SoC; see Table 1 below) is more aligned

	to clinical expectation and experience of seeing patients responding and staying in response. The clinical expert also stated that, although it is not possible to confidently estimate longer-term PFS at 10 years, it is reasonable to assume that for those patients who remain progression-free for 3-5 years, they would be expected to continue responding over the long term. MSD considers this clinical opinion to further support the choice of log-normal PFS extrapolation, whereby approximately 7% of patients treated with pembrolizumab are progression free at 5 years and 4% at 10 years (see Table 1 above). MSD considers fitting the log-normal to both the intervention and comparator arms for PFS to be conservative when considering alternative PFS selections. Applying the log-normal distribution to the pembrolizumab arm, and Weibull to the SoC arm (according to best statistical and visual fit for each arm), alongside clinical opinion of a longer tail in PFS for patients treated with pembrolizumab- results in an incremental QALY gain of 0.75 and hence a lower ICER of £46,807. Therefore, applying the log normal fitting to the UK SoC arm for consistency with the best choice for the pembrolizumab arm, results in a conservative estimate of cost effective. In conclusion, given the rationale presented above, MSD believes there is a clear case for selecting log-normal as the appropriate parametric curve for extrapolation of PFS, based on the best fit to the pembrolizumab KM data and aligned with clinical opinion.
Issue 2: Treatment switching	
Should treatment switching be adjusted for?	**MSD believes that treatment switching should be adjusted for (i.e. adjusting for use of subsequent anti-PD1/PD-L1 therapy in the UK SoC arm of KEYNOTE-045)** As noted in the ERG report, 40 patients who received UK SoC in the control arm of the KEYNOTE-045 trial also received anti-PD1/PDL1 treatment. Consequently, MSD implemented the 2-stage adjustment model without re-censoring, attempting to remove any additional benefit these patients may have received from a change in treatment, in terms of overall survival. MSD considers this to be a standard approach aligned with previous pembrolizumab submissions to NICE, also reflecting

	the ERG's preferred approach at the time of the original appraisal of TA519[1]. The ERG has already noted that re-censoring can lead to a loss of information and may not always be beneficial to the analysis MSD does not agree that it would be appropriate to use the ITT analysis for decision making in this appraisal, without adjusting for treatment switching. As mentioned in the Technical report, the ERG acknowledges that failing to adjust for subsequent therapy is "*not ideal, as it is likely that some patients who switched did receive a benefit from the treatment*." The ERG also states that "*not adjusting for this benefit introduces bias which favours the control arm*". In the ERG report, it had been stated that this bias favouring the control arm *"may be stronger than the potential biases when the 2-stage method is used*". The Technical report inaccurately states that the ERG *"Looked at data from a 2013 study by Bellmunt et al, which reported KEYNOTE-045 data from an older data cut and gave the outcomes for the vinflunine arm"*. This is incorrect; the Bellmunt study reports results from a different Phase III clinical[2] trial and does not discuss results from KEYNOTE-045. In the Technical report it is stated that the ERG compared both the ITT and 2-stage data from UK SoC arm of the KEYNOTE-045 trial with the vinflunine arm of the trial by Bellmunt et al. The ERG's clinical advisors stated that within this comparison they would expect patients in the UK SoC arm of the KEYNOTE-045 to have similar or slightly superior overall survival compared to the vinflunine patients. There was a concern, highlighted in the ERG report, that a comparison of the observed data demonstrates that the 2-stage adjustment may penalise the survival times too severely, whilst the ITT may be too optimistic. Although the median OS in the vinflunine arm of the Bellmunt et al study is closer to the median OS from the UK SoC arm of the KEYNOTE-045 ITT population (rather than the UK SoC arm of the KEYNOTE-045 2-stage adjusted population), it is noteworthy that in terms of 12, 24 and 30 month OS, there is better consistency with the UK SoC arm of the 2-stage adjusted population from KEYNOTE-045. Nevertheless, having looked further at the Bellmunt et al study, MSD has concerns that based on the limited patient characteristics available in the publication, it is potentially inappropriate to consider the two study populations as analogous and therefore draw cross-trial comparisons. Full details on the number of prior therapies that patients received in the Bellmunt et al study were also not reported. Additionally, when comparing the baseline characteristics of the populations included in the Bellmunt study and in KEYNOTE-045, some important differences exist: a

	greater proportion of the study population in KEYNOTE-045 was >65 years old (54% vs. 47% in Bellmunt study) or had had visceral involvement (85.7% vs. 74% in Bellmunt study); KEYNOTE-045 recruited patients with an ECOG status of 0 (39%), 1 (59.1%) and 2 (1.5%) whereas Bellmunt study only included ECOG status of 0 (28%) and 1 (72%). These differences could have impacted the outcomes of the studies in several ways (e.g. heterogeneity of the results, subgroup analyses, over or underestimation of treatment effect) and therefore MSD considers that any assumptions based on this cross-trial comparison should be interpreted with caution.
If so, should the 2-stage approach be used?	**MSD believes a 2-stage model is the most appropriate statistical approach.** It must be noted that the use of a 2-stage model follows the precedent set in the original appraisal of TA519 and was agreed by the Committee as the most appropriate patient population upon which to base decision making. The ERG report confirms that alternative methods of adjusting for treatment switching were discussed in the previous review of this indication and were deemed not beneficial (RPSFT or IPCW). The use of the 2-stage adjustment is also consistent with the approach taken by MSD in all other NICE appraisals of pembrolizumab when it has been necessary to adjust data in the comparator arm due to within trial switching or subsequent therapy usage which was inconsistent with standard clinical practice**.** In the Technical report, the ERG has noted that some of these patients switched upon disease progression, whilst some did not. In total, 40 patients who received UK SoC in the control arm of the KEYNOTE-045 trial also received anti-PD1/PDL1 treatment; of these 40 patients, 25 patients switched upon disease progression, and 15 patients switched at a different stage or did not experience documented disease progression. MSD can confirm that the 2-stage adjustment method involved calculating an acceleration factor from an analysis of the survival times of the 25 patients who did switch upon disease progression, compared to those who did not switch upon disease progression, adjusting for covariate differences. The 15 patients who switched at a time other than disease progression were not used in the calculation of the acceleration factor and the survival times for these 15 patients were not adjusted; instead the within trial observed survival times for these 15 patients were used when these patients were included in the 2-stage model. MSD statistical team has confirmed that these 15 patients who switched at a point other than disease progression, would only have been adjusted for in alternative adjustment analyses (e.g. RPSFT or IPCW), but not in the 2-stage adjustment.

	As noted by the ERG, the magnitude of the acceleration factor applied during 2-stage adjustment has increased in the analysis presented with this submission, compared with that included at the time of the original appraisal for this indication. The previous estimate of the acceleration factor was 3.86 based on 14 patients, whereas the current estimate of 5.37 is based on 25 patients. MSD acknowledges this increase in the magnitude of the acceleration factor; however, we consider this unsurprising, given the analysis still involves a limited number of patients and calculations are sensitive to small numbers. This sensitivity is reflected in the wide confidence intervals. Nevertheless, the fact that this adjusted analysis is based on the longest follow-up data we have from KEYNOTE-045 (~4 years based on the first patient randomised), makes us consider this more reliable than data based on shorter follow-up. The approach taken when applying the 2-stage adjustment method is entirely consistent with the approach taken in previous pembrolizumab appraisals, so MSD believes that the 2-stage model should be used as base-case approach. The same variables (age, gender, ECOG at secondary baseline [0, $\geq$1], time to progression, liver metastases, time from last prior chemotherapy [<3 vs. $\geq$3 months], haemoglobin at secondary baseline and site of primary tumour) have been used as per the original submission. The method has been followed appropriately, with adjustment made based on whether patients switched at the time of disease progression or not and an average effect applied accordingly to all patients classified as eligible for having their survival time adjusted under the 2-stage method.
Issue 3: Choice of extrapolation curve and cut-off point for overall survival (OS)	
Is 24 weeks or 40 weeks the more appropriate choice of cut-off for extrapolation of OS data?	**MSD is already in agreement that 24-weeks is an appropriate choice of cut-off for OS extrapolation**. The OS cumulative hazard curves start separating from week 24 (see company submission Appendix F, Figure 3), followed by a clearer change in the slope after around 40 weeks. To remain consistent with the ERG preference from the original appraisal, as reflected in the Terms of Engagement (ToE) document, the MSD base case in this CDF guidance review submission reflected OS extrapolation from a 24-week cut-off point. Extrapolation from a 40-week cut-off point was presented only as a scenario analysis in our submission.

In the company's extrapolation, is the proportion of people on the pembrolizumab arm who are still alive after 10 years plausible?	**MSD believes that at 10 years it is plausible that a proportion of patients remain alive.** Using the log-logistic extrapolation for OS as per the base-case in MSD's submission, 13.1% and 5.5% of patients treated with pembrolizumab are expected to be alive at 5 and 10 years, respectively. These predicted figures were confirmed by a clinical expert consulted by MSD as reflective of what can be expected to be seen in clinical practice. Clinical feedback also confirmed that, although it is very difficult to ascertain how many patients will be alive after 10 years since no-one has experience of this scenario, it is plausible that for a handful of patients who continue to respond after few years, they would be expected to remain in response and alive when treated with pembrolizumab. This consideration was also highlighted by the ERG's clinical experts.
What proportion of patients in the UK SoC arm would you expect to be alive at 10 years?	**MSD believes that at 10 years, it is plausible to have 1-2% patients still alive in the UK SoC arm.** The clinical expert MSD consulted confirmed that although there is no direct experience of people being alive at 10 years, the prediction made by the log-logistic distribution (1.36% at 10 years) seems reasonable for the UK SoC arm.
Are there any other long-term data for OS available for immunotherapies in this indication, or for other urothelial carcinoma stages/sub-groups?	**MSD is not aware of any other long-term data for OS in for immunotherapies in this indication or for other urothelial carcinoma stages/subgroups.** This was also confirmed by the clinical expert consulted by MSD. He did however mention that his experience with other IOs in urothelial cancer is consistent with the outcomes seen with pembrolizumab in this disease area but also across different tumour types; i.e. a handful of patients remain in response after taking pembrolizumab.
Which distribution is most appropriate for modelling OS?	**MSD believes that a log-logistic distribution is most appropriate for modelling OS.** Both the MSD and ERG base cases include the log-logistic distribution for modelling OS, which is consistent with the ToE. With the additional data collection (November 2018 data-cut), the Gompertz curve has the closest fit based on AIC/BIC statistics; however, there is an implausible long-term effect for UK SoC (6.3% survival throughout a lifetime time horizon from year 5 onwards; see Table 2). Clinical experts validated the clinical implausibility of the Gompertz curve, as they would

	not expect a patient on UK SoC to have the same OS survival of ~ 6% from year 5 and continuing for the lifetime of the model. The log-logistic parametric curve provides the 2nd best fitting goodness-of-fit data for both the pembrolizumab and UK SoC arms, which also results in more realistic long-term survival estimates that reflect clinical practice. As per Table 2 below, the 5-year survival for the UK SoC arm is predicted as 3.25% with the log-logistic curve, which is aligned with the 2-3% figure suggested by expert clinical opinion and 5-11% accepted by the committee during the original appraisal of TA519. In the scenario analyses presented by the ERG, MSD considers it inappropriate to include parametric curves for OS extrapolation which do not reflect the clinically held view that a proportion of patients experience long-term survival when treated with pembrolizumab. The Technical report confirms that according to the ERG's clinical advisor, *"some sustained long-term benefit could be plausible for patients receiving pembrolizumab"*, which supports the selection of the log curves". This position is also reflected in the feedback that MSD received through clinical consultation. MSD would therefore argue that only the log-normal curve should be included in scenario analyses.

Table 2. Long Term OS estimates for UK SoC

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.3012	0.2752	0.2517	0.2464	0.2427	0.2463	0.236
2 year	0.1066	0.1168	0.1131	0.1041	0.1134	0.1167	0.093
3 year	0.0377	0.0554	0.0667	0.0621	0.0815	0.0736	-
5 year	0.0047	0.0145	0.0317	0.0325	0.0662	0.0397	-
10 year	0.0000	0.0008	0.0099	0.0136	0.0632	0.0160	-
20 year	0.0000	0.0000	0.0026	0.0057	0.0631	0.0060	-
30 year	0.0000	0.0000	0.0010	0.0035	0.0631	0.0032	-
35 year	0.0000	0.0000	0.0007	0.0029	0.0631	0.0025	-

Issue 4: Treatment effect duration

Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate?

MSD believes that a 5-year duration of treatment effect for pembrolizumab it is the most appropriate for several reasons, as detailed below.

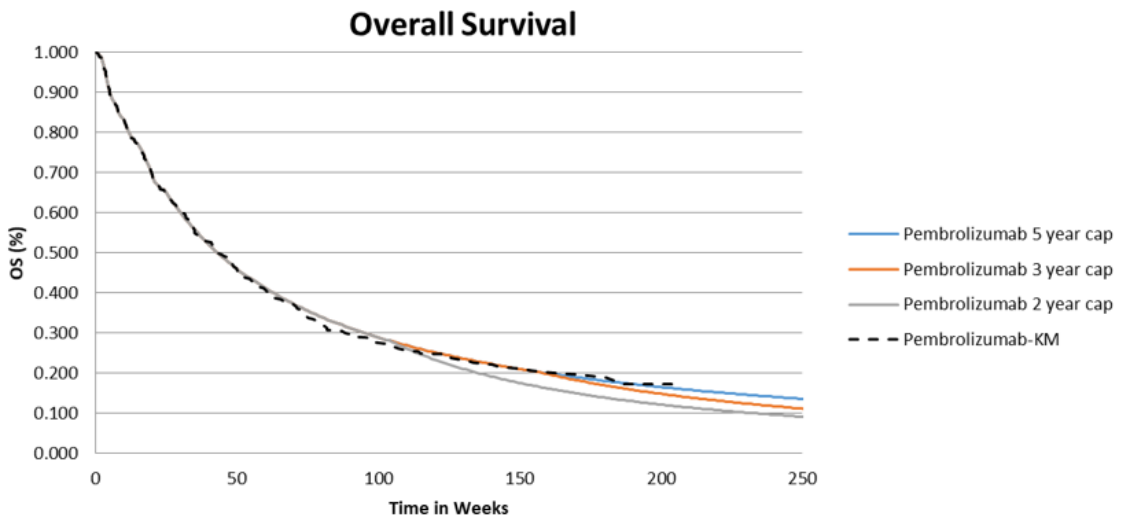
1. The sustained benefit of pembrolizumab over the duration of the follow-up period from KEYNOTE-045 (~4 years from the first patient randomised) lends support to a continued treatment effect beyond 3 years. A comparison of the hazard ratio (HR) of pembrolizumab vs UK SoC with 2-stage adjustment between the original data-cut from the original submission (i.e. September 2016 data-cut; HR = [redacted]; maximum follow-up of 1.7-years) and the latest data-cut which informs this CDF guidance review (i.e. November 2018 data-cut; HR = 0.64 ; maximum follow up of 4 years), shows that with additional 2.3-years of follow-up data, the HR decreases. This suggests a sustained treatment effect of pembrolizumab. This trend is consistently observed regardless of whether the comparison is made between pembrolizumab and the UK SoC comparator arm or the full KEYNOTE-045 comparator arm (i.e. including vinflunine), and also regardless of whether a comparison is

made with adjusted or unadjusted data in the control arm, to account for subsequent therapy (see Table 3 below). The improved treatment effect which we see below is considered clinically plausible by clinical experts in the field and further supports a treatment effect beyond three years.

Table 3. HRs from September 2016 and November 2018 data-cuts, including adjusted and unadjusted analyses

2. As can be seen in Figure 3 below, under the different scenarios of applying either a 2-year or 3-year duration of treatment effect for pembrolizumab, the extrapolation of OS in the pembrolizumab arm does not fit well to the observed pembrolizumab KM data from the November 2018 data-cut of KEYNOTE-045; both projections underestimate the OS KM curve, and consequently the treatment effect of pembrolizumab. MSD argues that the assumption of either a 2-year or 3-year treatment cap is inappropriate, as any longer-term benefit experienced by patients treated with pembrolizumab is not taken into consideration. Instead, a 5-year duration of treatment effect for pembrolizumab should be considered in the base-case. This position was supported by the clinical expert consulted by MSD, who confirmed that some patients respond well and remain in response, progression-free; hence a treatment effect of at least 5 years can be considered conservative.

Figure 3. Extrapolated OS curves at 2,3 and 5-year treatment cap



3. A 5-year duration of treatment effect for pembrolizumab is further supported by the time varying HR analyses of pembrolizumab vs. 2-stage adjusted UK SoC (see Figure 4 previously provided in Appendix G of the MSD' s submission for this CDF guidance review, and Figure 5 provided in MSD's response to ERG clarification questions [company response B2]). These data clearly show that the mean estimate of HR comparing pembrolizumab vs UK SoC is continually lower than 1 after week 8 and reaches a plateau of 0.62 from week 170. With regards to this plateau, the ERG state in the ERG report that "*so there is no clear evidence that the treatment effect fully wanes within the observed follow-up period*". MSD discussed this with a clinical expert, who confirmed that the plateau in the hazard ratio after week 170 (~3 years) is consistent with his clinical experience in this patient population, where those who are relapse-free after 2-3 years can expect long term survival and more favourable outcomes.

