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Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable: An Evidence Review Group perspective of a NICE Single Technology Appraisal

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Short running title: "Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable: An ERG perspective"

Abstract

As part of its Single Technology Appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer (Merck Sharp & Dohme) of pembrolizumab (Keytruda®) to submit evidence of its clinical and cost-effectiveness for the treatment of locally advanced or metastatic urothelial cancer where cisplatin is unsuitable. The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a detailed review of the evidence for the clinical and cost-effectiveness of the technology, based upon the company's submission to NICE. The clinical effectiveness evidence in the company's submission for pembrolizumab was based upon one Phase II, single-arm, open-label, non-randomised study (KEYNOTE-052). The evidence for the comparator (carboplatin plus gemcitabine) was based on four studies including one randomised controlled trial and three cohort studies. In the absence of head-to-head trials, the company conducted an indirect treatment comparison for both PFS and OS, by firstly adjusting cross-study differences using simulated treatment comparison approach and then synthesising the evidence based on an assumption of constant hazard ratios using a standard meta-analysis model and time-varying hazard ratios using fractional polynomial models. The treatment effect of pembrolizumab was more favourable in the adjusted population compared with the observed effect in the KEYNOTE-052 study. The company submitted a de novo partitioned survival cohort simulation model, which partitions the OS time into PFS and post-progression survival. The probabilistic incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with carboplatin plus gemcitabine was estimated to be £37,081 per quality-adjusted life year

(QALY) gained, based upon the results within the company's health economic model. Following a critique of the model, for their preferred base case the ERG corrected some minor model errors, chose a progression approach for estimating utilities, and revised the extrapolation of PFS and OS. The ERG's probabilistic base case ICER was estimated to be £67,068 per QALY gained. The ERG also undertook a range of exploratory sensitivity analyses which suggested that the ICER was highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab had the largest impacts upon the ICER. The NICE appraisal committee recommended pembrolizumab 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, provided that pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and the conditions of the managed access agreement for pembrolizumab are followed.

Key points for decision makers

- Pembrolizumab is an effective treatment option for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable, although the relative treatment efficacy is uncertain due to paucity of evidence.
- The choices of extrapolation for the overall survival of pembrolizumab and the stopping rule for pembrolizumab had the largest impacts upon the cost-effectiveness estimates, with the Evidence Review Group estimated cost per quality-adjusted life year gained ranging from £48,330 to £136,971 under plausible assumptions.
- Pembrolizumab was recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable, only if pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and the conditions of the managed access agreement for pembrolizumab are followed.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order for NICE to recommend their use within the NHS in England. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after their UK market authorisation.[1] Within the STA process, the company provides NICE with a written submission that summarises the company's estimates of the clinical and cost effectiveness of the technology, alongside the implemented mathematical model. This submission is reviewed by an external organisation independent of NICE (the Evidence Review Group [ERG]), which consults with clinical specialists and produces a report. After consideration of the company's submission, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee (AC) formulates preliminary guidance, the Appraisal Consultation Document (ACD), which indicates the initial decision of the AC regarding the recommendation (or not) of the technology. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a further ACD may be produced or a Final Appraisal Determination (FAD) issued, which is open to appeal. In this STA, NICE directly produced a FAD having considered the probability of an appeal.

This paper presents a summary of the ERG report [2] for the STA of pembrolizumab for untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable. A brief summary of the

resulting NICE guidance for the use of this technology in England is also provided. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, FAD and comments from consultees) can be found on the NICE website.[3]

2. The Decision Problem

Urothelial cancer may arise from the transitional cells in the endothelium of the bladder, renal pelvis, ureter, and urethra. In the UK, urothelial cancer accounts for approximately 90% bladder, renal pelvis, ureter and urethra cancers,[4] and bladder cancer is recognised as the 10th most common form of cancer, and the 7th most common cause of cancer mortality.[5] Bladder cancer is most frequent within an elderly population; in the UK 55% of bladder cancer is diagnosed in people aged 75 years and over (Cancer Research UK 2012 to 2014).[6] The survival in untreated bladder cancer patients is uncertain and survival data for patients with urothelial cancer are not available because of the scarcity of such data in the literature. However, it is known that survival rates for patients with bladder cancer are strongly correlated to disease stage at diagnosis. For patients with stage IV disease, the likelihood of survival is 35% and 28% at 1 year for men and women, respectively, and 9% and 11% at 5 years following initial diagnosis. There is variation in 5-year overall survival for patients with advanced or metastatic urothelial cancer, and the lowest 5-year survival rates suggested in the literature were 6% globally.[7]

