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Advising on new medicines for Scotland
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NHS SCOTLAND
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pembrolizumab 25mg/mL concentrate for solution for infusion and 50mg powder for concentrate for solution for infusion (Keytruda®) SMC No 1339/18

Merck Sharp & Dohme Limited

10 August 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the end of life and orphan equivalent process

pembrolizumab (Keytruda®) is not recommended for use within NHS Scotland.

Indication under review: as monotherapy, 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.

In an open-label, non-comparative phase II study of adults with advanced / metastatic urothelial cancer who had no previous treatment for advanced / metastatic disease and who were ineligible for first-line cisplatin-based therapy, treatment with pembrolizumab was associated with an objective response in 47% of patients with strongly positive PD-L1 expression (CPS≥10).

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

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Indication

As monotherapy, 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.[1, 2]

Dosing Information

The recommended dose of pembrolizumab for urothelial carcinoma is 200mg administered as an intravenous infusion over 30 minutes every three weeks.

Patients with previously untreated urothelial carcinoma should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test.

Patients should be treated until disease progression or unacceptable toxicity. Atypical responses (ie an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.Please refer to the summary of product characteristics for advice on treatment modification for adverse events.

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[1, 2]

Product availability date

24 August 2017
Pembrolizumab meets SMC orphan-equivalent criteria and end-of-life criteria for this indication.

Summary of evidence on comparative efficacy

Pembrolizumab is a monoclonal antibody which blocks the interaction between the programmed cell death-1 (PD-1) receptor and its ligands PD-L1 and PD-L2. This results in the functional activity of the target lymphocytes being enhanced to facilitate immune-mediated anti-tumour activity.[1, 2] Urothelial carcinoma occurs in the bladder (90%), renal pelvis (8%) and in the ureter and urethra (2%). The main histological subtype is transitional cell carcinoma.[3]

This submission relates to the treatment of locally advanced or metastatic urothelial cancer in adults who have not received any systemic treatment for their advanced / metastatic disease and who are ineligible for cisplatin-based regimens, and whose tumours are strongly positive for PD-L1 expression (CPS≥10). Pembrolizumab has previously been reviewed by SMC for the treatment of urothelial cancer in adults who have received prior platinum-containing chemotherapy (SMC ID 1291/18).

The key evidence for this indication is the multi-centre, single-arm, phase II study, KEYNOTE-052.[3, 4] The study recruited adults (≥18 years of age) with urothelial carcinoma of the bladder, urethra, renal pelvis or ureter (cytologically or histologically confirmed). Transitional cell and mixed transitional / non-transitional cell histologies were allowed. Patients had measurable disease, based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2 as assessed within 10 days prior to treatment initiation. Patients were ineligible to receive cisplatin-based chemotherapy, meeting at least one of the following criteria:

- ECOG Performance Status of 2 (the proportion of these patients was limited to approximately 50% of the total population)
- Creatinine clearance (calculated or measured) <60mL/min but ≥30mL/min
- Grade ≥2 audiometric hearing loss
- Grade ≥2 peripheral neuropathy
- New York Heart Association (NYHA) Class III heart failure.[3, 4]

All patients received pembrolizumab administered at the licensed dose of 200mg by intravenous (IV) infusion every three weeks.[3] Treatment was continued until RECIST-confirmed disease progression, intolerable toxic effects, doctor or patient decision to withdraw, inter-current illness preventing further treatment, confirmed pregnancy, non-compliance with trial procedures, loss to follow up, or completion of 24 months of treatment. Clinically stable patients with progressive disease who were judged by the investigator to be benefiting from pembrolizumab could remain on treatment until subsequent progression. Patients receiving pembrolizumab who attained a complete response and had been on treatment for at least 24 weeks could discontinue treatment. Patients who stopped study treatment after 24 months, for reasons other than progressive disease or intolerability, or participants who attained a complete response and stopped study treatment, were eligible for up to one year of retreatment upon experiencing progressive disease.[3, 4]

The primary outcome was objective response rate (ORR) defined as the proportion of patients who achieved a complete or partial response (based on RECIST version 1.1), as assessed by independent central radiology review.[3, 4] This was analysed in the all-patients treated group, all patients who received at least one dose of study treatment. Outcomes were also assessed in populations defined by their PD-L1 expression status: positive group (combined [tumour and immune cells] positive score ≥1%), and strongly positive group (combined positive score ≥10%).[3]

KEYNOTE-052 is ongoing, with study completion likely in June 2018. At the second interim analysis (data cut-off 9 March 2017), median follow up was 9.5 months (range 0.1 to 22.7 months); ORR results are presented in Table 1.

