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Pembrolizumab for previously treated advanced or metastatic urothelial cancer: An Evidence Review Group perspective of a NICE Single Technology Appraisal

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Short running header: P**embrolizumab for previously treated advanced or metastatic urothelial cancer: an ERG perspective**

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Abstract

Pembrolizumab is an intravenously administered monoclonal antibody licensed for locally advanced or metastatic urothelial carcinoma after platinum containing chemotherapy. This summary presents the perspective of Warwick Evidence, the Evidence Review Group (ERG) appointed by the National Institute of Health and Care Excellence (NICE) for the single technology appraisal of pembrolizumab for this indication. Pembrolizumab is manufactured by Merck, Sharp and Dohme (MSD).

The major source of clinical effectiveness was the KEYNOTE-045 trial, where 542 patients received either pembrolizumab or clinician's choice of docetaxel, paclitaxel or vinflunine as a second-line treatment. No indirect treatment comparison was performed. The clinical effectiveness was assessed using hazard ratios for overall survival (OS) and progression-free survival (PFS) of the intention-to-treat (ITT) population, together with the subpopulations positive for programmed cell death 1 ligand 1 (PD-L1) expression (combined positive score (CPS) ≥1%) and strongly positive for PD-L1 expression (CPS≥10%). In the ITT population, OS improved with pembrolizumab (HR 0.73, 95% CI: 0.59, 0.91) while PFS outcomes showed no difference (HR 0.98, 95% CI: 0.81, 1.19). Pembrolizumab demonstrated a better safety profile than its combined comparators, with fewer patients experiencing adverse events (60.9% vs 90.2%). Similar results were observed in populations expressing PD-L1.

MSD estimated the cost-effectiveness of pembrolizumab using a *de novo* partitioned survival model. The model had three health states: pre-progression, post-progression and death, where OS and PFS estimates excluded patients who received vinflunine. The largest uncertainty was over the selection of the parametric models used to extrapolate OS and PFS and the time-point when to begin their extrapolation. The company preferences for extrapolation were not well-supported and the ERG disagreed with their selection for OS. Utility values were also contentious, with the company preferring to use pooled time-to-death based utilities pooled across treatment arms, whilst the ERG preferred pooled progression based utilities. The company preferred to use data of patients receiving vinflunine when calculating the utility values, which the ERG disagreed with as this is not recommended treatment within the United Kingdom. The company assumed a lifetime treatment effect for their model, however, the lack of evidence made it difficult to confidently provide a realistic estimate of treatment effect duration. Various durations were explored (3, 5 and 10 years).

The first appraisal committee meeting concluded that pembrolizumab was not cost-effective largely due to uncertainty in the OS and PFS extrapolations. The company's second submission included an additional 4 months follow-up to survival data. The company in this new submission maintained their original assumptions in their base-case analysis, changing only the choice of parametric curve for PFS. This change resulted in the OS and PFS curves intersecting at 6 years in the pembrolizumab arm, at which point PFS identically followed OS. This resulted in no patients in the post-progression health

state beyond this time-point, and therefore, the majority of pembrolizumab's benefit came from pre-progression survival. Given the unclear PFS benefit, the ERG found this implausible and maintained their original base-case model assumptions. Considerable uncertainty remained over the specification of the extrapolations and the duration of treatment effect.

Based on a new-value proposition submitted by the company, the appraisal committee concluded that pembrolizumab had plausible potential to be cost-effective. Pembrolizumab was referred for funding through the Cancer Drugs Fund, so that further data could be collected with the aim of diminishing the outstanding uncertainties pertaining to its clinical effectiveness.