2.1 Current Treatment

In the UK the current first line treatment for patients with locally advanced or metastatic urothelial carcinoma who are cisplatin ineligible is carboplatin in combination with gemcitabine.[8] Some patients may alternatively receive best supportive care (BSC). Atezolizumab has a marketing authorisation for untreated locally advanced or metastatic urothelial carcinoma when cisplatin is unsuitable. However, because of substantial uncertainty in the clinical effectiveness evidence, NICE recommended atezolizumab for use within the Cancer Drugs Fund only [9] and hence atezolizumab was not considered to be standard practice for the purpose of this appraisal.

Pembrolizumab (Keytruda®) is a monoclonal antibody of the IgG4/kappa isotype designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. Pembrolizumab as a monotherapy is licenced for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy. It is given by intravenous infusion at a fixed dose of 200mg every three weeks. Treatment should be continued until disease progression or unacceptable toxicity.[10] The original anticipated NHS list price was £2,630 per 100 mg vial.[3] The company has a commercial arrangement, which makes pembrolizumab available to the NHS with a discount. Unless otherwise stated, all results presented here used the discount.

3. The Independent ERG Review

The company provided a submission to NICE on the clinical effectiveness and cost effectiveness of pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable.[3] This submission was critically appraised by the ERG. In addition, the ERG identified areas requiring clarification, for which the company provided additional evidence prior to completion of the ERG report.[3]

3.1 Clinical Evidence Provided by the Company

The company's submission (CS) included a systematic review of the clinical effectiveness evidence. The KEYNOTE-052 study provided the main supporting clinical effectiveness evidence for this submission and is a Phase II, single-arm, open-label, non-randomised study.[11] KEYNOTE-052 was designed to test the efficacy and safety of pembrolizumab in patients with advanced/unresectable or metastatic urothelial cancer where cisplatin is unsuitable. The KEYNOTE-052 study is ongoing, and different data cut-off points are used in the CS [3] (9th March 2017), and Balar et al. (2017) [11] and the European Public Assessment Report (EPAR) [10] (both 1st Sept 2016).

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

The primary outcome of the KEYNOTE-052 study was objective response rate (ORR) with overall survival (OS) and progression-free survival (PFS) being secondary endpoints. At the data cut-off point of 9th March 2017, median OS was 11.0 months (95% confidence interval (CI): 10.0-13.6 months) and there were 188 deaths. Median PFS was 2.3 months (95% CI: 2.1-3.4 months) and ORR was 29.2% (95% CI: 24.6%-34.1%).

All participants were monitored for adverse events (AEs) for 30 days following the end of treatment (this was 90 days for serious adverse event (SAE) monitoring, unless the participant initiated a new treatment, in which case it was 30 days after the end of treatment). At the data cut-off point of 9th March 2017, patients had spent a median of 3.40 months (range 0.03-22.01 months) on treatment with pembrolizumab, with a mean of 8.20 months (standard deviation 6.84). The number of study medication administrations had median 5.00 doses (range 1.00-33.00 doses). Incidence of any adverse event (AE) was reported in the CS as being 97.6%, and incidence of treatment-related AEs was reported in the CS

as being 65.7%. The most common AEs were reported in the CS as being fatigue (33%), decreased appetite (24.1%), constipation (22.4%), urinary tract infection (21.6%), haematuria (15.7%) and an increase in blood creatinine (13.8%). The most common treatment-related AEs were reported in the CS as being fatigue (18.1%) and pruritus (16.8%). The CS reported 20 (5.4%) cases of mortality from AEs.