Although the upper confidence interval crosses 1 at around 63 weeks in Figure 4, the Technical report states that the ERG has indicated that this "*may have been partially due to the small number of patients remaining at risk, so this wasn't strong evidence of a loss of effect*". The HR analysis without adjusting for PD1/PD-L1 subsequent therapy use in the UK SoC arm is also presented in Figure 5 below, which shows consistency with the adjusted data as a plateau is reached with the HR continuously lower than 1. It is important to note that in this plot, the true treatment effect will be diluted by patients receiving subsequent therapy with PD-1/PD-L1 agents in UK SoC arm. Subsequent therapy usage can plausibly explain the higher HR observed from week 30 to 70 when comparing HRs based on unadjusted OS in the UK SoC arm (Figure 5) with HRs based on adjusted OS in the UK SoC arm (Figure 4), and the earlier timepoint that the upper 95% CI crosses 1 (See Figure 4 and 5).

MSD urges that this evidence, based on the most recent data-cut from KEYNOTE-045, should be taken into consideration by the ERG and Committee. This analysis supports the position that pembrolizumab provides a survival benefit beyond 3 years, and therefore a treatment waning cap of 5 years is appropriate for the base-case and could even be considered a conservative assumption.

Figure 4. Time varying HR for pembrolizumab vs. 2-stage adjusted UK SoC with 95% CI

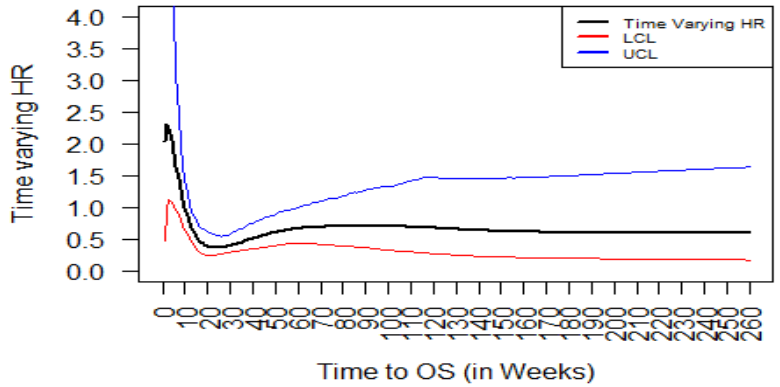
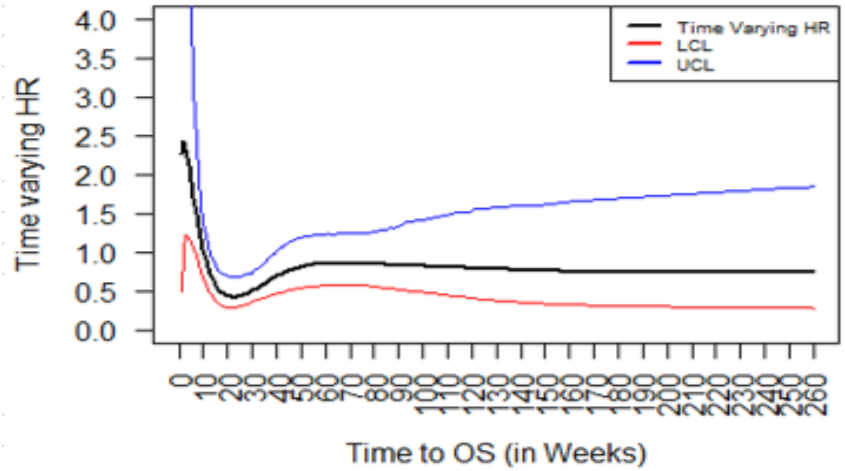


Figure 5. Time-varying HR for pembrolizumab vs. unadjusted UK SoC with 95% CI



4. Further evidence of a 5-year treatment duration being accepted for IO therapy in this patient population comes from the NICE appraisal of TA525[3] (Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) published in June 2018 and the NICE appraisal of TA584[2] (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer) published in June 2019. In both appraisals, which were evaluated by committee D, a 3-year treatment effect ***after stopping treatment*** was considered appropriate by the committee. As stated in the technical report for this CDF review, '*the committee was aware that the duration of treatment effect after the implementation of a stopping rule is an area of uncertainty for new immunotherapies'.* A 2-year stopping rule is implemented in KEYNOTE-045 and in the economic model; therefore, MSD's preferred 5-year cap on treatment effect (from the start of treatment), as reflected in our base case, is equivalent to a 3-year treatment cap after stopping treatment; consistent with TA525 and TA584.

Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?	**Long term follow-up data are available across the pembrolizumab clinical study program.** The only available and robust evidence of the long-erm treatment effect of pembrolizumab in the indication under consideration is provided with the results obtained from the November 2018 data-cut of KEYNOTE-045; OS, PFS and ToT data were presented in MSD's submission document for the CDF guidance review, and this is further supplemented with the additional data provided as part of this response to the technical engagement questions (see duration of response [DOR], objective response rate [ORR] and follow-up information provided in Tables 4-6 and Figure 6_below, and further explained below). The November 2018 data-cut reflects more than 4 years of data from the first patient randomised (November 2014) and more than 3 years from the last patient randomised (October 2015). Data supporting a long-term survival benefit associated with pembrolizumab treatment is available from studies across the pembrolizumab clinical study program. Specifically, supportive data is available from KEYNOTE-001 (melanoma and NSCLC cohorts), KEYNOTE-006 (melanoma population), and KEYNOTE-024 (in a previously treated NSCLC population). These studies are further described below. The rationale for presenting such evidence with this response is based on the views and experience of the clinical expert that MSD consulted; it was acknowledged that a long-term treatment effect associated with pembrolizumab translates across a variety of tumour types, especially for those patients remaining progression-free, who maintain a response at 2 and 3-years. The clinical expert also indicated that based on experience with IO therapies in urothelial cancer, some patients with a response who stop treatment due to toxicity can remain progression-free for quite some time beyond the cessation of therapy, thus indicating a long-term treatment effect. 1. KEYNOTE-001[5] (Phase 1b) Evidence included in the recently published KEYNOTE-001 study, provides the longest efficacy and follow-up (median of 60.6 months) in advanced NSCLC. The study recruited both treatment naïve and previously treated patients. The estimated

	5-year OS was 15.5% for previously treated patients and 25% for the same population with a PD-L1 tumour proportion score of ≥50%. Additionally, in the melanoma cohort[6] of the same study with a median follow-up of 55 months, the estimated 5-year OS was 34% in all patients (both naïve and previously treated). Although the median response duration was not reached, the longest response was still ongoing at 66 months. 2. KEYNOTE-006[7] (Phase III) In addition to the KEYNOTE-001, post-hoc 5-year results are available from KEYNOTE-006; an open-label, randomised, controlled study that investigated PFS and OS outcomes for pembrolizumab vs. ipilimumab in patients with ipilimumab-naive stage III or IV melanoma. KEYNOTE-006 has more similarities with the study design of KEYNOTE-045, since patients were treated with pembrolizumab for a maximum duration of 2 years of pembrolizumab before entering follow-up. After a median follow-up of 57.7 months in surviving patients, the median OS was 32.7 months in the pembrolizumab groups and the 5-year OS was 38.7% (similar to KEYNOTE-001 (34%), supporting an ongoing durable response. For patients who completed the protocol specified treatment of 2 years with at least stable disease, results from the analysis of KEYNOTE-006[7] data show that in 74% of these patients had on-going disease control. Furthermore, patients with complete response had a 24-month PFS after stopping treatment of 85.4%. These results are consistent with the durable responses observed in KEYNOTE-001, whereby the 24-month disease-free survival of 90%[9] was seen in patients who discontinued pembrolizumab after achieving a complete response. These results relating to pembrolizumab treatment in other tumour types provide insights into the potential long-term durability associated with pembrolizumab treatment in urothelial cancer following the implementation of a 2- year stopping rule and that this treatment effect may continue for at least another 2 years for the majority of patients, therefore further supporting the choice of a 5-year treatment effect cap from the start of treatment.

	3. KEYNOTE-024[8] (Phase III) In this randomised, open-label study, pembrolizumab was compared to platinum-based chemotherapy in NSCLC patients. Based on a median follow-up of 25.2 months, the median OS was 30.0 months, with an OS HR of 0.63 as compared to chemotherapy. Furthermore, 82 patients form the chemotherapy arm switched to pembrolizumab and, when adjusting the results for switching, the HR was 0.49. Despite being based on different tumour types, the evidence from the above mentioned pembrolizumab clinical studies clearly add to the body of evidence and provide support for the durable long-term treatment effect associated with pembrolizumab. In our submission for this CDF guidance review of TA519, MSD submitted only OS, PFS and Time on Treatment (ToT) data based on the November 2018 data-cut from KEYNOTE-045, as agreed between NICE and MSD as the data which would most appropriately address the areas of uncertainty as highlighted in the ToE document. However, data concerning DOR, ORR and follow-up duration are available based on the November 2018 data-cut, and MSD are submitting this data as part of this response to the Technical engagement consultation, for consideration by the NICE technical team, ERG and Committee, as further supportive evidence of a long-term, durable response associated with pembrolizumab therapy (see Tables 4 – 6 and Figure 6). We report that the median DOR for responders was 29.7 months in the pembrolizumab arm vs 4.4 months in the control arm (see Table 4 below). The 36-month OS rate is 20.7% in the pembrolizumab arm vs 11.0 % in the control arm, and the 36-month DOR rate is 44% in the pembrolizumab arm, all of which are meaningful (based on KM data). A greater proportion of responses lasted ≥24 months (56.8% vs 28.3%, based on KM data); the median survival follow-up for responders was 39.6 months for pembrolizumab and 17.7 months for control (see Table 5 below). Additionally, the ORR was higher with pembrolizumab vs control (21.1% vs 11.0%) (see Table 6). Figure 6 shows that many responses in the pembrolizumab arm continued beyond 150 weeks (~3 years), and with further follow-up (i.e. beyond 30 November 2018) clinicians recognised that it is likely that some of these responses would be noted to go on even further.

Table 4. Summary of time to response and response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - All Subjects (ITT Population) – November 2018 data-cut

	Control (N=272)	Pembrolizumab (N=270)
Number of Subjects with Response†	30	57
Time to Response† (months)		
Mean (SD)	2.4 (0.8)	2.6 (1.1)
Median (Range)	2.1 (1.7-4.9)	2.1 (1.4-6.3)
Response Duration‡ (months)		
Median (Range)§	4.4 (1.4+ - 42.8+)	29.7 (1.6+ - 42.7+)
Number of Subjects with Response ≥ 6 Months (%)‡	8 (47)	46 (84)
Number of Subjects with Response ≥ 12 Months (%)‡	5 (35)	35 (68)

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

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

§ *"+" indicates the response duration is censored.*

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cut-off Date: 30NOV2018

Table 5. Summary of follow-up duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed CR or PR: All subjects (ITT Population) – November 2018 data-cut

	Control (N=30)	Pembrolizumab (N=57)	Total (N=87)
Follow-up duration(months)†			
Median (Range)	17.7(7.3-45.8)	39.6(11.1-46.2)	38(7.3-46.2)
Mean (SD)	23.3(14.4)	35.3(10)	31.1(12.9)

† *Follow-up duration is defined as the time from randomization to the date of death or the database cut-off date if the patient was still alive.*

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cut-off Date: 30NOV2018.

Table 6: Summary of Best Overall Response Based on RECIST 1.1 per Central Radiology Assessment - All Subjects (ITT population)

Response Evaluation		Control			Pembrolizumab	
		(N=272)			(N=270)	
	n	%	95% CI[†]	n	%	95% CI[†]
Complete Response (CR)	8	2.9	(1.3, 5.7)	26	9.6	(6.4, 13.8)
Partial Response (PR)	22	8.1	(5.1, 12.0)	31	11.5	(7.9, 15.9)
Objective Response (CR+PR)	**30**	**11.0**	**(7.6, 15.4)**	**57**	**21.1**	**(16.4, 26.5)**
Stable Disease(SD)	92	33.8	(28.2, 39.8)	47	17.4	(13.1, 22.5)
Disease Control (CR+PR+SD)	**122**	**44.9**	**(38.8, 51.0)**	**104**	**38.5**	**(32.7, 44.6)**
Progressive Disease(PD)	90	33.1	(27.5, 39.0)	131	48.5	(42.4, 54.7)
Non-evaluable (NE)	9	3.3	(1.5, 6.2)	4	1.5	(0.4, 3.7)
No Assessment	51	18.8	(14.3, 23.9)	31	11.5	(7.9, 15.9)

Confirmed responses are included.

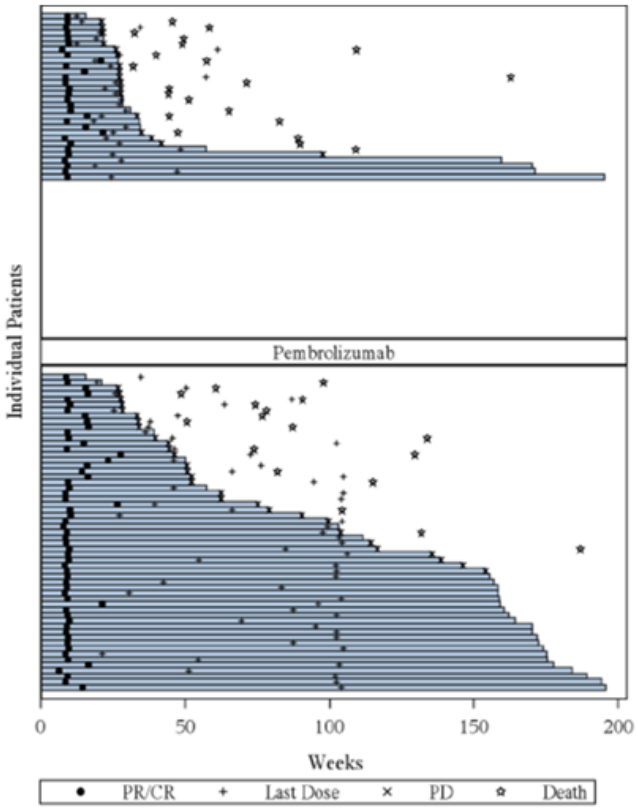
[†] *Based on binomial exact confidence interval method.*

Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.

No Assessment: subject had no post-baseline imaging.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cutoff Date: 30NOV2018

Figure 6. Plot of time to response and time to progression based on RECIST 1.1 per Central Radiology Assessment (ITT)



Recently, Fradet et al[10], in an updated analysis of KEYNOTE-045, examined OS by best overall response (Poster ASCO 2018) and showed that patients who experienced a complete or partial response when treated with pembrolizumab had

	significantly longer OS (HR = 0.14 (95% CI 0.06-0.33, p<0.00001) and PFS (HR=0.27, 95% CI 0.14-0.51, p<0.0001) compared to chemotherapy. Similar results were not seen in patients experiencing stable or progressive disease. This suggests that patients who respond to immunotherapy do experience significantly longer survival, as also confirmed by the clinical expert consulted.
Issue 5: PD-L1 expression sub-groups	
Does pembrolizumab have a different effect in different PD-L1 sub-groups?	**MSD believes pembrolizumab does not have a different effect in different PD-L1 subgroups**. At the time of the original appraisal of TA519[1], the Committee concluded that *"Cost-effectiveness analyses based on PD-L1 expression are not useful for decision-making"*. At that time, cost-effectiveness results from the model produced ICERs that were counterintuitive to the clinical evidence base. This situation remains unchanged based on the latest data-cut from KEYNOTE-045 (dated November 2018), and consequently MSD does not consider the new data-cut to offer additional evidence to justify decision making based on PD-L1 subgroups. MSD's position, as supported by clinical expert validation, is that PD-L1 acts only as a prognostic factor rather than a predictive biomarker in the population of relevance covered by this CDF guidance review. Consequently, MSD believe that the same conclusions hold, in relation to PD-L1 subgroups, as reached by the Committee at the time of the original appraisal of TA519
What are the ICERs for each PD-L1 expression sub-group?	**MSD does not believe appropriate to produce ICERs results based on PD-L1 subgroups adjusted for treatment switching.** To meet the request of the NICE technical team, MSD is providing results of the cost-effective analyses for the PD-L1 subgroups of relevance (CPS≥1 and CPS≥10), based on the unadjusted (ITT) population, as can be obtained from the current version of the economic model. The results presented are based on the MSD base case model settings (see results below in Table 7). The clinical effectiveness data had been previously provided by MSD during the clarification question stage (please

refer the MSD response to clarification question A1). The results in Table 7 and Table 8, show that pembrolizumab is cost-effective in both the CPS≥1 and CPS≥10 PD-L1 subgroups, producing similar results.