Table 1: Primary efficacy endpoint in KEYNOTE-052 (data cut-off March 2017)[3]

	ORR	CR	PR
All-patients treated (n=370)	29%	7.3%	22%
PD-L1 positive (PD-L1 CPS≥1%) population (n=282)	33%	8.5%	24%
PD-L1 strongly-positive (PD-L1 CPS ≥10%) population (n=110)	47%	16%	31%

ORR = objective response rate, CR= complete response, PR = partial response, PD-L1 = programmed cell death-ligand 1, CPS = combined positive score.

Secondary endpoints included progression free survival (PFS), overall survival, time to response, and duration of response. These are summarised in Table 2 for the all-patients treated population.

Table 2: Secondary outcomes in KEYNOTE-052 (data cut-off March 2017)[3]

Secondary endpoint		All-patients treated population (n=370)
Response	Number in response	108
	Median time to response (range)	2.1 months (1.3 to 9.0)
	Median duration of response	NR
	Proportion with duration of response ≥6 months	82%
PFS	Event rate	77%
	Median (95% CI)	2.3 months (2.1 to 3.4)
	PFS at 6 months	34%
	PFS at 12 months	22%
OS	Event rate	51%
	Median (95% CI)	11.0 months (10.0 to 13.6)
	OS at 6 months	67%
	OS at 12 months	47%

Medians and survival rates at landmarks estimated by Kaplan-Meier method. NR = not reached, PFS = progression-free survival, OS = overall survival, CI = confidence interval

Median OS in the PD-L1 strongly-positive (PD-L1 CPS ≥10%) population (n=110) was 19 months (95% CI: 12 to not reached) and the 12-month OS rate was 61%.[1]

Patient reported outcomes were collected using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EuroQol 5-dimension (EQ-5D) instruments. Compliance rate and completion rate were assessed in the Full Analysis Set population (patients who received at least one dose of study medication and completed at least one instrument; n=367).[3] Compliance rates for both EORTC QLQ-C30 and EQ-5D were 90% or above at baseline and over 86% at week 9. Completion rates remained above 70% until week 9, when they dropped as patients discontinued the study due to disease progression, physician decision, adverse events, or death.[3]

At week 9, general health status, measured by EORTC QLQ-C30, was improved (increase ≥10 points) in 31% of patients and stable in 42% of patients. Mean global health status by visit increased at each study visit, but magnitude in improvement was less than 10 points (usual minimal clinically important improvement) up to week 21 / 27 visits. Majority improvement or stable quality of life outcomes were observed for all EORTC functioning and symptom domains. An improved quality of life was registered for patients who remained on treatment, although scores after week 9 should be interpreted with caution due to the small sample size.[3]

In a similar pattern to EORTC quality of life outcomes, EQ-5D visual analogue and utility scores were reported to be stable over time.[3]

Summary of evidence on comparative safety

No comparative safety data are available for the population under review.

In the overall KEYNOTE-052 study population, treatment-related adverse events (AEs) were reported in 66% of patientsand were at least grade 3 in severity in 19% of patients. Discontinuation due to treatment-related AEs occurred in 7% of patients.[7]

The most commonly reported treatment-related AEs were fatigue (18%), pruritus (17%), rash (12%), decreased appetite (10%), hypothyroidism (10%), diarrhoea (8.6%), and nausea (8.4%). Individual treatment-related AEs of at least grade 3 in severity occurred in less than 3% of patients. The most common immune-mediated AEs of interest were hypothyroidism (11%), pneumonitis (3%), hyperthyroidism (3%), colitis (2%) and adrenal insufficiency (2%).[7]

There was one death attributed to a treatment-related adverse event; myositis in a patient over 80 years old.[7]

The European Medicines Agency (EMA) noted that safety data were generally consistent with those previously reported in other indications.[3]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Patients with advanced or metastatic urothelial carcinoma will generally receive platinum-based combination chemotherapy (first-line) and despite responses of 40% to 60% almost all patients will have disease progression at a median of around eight months. The preferred platinum agent is cisplatin. Around half of patients are not suitable for cisplatin (for reasons such as poor performance status and inadequate renal function) and these patients may be considered for carboplatin-based chemotherapy regimen (ie gemcitabine / carboplatin) with response rate of approximately 40% and median progression free survival of around six months. Patients not eligible for platinum-regimens may receive single agent taxane or gemcitabine. Patients considered not fit enough for chemotherapy would most likely be managed with best supportive care.[8] Pembrolizumab is one of three immunotherapies licensed for the treatment of urothelial cancer, however, no targeted therapies are available in NHS Scotland for the specific indication under review; patients who are ineligible for first-line cisplatin-based therapy .[9, 10]

Clinical experts consulted by SMC considered that pembrolizumab addressed an unmet need in this therapeutic area, namely the lack of effective treatment options for patients who are otherwise not suitable to receive platinum-based chemotherapy.