In the absence of head-to-head evidence, the company conducted an indirect treatment comparison (ITC) for both PFS and OS, by firstly adjusting cross-study differences using a simulated treatment comparison (STC) approach [12] and then synthesising the evidence based on an assumption of constant hazard ratios using a standard meta-analysis model and time-varying hazard ratios using fractional polynomial models. Four studies of carboplatin plus gemcitabine were presented in the CS, including one randomised controlled trial [13] and three cohort studies.[14-16] There was considerable heterogeneity between the comparator studies with regard to patients and dosage and administration of gemcitabine and carboplatin. Median OS ranged from 7.2 months (95% CI: 5.9-8.5 months) to 10 months (95% CI: not reported (NR)). PFS ranged from 4.4 months (95% CI: 1.03-7.75 months) to 5.8 months (95% CI: NR).

The STC approach included four prognostic factors: ECOG ≥2; renal failure; presence of liver metastases or visceral metastases, and primary tumour site (upper or lower). The absolute treatment effect of pembrolizumab was more favourable in the adjusted population compared with the observed effect in the KEYNOTE-052 study.

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

3.1.1 Critique of the Clinical Evidence and Interpretation

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

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

The ERG had concerns that the company's population adjustment approach to balance the cross-study differences between KEYNOTE-052 and carboplatin plus gemcitabine studies lacked validity. The company's adjustments suggested that patients in KEYNOTE-052 were less fit compared with the patients in each of the carboplatin plus gemcitabine studies. However, this was not supported by the reported summary of patient baseline characteristics from the included studies. The ERG's clinical advisors also confirmed that patients in KEYNOTE-052 were not more frail compared with the patients in the comparator studies. The ERG noted that there was no evidence by subgroup for the comparator; hence it was not appropriate to conduct the ITC for the subgroups.

3.2 Cost-Effectiveness Evidence Provided by the Company

The company submitted a de novo partitioned survival cohort simulation model, which included three states: (i) progression-free; (ii) progressed disease and (iii) death. The model adopted a weekly cycle length and a 20-year time horizon. The incremental health gains, costs and cost-effectiveness of pembrolizumab were evaluated from the perspective of the UK NHS and Personal Social Services (PSS). To estimate the long-term OS and PFS for the pembrolizumab group, data from the KEYNOTE-052 study were extrapolated using a piecewise approach with parametric distributions (i.e. a hybrid Kaplan-Meier (KM) approach). The company used the KM data up until 32 weeks and fitted a log normal distribution to the KM data from 32 weeks onwards as the base case for OS. The base case for PFS used KM data up until 9 weeks and fitted a Weibull distribution to the KM data from 9 weeks onwards. The fractional polynomial model with p1=p2=0 for OS and PS was used to estimate the relative treatment effect (i.e. time-varying hazard ratios) of pembrolizumab versus carboplatin plus gemcitabine. The PFS and OS for the carboplatin plus gemcitabine arm were modelled by applying the time-varying hazard ratios to the extrapolated PFS and OS of pembrolizumab arm, respectively.

The estimated PFS for carboplatin plus gemcitabine was used as a proxy for time on treatment, and patients were assumed to receive no more than 6 cycles. Time on treatment data from the KEYNOTE-052 study were extrapolated using standard parametric distributions to estimate time on pembrolizumab (a Gompertz distribution was used in the base case), and patients could receive a maximum of 24 months treatment in the model. In addition to the drug acquisition costs for pembrolizumab, carboplatin and gemcitabine, the model included costs for drug administration, subsequent treatment (a taxane or BSC, based on the latest UK market share estimates), disease management, end of life care and costs associated with treating adverse events. All costs are based on published sources and were valued at

2015/16 prices. Health-related quality of life data from the KEYNOTE-052 trial were used within the model (see Table 1). The company estimated the utility values in two different ways: (i) based on patients' disease state, so that patients had a different utility in the progression-free health state and the progressed disease health state; and (ii) based on patients' time to death. The latter was used within the company's base case. All costs and health outcomes are discounted at a rate of 3.5% per annum.