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Key points for decision makers:

- Pembrolizumab improved overall survival compared with the combined performance of vinflunine, docetaxel and paclitaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy as demonstrated in the KEYNOTE-045 clinical trial while no benefit was observed on progression-free survival.
- Pembrolizumab has a better safety profile compared with conventional cytotoxic chemotherapy.
- Considerable uncertainty remains over the long-term benefits of pembrolizumab, particularly the duration of treatment effect and the selection of parametric curve used for extrapolation.
- Pembrolizumab is potentially cost effective and is recommended for use within the Cancer Drugs Fund for patients with locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy only if pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression, and if the conditions in the managed access agreement for pembrolizumab have been followed.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing guidance on whether health technologies (such as drugs, medical devices or diagnostics) should be made available within the National Health Service (NHS) in England and Wales. The single technology appraisal (STA) process was specifically designed to appraise a single product for a single indication. The manufacturer of the health technology submits a report, which is critically reviewed by an independent evidence review group (ERG). The ERG produce their own report, which is considered by a NICE appraisal committee alongside the manufacturer's report and any other evidence available such as statements from clinical experts and other consultees. The appraisal committee is made up of members of academia, the NHS, patient organisations and pharmaceutical companies, and determines if the drug is clinically effective and cost-effective and whether it is recommended within NHS as part of routine care. After the committee meeting, an appraisal consultation document (ACD) is produced providing draft recommendations. Once recommendations are finalised a final appraisal determination (FAD) is produced, concluding the STA. A detailed description of the appraisal process can be found on the NICE website [1].

This article summarises the ERG (Warwick Evidence, University of Warwick) critique of Merck, Sharp and Dohme's (MSD) submission of pembrolizumab (Keytruda®) for patients with previously treated advanced or metastatic urothelial cancer. Feedback from the committee's decision making process are included along with a brief description of the NICE guidance that was developed [2].

2. ERG critique of the Decision Problem defined by the company

Urothelial cancer arises from the transitional cells, which stretch as the organ they are part of expands. These are largely found in the urinary system, with urothelial cancer including cancers of the bladder, renal pelvis, ureter and urethra. Bladder cancer is the most common of these, being among the ten most common cancers in the United Kingdom (UK), with over 10,000 cases diagnosed every year [3]. Urothelial cancer accounts for approximately 90% of bladder, renal pelvis, ureter and urethral cancers [4]. After age, smoking is the most significant risk factor of bladder cancer, with a 2-6 times increased associated risk [5]. Symptoms include haematuria (blood in urine), pain when passing urine and increased frequency of urination [6].

The staging of bladder cancer is performed using the Tumour-Node-Metastasis (TNM) classification, which combines information of tumour size, the involvement of lymph nodes and the presence of distant metastases into a single stage between 0 and IV [7]. Urothelial bladder cancer can be classed as muscle invasive or non-muscle invasive depending on whether the cancer has grown into the local

muscle layer. Approximately 15% of new cases are stage IV cancer [8], where prognosis is poor with five year overall survival (OS) rates of 9% for men and 11% for women [9].

Current NICE guidelines for the treatment of muscle invasive urothelial cancer include radical surgical resection such as cystectomy, radiotherapy or chemo-radiotherapy [10]. For patients with advanced or metastatic disease, first-line treatment is a platinum-based chemotherapy. After progression, second-line treatment for metastatic urothelial cancer is less clear. For those suitable for receiving an active treatment, options are retreatment with first-line platinum based chemotherapy or a taxane (paclitaxel or docetaxel). In 2013, vinflunine was not recommended by NICE for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy [11]. Patients who are ineligible for platinum chemotherapy may be offered best supportive care (BSC) to relieve pain and other symptoms.

In recent years, a novel class of immunotherapy treatments, such as pembrolizumab, nivolumab or atezolizumab, have shown great promise in cancer treatment. These treatments act as immune checkpoint inhibitors with the aim of boosting anti-tumour immunity rather than of directly targeting cancer cells or acting as traditional cytotoxic chemotherapies. Whilst the effect of cytotoxic chemotherapies is often observed soon after treatment administration, immunotherapies have a more delayed onset of action. This delayed reaction can partly explain why, when an immunotherapy is compared with a chemotherapy, the immunotherapy may initially appear inferior, particularly for progression free survival (PFS), but may become superior after a certain period of time has passed. This difference in mechanism of action can mean a traditional hazard ratio (HR) is not very informative.