Prognosis is poor, median overall survival with carboplatin plus gemcitabine was 9.3 months in one study.[11] Pembrolizumab meets SMC end-of-life criteria for this indication; it also meets SMC orphan-equivalent criteria.

In KEYNOTE-052, 29% of patients had an objective tumour response when treated with pembrolizumab. The ORR was highest in the subgroup of patients with PD-L1 combined positive score ≥10% (47%). In all patients, at median follow up of 9.5 months, median overall survival was 11 months and median PFS was 2.3 months. Median OS was 19 months in the PD-L1 strongly-positive (PD-L1 CPS ≥10%)

population. Quality of life measures were either stable or tended to report an improvement following treatment.[3]

KEYNOTE-052 had a number of limitations. As a single-arm study, the magnitude of the treatment effect is unknown. The primary outcome was ORR which, although acceptable for a phase II study, is not sufficient to demonstrate clinical benefit. Duration of response, PFS and overall survival were secondary outcomes. To date, only results from interim analyses are available. Length of follow-up of the study was sufficient to estimate median PFS and overall survival, but not median duration of response. The overall survival data are relatively immature with approximately half of patients censored at the data cut-off. The results of patient-reported outcomes should be treated cautiously given the open-label, single-arm design of the study.

The phase III study KEYNOTE-361, is currently recruiting patients and is expected to provide comparative data for pembrolizumab and platinum-based chemotherapy in the next two years. The study includes a subgroup who are cisplatin ineligible.[12, 13]

The EMA noted that the ORR from the interim data analyses of KEYNOTE-052 were slightly lower when naively compared with historical data for chemotherapy.[3] To support the economic case made to SMC, the submitting company presented an indirect comparison of pembrolizumab and gemcitabine / carboplatin when used as a first-line treatment for advanced urothelial carcinoma in patients considered ineligible for cisplatin-based regimens. In the absence of a common comparator, simulated treatment comparisons (STC) were used to predict overall survival and PFS with pembrolizumab, for patients enrolled in four gemcitabine / carboplatin studies. Using individual patient level data from patients treated with pembrolizumab in KEYNOTE-052, PFS with pembrolizumab was predicted from two gemcitabine / carboplatin studies, overall survival with pembrolizumab was predicted from four gemcitabine / carboplatin studies. A network meta-analysis (NMA) was then performed with fixed (PFS and overall survival) and random effects models (overall survival only) using the simulated data from the single-arm studies. The results of the NMA indicated that the hazard ratios for both PFS and OS increased over time suggesting that the comparative efficacy of pembrolizumab decreased over time. For PFS there was insufficient evidence of a difference between treatments; credible intervals included or approached one one at all-time points. The modelled credible intervals for overall survival excluded one at all time points. The gemcitabine / carboplatin studies did not report the PD-L1 status for each patient and therefore it is unclear how closely the patient population used in the NMA matched the licensed population or pembrolizumab.

The validity of the indirect comparisons rely on the strength of the prediction models that the company used. Five prognostic variables were included in the models (ECOG performance status ≥2, presence of liver metastases, poor renal function, presence of visceral metastases, and primary tumour site in upper urinary tract). There are limited data for pembrolizumab from KEYNOTE-052 to determine modifiers of its treatment effect which should have been included in the prediction model. Differences in the maturity of survival data and in the criteria for ineligibility for cisplatin were identified and were not accounted for in the indirect comparisons.

The economic case also included a two-year stopping rule for pembrolizumab treatment. Although this was part of the KEYNOTE-052 study protocol, the licence for pembrolizumab does not stipulate one.

Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to the sustained tumour responses with treatment.

Currently patients with locally advanced or metastatic urothelial carcinoma are not tested for PDL1 status. Therefore the introduction of pembrolizumab is likely to have some service implications for pathology laboratories.