[Table 1 about here]

The probabilistic incremental cost-effectiveness ratio (ICER) for pembrolizumab compared with carboplatin plus gemcitabine was estimated to be £37,081 per quality-adjusted life year (QALY) gained, based upon the results within the company's health economic model. The CS argued that pembrolizumab satisfied NICE's criteria for life-extending therapies at the end of life.

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The company's health economic model structure was generally appropriate for the decision problem defined in the NICE final scope, though it should be noted that the only comparator tested within the economic evaluation was carboplatin plus gemcitabine. This was because there was no evidence for BSC and the evidence for atezolizumab was too uncertain to enable a useful comparison. The model was generally well described within the report. However, the STC lacked validity and there was substantial uncertainty around the extrapolation of the survival curves. The company undertook limited analyses to assess the impact of this uncertainty upon the model results, leading to an underestimate in the uncertainty around the ICER.

3.3 Additional Work Undertaken by the ERG

3.3.1 The ERG's suggested base case

1) Correction of model errors

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

2) Utility by progression status

The ERG preferred utility by progression status rather than by time to death within the base case, since the estimated utilities via the latter method were implausibly high for this patient group. This analysis substantially reduced the QALYs associated with pembrolizumab, hence the ICER associated with pembrolizumab compared with carboplatin plus gemcitabine increased to £42,588 per QALY gained.

3) Extrapolation of OS and PFS using unadjusted data

The ERG had concerns about the validity of the STC undertaken by the company. Given that we did not have the individual patient-level data (IPD) to undertake our own population adjustment analyses, the ERG used a naïve indirect comparison based on the carboplatin plus gemcitabine arm from De Santis (2012) [13] and KEYNOTE-052. The reason to only include De Santis (2012) [13] for the comparator was because the ERG believed that it may not be appropriate to synthesise the evidence from the four carboplatin plus gemcitabine studies due to the heterogeneity with regard to patients and dosage and administration of gemcitabine and carboplatin; and De Santis (2012) [13] was the largest and most rigorously conducted study in the population of interest. The ERG noted that the naïve indirect comparison did not adjust for bias due to cross-study differences. The bias due to imbalance in the observables may be minimal in this case because De Santis (2012) [13] and KEYNOTE-052 had similar patient baseline characteristic distributions. The results of the naïve indirect comparison should be interpreted with caution as it did not account for residual bias.

For carboplatin plus gemcitabine, only the OS KM curve was reported in the published paper. The ERG obtained the PFS KM curve from the first author of the paper. The ERG reconstructed IPD from these KM curves and the observed pembrolizumab data in KEYNOTE-052 for both OS and PFS using the algorithm proposed by Guyot et al. (2012).[17] These curves were extrapolated using standard parametric distributions including exponential, Weibull, log logistic, log normal, Gompertz, gamma and generalised gamma and natural cubic spline models by Royston and Parmar (2002) [18] with knots={1, 2, 3} based on modelling the log of the cumulative hazard function. Based on assessing both internal and external validity, the ERG's preferred model choices for pembrolizumab OS was log normal; pembrolizumab PFS was spline with knots=3; carboplatin plus gemcitabine OS was spline with knots=2; and carboplatin plus gemcitabine PFS was spline with knots=3.

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

4) Stopping rule/effectiveness of pembrolizumab after 24 months

Given that a 2-year stopping rule has also been used within other indications, and this was how the company suggested pembrolizumab would be used, the ERG had used this stopping rule in their base case. However, the ERG did not agree that it was reasonable to discontinue the acquisition cost of pembrolizumab at 24 months within the model, whilst making use of the extrapolated PFS and OS from the study where patients did not discontinue treatment, as this was highly likely to overestimate the benefits of the treatment. Within their base case, the ERG had discontinued the acquisition cost of

pembrolizumab at 24 months, whilst using the hazard for carboplatin and gemcitabine within the pembrolizumab group beyond 24 months. Alternative assumptions were tested within the ERG's scenario analyses. As the hazards for the pembrolizumab survival curves were similar to those for the carboplatin plus gemcitabine survival curves beyond 24 months, this analysis did not impact upon the model results substantially.