Pembrolizumab blocks a protein called programmed cell death 1 (PD-1) which is found on T-cells. PD-1 interacts with its ligands (programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2)) which are often found on the surface of tumour cells. This interaction prevents the body from attacking its own cells. By disabling this protein, the immune system is then able to recognise cancer cells and attack them accordingly. Pembrolizumab is currently recommended in routine commissioning by NICE for the treatment of patients with PD-L1 positive non-small-cell lung cancer (NSCLC) who have received prior chemotherapy [12] and for patients with advanced melanoma after disease progression with ipilimumab [13]. It has also been recommended for inclusion in the Cancer Drugs Fund (CDF) for untreated metastatic NSCLC in adults with PD-L1 tumour proportion score of at least 50% [14].

The review by the ERG of the company submission for pembrolizumab began in February, 2017, which means the benefit/risk balance of pembrolizumab in this indication was not yet determined by the European regulatory authorities. However, on the 22nd of July 2017, the European Medicines Agency (EMA) extended the approval of pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy. This summary describes the clinical and cost-effectiveness review of pembrolizumab for treating locally advanced or metastatic urothelial cancer in adults who failed prior platinum-based regimen. A separate appraisal of pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable ID1209 is planned in 2018 (TA 10215) [15].

3. Submitted evidence and ERG critique of the company's original submission and outcome following first appraisal committee.

MSD submitted a report and an economic model containing clinical and cost-effectiveness information investigating the use pembrolizumab for patients with previously treated advanced or metastatic urothelial cancer.

3.1 Submitted clinical evidence and ERG critique

The company undertook a systematic review to determine the clinical effectiveness of pembrolizumab. The KEYNOTE-045 phase III randomized control trial (RCT) was the only study found. Hence, all clinical evidence presented by the company came from this trial, with the initial submission based on the second interim analysis (IA2) with median follow-up of 14.1 months (range 9.9 to 22.1 months) [16].

KEYNOTE-045 recruited 542 patients from 120 centres across 29 countries, with 272 allocated to pembrolizumab and 270 to investigators' treatment choice (docetaxel, paclitaxel or vinflunine) [16]. Prior to randomisation, all subjects were allocated to one of these three control treatments in case they were randomized to the control arm. Patients were stratified on four factors: Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs 2), liver metastases (presence vs absence), haemoglobin (≥ 10g/dL vs <10g/dL) and time from most recent chemotherapy (<90 days vs ≥ 90 days). There were no significant differences in baseline characteristics between the two arms.

Pembrolizumab was administered intravenously with a 200mg dose every 3 weeks. For the control arm dosages were based on patients' body surface areas and were 175mg/m^2, 75mg/m^2 and 320mg/m^2 every 3 weeks for paclitaxel, docetaxel and vinflunine respectively. Patients in the control arm were

eligible to switch to an anti PD-1 treatment, including pembrolizumab, following disease progression. Those in the intervention arm would remain on treatment until disease progression, unacceptable toxicity, physician's decision or 24 months. A total of 33 patients switched from the control arm with only 22 of these meeting the eligibility criteria for switching.

BSC was not considered among the clinical evidence, despite its inclusion in the final scope produced by NICE. The ERG felt BSC was still a relevant comparator, and that there was potential for patients ineligible for chemotherapy to benefit from pembrolizumab due to its better safety profile. However, there was a lack of data to enable a direct or indirect comparison of pembrolizumab to BSC.

Six co-primary endpoints were pre-specified by the company. These were OS and PFS in the intention-to-treat (ITT) population and two sub-populations of patients according to PD-L1 expression (those positive for PD-L1 expression defined as a combined positive score (CPS) ≥1%; those strongly positive defined as a CPS ≥10%) . OS was defined as time from randomisation until death from any cause. PFS was defined as the time until the date of first documentation of disease progression or death due to any cause, whichever occurred first, and was assessed by blinded independent central radiological review according to Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 [17]. If no events were reported, patients were censored at the date of the previous follow-up. Secondary endpoints included objective response rate (ORR), duration of response (DOR) and safety.