Pembrolizumab PD-L1 sub-group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
UK SoC	[redacted]	1.30	0.88				
CPS≥1	[redacted]	2.41	1.67	£35,523	1.11	0.78	£45,370

Table 7: ICER results for PD-L1 subgroup (CPS≥1) based on unadjusted (ITT) population

Table 8: ICER results for PD-L1 subgroup (CPS≥10) based on unadjusted (ITT) population

Pembrolizumab PD-L1 sub-group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
UK SoC	[redacted]	1.42	0.94				
CPS≥10	[redacted]	2.40	1.64	£32,617	0.99	0.70	£46,485

With respect the request for results of cost-effectiveness analyses for the PD-L1 expression subgroups incorporating the 2-stage adjusted approach to account for subsequent therapy usage in the UK SoC arm, MSD are unable to provide these analyses. Having consulted with our statistical team, they have confirmed that there were too few subjects who received subsequent anti-PD1/PD-L1 therapy in the relevant PD-L1 subgroups (CPS≥1%: 9 subjects and CPS≥10%: 7 subjects), for the model to run properly and be robust. In order the run such analyses, the MSD statistical team use a cut-off requiring a minimum of 10 subjects who switched following documented disease progression. Specifically, for all subsequent therapy 2-stage adjustment work undertaken in relation to KEYNOTE-045, a minimum of 10 subjects who received subsequent anti-PD1/PD-L1 therapy following documented disease progression has been used as a cut-off, to determine whether 2-stage models would be run for a given population. This has been done to mitigate the issue of high variability and sensitivity of

	acceleration factors and subsequent therapy adjustments, due to small sample sizes and small numbers of subjects receiving subsequent therapy. This approach was also applied for previous data-cuts and across several pembrolizumab indications Based on these considerations, MSD considers that it would be inappropriate to attempt to run 2-stage adjusted analyses based on the above-mentioned PD-L1 subgroups, as any such analyses are likely to produce biased and unreliable results, which will not be useful to inform the economic model and therefore decision making.
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	8: Reck M, Rodríguez-Abreu D, Robinson A, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. 9: Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, Hwu WJ, Weber JS, Gangadhar TC, Joseph RW, Dronca R. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. Journal of clinical oncology. 2017 Dec 28;36(17):1668-74. 10: Fradet et al, Pembrolizumab versus Investigator's Choice (Paclitaxel, Docetaxel, or Vinflunine) in Advanced Urothelial Cancer: Two-year follow-up from the phase 3 KEYNOTE-045 Trial, Poster presented at the ASCO Annual Meeting, June 1-5, 2018; Chicago, Illinois

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Tuesday 1 October 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
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About you

Your name	**Prof Peter Clark**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England and Improvement**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Choice of extrapolation for progression-free survival (PFS)	
Is the log-normal distribution or the Weibull distribution the most appropriate extrapolation of PFS, for both the pembrolizumab and UK standard of care (SoC) arms?	**The Weibull extrapolation was the committee's preferred distribution methodology when this topic was first appraised. The Weibull remains the ERG's preferred distribution for this re-appraisal and the ERG's case for concluding this is persuasive. There is no robust change in the evidence to necessitate a change to a different methodology for modelling PFS.**
Issue 2: Treatment switching	
Should treatment switching be adjusted for?	**The original trial design of Keynote-045 did not allow crossover from standard care chemotherapy to pembrolizumab. The trial protocol subsequently underwent an amendment to allow such cross over whether it was before or after disease progression on standard chemotherapy.** **In this appraisal it is reasonable to allow for cross over to pembrolizumab from chemotherapy whilst recognising the uncertainty that this brings. It is also reasonable to allow for the effect of any patients treated with pembrolizumab who at 2 years discontinued pembrolizumab and who then were re-treated with pembrolizumab/atezolizumab/nivolumab/any other anti-PD1 or anti-PD-L1 drug. Whether the protocol allowed this is immaterial. If it happened (and it is likely to have done so), then it too must be allowed for in the analyses depending on whether NICE still stipulates a maximum 2 year treatment duration, this policy being the company's submitted position. If NICE continues to wish to appraise according to a maximum 2 year treatment duration, then the benefit on survival of further immunotherapy must be considered (difficult as this may be) and excluded from the pembrolizumab arm. If re-treatment after a 2 year initial**

	treatment period is recommended by NICE, then the cost of such an approach must also be included in the cost effective analyses. **The papers for this appraisal did not include any information as to the numbers of patients in the pembrolizumab arm who received further immunotherapy. The company should be asked to submit this information.**
If so, should the 2-stage approach be used?	**Allowing for cross over always introduces uncertainty. NHS E&I notes the ERG's detailed arguments and conclusion that a 2 stage approach is appropriate. The timing of the 2 stage approach is always going to be a matter of judgment and it is the committee's judgement that matters.**
Issue 3: Choice of extrapolation curve and cut-off point for overall survival (OS)	
Is 24 weeks or 40 weeks the more appropriate choice of cut-off for extrapolation of OS data?	**NHS E&I note the attention that the ERG has given to this issue and sees no reason for not supporting the ERG's approach. Please also see comment immediately above.**
In the company's extrapolation, is the proportion of people on the pembrolizumab arm who are still alive after 10 years plausible? What proportion of patients in the pembrolizumab arm would you expect to be alive at 10 years?	**NHS E&I notes that both the company and the ERG have opted for use of the log logistic distribution in extrapolating overall survival. There is always a very small number of patients treated with standard chemotherapy who do very well (and against general expectation). It is biologically plausible that patients treated with pembrolizumab will do better (even with a 2 year treatment duration) as the immunotherapy works by changing the patient's immune system's reaction to the cancer. It is therefore biologically plausible that there will be a small/modest number of long term survivors following treatment with pembrolizumab.** **The company's (longer than 5 year) modelling survival curves were in the appendices and were not included in the technical papers distributed to NHS E&I. Hence a more specific comment cannot be made in relation to the technical team's question.** **The other factor to remember is that patients with urothelial cancer have significant comorbidities, many of which are as a consequence of smoking tobacco for many years.**

	The median age in the CDF use of pembrolizumab in this indication was 70 years and hence the number of 10 year survivors with pembrolizumab will be small though significantly greater than with standard chemotherapy.
What proportion of patients in the UK SoC arm would you expect to be alive at 10 years?	**See above**
Are there any other long-term data for OS available for immunotherapies in this indication, or for other urothelial carcinoma stages/sub-groups?	**None that NHS E&I is aware of.**
Which distribution is most appropriate for modelling OS?	**The log logistic has been chosen by the company and by the ERG and fits in with biological plausibility.**
Issue 4: Treatment effect duration	
Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate?	**Definition of what is meant by 3 or 5 year treatment effect duration is very important. NHS E&I assumes that 3 year treatment effect refers to the long term effect following 2 years of treatment and then 1 year of follow-up (2+1). Similarly the 5 year treatment effect duration is mathematically portrayed as 2+3. This is a very relevant issue given the maximum 2 year treatment duration that NHS E&I would commission and the biological plausibility of a treatment effect (recruitment of the immune system) enduring at least for a time after treatment has stopped in responding patients.** **There are long term (5 year) data for patients treated with immunotherapy in melanoma and non small cell lung cancer which show continued long term benefit. Use of this to justify a 5 year duration of treatment effect (2+3) has to be cautious in view of which parallel is chosen in terms of which other cancer. Melanoma and NSCLC are completely different**

	diseases when compared with urothelial cancer. There has always been an immunological avenue for treating melanoma (eg interleukin) and lung cancer is a very mutation-rich cancer. In addition, it is known that pembrolizumab does not work in every disease and has failed in trials in triple negative breast cancer, hepatocellular carcinoma, gastric/gastro-oesophageal junction cancer and myeloma. Furthermore, the melanoma studies and the Keynote001 studies in lung cancer quoted by the company used a policy of open treatment duration with pembrolizumab rather than the 2 year maximum treatment duration subsequently employed in most pembrolizumab trials. The case that the company is making is still for a maximum of 2 years use of pembrolizumab in this urothelial indication. **Since the follow-up data now submitted by the company is reasonably robust to 3 years (where rates of overall survival are about 20% with pembrolizumab, 12% with chemotherapy after adjustment for cross over and 8% ITT and without any such adjustment) plus there is a fixed 2 year treatment duration policy plus relapses still occur in those patients who do well and discontinue treatment at 2 years, it is reasonable for the ERG and the Technology Appraisal Committee to be currently cautious and assume a duration of treatment effect to be more in line with 3 (2+1) years than 5 (2+3) years.**
Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?	**Nil that NHS E&I is aware of.**
Issue 5: PD-L1 expression sub-groups	

Does pembrolizumab have a different effect in different PD-L1 sub-groups?	**There is plausibility for benefit to be greater in patients whose tumours have higher PD-L1 expression. The EMA has limited use of atezolizumab and pembrolizumab in 1st line urothelial patients to only those with higher levels of PD-L1 expression. The difficulty in this set of Keynote045 data here is that the numbers in the known PD-L1 subgroups are modest and the size of the comparator group has already been significantly reduced due to the exclusion of the vinflunine patients. The opportunity for robust decision making is therefore limited.**
What are the ICERs for each PD-L1 expression sub-group?	This is one for the company.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Tuesday 1 October 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	[redacted], **Action Bladder Cancer UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Questions for engagement

Issue 1: Choice of extrapolation for progression-free survival (PFS)	
Is the log-normal distribution or the Weibull distribution the most appropriate extrapolation of PFS, for both the pembrolizumab and UK standard of care (SoC) arms?	**n/k (not qualified to comment).** Note that these technical issues are, I believe, beyond the scope for Patient Experts to reasonably comment. However, the fact that Pembrolizumab has reduced the risk of death in the whole population by 26% compared with SoC (49% in patients strongly positive in PDL-1) is welcomed and we strongly support the continued availability of Pembrolizumab.
Issue 2: Treatment switching	
Should treatment switching be adjusted for?	**n/k**
If so, should the 2-stage approach be used?	**n/k**
Issue 3: Choice of extrapolation curve and cut-off point for overall survival (OS)	
Is 24 weeks or 40 weeks the more appropriate choice of cut-off for extrapolation of OS data?	**n/k**
In the company's extrapolation, is the proportion of people on the pembrolizumab arm who are still alive after 10 years plausible? What proportion of patients in the pembrolizumab arm would you expect to be alive at 10 years?	**n/k**

What proportion of patients in the UK SoC arm would you expect to be alive at 10 years?	**n/k**
Are there any other long-term data for OS available for immunotherapies in this indication, or for other urothelial carcinoma stages/sub-groups?	**n/k**
Which distribution is most appropriate for modelling OS?	**n/k**
Issue 4: Treatment effect duration	
Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate?	n/k Our aim would be to make the treatment available to patients to achieve best OS and PFS, for the longest duration, irrespective of cost.
Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?	n/k
Issue 5: PD-L1 expression sub-groups	
Does pembrolizumab have a different effect in different PD-L1 sub-groups?	It would seem so; "The updated data showed that pembrolizumab, when compared to UK SoC (excluding vinflunine), reduced the risk of death by 26% in the entire population, by 42% in patients with PD-L1 Combined Positive Score (CPS)≥1%, and by 49% in patients strongly positive for PD-L1, CPS≥10%."

What are the ICERs for each PD-L1 expression sub-group?	n/k

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Choice of extrapolation for progression-free survival (PFS)	
Is the log-normal distribution or the Weibull distribution the most appropriate extrapolation of PFS, for both the pembrolizumab and UK standard of care (SoC) arms?	
Issue 2: Treatment switching	
Should treatment switching be adjusted for?	**Yes**
If so, should the 2-stage approach be used?	**Yes (although this is not my area of expertise).**
Issue 3: Choice of extrapolation curve and cut-off point for overall survival (OS)	
Is 24 weeks or 40 weeks the more appropriate choice of cut-off for extrapolation of OS data?	**40 weeks**
In the company's extrapolation, is the proportion of people on the pembrolizumab arm who are still alive after 10 years plausible? What proportion of patients in the pembrolizumab arm would you expect to be alive at 10 years?	**There is no direct evidence to support 10-year survival. The most recent updates on Keynote-045 (presented at the ESMO meeting in Barcelona on 30 Sep 2019) show 20.7% of patients are still alive at 36 months on pembrolizumab – so the 10 year estimate should definitely be lower than this. I would suggest that it is implausible that more than 5% will be alive at 10 years.**
What proportion of patients in the UK SoC arm would you expect to be alive at 10 years?	**There are very rare long term survivors after second line therapy. Our experts estimate 1 – 2 %.**

Are there any other long-term data for OS available for immunotherapies in this indication, or for other urothelial carcinoma stages/sub-groups?	**The most mature data in this specific indication are from the recently presented update on kn-045 (20.7% alive at 36 months). The 30-month os update for ImVigor 211 (the similar trial of atezolizumab) show 18% alive on the atezolizumab arm (ESMO congress, 30 sep 2019). Although there are other, earlier, trials in related indications our expects are not aware of longer term follow up results.**
Which distribution is most appropriate for modelling OS?	
Issue 4: Treatment effect duration	
Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate?	The impact of stopping immunotherapy at 2 years is unknown in any disease type. The follow up of KN-045 is too immature to estimate whether this will result in any drop off of effect (and it is very likely many patients will receive further immunotherapy on progression after stopping at 2 years, so even these data will be unreliable). Our experts believe the reasonable view is that there will be some patients who continue to benefit at 5 years, but definitely not all. The median duration of response on pembrolizumab in KN-045 is 29.7 months, and it is clear, therefore, that the effects of treatment on disease control are less than permanent for most patients who respond. Given that we now had data at 3 years, this seems a reasonable duration of treatment effect.
Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?	See above. The poster describing the long term follow up is now available on the MSD website (abstract 918P, ESMO, Barcelona 30 Sep 2019).
Issue 5: PD-L1 expression sub-groups	

Does pembrolizumab have a different effect in different PD-L1 sub-groups?	Yes, but not in this indication / stage of the disease. This appears to be the case regardless of the choice of drug or test in the post platinum setting. PD-L1 status does appear to be weakly prognostic however and this may impact on ICER.
What are the ICERs for each PD-L1 expression sub-group?	

ERG Comments on Company Response to Technical Engagement (CDF Review of TA519) [ID1536]

Produced by	Warwick Evidence
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Date completed	9th October 2019

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Declared competing interests of the authors

None

Issue 1: Choice of extrapolation for progression-free survival (PFS)

ERG response

The company begins with disagreeing with the ERG's approach to interpreting the differences in AIC and BIC values when distinguishing between different parametric models. Burnham and Anderson [1] state that models with a difference of less than 2 units from the lowest AIC all have "substantial support", meanwhile Raftery [2] states that a difference of less than 2 units from the model with the lowest BIC is only "weak evidence" of a difference. Based on these two routine definitions, the ERG maintain their interpretation of the differences in AIC and BIC for the models considered in this appraisal.

The ERG present again the table of the AIC and BIC values for the parametric curves fitted to the PFS data from 21 weeks. The best fit (lowest score) is underlined in each column, with models with scores greater than 2 units difference greyed out. It is clear that the only parametric curve that is consistently among the best fitting models to both arms according to both AIC and BIC is the Weibull curve.

Table 1 AIC and BIC scores for parametric fits to post 21-week PFS data from KEYNOTE-045:

	Model for pembrolizumab for week 21+ in overall population		Model for control for week 21+ in overall population	
	AIC	BIC	AIC	BIC
Exponential	529.4	531.8	**383.5**	**385.4**
Weibull	**525.4**	**530.2**	**382.8**	**386.6**
Gompertz	**524.2**	**529.0**	**383.9**	387.7
Llogistic	**523.9**	**528.7**	385.5	389.3
Lnormal	**523.5**	**528.3**	385.8	389.6
GenGamma	**525.5**	532.7	**384.7**	390.3

Lowest values in each column are underlined. Values with a difference ≥2 from the lowest value in each column are greyed out.

Secondly, the company comment that the log-normal curve is "clearly a better fit" to the pembrolizumab PFS data. This is a subjective statement, particularly as the curves are almost indistinguishable for the first 30 months of follow-up. Beyond 30 months (130 weeks) there are 29 patients at risk in the pembrolizumab arm experiencing 5 PFS events. No PFS events occur beyond 36 months, and it is unclear to the ERG how many patients remain at risk after this point. Due to the fact that at this late stage of trial follow-up, a single event can be very influential to the visual fit of a parametric curve, it may be misleading to consider fits to tail data when selecting a parametric fit. For the follow-up period, where there are substantial numbers of patients contributing information, there is little to choose between visual fit of the Weibull and log-normal PFS curves.

Finally, the company state that the extrapolation of the log-normal curve at 5 years is more plausible than that of the Weibull curve according to their clinical expert. The ERG accept that the log-normal scenario could be considered plausible, however it is not supported by evidence. The ERG maintain that the Weibull curve is the better fit to the observed data from KEYNOTE-045 beyond 2 years, hence the reason for selecting this curve in our base-case analysis. (see Table 2).

The ERG also note considerable inconsistency in the company's modelling of PFS. In their original submission for TA 519, the company selected an exponential curve for the PFS extrapolation, a curve which does not maintain an extended tail predicting 0% of pembrolizumab patients being in the progression-free health state at 10 years. Following AC1, the company then changed to a Gompertz distribution for the PFS curve, another curve which again does not have similar extended behaviour to that of the log-normal, this time predicting 10% of pembrolizumab patients in the progression-free health state at 10 years.

Table 2: A comparison of Weibull and log-normal curves fitted to PFS data from 21 weeks to observed data from KEYNOTE-045.

	UK SoC			Pembrolizumab		
	Weibull	Log normal	Observed in KN045	Weibull	Log normal	Observed in KN045
1 year	0.0979	0.0919	11%	0.2033	0.1939	18.8%
2 year	0.0233	0.0375	2%	0.1290	0.1313	13%
3 year	0.0065	0.0213	Insufficient follow-up (but <1.5%)	0.0879	0.1015	Insufficient follow-up (but <10%)
5 year	0.0006	0.0098	Insufficient follow-up	0.0450	0.0706	Insufficient follow-up
10 year	0.0000	0.0030	Insufficient follow-up	0.0109	0.0398	Insufficient follow-up

Issue 2: Treatment switching

ERG response

The company maintain their preference to implement the 2-stage adjustment for patients who received an anti-PD1/PD-L1 therapy following disease progression in the control arm. The ERG have already stated that failing to adjust at all for this treatment switching may introduce bias into the economic analysis, favouring the control arm. However, the ERG remain unconvinced that the 2-stage analysis offers significant benefit over the ITT analysis, due to the previously mentioned problems associated with it.