3.3.2 The ERG's sensitivity analysis

The ERG had re-run the deterministic univariate sensitivity analyses undertaken by the company using the new ERG base case. This suggested that the parameters varied by the company in their univariate sensitivity analysis did not impact upon the ERG's model results substantially, with the weekly cost in the progression-free state following pembrolizumab treatment having the largest impact upon the model results. This analysis resulted in ICERs for pembrolizumab versus carboplatin plus gemcitabine in the range £61,647 to £67,019 per QALY gained.

The ERG had also undertaken some additional sensitivity analyses which were not undertaken by the company, to assess plausible alternative assumptions. These analyses showed that the ICER was highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab had the largest impacts upon the ICER. There were four alternative curves that the ERG tested (three spline models and generalised gamma) which provided a good statistical fit (based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC)) and visual fit to the pembrolizumab OS data, and for which our clinicians suggested all could be clinically plausible since long-term survival was unknown. These resulted in ICERs for pembrolizumab versus carboplatin plus gemcitabine ranging from £48,330 to £97,140 per QALY gained. Using the log normal distribution for pembrolizumab OS, as in the ERG base case, and assuming no stopping rule for pembrolizumab, increased the ICER to £84,905 or £136,971 per QALY gained, dependent upon the time on treatment curve extrapolation assumptions. Whilst lowering the cost of carboplatin did not substantially impact upon the model results, it should be noted that the direction of effect is to increase the ICER.

3.4 Conclusions of the ERG Report

The systematic review presented in the CS appears to be comprehensive. The health economic model submitted by the company was generally well described and justified. Due to the lack of head-to-head studies, the relative treatment effect of pembrolizumab was uncertain. The ERG believed that the company's STC lacked validity, and because of this the benefits of pembrolizumab were likely to be overestimated within the company's health economic model. There was also substantial uncertainty around the extrapolation of the survival curves. In addition, it was unclear whether a treatment stopping rule would be applied in practice, and if so it was unknown what impact this would have upon treatment effectiveness. These structural uncertainties were insufficiently explored by the company within their

scenario analyses, and hence the full range of plausible ICERs given the available evidence was not presented by the company.

The ERG's probabilistic base case ICER was £67,068 per QALY gained. The scenario analyses run by the ERG suggested that the ICER was highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab had the largest impacts upon the ICER, with a cost per QALY gained for pembrolizumab versus carboplatin plus gemcitabine ranging from £48,330 to £136,971 per QALY gained under plausible assumptions. Pembrolizumab did appear to satisfy NICE's end of life criteria.

4. Key Methodological Issues

The key methodological issues in the evidence base were the ITC analysis and the use of a stopping rule for pembrolizumab at 24 months of treatment. STC is one of the population adjustment methods that could be used to balance the cross-study differences when performing an ITC analysis. However, the method is not without limitations.[12] The company's ITC analysis lacked validity as the adjusted results suggested that patients in KEYNOTE-052 were less fit compared with the patients in each of the carboplatin plus gemcitabine studies, which was not supported by the reported summary of patient baseline characteristics from the included studies. Given that the ERG did not have access to the IPD in order to undertake their own ITC analysis to provide more valid estimates and given that in the largest RCT (De Santis (2012) [13]) the baseline characteristics were similar to KEYNOTE-052, the ERG preferred base case used analysis naïve indirect comparison using KEYNOTE-052 and De Santis (2012) [13] within the health economic model.

The company suggested the use of a stopping rule for pembrolizumab at 24 months of treatment, and this is the protocol for the KEYNOTE study. However, there is no mention of a stopping rule in the Summary of Product Characteristics (SmPC) for pembrolizumab. The clinical advisors to the ERG suggested that there is uncertainty about whether a stopping rule would be implemented in clinical practice. Moreover, no patients were followed up beyond 24 months within the KEYNOTE study at the data cut-off point (9th March 2017) and hence there was no evidence about the impact of a stopping rule upon treatment effectiveness.