Pembrolizumab was associated with a statistically significant improvement in OS (HR for death 0.73, 95% CI [0.59, 0.91], p=0.002) under the ITT analysis. Median OS was 10.3 months for pembrolizumab and 7.4 months for the control arm. Three methods, which accounted for treatment switching (two-stage, rank preserving structural failure time (RPSFT) and inverse probability of censoring weighting (IPCW)), were investigated and all methods lowered the HR estimate(range: 0.68 to 0.70) [18].

No statistically significant difference was observed when examining PFS with a HR of 0.98 (95% CI [0.81, 1.19]), p=0.416. Median PFS was 2.1 months for pembrolizumab and 3.3 months for the control group. However, at 12 months PFS was 16.8% for pembrolizumab and 6.2% for control. Pembrolizumab had a significantly improved ORR of 21.1% compared with 11.4% for the control arm (p=0.0011) up to IA2. The median DOR was not reached in the pembrolizumab arm, compared with 4.3 months for the control arm.

Other primary investigations of subgroups based on tumour PD-L1 expression level found that the results were consistent with those of the ITT population. The benefit of pembrolizumab appeared to be even greater, with OS HR for CPS ≥1% of 0.61 (0.43, 0.86) and for CPS ≥10% of 0.57 (0.37,

0.88), however, the study was not powered to detect differences between the different subgroups. For the PD-L1 negative subgroup, the results were inconclusive with a HR of 0.89 (0.66, 1.20) leading the ERG to refrain from drawing conclusions based on PD-L1 status.

Incidence of adverse events (AEs) between the arms was similar (93.2% pembrolizumab vs 98.0% control) but in the pembrolizumab arm fewer patients experienced grade 3-5 drug related AEs (15.0% vs 49.4%), and fewer discontinued treatment due to drug related AEs (5.6% vs 11.0%). More patients in the pembrolizumab arm had pruritus (23.3% vs 5.5%), but generally AEs were balanced or more prevalent in the control arm. Similarly, the number of serious adverse events (SAEs) and the number of discontinuations due to SAEs between arms were comparable between arms, though less drug related SAEs were observed in the pembrolizumab arm (10.2% vs 22.4%).

The company submission also indicated that AEs of special interest (AEOSI) are immune mediated events and infusion related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab. There were 45 (16.9%) subjects in the pembrolizumab arm with 1 or more AEOSIs. The only AEOSI of grade 3, 4, or 5 severity that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2.3% of the patients), colitis (1.1%), and nephritis (0.8%).

The company attempted to present indirect and mixed treatment comparisons, but no network meta-analysis was undertaken owing to a disconnected network.

Overall, the quality of the systematic review was acceptable, and the ERG agreed a network meta-analysis was not suitable. The KEYNOTE 045-trial was of good quality but overall was at high-risk of bias as neither participants nor personnel were blinded. Blinding occurred only when disease progression status was assessed. Randomisation was acceptable, though stratification did not account for response to previous chemotherapy or any geographical factor such as study centre, as were used in a previous STA (TA272) [11].

The generalisability of the results to the UK population was unclear due to KEYNOTE-045 having only four (<1%) patients from the UK, meaning the vast majority of patients came from different countries with different healthcare systems, in addition to different environmental and lifestyle factors. Despite this, patients seemed broadly similar to those likely to receive pembrolizumab in the UK, with 13.8% from Western Europe, and 41% from Europe. The baseline characteristics were largely similar, though slightly fewer subjects in the pembrolizumab arm were in the PD-L1 ≥10% group (28.5% vs 33.8%) [16].