Firstly, the resulting survival times for the adjusted control arm population appeared to be too severely penalised, with the OS appearing slightly worse for the control arm than that of an external study published by Bellmunt et al. [3], whereas the ERG's clinical advisor expected that patients in the UKSoC arm would have similar or slightly better OS. The company state that it is potentially inappropriate to compare the two populations. However, the Bellmunt et al. study remains the most relevant source of data located by the ERG, and the ERG's clinical advisor was happy to draw comparisons between the populations despite the differences in baseline characteristics.

Secondly, the methodology underlying the 2-stage adjustment also suggest it may not be the right solution. It assumes that all 25 patients who switched to anti-PD1/PD-L1 treatment received the

same OS benefit, in terms of a time ratio/acceleration factor. Given that immunotherapies are not effective in all patients, it is likely that some patients actually received no benefit from switching treatments, however this option is not compatible with the company's implementation of the 2-stage adjustment.

Furthermore, as there was no pre-specified rule on treatment switching and the company were unable to provide clear rationale why some patients switched whilst others did not, there is a strong possibility of selection bias in patients who switched versus those who did not, which may not be captured in the company's adjustment. The acceleration factor could be capturing the benefits of a prognostic factor alongside any potential treatment benefit. The acceleration factor itself remains associated with a large level of uncertainty, with a confidence interval of 3.231 to 10.094 around the estimate of 5.370.

Given the influence of this parameter, and lack of other options, the ERG maintain the position of encouraging the committee to also consider ICERs from the unadjusted ITT population alongside those from the 2-stage adjusted in the decision-making process. An alternative approach would be to apply the 2-stage method only to patients who have some level of response to their anti-PD1/PD-L1 treatment after switching from UK SoC.

Issue 3: Choice of extrapolation curve and cut-off point for overall survival (OS)

ERG Response

The ERG agree with the majority of the comments made by the company in this issue, though the ERG think that the company's upper estimate of 2% survival at 10 years in the UK SoC arm may be too optimistic based on comments from the ERG's clinical advisor. As with the company's preferred PFS extrapolation, their preferred OS curve and anticipated long-term survival profile is plausible but remains unsupported by evidence. The company also appear to exclude the generalised gamma curve, despite it providing similar extrapolations to the log curves. The ERG would like to highlight the considerable uncertainty that remains for long-term OS, and maintain the view that log-normal, log-logistic and generalised gamma curves could all be considered plausible, with the Weibull curve presenting a plausible scenario if no patients experience the long-term survival benefit described by the company.

Issue 4: Treatment effect duration

Point 1: The improvement of the hazard ratio from previous to current data-cut suggests a sustained treatment effect.

ERG Response

The ERG disagree with the company's interpretation of this information. We accept that the hazard ratio has improved with the extended follow-up, however this may not be attributable to the relative treatment effects beyond three years. It is far more likely explained by the greater completeness of follow-up of patients prior to 3 years of each patients' follow-up, i.e. those who were recruited later in the trial. This is supported by the fact that no death events occurred in the 2-stage adjusted UK SoC population beyond 3 years, and just one death event in the unadjusted UK

SoC population. Hence, the follow-up beyond 3 years is unlikely to be influential on the overall trial hazard ratio.

Point 2: The 2- and 3-year effect duration extrapolations are not good matches to the OS data

ERG Response

By comparing the pembrolizumab OS survival extrapolation to the observed data, the company disregard the impact that the choice of parametric curve may have on such an assessment. This affects not only the initial pembrolizumab fit, but also the estimate of the UK SoC hazard rate, which is reverted to after 2/3/5 years. Despite this, we acknowledge that the two-year effect duration applied to the log-logistic curve appears to not fit well to the observed data.

However, the three-year duration is a better fit, and only deviates from the observed data in the tail. As discussed in the PFS section, fitting well to tail data where there are few people at risk and few events can be misleading and result in the incorrect selection of model assumptions.

Point 3: The time varying hazard ratio analysis supports a 5-year treatment effect.

ERG Response

The ERG have already commented on this analysis, and how the data available does not allow for a meaningful hazard ratio to be calculated beyond two years of trial follow-up for the 2-stage adjusted UK SoC population. It is unclear to the ERG how the company interprets this analysis as support for a 5-year treatment effect.

Point 4: Atezolizumab appraisals TA525 and TA584 support 5-year effect duration.

ERG Response

The relevance of TA584 is unclear as it is a different treatment being used for a different disease. TA525 is at least for the same indication so can be considered more relevant. The ERG were unable to scrutinise the evidence underlying the committee's decision to prefer a 3-year post-stopping-treatment duration effect of atezolizumab. However, the company's assumption that this is equivalent to a 5-year stopping rule is likely to be incorrect. Given that the mean time on treatment in KEYNOTE-045 was 6.84 months, and that from 43 weeks consistently less than 50% of the patients who were still alive in the pembrolizumab arm were still receiving pembrolizumab, a 5-year effect duration provides additional benefit than a 3-year post-stopping-treatment effect rule would provide.

The company also provide additional evidence of long-term pembrolizumab efficacy from various sources.

1. KEYNOTE-001 – This was presented previously, and already criticised by the ERG for lack of relevance and transferability.
2. KEYNOTE-006 – This study of pembrolizumab vs ipilimumab in melanoma is also of limited relevance, given the different disease and comparator. The evidence provided by the company also does not provide any support for a sustained effect of pembrolizumab relative to the comparator, which is the key consideration here.
3. KEYNOTE-024 – The information on this study of pembrolizumab vs platinum-based chemotherapy in NSCLC included in their response does not provide any evidence for or against a duration of treatment effect.

4. KEYNOTE-045 – The company provides some additional information from the pivotal trial in this appraisal related to the patients with prolonged response, though much of the information is not related to the long-term survival profile, and is just relevant to the benefits of pembrolizumab within the first three years of follow-up. The ERG agree that there is evidence of a sustained response of pembrolizumab, but the same is also true for those who respond on UK SoC. Whilst there are fewer responders on UK SoC, there is no evidence that suggests that the hazard rate beyond 3 years for these long-term responders is different across the two treatment arms. Based on the percentages provided by the company, in the UK SoC arm 80.9% (28.3%/35.0%) of responders at 12 months maintain a response at 24 months, compared to 83.5% (56.8%/68.0%) in the pembrolizumab arm. This suggests that the long-term responders in both arms may experience similar outcomes.

Finally, the company refer to a poster by Fradet et al., who present an analysis of OS by best overall response. This evidence is again not relevant to the post 3-year treatment effect, as it will be dominated by the events occurring in the first 3 years of KEYNOTE-045, and is not specific to patients with long term responses.

ERG Conclusion

The majority of information provided by the company is unrelated to the estimation of a relative benefit of pembrolizumab to UK SoC beyond 3 years.

The maximum follow-up from KEYNOTE-045 is 4 years, however only 1 death occurs in UK SoC beyond 3 years in the unadjusted/ITT arm, with no events occurring after this point in the 2-stage adjusted analysis. Hence, any estimation of a relative treatment effect of pembrolizumab compared to UK SoC is not possible beyond this point. The ERG maintain their preference for a 3-year effect duration over a 5-year duration, based on the evidence presented here and as previously discussed in this CDF review.

Issue 5: PD-L1 expression sub-groups

The company believe that pembrolizumab does not have a different effect in different PD-L1 subgroups.

The ERG are unable to draw a clear conclusion based on the existing evidence from KEYNOTE-045. The hazard ratios across both of the PD-L1 subgroups (CPS ≥1% HR = 0.58 [95% CI: 0.40, 0.84] and CPS ≥10% HR = 0.51 [95% CI: 0.32, 0.81]), are lower than the hazard ratio for the ITT population (HR = 0.74 [95% CI: 0.59, 0.94]) suggesting there may be greater benefit in patients with higher PD-L1 CPS expression. The ERG are not aware that the company have presented a formal statistical test of the interactive effect of pembrolizumab with the PD-L1 subgroups using the most recent data cut. However, it is possible that any analysis may be underpowered as the trial was not designed to compare the efficacy across the groups, and so a formal test may still be inconclusive.

The ERG conducted a brief search to assess if any relevant external evidence existed. A meta-analysis by Shen et al. suggests PD-1/L1 inhibitors may be more effective in patients with PD-L1 expression across different cancer types [4]. Similarly, a meta-analysis by Ghate et al. of urothelial cancer studies suggests that PD-L1 expression may be a prognostic factor [5]. In KEYNOTE-061, pembrolizumab was compared to paclitaxel in patients with previously treated advanced gastric or gastroesophageal junction cancer. The inclusion criteria of the trial was changed during the recruitment phase so patients with PD-L1 CPS <1% were no longer recruited, based on the

performance of pembrolizumab observed within the trial [6], however it is unclear whether this is transferrable to urothelial cancer.

The ERG have verified the ICERs produced by the company for the subgroups, and present the equivalent analyses using our own base case assumptions. The assumptions have not been adjusted for the specific subgroups, and it is possible that a different combination of assumptions may be more representative of the patient pathway in the subgroups.

Table 3: ICER results for overall population using unadjusted (ITT) population.

Pembrolizumab Overall	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case parameters							
UK SoC	[redacted]	1.4	0.93				
Pembrolizumab	[redacted]	2.18	1.48	£31,016	0.78	0.55	£56,422
ERG base case parameters							
UK SoC	[redacted]	1.4	0.93				
Pembrolizumab	[redacted]	2.07	1.39	£30,001	0.67	0.46	£65,469

Table 4: ICER results for PD-L1 subgroup (CPS≥1%) using unadjusted (ITT) population

Pembrolizumab PD-L1 sub-group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case parameters							
UK SoC	[redacted]	1.3	0.88				
CPS≥1	[redacted]	2.41	1.67	£35,523	1.11	0.78	£45,370
ERG base case parameters							
UK SoC	[redacted]	1.3	0.87				
CPS≥1	[redacted]	2.2	1.52	£34,029	0.9	0.65	£52,214

Table 5: ICER results for PD-L1 subgroup (CPS≥10%) using unadjusted (ITT) population

Pembrolizumab PD-L1 sub-group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case parameters							
UK SoC	[redacted]	1.42	0.94				
CPS≥10	[redacted]	2.4	1.64	£32,617	0.99	0.7	£46,485
ERG base case parameters							
UK SoC	[redacted]	1.42	0.93				
CPS≥10	[redacted]	2.21	1.5	£31,126	0.79	0.57	£54,598

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Technical report

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [Cancer Drugs Fund Review of TA519]

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team, chair and vice chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission, the terms of engagement for the CDF review (ToE) and the original appraisal (TA519)
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts
- the evidence review group (ERG) report
- the committee discussion in the original appraisal (TA519)
- the terms of engagement for the CDF review

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Appraisal background

Marketing authorisation (MA):

'[Pembrolizumab] as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy'

Based on scope:

Population

As in MA, but limited to people for whom cisplatin is suitable in first line
(there is a separate indication for those who are not eligible for cisplatin)

Comparators

Docetaxel, paclitaxel, best supportive care

Outcomes

Includes overall survival and progression-free survival

TA519: History of the appraisal

- Dec 16 – Originally scoped
- May 17, Oct 17 – ACM1, ACM2
- Jan 18 – New value proposition
- Apr 18 – Available in CDF

Further data collection:

- Managed access agreement
- Additional data from KEYNOTE-045

Nov 18 – CDF review

1.2 Treatment pathway

Locally advanced or metastatic urothelial carcinoma pathway

First line

Platinum-based therapy, such as:
- Cisplatin + gemcitabine
- Accelerated MVAC + G-CSF

When cisplatin is unsuitable:
- Carboplatin + gemcitabine

(Indication subject to a separate appraisal)

*Disease progression on/ after **platinum**-based therapy*

Second line

Taxanes (paclitaxel, docetaxel)

Best supportive care

Pembrolizumab
Access through CDF (TA519), subject of this review

Since original appraisal, atezolizumab recommended for routine commissioning (TA525), nivolumab not recommended (TA530)

This follows the original scope in TA519 (section 6.25 of process guide, no changes to scope allowed), and shows positioning of interventions which have been appraised since.
Re-treatment with first line chemotherapy removed (as per TA519 FAD section 3.4).

FAD: final appraisal determination; G-CSF: granulocyte-colony stimulating factor; MVAC: methotrexate, vinblastine, doxorubicin and cisplatin

1.3 Key considerations from original appraisal

Committee preference from original appraisal:	Did company follow/ address this in CDF review?
End of life criteria apply	N/A (criteria still met)
UK standard of care (SoC) includes paclitaxel and docetaxel (vinflunine excluded), but best supportive care should be comparator also	X (presented paclitaxel and docetaxel)
2-year stopping rule	✓ (stopping rule still applies)
Lifetime treatment effect implausible, treatment effect duration capped at 3 or 5 years	**✓ (5 years base case, 3 and 10 years as scenarios)**
Weibull curve for progression-free survival (PFS) extrapolation	X
2-phase piecewise approach for OS	✓
Best time to switch to parametric curve uncertain (24 weeks or 40 weeks)	✓(24 weeks in base case, 40 weeks scenario analysis)
Several plausible OS curves, considered log-logistic (ERG preferred) and log-normal (company preferred)	**✓ (but 4 curves considered plausible by ERG with newer data cut)**
Simplified 2-stage method to adjust for treatment switching	**✓(but ERG had concerns so presented alternative)**
Utility estimates should be based on progression state (not on time-to-death), pooled across treatment arms, and exclude vinflunine	✓

1.4 Clinical trial – KEYNOTE-045

Additional 22 months of data collection in trial (cut-off Nov 2018) compared to last data seen by committee

KEYNOTE-045	Phase III RCT, n = 542
Population	People with metastatic or locally advanced/ unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy. ECOG performance status of 0, 1 or 2
Intervention	Pembrolizumab 200 mg IV every 3 weeks
Comparator	One of the following, IV every 3 weeks: • Paclitaxel 175 mg/m^2 • Docetaxel 75 mg/m^2 • Vinflunine 320 mg/m^2 (not in UK SoC)
Primary outcome	OS and PFS (per RECIST 1.1)
Key subgroups	PD-L1 positive tumours (CPS≥1%), strongly PD-L1 positive tumours (CPS≥10%)

Key abbreviations in appraisal	
SoC	Comparator arm of KEYNOTE-045 = paclitaxel, docetaxel or vinflunine
UK SoC	Committee preferred comparator in original appraisal = paclitaxel or docetaxel
ITT	Trial results that have not been adjusted for treatment switching (relevant to analyses with and without vinflunine included in comparator arm)

CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumours

1.5 Updated clinical trial results – overall survival

Pembrolizumab versus UK SoC – adjusted for treatment switch to anti-PD-L1 treatment in UK SoC arm using 2-stage analysis

		Updated results from KEYNOTE-045 (cut-off Nov 2018, database lock Mar 2019)			Results from KEYNOTE-045 presented in first appraisal committee meeting of TA519		
Treatment	N	Median OS (months) (95% CI)	Treatment vs. Control		Median OS (months) (95% CI)	Treatment vs. Control	
			Hazard ratio (95% CI)	p-value		Hazard ratio (95% CI)	p-value
Control (UK SoC)	182	7.0 (5.5, 8.7)	---	---	7.4 (6.1, 8.3)	---	---
Control (UK SoC), adjusted ¶	182	6.2 (5.2, 7.4)	---	---	6.9 (5.3, 8.1)	---	---
Pembrolizumab (200 mg Q3W)	188	10.1 (7.6, 12.9)	**0.64 (0.49, 0.81)**	0.0139	10.3 (8.0, 11.8)	[redacted]	Unknown

¶Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

CI: confidence interval; Q3W: every 3 weeks

1.6 Updated clinical trial results – progression-free survival

Pembrolizumab versus UK SoC – no adjustment for treatment switching

		Updated results from KEYNOTE-045 (cut-off Nov 2018, database lock Mar 2019)			Results from KEYNOTE-045 presented in first appraisal committee meeting of TA519		
Treatment	N	Median PFS (months) (95% CI)	Treatment vs. Control		Median PFS (months) (95% CI)	Treatment vs. Control	
			Hazard ratio (95% CI)	p-value		Hazard ratio (95% CI)	p-value
Control (UK SoC)	182	3.3 (2.3, 3.5)	---	---	3.3 (2.3, 3.4)	---	---
Pembrolizumab (200 mg Q3W)	188	2.1 (2.0, 2.2)	**0.95 (0.76, 1.19)**	0.6183	2.1 (2.0, 2.2)	[redacted]	0.956

2. Remaining issues after data collection in CDF period, to be addressed in this review

#	Issue	Matches ToE?	Why this is being explored in CDF review	Technical team consideration
1	PFS extrapolation	X	• Additional data from KEYNOTE-045 can better inform extrapolation • Company & ERG use different approaches	Weibull most appropriate
2	Treatment switching	-	• 2-stage adjustment used in original appraisal associated with uncertainties • Adjustment now a bigger driver of ICER (compared to original appraisal)	Both the 2-stage adjustment and analyses without adjustment should be considered during decision-making
3	OS extrapolation	✓	• Additional data from KEYNOTE-045 can better inform extrapolation • ERG identify multiple plausible approaches	Committee may wish to consider ICERs from each of the 4 plausible extrapolation distributions
4	Treatment effect duration	?	• Additional data has not resolved uncertainty • Company & ERG use different approaches	3-year treatment effect appears most plausible, committee may wish to consider 5-year and conservative 2-year scenario analysis
5	PD-L1 expression sub-groups	-	• TA519 = pembrolizumab has better effect in patients with high Combined Positive Score (CPS) • New data = potentially relevant evidence on PD-L1 subgroups	Technical team considers it relevant to reconsider sub-groups in light of the updated clinical data

3. Summary of the technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

3.1 In summary, the technical team considered the following:

Issue 1 The Weibull extrapolation should be used for progression-free survival (PFS).