The company also assumed that there were no costs of pembrolizumab beyond 24 months, whilst the effectiveness was extrapolated based on the trial evidence where patients did not discontinue treatment. The ERG believed that this was highly likely to underestimate the cost-effectiveness of pembrolizumab. Within their base case, the ERG discontinued the acquisition cost of pembrolizumab at 24 months, whilst using the hazard for carboplatin and gemcitabine within the pembrolizumab group beyond 24 months, although other scenarios were also tested due to the uncertainty around this.

5. National Institute for Health and Care Excellence Guidance

In June 2018, on the basis of the evidence available (including verbal testimony of invited clinical experts and patient representatives), the Appraisal Committee (AC) published guidance that pembrolizumab can be used within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable. This recommendation was conditional on pembrolizumab being stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and the conditions of the managed access agreement for pembrolizumab are followed.

5.1 Consideration of Clinical and Cost-Effectiveness Issues Included in the Final Appraisal Determination (FAD)

This section summarises the key issues considered by the Appraisal Committee. The full list of the issues considered by the AC can be found in the FAD.[3]

5.1.1 Uncertainties in the Clinical Evidence

The AC was concerned that in the absence of head-to-head trials comparing pembrolizumab with other treatments, it was difficult to assess pembrolizumab's relative treatment benefit. The trial data were immature so there is considerable uncertainty about the long-term benefits. The AC concluded that pembrolizumab appeared to be an effective treatment option for people with untreated disease when cisplatin is unsuitable. However, there was considerable uncertainty about the size of the clinical benefit compared with other treatments and the duration of these benefits.

The AC concluded that the results of the STC lacked validity and because of the limitations in the STC and in the evidence networks, the network meta-analyses were unlikely to provide a robust estimate of relative effectiveness.

5.1.2 Uncertainties in the Economic Modelling

The AC recognised that the extrapolation of OS was highly uncertain, and had a substantial effect on cost effectiveness. It concluded that although the ERG's approach produced more plausible estimates for the comparator arm, it was based on an unadjusted comparison. Therefore the AC considered both the company's and the ERG's approaches in its decision-making.

The AC was concerned that the utility values based on time to death performed by the company results in higher utility values for people living longer than 180 days than the average value for PFS from the trial, and considered that it was more appropriate to use the progression state based utility values.

6. Appraisal Committee's Key Conclusion

The AC concluded that pembrolizumab appears to be effective in a single-arm clinical trial (KEYNOTE-052), but it is difficult to establish the relative treatment effect because of the lack of head-

to-head trials comparing with other treatments. The long-term benefits of pembrolizumab are uncertain because the trial is ongoing and this leads to uncertain estimate of cost effectiveness. The AC concluded that the most likely ICER for pembrolizumab compared with carboplatin plus gemcitabine was in the range from £43,702 to £65,642 per QALY gained, but could be higher. The AC agreed that pembrolizumab met the criteria to be considered as a life-extending end of life treatment, and longer follow-up data from KEYNOTE-052 and data from KEYNOTE-361, which directly compares pembrolizumab with other treatment, would help to address some of the uncertainties in the treatment effects. The AC therefore recommended pembrolizumab for the use within the Cancer Drugs Fund while further data are collected.

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This summary of the ERG report was compiled after NICE issued the FAD. All authors have commented on the submitted manuscript and have given their approval for the final version to be published. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of NICE or the Department of Health. Any errors are the responsibility of the authors. The authors would like to thank Mark Clowes for critiquing the literature searches undertaken by the company and Jonathan Shamash for providing clinical advice to the ERG.

Author contributions

HS and AR critiqued the mathematical model provided and the cost-effectiveness analyses submitted by the company. EK and EH critiqued the clinical effectiveness data reported by the company. SR critiqued the STC and ITC performed by the company and conducted the addition analysis for extrapolation. CA provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document. SR acts as the guarantor of the manuscript. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflicts of Interest

SR, HZ, EH, EK, AR and CA have no conflicts of interest to declare.

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