Additionally, the ERG believed that allowing investigators choice of three drugs within the control arm was not conventional and may introduce heterogeneity. The extent of the missingness of data was not always clear: the ERG found that in the reporting of ORR, 19% and 26% of the pembrolizumab and standard of care (SOC) arms, respectively appeared to be missing, which could bias results. The outcomes selected for the trial conformed to those identified by NICE in the decision problem; however, the selection of six primary outcomes was of concern, increasing the risk of a type 1 error. This was extended by further planned analyses of 17 subgroups, with a failure to account for multiplicity. In addition, whilst the company identified that the assumption of proportional hazards was not met between the treatment arms, they proceeded to present hazard ratios and associated p-values, without concern of their misrepresentation of the treatment profiles.

The assumptions of the considered methods to adjust for treatment switching (2-stage, RPSFT and IPCW) were not fulfilled in the trial, and their degree of improvement over the unadjusted analysis is unclear.

3.2 Submitted Cost Effectiveness Evidence and ERG critique

The company submission included a systematic review of the literature in order to identify cost-effectiveness studies that assessed pembrolizumab for patients with advanced or metastatic urothelial cancer. Even though the review was deemed satisfactory by the ERG, the review did not identify any relevant published studies. Hence, the company developed a *de novo* economic model which compared pembrolizumab with UK standard of care (UK-SOC) from an NHS viewpoint. The model used a starting age for patients of 65.5 years, was not separated by gender, had a lifetime horizon, a weekly cycle length and a half-cycle correction was incorporated The UK-SOC consisted of either paclitaxel or docetaxel since vinflunine is not recommended within the NHS. The model excluded patients who were randomised to the control arm and allocated vinflunine. However, patients allocated to vinflunine were included in the company base-case for the calculation of utility values and AE frequency. The model used a partitioned survival approach containing three health states: pre-progression, post-progression and death. The partitioned survival model fits parametric models to OS and PFS data for each arm of the KEYNOTE-045 trial. From these models the predicted proportion of patients in each of the three health states at each weekly cycle were estimated. All patients began in the pre-progression health state, and could either remain in this health state or transition to the post-progression or death health states. The economic model allowed the parametric curve to be fitted only to data occurring beyond a particular timepoint (e.g. 32 weeks), before which the Kaplan-Meier data were used to estimate the number of patients in each health state.

Various parametric models were fitted and their Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values compared to select the company's base-case model, with lower AIC/BIC suggesting a better fitting model. In the original submission, the company fitted a log-normal parametric model, with the 2-stage method to account for treatment switching, beginning at 40 weeks for OS. An exponential model was chosen for PFS, starting from 21 weeks. The parametric models were extrapolated so that the model extended for a 35-year time horizon.

Plausibility of the long-term OS predictions were also verified using Cancer Research UK (CRUK) data [19]. For both OS and PFS the economic model only allowed models of the same parametric type to be fitted to both treatment arms. Time on treatment was also modelled parametrically, however the treatment arms were able to be fitted with models of different parametric form to each other. The maximum treatment duration for pembrolizumab was two years, based on the design of the KEYNOTE-045 trial, and 18 weeks for UK-SOC. General population mortality was estimated from the latest UK life tables from the Office of National Statistics [20].

Drug costs were based on the December 2016 electronic market information tool [21], and the manufacturer's price for pembrolizumab. A confidential patient access scheme (PAS) was also included in the model. Administration costs were based on intravenous infusion in a hospital setting for both arms. Additional costs of subsequent therapies, AEs, resource use, monitoring and terminal care were also included and obtained from NHS reference costs [22, 23], the vinflunine NICE STA [11] and a study by Brown et al (2013) [24]. A discount rate of 3.5% per year was applied to both costs and utility values. All costs were valued at 2016 prices.

Utility values were obtained using the EQ-5D-3L questionnaire, and based on time-to-death utilities categorised into <30, 30-90, 90-180, 180-360 and ≥360 days. Quality-adjusted life years (QALYs) were adjusted for the effects of ageing and grade 3+ AEs, with the effects pooled for both treatment arms. The prevalence and disutility of AEs were obtained from the full trial population of KEYNOTE-045, which also included febrile neutropenia and grade 2 diarrhoea.