Issue 2 Both the 2-stage and ITT analyses should be considered during decision-making.

Issue 3 **24-week cut-off should be used for extrapolating overall survival (OS) data. There are several plausible OS extrapolations.**

Issue 4 **3-year treatment effect (2+1, which represents 2 years of treatment and 1 year of follow-up) appears most plausible, but committee may wish to consider 5-year effect also, as well as the conservative 2-year scenario analysis.**

Issue 5 **The committee may wish to consider if PD-L1 sub-group results are appropriate and reliable for decision-making in light of updated data.**

3.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The Systemic Anti-Cancer Therapy (SACT) data collection period was limited (9 months), which was too short to collect data on overall survival and treatment duration. This means there is limited real-world data on the use of the drug in this indication for the population in England, increasing the uncertainty associated with estimations of treatment effect size and duration.

- There is no long-term overall data available for immunotherapies in this indication.

- As in TA519, the company submitted clinical and cost-effectiveness analyses comparing pembrolizumab with paclitaxel or docetaxel; comparisons excluded vinflunine to represent UK standard of care (SoC). Although best supportive care was a comparator in the NICE scope and the ToE for this appraisal, the company did not submit analyses comparing pembrolizumab with best supportive care. However, it should be noted that the ToE indicated the ERG base case model from the original appraisal should be used. This was based on the company's submitted model, which did not include best supportive care as a comparator.

3.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for pembrolizumab. This commercial arrangement has

been updated since the original appraisal, and replaces the confidential discount that was applicable during the CDF-funded period.

3.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £53,678–65,469 per QALY gained (see Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate).

3.5 It was decided in TA519 that the end-of-life criteria were met (see TA519 FAD sections 3.24 and 3.25).

3.6 The technology is not considered innovative (see Table 3: Other issues for information).

3.7 No equality issues were identified (see Table 3: Other issues for information).

4. Key issues for consideration

Issue 1 – Choice of extrapolation for progression-free survival (PFS)

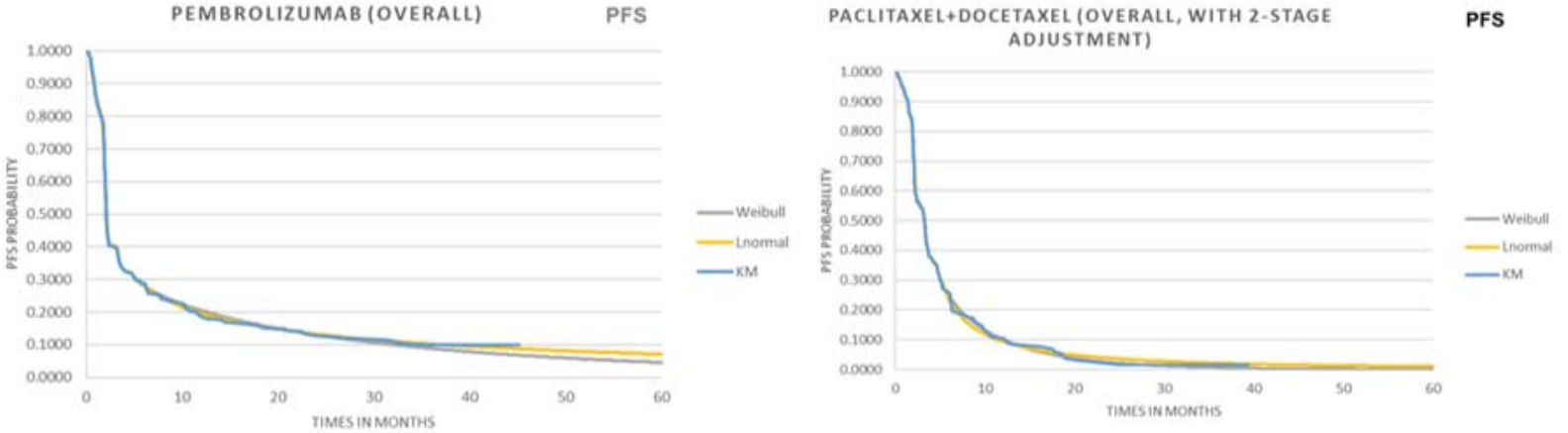
Questions for engagement	1. Is the log-normal distribution or the Weibull distribution the most appropriate extrapolation of PFS, for both the pembrolizumab and UK standard of care (SoC) arms?
Background/description of issue	**TA519:** In the original appraisal, the committee understood that pembrolizumab did not significantly reduce the risk of a PFS event, compared to UK SoC (excluding vinflunine) (hazard ratio [95% CI] = 0.98 [0.81 to 1.19]). The company extrapolated the Kaplan-Meier PFS data after 21 weeks using the Gompertz curve. The ERG agreed with the use of Kaplan-Meier data up until week 21 (where the curves of the cumulative hazard plot crossed). However, it preferred extrapolation with a Weibull curve because it believed this had the most plausible balance of pre-progression and post-progression survival benefits. The committee preferred the ERG's piecewise approach of extrapolating the trial data at 21 weeks using a Weibull curve. **CDF review:** As part of the CDF managed access arrangement, additional PFS data was collected from KEYNOTE-045. Because of the availability of this new evidence, both the company and ERG reconsidered the choice of PFS extrapolation. The updated data indicates that pembrolizumab does not significantly reduce the risk of a PFS event compared to UK SoC (hazard ratio [95% CI] = 0.95 [0.76 to 1.19]). Taking into account the updated data cut (November 2018), both the company and the ERG maintained a piecewise approach, with parametric extrapolation beyond 21 weeks. **The company** chose the log-normal parametric function as their base case for extrapolating PFS for the pembrolizumab arm. This choice was made based on statistical and visual fit to the updated KEYNOTE-045 data. The company did not find a clear extrapolation choice for the UK SoC arm, so it used the log-normal curve in its base case to be consistent with

	the pembrolizumab arm. The company presented a scenario analysis using the Weibull extrapolation of both arms, as it was the ERG and committee's recommended extrapolation in the original appraisal. Considering the most recent data cut, the **ERG** still preferred the Weibull function for extrapolating PFS for both the pembrolizumab and UK SoC arms. It considered that the Weibull is a better statistical fit to the UK SoC arm and among the best fitting curves of the pembrolizumab arm. While the ERG accepted that the log-normal model has the best statistical fit for the pembrolizumab arm, it considered that there is only a small difference in statisical fit between several of the distributions, and that four curves (log-normal, log-logistic, Weibull, Gompertz) could be reasonable. The ERG disagreed with the company's choice to prioritise the fit to the pembrolizumab arm, rather than the UK SoC arm, and aimed to find the curve which was consistently among the best fitting for both arms. It considered that the Weibull distribution is most consistent with the KEYNOTE-045 trial and was a reasonable visual fit to the cumulative hazard plots provided by the company.
Why this issue is important	The length of time spent in the progression-free health state and the progressed disease state may affect the overall number of QALYs for pembrolizumab and comparators, which impacts the ICER.
Technical team preliminary judgement and rationale	It is acceptable to extrapolate the Kaplan-Meier PFS data after 21 weeks. For both the pembrolizumab and UK SoC arms from the clinical trial, it is appropriate to use a Weibull extrapolation.
Summary of comments	Comments received from company: *- Most appropriate extrapolation curve of PFS is log-normal. Selected based on AIC/BIC statistics and visual inspection, acknowledge that for UK SoC arm, Weibull extrapolation is one of the best fitting curves based on these selection criteria within observed trial period, but extrapolation is 4th best fitting to observed data in pembrolizumab arm based on statistics criteria. Log-normal best fitting, results in extrapolated curve more aligned to clinical expectation.* *- ERG's justification for parametric curve selection based on AIC/BIC in UK SoC not robust. ERG stated that as difference in AIC/BIC is <2 for various curves when fitted to pembrolizumab KM data, all curves should be considered under equal merit. Do not consider this a standard interpretation of AIC/BIC. Differences between Weibull and log-normal curves for UK SoC arm modest within observed trial period and in longer-term prediction: log-normal PFS predictions in UK SoC arm are 1% higher at year 2, 3, 4, and 5 and 0.3% higher at 10 years. Curve choice has greater impact on longer-term extrapolation in pembrolizumab arm. Log-normal best fitting, and results in extrapolated curve more aligned to clinical expectation.*

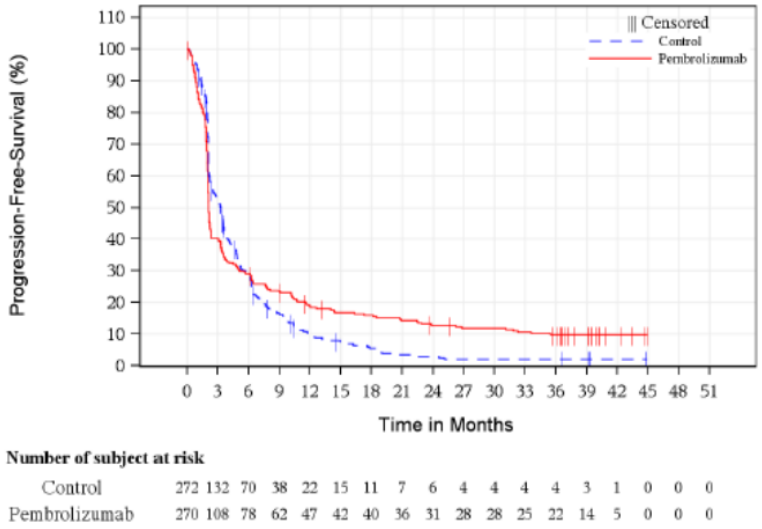
PFS – AIC/BIC statistics (note: highlighting company's own, does not indicate confidential information)*:*

	PFS - UK SOC			PFS - Pembrolizumab		
	Weibull	Log normal	Observed in KN045	Weibull	Log normal	Observed in KN045
1 year	0.0979	0.0919	0.11	0.2033	0.1939	0.188
2 year	0.0233	0.0375	0.02	0.1290	0.1313	0.13
3 year	0.0065	0.0213	Insufficient follow-up (but <0.015)	0.0879	0.1015	Insufficient follow-up (but <0.10)
5 year	0.0006	0.0098	-	0.0450	0.0706	-
10 year	0.0000	0.0030	-	0.0109	0.0398	-

- Log-normal is better visual fit to pembrolizumab KM data. Weibull overestimates KM curve for pembrolizumab between months 10-17, but underestimates towards end of observed period (month 30 onward). Distinct difference in longer-term predictions for pembrolizumab based on choice of curve, with Weibull penalizing projected PFS in pembrolizumab arm (3% lower than log-normal).



- Clinical expert confirmed approach of selecting extrapolation based on best fit to pembrolizumab KM data and applying same curve to UK SoC arm for consistency was reasonable and appropriate, considering UK SoC curves overlap closely.

	Allows emphasis on understanding pembrolizumab extrapolation tails, therefore longer-term expectations in PFS when using pembrolizumab. With immunotherapies in this population, clinicians expect to see extended tail in PFS curve (not drastic shift in median PFS), aligned to what is seen with pembrolizumab in different tumour types. Flat long tail of PFS curve in pembrolizumab arm from KEYNOTE-045 demonstrated from Nov 2018 data cut. Expert's opinion was that log-normal curve better reflects handful of patients responding and remaining progression-free, leading to a longer tail in the survival curve. *KM estimates of PFS based on RECIST 1.1. per Central radiology Assessment (Primary Censoring rule) – ITT population:*  *- Consider fitting log-normal to both arms to be conservative, e.g. with log-normal for pembrolizumab and Weibull for SoC (best statistical and visual fit for each) instead of log-normal for both arms, results in incremental QALY gain of 0.75 and a lower ICER of £46,807.* ERG's critique of company's comments: *- Clear that only Weibull consistently among best fitting to both arms according to both AIC and BIC. Considerable inconsistency in company's modelling of PFS compared to TA519.* *- Company comment that log-normal "clearly a better fit" to pembrolizumab is subjective, particularly as curves almost indistinguishable for first 30 months of follow-up. Beyond 36 months, unclear how many still at risk, single event can be*

	very influential to visual fit at late stage of follow-up, may be misleading to consider fits to tail data when selecting a parametric fit. Comments received from patient organisations: *- Technical issues beyond scope for patient experts to reasonably comment. However, fact that pembrolizumab has reduced risk of death in whole population by 26% compared with SoC (49% in patients strongly positive in PD-L1) is welcomed, we strongly support continued availability.* Comments received from NHS commissioning expert: *- Weibull extrapolation was committee's preferred methodology when topic was first appraised, remains ERG's preferred distribution and case for concluding this is persuasive. No robust change in evidence to necessitate a change to a different methodology for modelling PFS.*
Technical team judgement after engagement	It is acceptable to extrapolate the Kaplan-Meier PFS data after 21 weeks. For both the pembrolizumab and UK SoC arms from the clinical trial, it is appropriate to use a Weibull extrapolation.

Issue 2 – Treatment switching

Questions for engagement	2. Should treatment switching be adjusted for? 3. If so, should the 2-stage approach be used?
Background/description of issue	**TA519:** Some patients on the chemotherapy arm in KEYNOTE-045 switched to anti-PD-L1/PD-1 treatment (including pembrolizumab). Several techniques to adjust overall survival for the chemotherapy arm to account for subsequent immunotherapy were investigated in TA519. The company and ERG used the 2-stage method (although they acknowledged the method had some disadvantages). The committee concluded that the 2-stage method was appropriate. **CDF review:** The 2-stage technique calculates an acceleration factor for SoC 'crossover' patients to estimate event times had they not received subsequent anti-PD-L1/anti-PD-1 therapy. In the CDF review, this factor was 5.37 (based on 25 patients), compared to the estimate used in TA519, which was 3.86 (based on 14 patients). Because this acceleration factor was much larger than in the original appraisal, as well as applied to more patients, the ERG investigated its impact on results. In KEYNOTE-045, 40 people received anti-PD-L1/ PD-1 treatment after UK SoC. In their updated submission, the **company** maintained the 2-stage technique to remove any additional OS benefit these patients may have received from change in treatment. While this approach was used in TA519, the **ERG** was concerned about the larger magnitude of the acceleration factor from the new data cut. A larger acceleration factor meant the adjustment for treatment switching had a much greater influence on the OS, and thus on the costs and benefits which informed the ICER. Because the adjustment for treatment switching has a greater impact on the ICER in the CDF review than in the original appraisal, the ERG revisited the uncertainties associated with the approach. The 2-stage approach assumed uniform treatment effect, but the ERG considered that it was unlikely that all patients who switched benefited from the anti-PD-L1/PD-L treatment. The estimated acceleration factor had a wide confidence interval (estimate: 5.37, 95% confidence interval: 3.231 to 10.094), which implied a large amount of uncertainty. The company were asked by the ERG to estimate

the acceleration factor including data from the full SoC (i.e. including vinflunine patients), as an attempt to reduce the uncertainty by increasing the sample size. The estimate was consistent with the UK SoC analysis, but still had a wide confidence interval (estimate: 5.320; 95% confidence interval: 3.443 to 8.446). Some of the eligible people in the trial switched treatment on disease progression, while others did not. The ERG indicated that if treatment switching was not random, the acceleration factor might include the effect of an unknown prognostic factor, not just the effect of treatment switching.

Because of the concerns with the acceleration factor, the ERG investigated not adjusting for treatment switching (referred to as an 'ITT analysis[1]'). The ERG considered that this approach is also not ideal, as it is likely that some patients who switched did receive a benefit for the treatment. Not adjusting for this benefit introduces bias which favours the control arm.

The ERG looked at data from a 2013 study by Bellmunt et al., which reported phase III trial data from another trial in second-line treatment of patients with advanced urothelial carcinoma who progressed after a platinum-containing regimen (vinflunine versus best supportive care). The ERG also sought the opinion of a clinical advisor. The clinical advisor looked at the data reported by Bellmunt et al. and compared it to the 2-stage adjusted and ITT data for the UK SoC arm. The clinical advisor stated they would expect patients in the UK SoC arm of the KEYNOTE-045 to have similar or slightly superior overall survival compared to the vinflunine patients included in the Bellmunt et al. study.