The ERG noticed that the initial model provided by the company allowed the maximum treatment duration of UK-SOC to reach 58 weeks. The company corrected this error and issued a new economic model in the clarification stage.

The economic model produced a deterministic ICER of £45,833/QALY, with pembrolizumab being more effective and more expensive than UKSOC. One way sensitivity analyses (OWSA) found that the ICER was most sensitive to the parameter values of the log-normal distributions modelling OS for

both treatment arms and also the discount rate applied to health outcomes. The probabilistic ICER was £46,194/QALY [25].

The ERG had a number of concerns around the assumptions of the economic model. The most influential factor was the choice of survival model fitted to the OS data. Firstly, the choice of the 40-week cut-off point had limited justification. The ERG agreed that a two-phase piecewise model was suitable, but did not agree with the choice of a 40 week cut-off point. The ERG believed that an earlier cut-off point would have been more beneficial, maximizing the data that the parametric model fitted. Despite the fact that the assumption of switching to a common treatment, made by the two-stage adjustment method, was not met in the trial, and that only 22 (12%) subjects in the UK-SOC arm switched, the ERG thought that the 2-stage model offered an improvement over an ITT analysis. The AIC and BIC values were remarkably similar across the various parametric models, concluding the models fitted the data equally well.

The comparison of 5-year survival predictions to CRUK data was also problematic due to the lack of information on the CRUK population. The ERG's clinical experts felt that patients in KEYNOTE-045 would have a worse prognosis since they have had a progression or recurrence of the cancer following first-line platinum-containing regimen and, most importantly, they also had a very high proportion (87.3%) of people with visceral metastasis. The ERG conducted a literature search and found two studies [26, 27] that presented long-term survival of patients more similar to those in KEYNOTE-045 and estimated that the 5-year OS of UK-SOC patients to be between 2% and 6.8%, rather than the 9-11% estimated by the company based on the CRUK data.

The inability to fit parametric curves of different types to the treatment arms for OS was a major limitation. Pembrolizumab is not a chemotherapy treatment, having a different biological mechanism of action to the UK-SOC treatments. The hypothesis behind immunotherapies is that they "raise the tail" or noticeably increase the long-term survival rates, as seen with nivolumab for NSCLC [28], rather than extending a patient's expected survival by an extra couple of months as with typical second-line care. The ERG believes that in this case it may not be appropriate to assume that both arms of the trial should be fitted with the same model type. The ERG acknowledges that fitting the same model type to each arm reduces any selection bias that may occur; however, this may result in the fitting of a compromised model, which does not fit either arm well. The ERG has similar criticisms with the PFS modelling including the cut-point and parametric model selection.

The company used utility values based on time-to-death stating that typical progression based values would fail to properly capture any decline in health prior to death. However, no strong justification for the time period categories was provided, and the company revealed that utility scores were averaged

from all eligible questionnaires, and not weighted per person. The ERG feels this could result in bias due to a possible relationship between questionnaire response and health status.

Additional concerns included the fact that AE prevalence, disutilities and other utility values were taken from the full trial population rather than excluding vinflunine patients. The company also did not provide any age-related disutility for persons over the age of 75 years. The decision to exclude vinflunine patients to assess UK suitability was appropriate; however, the company did not acknowledge the potential bias that this might incur, as the effects of randomisation are undone, which could potentially be inflated by the clinician's preference of treatments when allocating to patients, prior to randomisation.

The ERG produced their own base-case economic model with the following key changes:

- A 24 week cut-off for partitioned OS model - to maximise the data fitted to the OS parametric model.
- A log-logistic model for OS due to goodness of fit and 5 year survival estimates - had competitive AIC scores.
- Progression based utility values.
- EQ-5D utility values excluding patients receiving vinflunine.
- Distribution of patients within UK-SOC arm based on UK market share.
- Age related disutility values generated using algorithm from Ara and Brazier (2010) [29].
- The ERG's base-case model raised the deterministic ICER above that of the companies base-case ICER to £51,235/QALY [25].

The median OS observed in the UK-SOC arm of KEYNOTE-045 after adjusting for treatment switching was 6.9 months, whereas the median OS in the pembrolizumab arm was 10.3 months. The company's economic model estimated that the mean survival with pembrolizumab was 33.7 months, compared with 19.5 months with UK-SOC. Hence the committee concluded the pembrolizumab would extend life by more than three months and met the criteria to be considered as an end-of-life treatment [14].

3.3 Summary of ERG Review

The presented clinical evidence from KEYNOTE-045 suggested that pembrolizumab is more effective than SOC in the treatment of previously treated advanced or metastatic urothelial cancer. The evidence suggests a better safety profile and a lower risk of death for pembrolizumab in both the ITT population and also the PD-L1 positive and strongly positive subgroups. Whilst no significant

difference was found in PFS HR, examination of the PFS survival data suggests a long-term benefit for those on pembrolizumab. This benefit is more significant when comparing the OS of both arms.

Under the company's base-case model, with a PAS discount, pembrolizumab had an ICER of £45,833/QALY. The ERG's base-case model suggested that the ICER was £51,235/QALY. The true cost-effectiveness of pembrolizumab remains uncertain due to the lack of long-term survival data and of established methods for modelling emerging immunotherapy treatments. In particular, the optimal choice for both the cut-off point for fitting a parametric model and the parametric model was not obvious. The constraints of fitting the same parametric type model to both arms meant that the sensitivity analyses were limited.

3.4 Outcome following first appraisal committee

Following the first appraisal committee (AC) meeting (31/05/2017), NICE issued an ACD which concluded that pembrolizumab was not recommended for treating adults with previously treated advanced or metastatic urothelial cancer. The committee accepted that pembrolizumab offered clinical benefit, however they expressed concern over the uncertainty of the cost-effectiveness, concluding "all plausible estimates are higher than what NICE normally considers acceptable for end-of-life treatments", and that "there are also other plausible scenarios and assumptions not fully accounted for which would increase the estimate further". The committee felt that both the company's and ERG's preferred models underestimated the ICER.

The ACD also contained preferences of the committee over the settings within the economic model. These included reducing the duration of treatment effect, using progression-based utilities, the exclusion of utility data from participants on vinflunine, and using the UK market share to estimate the UK-SOC costs.

4. Company's subsequent submission, ERG critique, and outcomes following appraisal committee

4.1 Second submission

A number of organisations commented on the ACD, emphasising the clinical benefit of pembrolizumab. The company responded to the ACD presenting new economic analyses based on the results of an additional four months OS and PFS data, and an updated PAS discount.

The company's new base-case analysis maintained the 40 week cut-off for OS, and justified their decision of log-normal based on AIC and clinical plausibility. The company also supported the

lifetime treatment effect and their choice of time-to-death based utilities giving examples of their use in other technology appraisals. The only change in model specification of the company's base-case was the choice of parametric fit for PFS, choosing a Gompertz model. However, no justification for this change was provided. The company's revised base-case ICER was now £48,601/QALY [25].

The ERG noted that the combination of parametric curves chosen by the company meant that the PFS and OS curves for the pembrolizumab arm crossed at approximately six years, suggesting there were less patients alive, than who were alive and progression free. A correction was made within the model, forcing the PFS curve to follow the OS prediction from the point of intersection. This resulted in no patients being in the post-progression health state after six years for the pembrolizumab arm. The ERG felt this to be implausible, and investigated the balance of treatment benefit of pembrolizumab split into the pre- and post-progression health states. The ERG expected that due to the mechanism of action of pembrolizumab, a majority of its benefit would be observed in the post-progressive health state when compared with chemotherapies. Hence, the ERG selected a Weibull distribution for PFS, as it not only solved the crossing curves issue, but also provided a plausible estimate of 61% of treatment benefit coming from post-progression survival. This is compared with the company's base-case analysis which suggests that participants on pembrolizumab experience worse survival than those on UK-SOC in the post-progressive group. Visual inspection of log-cumulative hazard plot suggested equivalence of fit to later events, but superior fitting for Weibull to early events.