Table A: Comparison between OS data from Bellmunt et al. (2013) and KEYNOTE-045 (unadjusted and adjusted for treatment switching)

	Bellmunt (2013)	ITT approach	2-stage adjustment
Median OS	6.9 months	7.0 months	6.2 months
12-month OS	27%	32%	25%
24-month OS	11%	16%	10%
30-month OS	5.5%	12%	7.7%

The ERG considered that the ITT approach may overestimate survival time in the UK SoC arm and that the 2-stage adjustment approach might underestimate survival times too much. The ERG used the 2-stage method in its base case but presented the ITT analysis as a scenario analysis. The ERG advised that the 2-stage adjusted analysis and the ITT

[1] ITT analysis in this instance means not adjusting for treatment switching (rather than using the original SoC arm from the trial instead of the UK SoC arm)

	analysis should be carefully considered, as it believed that the true OS benefit lay somewhere between the OS result of the two methods. The technical team are aware that in a previous appraisal in the indication (nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy, TA530), clinical experts advised that mean life expectancy after treatment with platinum-based therapy was around 12 months, and that survival at 5 years is uncommon (approximately 2-3% for taxanes or best supportive care).
Why this issue is important	Finding the base case survival to use for UK SoC is important to make the most realistic comparison between pembrolizumab and UK SoC. This is especially important due to the immaturity of the clinical trial data (see Issue 3 – Choice of extrapolation curve and cut-off point for overall survival). When the ERG's ITT approach is used instead of adjusting for treatment switching, the company's base case ICER increases to £65,469.
Technical team preliminary judgement and rationale	The additional KEYNOTE-045 data is likely to affect the impact of the 2-stage method on the ICER. Because of this, it is relevant to reconsider the adjustment for treatment switching in the CDF review. Both the 2-stage and ITT analyses should be considered during decision-making.
Summary of comments	Comments received from company: *- Treatment switching should be adjusted for, approach taken is in line with previous pembrolizumab submissions and ERG's preferred approach in TA519. Not appropriate to use ITT analysis for decision making in this appraisal.* *- Potentially inappropriate to consider Bellmunt and KEYNOTE-045 study populations as analogous and draw cross-trial comparisons, e.g. different age distribution and ECOG inclusion criteria. Interpret assumptions based on cross-trial comparison with caution.* *- 40 patients who received UK SoC in KEYNOTE-045 control arm also received anti-PD1/PDL1 treatment (of these, 25 switched upon disease progression, 15 switched at different stage/did not experience documented disease progression). Acceleration factor calculated from analysis of survival times of 25 patients who switched upon disease progression, compared to those who did not switch upon disease progression, adjusting for covariate differences (15 patients who switched at another time not used in calculation of acceleration factor and their survival times not adjusted; instead the within trial observed survival times for these patients used when these patients were included in the 2-stage model. Would only have been adjusted for in alternative adjustment analyses (e.g. RPSFT or IPCW), but not in 2-stage adjustment).* *- Acknowledge increase in magnitude acceleration factor but consider unsurprising - analysis still involves limited patient numbers, calculations sensitive to small numbers. Sensitivity is reflected in the wide confidence intervals. Adjusted analysis*

	based on longest follow up data available from KEYNOTE-045, so consider it more reliable than data based on shorter follow up. ERG's critique of company's comments: *- Issues with 2-stage: survival times for UK SoC too severely penalised; assumes switchers to anti-PD-1/PD-L1 received same OS benefit in terms of a time ratio/acceleration factor (IOs not effective in all patients, likely some received no benefit from switching). No pre-specified rule on treatment switching and no clear rationale why some switched and others didn't means there is possible selection bias, and the influential acceleration factor maybe capturing benefits of prognostic factor not just treatment benefit.* Comments received from professional groups: *- Indicated that treatment switching should be adjusted for, and 2-stage approach should be used.* Comments received from NHS commissioning expert: *- Original trial design of KEYNOTE-045 did not allow crossover from standard care chemotherapy to pembrolizumab. Trial protocol underwent an amendment to allow such cross over whether it was before or after disease progression on standard chemotherapy.* *- Reasonable to allow for cross over to pembrolizumab from chemotherapy whilst recognising uncertainty this brings.* *- Allowing for cross over always introduces uncertainty. Noted ERG's arguments and conclusion that 2-stage approach is appropriate.*
Technical team judgement after engagement	ICERs from both the 2-stage adjusted approach and the ITT approach for switching from UK SoC should be carefully considered.

Issue 3 – Choice of extrapolation curve and cut-off point for overall survival (OS)

Questions for engagement	4. Is 24 weeks or 40 weeks the more appropriate choice of cut-off for extrapolation of OS data? 5. In the company's extrapolation, is the proportion of people on the pembrolizumab arm who are still alive after 10 years plausible? What proportion of patients in the pembrolizumab arm would you expect to be alive at 10 years? 6. What proportion of patients in the UK SoC arm would you expect to be alive at 10 years? 7. Are there any other long-term data for OS available for immunotherapies in this indication, or for other urothelial carcinoma stages/sub-groups? 8. Which distribution is most appropriate for modelling OS?
Background/description of issue	**TA519:** Some of the key areas of uncertainty in the original appraisal were around overall survival. • The ICER was most sensitive to the curve used to extrapolate OS. There were several plausible curves. The company's preference was the log-normal parametric curve for both the pembrolizumab and UK SoC arms, while the ERG's preference was the log-logistic curve for both arms. Clinical expert opinion indicated that long-term survival of people with metastatic disease in this indication was not well-known, due to variation in UK clinical practice. The committee decided that long-term survival was uncertain, and it would consider both the company and ERG's preferred OS extrapolation in its decision-making. • Data from KEYNOTE-045 showed that the proportional hazards assumption did not hold. Because of this, the committee considered it was appropriate to use a 2-phase piecewise model for OS. However, the company and the ERG disagreed at what point the observed data should switch to a parametric curve. The committee considered that it was unclear which time point (week 24 or week 40) was the most plausible point to switch to extrapolation for OS. The committee took both time points into consideration in its decision-making. **CDF review:** The CDF period allowed for longer period of follow-up data to be collected from KEYNOTE-045. However, this data is still immature so there is remaining uncertainty around long-term survival. Because of this, the company and the ERG investigated extrapolations to fit the longer follow-up period of OS data for both arms in the trial. The company and the ERG agreed that a 2-phase piecewise model for OS remained appropriate. They both used the new evidence to inform the choice of cut-off point for OS data

	Cut-off point for OS The **company** began OS extrapolation at 24 weeks, in line with the ToE and the ERG's preferred approach in the original appraisal. The company presented a scenario with extrapolation from 40 weeks because it thought, while the cumulative hazard curves started to separate from week 24, there was a clearer change in the slope after 40 weeks. The **ERG** rejected using 40 weeks as a cut-off point, as it considered the hazard on the UK SoC arm immediately after this did not reflect the long-term hazard. It preferred the 24-week cut point used in the company's base case. The ERG compared alternative cut-off options (16, 24, and 32 weeks) and found the impact of the choice on the long-term extrapolation was not large. After reviewing evidence based on the new data cut, the ERG concluded there was little to distinguish between the 16, 24, and 32-week cut-off points. *Choice of OS extrapolation* The **company's** base case choice of extrapolation distribution for OS was the log-logistic curve, in line with the ERG's preference in TA519. The company based this choice on statistical and visual fit to the data from the updated cut. The company highlighted that using this distribution gives a 3.2% 5-year survival rate for the UK SoC arm, which was consistent with the 2-3% figure suggested by a clinical expert in TA519 (FAD section 3.15). The **ERG** looked at the cumulative hazard plot for different OS extrapolation curves based on the updated clinical data and concluded that the Weibull, log-normal, log-logistic and generalised gamma curves are all plausible. The ERG indicated that reliance on goodness-of-fit statistics alone should be avoided for immature data, and highlighted that OS data from KEYNOTE-045 was less mature than PFS data. The ERG considered: • Gompertz was not appropriate, despite having the best statistical fit to the observed data, because the underlying shape resulted in implausible long-term extrapolation. • Log-normal and log-logistic had the next-best statistical fit, but behaviour in their extrapolation tails needed to be considered. Over time, both had sharply decreasing hazards, meaning a small number of patients will live for a long time. • Weibull also had a decreasing hazard rate, but this remained higher than those of the two log models. • Log-normal, log-logistic and Weibull had similar predictions for the first few years of trial follow-up, but there were differences in their long-term predictions, particularly for the pembrolizumab arm. • The proportion of patients alive at 10 years was unknown. If long-term survival was plausible, generalized gamma was most suitable, as it was most optimistic for both arms. A log curve may also have been appropriate if long-term

	survival was plausible, as log-normal and log-logistic curves were optimistic for pembrolizumab and pessimistic for UK SoC. If long-term survival was not plausible, the Weibull was most suitable, as it was pessimistic for both arms. • According to the ERG's clinical advisor, some sustained long-term benefit could be plausible for patients receiving pembrolizumab. This supported the selection of one of the two log curves. As a result of these considerations, the ERG used a log-logistic extrapolation of OS in their base case, but explored the other three plausible distributions (log-normal, Weibull, generalized gamma) in scenario analyses.
Why this issue is important	Predictions for UK SoC patients are similar across most of the parametric curves explored by the company and ERG. As there is still uncertainty over long-term efficacy of pembrolizumab in this population, it remains difficult to select the optimal curve for extrapolation. There is also no long-term data available for immunotherapies in this area, so this remains a key area of uncertainty even after data collection in the CDF period. The modelled long-term benefits and costs will impact the ICER. For example, changing to log-normal instead of log-logistic for OS extrapolation increases the ICER to £58,705, while using generalized gamma instead of log-logistic increases the ICER to £55,202.
Technical team preliminary judgement and rationale	A 24-week cut-off for OS trial data should be used. In light of the updated OS data from the data cut presented in the company's submission, the log-logistic curve used in the company and ERG's base cases could be plausible. But despite further data collection in KEYNOTE-045, OS data is still immature, so it may be relevant to consider ICERs from each of the 4 plausible extrapolation distributions. Further information may be needed on the plausibility of long-term survival after pembrolizumab in this indication to inform the choice of extrapolation.
Summary of comments	Comments received from company: *- Already agree that 24 weeks is an appropriate choice of cut-off for OS extrapolation, 40-week cut off presented only as a scenario analysis. Reiterated that OS cumulative hazard curves start separating from week 24, clearer change in slope after around 40 weeks.* *- Plausible that 1-2% of patients remain alive at 10 years, based on clinical expert consulted who confirmed that prediction by log-logistic (1.36% at 10 years) seemed reasonable for UK SoC arm. They also confirmed that predicted figures for pembrolizumab arm with log-logistic (13.1% at 5 years, 5.5% at 10 years) reflect what can be expected to be seen in clinical practice. Difficult to ascertain how many patients will be alive after 10 years as no one has experience of this scenario - plausible that, for handful of patients who continue to respond after a few years, they would be expected to remain in response and alive when treated with pembrolizumab. MSD not aware of other long-term OS data, but clinical expert's experience with other immunotherapies in urothelial cancer consistent with outcomes seen with pembrolizumab in this disease area and across different tumour types.*

- Log-logistic most appropriate for modelling OS. With latest data, Gompertz has closest fit based on AIC/BIC, but implausible long-term effect for UK SoC. Log-logistic provided 2nd best fitting goodness-of-fit data for both arms, results in more realistic long-term survival estimates reflecting clinical practice. 5-year survival for UK SoC predicted as 3.25% with log-logistic, aligned with 2-3% figure suggested by expert clinical opinion and 5-11% accepted by committee in TA519.

Long-term OS estimates for UK SoC (highlighting company's own, does not represent confidential information):

	Exponential	Weibull	Log normal	Log logistic	Gompertz	Gen Gamma	Observed in KN045
1 year	0.3012	0.2752	0.2517	0.2464	0.2427	0.2463	0.236
2 year	0.1066	0.1168	0.1131	0.1041	0.1134	0.1167	0.093
3 year	0.0377	0.0554	0.0667	0.0621	0.0815	0.0736	-
5 year	0.0047	0.0145	0.0317	0.0325	0.0662	0.0397	-
10 year	0.0000	0.0008	0.0099	0.0136	0.0632	0.0160	-
20 year	0.0000	0.0000	0.0026	0.0057	0.0631	0.0060	-
30 year	0.0000	0.0000	0.0010	0.0035	0.0631	0.0032	-
35 year	0.0000	0.0000	0.0007	0.0029	0.0631	0.0025	-

- Inappropriate to include parametric curves for OS extrapolation which do not reflect clinically held view that proportion of patients experience long-term survival with pembrolizumab. According to ERG's clinical advisor, '"some sustained long-term benefit could be plausible for patients receiving pembrolizumab", which supports the selection of the log curves', which is reflected in feedback MSD received through clinical consultation. Only log-normal should be included in scenario analyses.

ERG's critique of company's comments:

- Agree with majority of company's comments on issue, but company's upper estimate of 2% survival at 10 years in UK SoC arm may be too optimistic based on comments from ERG's clinical advisor.

- Company's preferred OS curve and anticipated long-term survival profile plausible but unsupported by evidence.

- Company appear to exclude generalised gamma despite it providing similar extrapolations to the log curves.

- Considerable uncertainty remains for long-term OS. Log-normal, log-logistic and generalised gamma could all be considered plausible, with Weibull as plausible scenario if no patients experience the long-term survival benefit described by company.

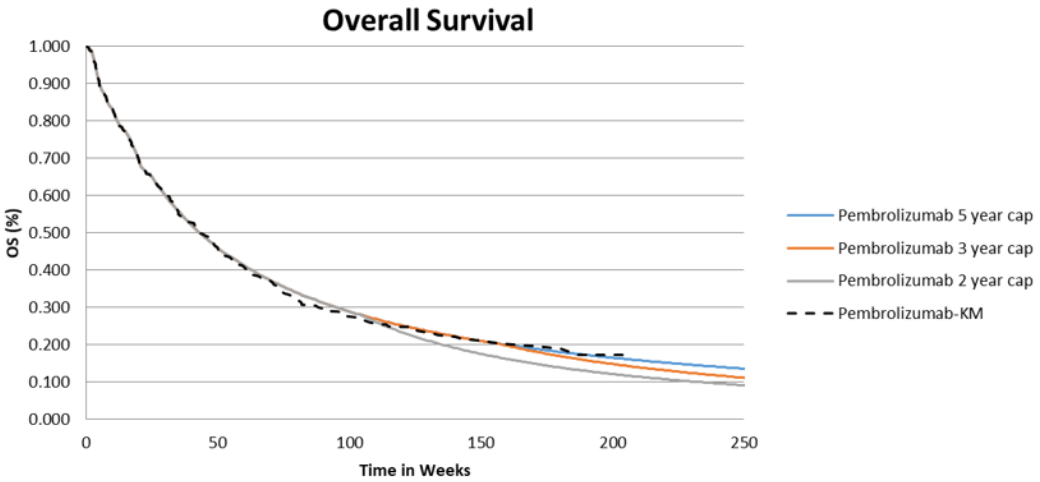
	Comments received from professional groups: *- 40 weeks is appropriate cut off.* *- No direct evidence to support 10-year survival. Most recent updates on KN-045 (presented at ESMO Barcelona 30 Sep 2019) show 20.7% of patients still alive at 36 months on pembrolizumab – so 10-year estimate should definitely be lower than this. Implausible that >5% will be alive at 10 years.* *- Very rare long-term survivors after second line therapy, our experts estimate 1-2%.* *- Most mature data in this indication are from recently presented update on KN-045 (20.7% alive at 36 months). The 30-month OS update for ImVigor 211 (the similar trial of atezolizumab) show 18% alive on atezolizumab arm (ESMO congress, 30 Sep 2019). Although there are other earlier trials in related indications our experts are not aware of longer term follow up results.* Comments received from NHS commissioning expert: *- See no reason for not supporting ERG's approach (24 week cut off).* *- Always a very small number of patients treated with standard chemotherapy who do very well (against general expectation). Biologically plausible that patients treated with pembrolizumab will do better (even with 2-year treatment duration) due to method of action, so biologically plausible that there will be small/modest number of long-term survivors following treatment.* *- Patients with urothelial cancer have significant comorbidities, many of which are as a consequence of smoking tobacco for many years. Median age 70 years in CDF use of pembrolizumab in indication, hence number of 10-year survivors with pembrolizumab will be small though significantly greater than with standard chemotherapy.* *- Log-logistic chosen by company and ERG, fits in with biological plausibility.*
Technical team judgement after engagement	Very low proportion (<5%) of survivors at 10 years biologically plausible. Log curves (log-logistic or log-normal), generalised gamma and Weibull curves for extrapolation of OS should be considered.

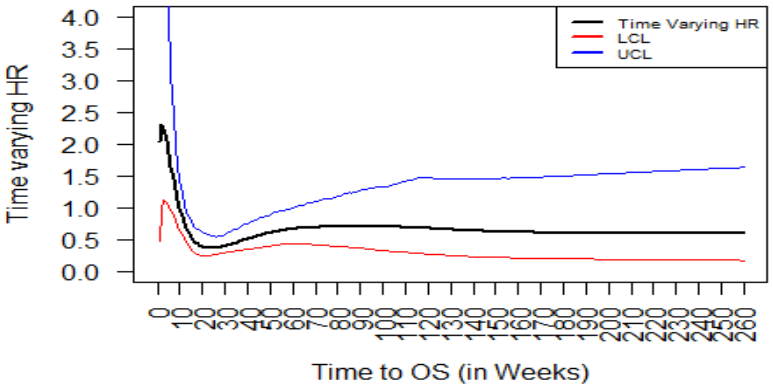
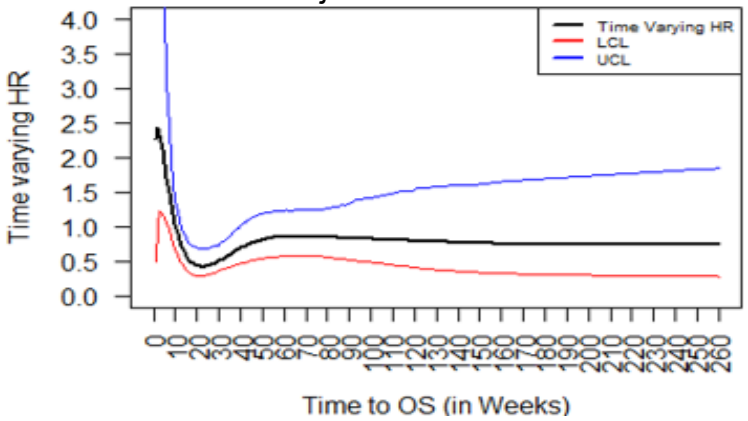
Issue 4 – Treatment effect duration

Questions for engagement	9. Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate? 10. Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?
Background/description of issue	**TA519:** In the original appraisal, the company assumed a lifetime treatment effect - in its base case, it assumed that pembrolizumab remained effective irrespective of time off treatment or implementation of a stopping rule (a 2-year stopping rule was implemented in KEYNOTE-045 as well as in the economic model). The company presented scenarios with different treatment effect durations. The committee was aware that the duration of treatment effect after implementation of a stopping rule is an area of uncertainty for new immunotherapies, but concluded that a lifetime continued treatment effect was implausible. **CDF review:** The additional data collected from KEYNOTE-045 since the entry of pembrolizumab into the CDF for this indication was considered as part of the CDF review, in an attempt to reduce uncertainty around the duration of treatment effect. Since TA519, subsequent data and publications on the treatment effect of immunotherapies might have become available, and could possibly have been used in the CDF review to validate some of the findings around treatment effect. The ToE for the review indicated the committee's preference from TA519 to cap the benefit of pembrolizumab at 3 years or 5 years (from the start of treatment), which was consistent with other appraisals of immunotherapies. The **company** selected a 5-year duration of treatment effect in its base case, supporting this choice with data from another pembrolizumab trial, KEYNOTE-001. That trial explored the use of pembrolizumab in non-small cell lung cancer (patients treated for ≥2 years continued to respond with 5-year survival at 75%), and melanoma (5-year survival rates in advanced

	melanoma were 34%, with 73% of responses ongoing). The company provided scenario analyses with 3-year and 10-year treatment effect. The **ERG** had several concerns with considering KEYNOTE-001 as evidence for treatment effect duration: • KEYNOTE-001 and KEYNOTE-045 study different types of cancer, so it may not be appropriate to make generalisations between them. • There was no limit on length of treatment with pembrolizumab for many patients in KEYNOTE-001, and under certain criteria patients could begin a second course of treatment; in contrast, KEYNOTE-045 restricted patients to 2 years of treatment. • There was no comparator in KEYNOTE-001, so it was not possible to know the relative treatment effect of pembrolizumab compared to other interventions. The ERG suggested that data on the duration of treatment response and number of responders from KEYNOTE-045 could have helped inform the decision about duration of treatment effect. This was not presented by the company for the data cut in their submission, although related data had been published from an earlier data cut (October 2017) in Fradet et al. (2019). This showed a maximum observed response of 2.5 years for pembrolizumab, compared to 2.49 years for the control arm (full trial SoC, i.e. included vinflunine). Pembrolizumab is most effective at 20-30 weeks (hazard ratios of 0.39 with adjustment for treatment switching, and 0.43 without), then the hazard ratio increases and plateaus. In analysis with adjustment for switching, the upper 95% confidence interval crossed 1 at around 63 weeks, suggesting there was no significant difference between the arms from this point. The ERG indicated this may have been partially due to the small number of patients remaining at risk, so this wasn't strong evidence of a loss of effect. The ERG looked at the data without the adjustment (with higher patient numbers), and found the upper 95% confidence interval crossed 1 earlier, at 39 weeks. The ERG suggested there was not enough evidence to tell if waning continued, or if treatment effect continued beyond 2 years. This was due to the small number of patients, and lack of survival events in the UK SoC arm. The ERG requested and carried out additional analyses to investigate treatment effect duration: • The company provided analysis with a flexible time varying hazard ratio (as trial results showed that the proportional hazards assumption was violated). In this analysis, the company used OS data with 2-stage treatment switching adjustment (see Issue 2 – Treatment switching), which affected the length of follow-up of UK SoC patients. The acceleration factor reduced the number of patients at risk of an event after 2 years on the UK SoC

	arm. The ERG indicated that, even without the adjustment, it was likely that there wouldn't be enough data to enable a conclusion on treatment effect beyond 2 years. • The company performed analyses varying the knot locations in the spline models. The ERG recreated patient-level data and fitted its own spline models to this. This indicated the same possible waning of treatment effect observed in the KEYNOTE-045 follow-up. The ERG used a 3-year treatment effect duration in their base case. Due to uncertainty around the duration of treatment effect of pembrolizumab in this indication, and no meaningful data available from the 2-stage adjustment beyond 2 years, the ERG carried out scenario analysis for a 2-year treatment effect duration. It also performed scenario analysis for 5-year and 10-year effect durations. The shortest of all treatment effect duration scenarios presented (a 3-year cap on treatment effect after stopping treatment, as opposed to a 5-year cap on treatment effect after stopping duration, or a lifetime treatment effect) was considered appropriate by a committee for a different immunotherapy in the indication (atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy, TA525).
Why this issue is important	The ongoing treatment effect influences the QALYs and thus the ICER. A 3-year treatment effect raises the ICER by £4,847 above the company's base case ICER. Starting from the company's base case (£47,123 with a 5-year effect duration), the resulting ICERs are £59,288 and £44,173 for 2-year and 10-year effect durations, respectively.
Technical team preliminary judgement and rationale	The technical team considers that there is uncertainty about the duration of pembrolizumab's relative treatment effect. The committee considered both 3-year and 5-year durations to be plausible in the original appraisal, but the available evidence from the later data cut does not strongly support a 5-year treatment effect duration. There is some publicly available evidence from a previous data cut to suggest the treatment effect duration for pembrolizumab in this indication could be less than 3 years, so it may be appropriate to consider the possibility of a treatment effect between 2 and 3 years. However, the technical team recognises that there is some evidence to suggest a 5-year treatment effect for pembrolizumab in other cancer types. The technical team considers a 3-year treatment effect duration to be the most plausible scenario it has seen. The technical team cannot conclude whether a 5-year treatment effect is plausible based on the evidence.

Summary of comments	Comments received from company: *- 5-year duration of treatment effect most appropriate. With additional 2.3-years of follow-up data (median 40.9 months, range 36.6-48.9 months*, presented at ESMO September 2019), HR decreases, suggesting sustained treatment effect of pembrolizumab. Trend observed regardless of whether comparison is made between pembrolizumab and UK SoC comparator arm or full KEYNOTE-045 comparator arm (i.e. including vinflunine), and regardless of whether comparison is made with adjusted or unadjusted data (i.e. ITT approach) in the control arm.* *HRs from September 2016 and November 2018 data-cuts, including adjusted and unadjusted analyses (provided by company in technical engagement response)*:* [redacted] *Extrapolated OS curves at 2,3 and 5-year treatment cap:*  *48.9 months is correct value – [redacted] confirmed as typographical error by company *- With 2-year or 3-year duration of treatment effect for pembrolizumab, extrapolation in pembrolizumab arm does not fit well to observed KM data from Nov 2018 data-cut; both projections underestimate OS KM curve and treatment effect of pembrolizumab. Assumption of 2-year or 3-year treatment effect cap inappropriate, as any longer-term benefit experienced by patients treated with pembrolizumab is not taken into consideration.* *- 5-year duration of treatment effect for pembrolizumab supported by time varying HR analyses of pembrolizumab vs. 2-stage adjusted UK SoC. Mean HR comparing pembrolizumab vs UK SoC continually <1 after week 8, reaches plateau of 0.62 from week 170. Clinical expert confirmed plateau in HR after week 170 (~3 years) is consistent with their clinical*

	experience in this patient population, where those who are relapse-free after 2-3 years can expect long-term survival and more favourable outcomes. HR analysis without adjusting for PD1/PD-L1 subsequent therapy use in the UK SoC arm shows consistency with adjusted data as a plateau is reached with HR continuously <1. *Time varying HR for pembrolizumab vs. 2-stage adjusted UK SoC with 95% CI:*  *Time-varying HR for pembrolizumab vs. unadjusted UK SoC with 95% CI:*  *- Evidence of a 5-year treatment duration being accepted for IO therapy in the patient population comes from NICE appraisal TA525 (Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) and NICE appraisal TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer). In both appraisals (evaluated by committee D), a 3-year treatment effect after stopping treatment was considered appropriate by the committee. As stated in the technical report for this CDF review, 'the committee was aware that the duration of treatment effect after the implementation of a stopping rule is an area of uncertainty for new immunotherapies'. A 2-year stopping rule is implemented in KEYNOTE-045 and in the economic model; therefore, MSD's preferred 5-year cap on treatment effect (from the start of treatment), as reflected in our base case, is equivalent to a 3-year treatment cap after stopping treatment; consistent with TA525 and TA584.* *- Only available robust evidence of long-term treatment effect of pembrolizumab in the indication are results from Nov 2018 KEYNOTE-045 data-cut. Have provided supplementary data on duration of response, objective response rate ORR and follow-up duration based on this data-cut, as further supportive evidence of a long-term, durable response associated with pembrolizumab therapy.* *- Median DOR for responders was 29.7 months in pembrolizumab arm vs 4.4 months in control arm. 36-month OS rate is 20.7% in pembrolizumab arm vs 11.0 % in control arm, and 36-month DOR rate is 44% in pembrolizumab arm, all of which*

are meaningful (based on KM data). Greater proportion of responses lasted ≥24 months (56.8% vs 28.3%, based on KM data); median survival follow-up for responders was 39.6 months for pembrolizumab and 17.7 months for control. ORR was higher with pembrolizumab vs control (21.1% vs 11.0%). Many responses in the pembrolizumab arm continued beyond 150 weeks (~3 years), and with further follow-up (i.e. beyond 30 Nov 2018) clinicians recognised it is likely that some of these responses would be noted to go on even further.

Summary of time to response and response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response - All Subjects (ITT Population) – Nov 2018 data-cut:

	Control (N=272)	Pembrolizumab (N=270)
Number of Subjects with Response†	30	57
Time to Response† (months)		
Mean (SD)	2.4 (0.8)	2.6 (1.1)
Median (Range)	2.1 (1.7-4.9)	2.1 (1.4-6.3)
Response Duration‡ (months)		
Median (Range)§	4.4 (1.4+ - 42.8+)	29.7 (1.6+ - 42.7+)
Number of Subjects with Response ≥ 6 Months (%)‡	8 (47)	46 (84)
Number of Subjects with Response ≥ 12 Months (%)‡	5 (35)	35 (68)

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

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

§ *"+" indicates the response duration is censored.*

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cut-off Date: 30NOV2018

Summary of follow-up duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed CR or PR: All subjects (ITT Population) – Nov 2018 data-cut:

	Control (N=30)	Pembrolizumab (N=57)	Total (N=87)
Follow-up duration(months)†			
Median (Range)	17.7(7.3-45.8)	39.6(11.1-46.2)	38(7.3-46.2)
Mean (SD)	23.3(14.4)	35.3(10)	31.1(12.9)

† *Follow-up duration is defined as the time from randomization to the date of death or the database cut-off date if the patient was still alive.*

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cut-off Date: 30NOV2018

Summary of Best Overall Response Based on RECIST 1.1 per Central Radiology Assessment - All Subjects (ITT population):

Response Evaluation		Control (N=272)			Pembrolizumab (N=270)	
	n	%	95% CI†	n	%	95% CI†
Complete Response (CR)	8	2.9	(1.3, 5.7)	26	9.6	(6.4, 13.8)
Partial Response (PR)	22	8.1	(5.1, 12.0)	31	11.5	(7.9, 15.9)
Objective Response (CR+PR)	**30**	**11.0**	**(7.6, 15.4)**	**57**	**21.1**	**(16.4, 26.5)**
Stable Disease(SD)	92	33.8	(28.2, 39.8)	47	17.4	(13.1, 22.5)
Disease Control (CR+PR+SD)	**122**	**44.9**	**(38.8, 51.0)**	**104**	**38.5**	**(32.7, 44.6)**
Progressive Disease(PD)	90	33.1	(27.5, 39.0)	131	48.5	(42.4, 54.7)
Non-evaluable (NE)	9	3.3	(1.5, 6.2)	4	1.5	(0.4, 3.7)
No Assessment	51	18.8	(14.3, 23.9)	31	11.5	(7.9, 15.9)

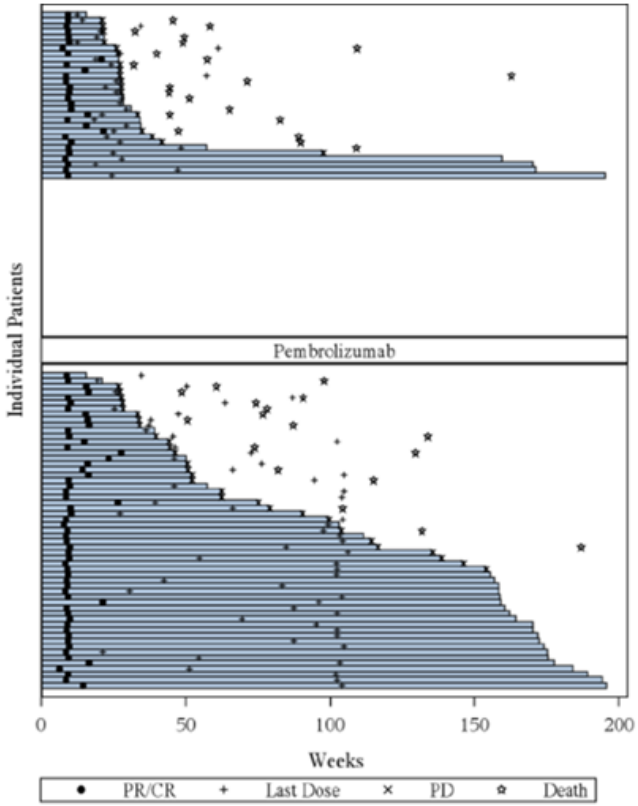
Confirmed responses are included.

† *Based on binomial exact confidence interval method.*

Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.

No Assessment: subject had no post-baseline imaging.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cutoff Date: 30NOV2018

	Plot of time to response and time to progression based on RECIST 1.1 per Central Radiology Assessment (ITT):  *- Fradet et al. examined OS by best overall response (Poster ASCO Chicago 2018), showed that patients who experienced a complete or partial response when treated with pembrolizumab had significantly longer OS (HR = 0.14 (95% CI 0.06 to 0.33, p<0.00001) and PFS (HR=0.27, 95% CI 0.14 to 0.51, p<0.0001) compared to chemotherapy. Similar results not seen in patients experiencing stable or progressive disease, suggesting that patients who respond to immunotherapy do experience significantly longer survival, as also confirmed by the clinical expert consulted.*

	- Data supporting long-term survival benefit associated with pembrolizumab available from studies across the pembrolizumab clinical study program. Despite being based on different tumour types, the evidence from pembrolizumab clinical studies clearly add to the body of evidence and provide support for the durable long-term treatment effect associated with pembrolizumab: • *KEYNOTE-001:* *– NSCLC (previously-treated), median follow-up 60.6 months, estimated 5-year OS 15.5% (25% in those with PD-L1 tumour proportion score of ≥50%)* *– Melanoma (naïve and previously-treated), median follow-up 55 months, estimated 5-year OS 34% in all patients, median response duration not reached, longest response still ongoing at 66 months. 24-month disease-free survival of 90% seen in patients who discontinued pembrolizumab after achieving a complete response.* • *KEYNOTE-006 (ipilimumab-naive stage III or IV melanoma):* *– Similarities with study design of KEYNOTE-045 - patients treated with pembrolizumab for maximum duration of 2 years of pembrolizumab before entering follow-up.* *– Median follow-up 57.7 months in surviving patients, median OS 32.7 months, 5-year OS 38.7%, supporting an ongoing durable response.* *– Patients with complete response had a 24-month PFS after stopping treatment of 85.4%.* • *KEYNOTE-024 (NSCLC)* *– Median follow-up 25.2 months, median OS 30.0 months, OS HR=0.63 compared to chemotherapy. When adjusting results for switching from chemotherapy arm to pembrolizumab (82 patients), HR was 0.49.* ERG's critique of company's comments: *Summary:* *- Majority of information provided by company unrelated to estimation of a relative benefit of pembrolizumab to UK SoC beyond 3 years.* *- Maximum follow-up from KEYNOTE-045 is 4 years, but only 1 death occurs in UK SoC beyond 3 years in the unadjusted (ITT) arm, with no events occurring after this in 2-stage adjusted analysis. Estimation of relative treatment effect of pembrolizumab compared to UK SoC not possible beyond this point. Maintain preference for a 3-year effect duration over a 5-year duration.* *Other ERG comments:*