The ERG considered the justification presented by the company for the 40-week cut-off, but found a supporting paper which recommended maximising the data used when fitting a parametric model, suggesting an earlier cut-point is favourable [30]. The company also justified its prioritisation of the use of AIC/BIC for model selection, referring to the NICE Technical Support Document (TSD) 14, however, the TSD describes how AIC/BIC do not inform "how suitable a parametric model is for the time period beyond the final trial follow-up" [31]. Hence, the ERG placed a stronger weighting on clinical plausibility, whilst also considered the fit to the observed data using AIC/BIC.

The ERG maintained its preference for progression based utilities, with the same concerns as in the initial submission. In response to the company's suggestion for unpooled progression based utilities, the ERG was concerned about the possibility of bias from the open label design. Any significant difference of effect on quality of life (QOL) between the treatments should be captured by the AE disutility, and there is no reason why any difference in QOL would continue beyond the course of treatment, hence the ERG favoured pooled progression based utilities. The ERG also reduced the duration of treatment effect, in line with the committee's preferred assumptions, as an exploratory analysis.

The ERG maintained all other assumptions from their initial preferred base-case analysis, and the resulting ICER of £52,892/QALY [25] was 9% higher than the company's ICER. Whilst the ERG agreed with the committee that there was a lack of evidence supporting a lifetime treatment effect, there was an equivalent lack of evidence to select any other duration of treatment effect. Hence the ERG explored the effects of varying this duration in a sensitivity analysis, but maintained a lifetime effect in their base-case. Overall, the ERG found that the additional evidence submitted and incorporate into the economic model did little to reduce the uncertainty over the cost-effectiveness of pembrolizumab. There remained no clear choice over the cut-point for the parametric models, nor the parametric model itself.

The NICE committee on 26th October 2017, discussed the issues around the cost-effectiveness of pembrolizumab in light of the new submission. Pembrolizumab was discussed again on 9th January 2018, with the company offering a new value proposition, with no change to the clinical evidence or modelling approaches. The committee concluded that there were substantial uncertainties associated with estimates of survival of patients receiving pembrolizumab therapy and that under the proposed managed access scheme in the CDF there was a reasonable expectation these might be resolved sufficiently to be able to gauge the cost-effectiveness of this treatment with further data collection.

4.2 Final outcome: NICE Guidance

NICE Guidance was published on the 25th April 2018, stating: "*Pembrolizumab is recommended for use within the Cancer Drugs Fund 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 guidance states that under the new value preposition, the company base-case ICER was £41,004/QALY and the ERG's was £44,504/QALY [32]. The guidance concludes stating "*pembrolizumab has plausible potential to be cost effective based on the evidence*" and "*that ongoing data collection in KEYNOTE-045 would reduce the uncertainty surrounding the overall survival extrapolation and the magnitude of any continued treatment effect*."

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6. Author Contributions:

DG, XA, PA, RC, TM, JP, MDS, JC and HM all formed part of the ERG report that this paper describes. DG produced the first draft of the manuscript, which was developed with assistance from XA, PA and HM. All authors commented on the manuscript and approved the final version. This summary has not been externally reviewed by PharmacoEconomics.

7. Compliance with Ethical Standards

7.1 Funding

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7.2 Conflicts of Interest

DG, XA, PA, RC, TM, JP, JC and HM have no other conflicts of interest that are directly relevant to the content of this article. MDS has received consulting fees/honoraria from Amgen, Astellas Pharma, AstraZeneca, Bayer AG, Bristol-Myers Squibb, Celgene, Dendreon, Eisai, ESSA Pharma, Ferring Pharmaceuticals, GlaxoSmithKline, Incyte, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Pierre Fabre Group, Roche, Sanofi, Seattle Genetics, Shionogi, Synthon, Takeda and Teva/Oncogenex.

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