	- Improved hazard ratio with extended follow-up likely explained by greater data completeness. *- By comparing pembrolizumab OS extrapolation to observed data, company disregards impact that curve choice may have on such an assessment. Affects initial pembrolizumab fit and estimate of UK SoC hazard rate, which is reverted to after 2/3/5 years. Despite this, ERG acknowledges that 2-year effect duration applied to log-logistic appears to not fit well to observed data. However, 3-year duration better fit, only deviates from observed data in tail.* *- Data available does not allow for meaningful hazard ratio to be calculated beyond 2 years of trial follow-up for 2-stage adjusted UK SoC population. Unclear how company interprets this analysis as support for 5-year treatment effect.* *- Relevance of TA584 unclear-different treatment, different disease. TA525 for same indication so more relevant, but assumption that 3-year post-stopping-treatment duration effect equivalent to 5-year stopping rule likely incorrect.* *- Trials in other indications brought up as supporting evidence lack relevance/transferability/do not provide support of sustained effect relative to comparator.* *- KN-045 – Agree evidence of sustained response of pembrolizumab, but same is true for those who respond on UK SoC. No evidence suggesting hazard rate beyond 3 years for long-term responders is different across treatment arms. Data suggests long-term responders in both arms experience similar outcomes.* <u>Comments received from professional groups:</u> *- Impact of stopping immunotherapy at 2 years unknown in any disease type. Follow up of KN-045 too immature to estimate whether this will result in any drop off of effect (very likely many patients will receive further immunotherapy on progression after stopping at 2 years, so even these data will be unreliable). Our experts believe the reasonable view is that there will be some patients who continue to benefit at 5 years, but definitely not all. Median duration of response on pembrolizumab in KN-045 is 29.7 months; it is clear that effects of treatment on disease control are less than permanent for most responders.* *Given that we now had data at 3 years, this seems a reasonable duration of treatment effect. ESMO poster could be used as evidence of duration of treatment effect.* <u>Comments received from patient organisations:</u> *- Our aim would be to make the treatment available to patients to achieve best OS and PFS, for the longest duration, irrespective of cost.* <u>Comments received from NHS commissioning expert:</u> *- Definition very important, NHS E&I assumes that 3-year treatment effect refers to long-term effect following 2 years of treatment and 1 year of follow-up (2+1). 5-year treatment effect duration portrayed as 2+3. Very relevant issue given*

	maximum 2-year treatment duration that NHS E&I would commission and biological plausibility of a treatment effect (recruitment of the immune system) enduring at least for a time after treatment has stopped in responding patients. *-There are long-term (5-year) data for immunotherapy in melanoma and NSCLC which show continued long-term benefit. Use of this to justify 5-year duration of treatment effect (2+3) has to be cautious in view of which parallel is chosen in terms of which other cancer. Melanoma and NSCLC are completely different diseases when compared with urothelial cancer. Pembrolizumab does not work in every disease and has failed in trials in several indications. Melanoma studies and KN-001 studies in lung cancer quoted by company used a policy of open treatment duration with pembrolizumab rather than 2-year maximum treatment duration subsequently employed in most pembrolizumab trials. Company still making case for maximum of 2 years use of pembrolizumab in this indication.* *- Follow-up data now reasonably robust to 3 years (where rates of overall survival are about 20% with pembrolizumab, 12% with chemotherapy after adjustment for cross over and 8% ITT and without any such adjustment) plus there is a fixed 2-year treatment duration policy plus relapses still occur in those patients who do well and discontinue treatment at 2 years, so it is reasonable for ERG and committee to be currently cautious and assume a duration of treatment effect more in line with 3 (2+1) years than 5 (2+3) years.*
Technical team judgement after engagement	3-year treatment effect (2+1, which represents 2 years of treatment and 1 year of follow-up) appears most plausible, but committee may wish to consider 5-year effect also, as well as consider the conservative 2-year scenario analysis.

Issue 5 – PD-L1 expression sub-groups

Questions for engagement	11. Does pembrolizumab have a different effect in different PD-L1 sub-groups? 12. What are the ICERs for each PD-L1 expression sub-group?
Background/description of issue	**TA519:** In the original appraisal, pembrolizumab appeared to be more effective for people with urothelial carcinoma expressing the PD-L1 protein than for people who do not express PD-L1. However, the cost-effectiveness results for this group were not reliable, as the ICERs behaved counterintuitively compared to clinical outcomes for the sub-groups. The committee judged that the cost-effectiveness results for the subgroups were inconsistent with the evidence seen in KEYNOTE-045, and did not find them plausible. Therefore, the committee did not consider the company's cost-effectiveness results to be reliable for decision-making and concluded that it could only make a recommendation for the whole population. **CDF review:** The technical team consider that it is relevant to reconsider the PD-L1 sub-groups in light of the updated evidence from the more recent KEYNOTE-045 data cut. It is aware that a recent appraisal in the disease area made a recommendation based on PD-L1 expression level (NICE TA522: Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable). The marketing authorisation for pembrolizumab in the indication does not have a PD-L1 expression requirement. The updated data showed that pembrolizumab, when compared to UK SoC (excluding vinflunine), reduced the risk of death by 26% in the entire population, by 42% in patients with PD-L1 Combined Positive Score (CPS)≥1%, and by 49% in patients strongly positive for PD-L1, CPS≥10%. This suggested that pembrolizumab had a better effect in patients with high CPS.
Why this issue is important	There could be different outcomes and resulting ICERs for pembrolizumab in PD-L1 expression sub-groups, so the intervention may be more or less cost-effective in these sub-groups compared to the whole population.
Technical team preliminary judgement and rationale	The technical team would like to see cost-effectiveness analyses based on PD-L1 expression sub-groups, for both the ITT and 2-stage adjusted approaches. The technical team consider that it is relevant to reconsider the PD-L1 sub-groups in light of the updated evidence from the more recent KEYNOTE-045 data cut. It is aware that the European Medicines Agency revised the marketing authorisation for pembrolizumab for untreated locally advanced or metastatic urothelial cancer when

<table>
<tr><td></td><td>cisplatin is unsuitable, to restrict patient eligibility to people with high levels of PD-L1. Although the regulator stated that there were no changes to how pembrolizumab should be used in patients with urothelial cancer who have had chemotherapy or in patients with other cancers for which this medicine is approved, the technical team considers that the role of PD-L1 expression remains unclear and that it would be useful to consider subgroups based on PD-L1 separately because there may be variations between them in their potential to benefit from treatment (see section 5.10 of NICE's Guide to the methods of technology appraisal). The scope for this review follows that of the original appraisal and allows for consideration of subgroups based on cancer histology and biological markers.</td></tr>
<tr><td>Summary of comments</td><td>Comments received from company:
- Pembrolizumab does not have different effect in different PD-L1 sub-groups - as supported by clinical expert validation, MSD's position is that PD-L1 acts only as prognostic factor rather than predictive biomarker in indication. Believe same conclusions on PD-L1 subgroups as reached by the committee in TA519 still hold, that "cost-effectiveness analyses based on PD-L1 expression are not useful for decision-making". At that time, cost-effectiveness results from model produced ICERs counterintuitive to clinical evidence base. Situation remains unchanged based on the latest data-cut. Do not consider new data to offer additional evidence to justify decision making based on PD-L1 subgroups.
- Have provided results as requested of analyses for PD-L1 sub-groups (CPS≥1 and CPS≥10) based on unadjusted (ITT) population. Pembrolizumab is cost-effective in both CPS≥1 and CPS≥10 PD-L1 subgroups, producing similar results.
ICER results for PD-L1 subgroup (CPS≥1) based on unadjusted (ITT) population:
<table>
<tr><th>Pembrolizumab PD-L1 sub-group</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>UK SoC</td><td>[redacted]</td><td>1.30</td><td>0.88</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CPS≥1</td><td></td><td>2.41</td><td>1.67</td><td>£35,523</td><td>1.11</td><td>0.78</td><td>£45,370</td></tr>
</table>
ICER results for PD-L1 subgroup (CPS≥10) based on unadjusted (ITT) population:
<table>
<tr><th>Pembrolizumab PD-L1 sub-group</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>UK SoC</td><td>[redacted]</td><td>1.42</td><td>0.94</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CPS≥10</td><td></td><td>2.40</td><td>1.64</td><td>£32,617</td><td>0.99</td><td>0.70</td><td>£46,485</td></tr>
</table>
- Could not provide analysis for PD-L1 sub-groups incorporating 2-stage adjustment for treatment switching, as too few subjects received subsequent anti-PD-L/PD-L1 therapy in PD-L1 sub-groups (CPS≥1%: 9 subjects, CPS≥10%: 7 subjects), for model to run properly and be robust (minimum of 10 subjects who received subsequent anti-PD1/PD-L1 therapy following documented disease progression used as a cut-off, to determine whether 2-stage models would be run for a given</td></tr>
</table>

	population (approach applied for previous data-cuts and across several pembrolizumab indications). Inappropriate to attempt to run 2-stage adjusted analyses based on PD-L1 sub-groups as likely to produced biased unreliable results, not useful to inform economic model or decision making. ERG's critique of company's comments: *- Unable to draw clear conclusion based on existing evidence from KEYNOTE-045. Hazard ratios CPS≥1% HR= 0.58 [95% CI: 0.40, 0.84] and CPS ≥10% HR= 0.51 [95% CI: 0.32, 0.81]), both lower than for ITT population (HR= 0.74 [95% CI: 0.59, 0.94]).* *- Not aware that company have presented any formal statistical test of interactive effect of pembrolizumab with PD-L1 subgroups using most recent data cut.* *- Meta-analysis by Shen et al. suggests PD-1/L1 inhibitors may be more effective in patients with PD-L1 expression across different cancer types. Meta-analysis by Ghate et al. of urothelial cancer studies suggests PD-L1 expression may be prognostic factor.* Comments received from professional groups: *- Yes* (pembrolizumab has a different effect in different PD-L1 sub-groups*), but not in this indication/stage. Appears to be the case regardless of choice of drug or test in post-platinum setting. PD-L1 status does appear weakly prognostic however and may impact ICER.* Comments received from patient organisations: *- It would seem so* (that pembrolizumab has a different effect in different PD-L1 sub-groups)*; "The updated data showed that pembrolizumab, when compared to UK SoC (excluding vinflunine), reduced the risk of death by 26% in the entire population, by 42% in patients with PD-L1 Combined Positive Score (CPS)≥1%, and by 49% in patients strongly positive for PD-L1, CPS≥10%."* Comments received from NHS commissioning expert: *- Plausible for benefit to be greater in patients whose tumours have higher PD-L1 expression. EMA limited use of atezolizumab and pembrolizumab in 1st line urothelial patients to only those with higher levels of PD-L1 expression. Difficulty in this set of KN-045 data is that the numbers in known PD-L1 subgroups modest and size of comparator group has already been significantly reduced due to exclusion of vinflunine patients. Opportunity for robust decision making is therefore limited.*
Technical team judgement after engagement	Committee may wish to consider if PD-L1 sub-group results are appropriate and reliable for decision-making in light of updated data.

5. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab

Alteration	Technical team rationale	ICER	Change from company base case ICER (which had 2-stage adjustment)
Scenario 1: 2-stage adjustment for treatment switching			
1. Company base case (2-stage adjustment for treatment switching)	**–**	**£47,123**	**–**
a) Weibull distribution to extrapolate PFS after 21 weeks	Technical team agreed with ERG's amendments. See page 21 of ERG report.	£48,518	+£1,395
b) 3-year treatment effect duration	Technical team agreed with ERG's 3-year duration of treatment effect. See page 26 of ERG report.	£51,970	+£4,847
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£53,678**	**+£6,555**
Scenario 2: no adjustment for treatment switching (ITT approach)			
2. Company base case, but without adjustment for treatment switching	Technical team considered ITT analysis without adjustment for treatment switching to be plausible.	**£56,422**	**+£9,299**
a) Weibull distribution to extrapolate PFS after 21 weeks	Technical team agreed with ERG's amendments. See page 21 of ERG report.	£58,850	+£11,727
b) 3-year treatment effect duration	Technical team agreed with ERG's 3-year duration of treatment effect. See page 26 of ERG report.	£62,400	+£15,277
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£65,469**	**+£18,346**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature evidence base	Despite 22 months of additional KEYNOTE-045 data, there is still a high level of uncertainty in long-term survival outcomes for this indication, both for pembrolizumab and immunotherapies in general. There is no long-term overall data available for immunotherapies in this indication. The proportion of patients in the pembrolizumab arm who are still alive after 10 years is unknown.	Lack of long-term data increases uncertainty in the decision.
Limited real-world data for use of the drug in NHS England	The Systemic Anti-Cancer Therapy (SACT) data collection period was limited (9 months), which was too short to collect meaningful data on overall survival and treatment duration.	Limited UK-specific data for OS presents challenges for comparisons between trial outcome and real-world outcomes. The impact of this on the ICER is unknown.
Best supportive care not included as a comparator	Best supportive care was included as a comparator in both the scope and the ToE. However, the ToE also indicated the ERG base case model from the original appraisal should be used. This was based on the company's submitted model for TA519, which did not include best supportive care as a comparator.	Outcomes and costs of best supportive care not illustrated, therefore not reflected in the ICER.

Table 3: Other issues for information

<table>
<tr><th>Issue</th><th>Comments</th></tr>
<tr><td>Stopping rule</td><td>The technology is subject to a 2-year stopping rule in this indication, as outlined in the recommendation in the original appraisal (TA519).</td></tr>
<tr><td>Time-on-treatment</td><td>For time-on-treatment, the company fitted separate parametric curves to the data for each arm of KEYNOTE-045. The approach was consistent with TA519.
The company used AIC and BIC statistics to select the best-fitting curve. It reported that generalised gamma had the lowest scores for both arms, but that it failed to converge for the pembrolizumab arm, so was only used for the UK SoC arm. As a result, the company chose the Weibull for the pembrolizumab arm extrapolation, as it was the second-best fit to the data.
The ERG had minor concerns that curves of different forms were used. However, because switching both arms to Weibull had a negligible impact on the analysis, the ERG accepted the company's assumptions around time-on-treatment.</td></tr>
<tr><td>Data from Public Health England</td><td>The SACT data was collected over 9 months for patients receiving the technology via the CDF. Patient baseline characteristics were similar to those in the KEYNOTE-045 trial. Details of patient status are outlined in Table B.
<u>Table B: SACT versus clinical trial data</u>
<table><tr><th></th><th>Public Health England report (SACT) (overall figures reported at end of 9-month data collection period) n=180</th></tr><tr><td>Still on treatment</td><td>43% (78)</td></tr><tr><td>Died</td><td>18% (32)</td></tr><tr><td>Disease progression with treatment stopped</td><td>31% (56)</td></tr></table>The ERG had no concerns over this data collected via the CDF.</td></tr>
<tr><td>Implementation of model</td><td>There were no changes to the model structure, population, intervention and comparators, perspective, time horizon or discounting in the model submitted by the company, which was</td></tr>
</table>

Issue	Comments
	accepted previously by the committee. The company followed the committee's preferred assumptions in the ToE, but made two main deviations: • Log-normal curve for extrapolation of PFS (see Issue 1 – Choice of extrapolation for progression-free survival) • Preferred 5-year duration of treatment effect, whereas in TA519, the committee suggested 3-year and 5-year possible durations of treatment effect (see Issue 4 – Treatment effect duration) In its critique, the ERG found some minor errors in the model, which the company corrected as part of their response to clarification. These changes did not affect the ICER. Both the ERG's report and the technical report were based on the corrected model.
Utilities and UK SoC	Utility estimates were updated from the original company submission, which used utility values based on time to death. They were in line with the ERG and committee preferred approach of using utility values based on progression state with current age-related disutility applied (consistent with the ToE). Similarly, to follow committee and ERG preferences, utility estimates excluded vinflunine data (as vinflunine is not used in the UK) and were pooled across treatment arms.
Resource use and costs	In line with the ToE, resource use and cost inputs used in the cost-effectiveness model were unchanged from the original appraisal, except for the inclusion of a new patient access scheme (PAS) discount for the technology.
Dosing of pembrolizumab	Pembrolizumab for this indication was recommended for use in the CDF based on a dosing of schedule of 200 mg every 3 weeks, presented in the original appraisal. Since then, the European Medicines Agency adopted a positive opinion for a new extended dosing schedule for pembrolizumab for all the monotherapy indications in the European Union, including the indication in this CDF review (Table 13 in the company submission). The company presented a scenario analysis with 100% of patients who receive pembrolizumab being treated with this dosing schedule (400 mg every 6 weeks), as part of their submission for this CDF review. The base case was 100% of the patients who receive pembrolizumab receiving 100 mg every 3 weeks (to match the original appraisal). The

Issue	Comments
	change in the dosing schedule led to a change in the ICER of +£529. The committee will take into account that this less frequent dosing has a small, upward effect on the ICER.
Innovation	Some of the consultees in the original appraisal considered the technology to be innovative, highlighting the lack of new treatment options for urothelial cancer for many years, and lack of improvement in outcomes, when compared to improvements in outcomes seen for other cancer types over the same timeframe. However, in the original appraisal, the company did not highlight any additional benefits that had not been captured in the QALY calculations.
End-of-life	In the original appraisal, the committee decided that pembrolizumab for this indication met the criteria for end-of-life treatment. This is because: • Life expectancy for people with locally advanced or metastatic urothelial carcinoma who have already had platinum-based therapy is less than 24 months when treated with UK SoC AND • Pembrolizumab extends life for this group of people, by more than 3 months compared to UK SoC The updated data from KEYNOTE-045 indicated that both these criteria still held.
Equality considerations	No equality issues were identified in the original appraisal. No new issues have been raised in this CDF review process.

Authors

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Lead team member

Malcolm Oswald

Lead team member