In patients who are ineligible for cisplatin-based chemotherapy, alternative treatment options are limited mainly to carboplatin-based chemotherapy administered on days 1 and 8 of a three-weekly cycle. Pembrolizumab would offer an advantage for patients with less frequent attendance at three-weekly intervals.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of pembrolizumab, as an orphan-equivalent and end-of-life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- The prognosis for patients is very poor and there is a significant symptom burden associated with advanced disease. The population who are cisplatin-ineligible are already frail and often have significant co-morbidities. Urothelial carcinoma can affect the physical health, mental health, and adversely affect finances of people living with the disease.
- Chemotherapy offered to patients in this population (ie carboplatin) is associated with significant toxicity, which is particularly difficult for this frail population to tolerate; quality of life whilst on treatment can worsen as a result.
- Pembrolizumab addresses the unmet need for an efficacious treatment with low toxicity, in a group of patients for whom the treatment options are limited.
- For the proportion of patients (approximately 30% of the population) who obtain an objective response, this has the potential to be of long duration. Pembrolizumab is expected to reduce disease-associated symptoms, and improve health-related quality of life, increasing patients' ability to self-care and deal with activities of daily living. This is of major significance to patients, families and carers.
- Compared with chemotherapy, pembrolizumab is very well tolerated. Detriment in quality of life due to side effects is a small risk; this is particularly valuable in this frail patient population.
- Patients who would be eligible for pembrolizumab in this indication are twice disadvantaged within the existing treatment pathway since they are unsuitable for cisplatin chemotherapy (preferred first-line treatment) and are also unable to access immunotherapy without first being treated with platinum chemotherapy.

Additional Patient and Carer Involvement

We received a patient group submission from Action Bladder Cancer UK. Action Bladder Cancer UK is a registered charity. Action Bladder Cancer UK has received 32% pharmaceutical company funding in the past two years with none from the submitting company. A representative from Action Bladder Cancer UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing pembrolizumab with gemcitabine / carboplatin in adult patients with locally advanced or metastatic urothelial carcinoma who have not received prior therapy and are considered cisplatin ineligible and whose tumours express PD-L1 with a combined positive score (CPS)≥10. Based on SMC clinical expert feedback the comparator seems reasonable but it is noted that there may be some patients for whom best supportive care may be an appropriate comparator.

A three-state partitioned survival model was used, with health states consisting of PFS, post-progression, and death. The time horizon was 20 years, and a weekly cycle length was adopted. Clinical data used in the economic analysis for PFS and overall survival (OS) estimation for pembrolizumab were based on extrapolation of the observed Kaplan-Meier data from the subgroup of patients in the KEYNOTE-052 study corresponding to the licensed indication using a piecewise approach, extrapolating from week 32 for OS using a log normal function and from week 9 for PFS using an exponential function (functions adopted were based on best statistical and visual fit). Due to a lack of head-to-head evidence, the STC and network meta-analysis (as described above) was used to estimate the treatment effect of gemcitabine / carboplatin compared with pembrolizumab for PFS and OS. A 1st order fractional polynomial model was used as the best fitting prognostic model to produce time varying HRs for PFS and for OS that worsened over time (for PFS 0.65 at 3 months, 0.93 at 15 months and 1.21 at 24 months, the final follow-up time point, and for OS 0.30 at 3 months, 0.44 at 15 months and 0.48 at 24 months).

Health-related quality of life data using the EQ-5D-3L were collected in the KEYNOTE-052 study, and a time-to-death analysis was adopted in the base case for utility estimation (with values estimated of 0.753, 0.685, 0.586, 0.548 and 0.421 for ≥360 days before death, 180 to 360 days, 90 to 180, 30 to 90 and less than 30 days to death respectively). A scenario analysis was performed using estimated utilities for the PFS and post progression health states (0.678 and 0.614 respectively, see table 3 for results). Disutilities associated with adverse events by treatment were also included derived from analysis of the EQ-5D data.

Treatment duration for pembrolizumab was estimated by extrapolating time on treatment data from KEYNOTE-052 (a Gompertz function was applied in the base case). Treatment with pembrolizumab is until progression or unacceptable toxicity. For gemcitabine / carboplatin, treatment is until disease progression, hence an assumption was made that treatment duration equates to time in the PFS state for the comparator, with a maximum treatment duration set at 18 weeks in line with clinical practice for gemcitabine / carboplatin. A stopping rule for pembrolizumab was implemented in which the maximum treatment duration was set at two years, in line with the KEYNOTE-052 study protocol.

Medicine acquisition and administration costs were included in the economic analysis. Subsequent therapy costs, consisting of docetaxel and paclitaxel were based on the proportion of patients receiving subsequent therapies in the KEYNOTE-052 study. Disease monitoring and management costs, adverse event management costs and terminal care were also included. A cost of £40 was included for PD-L1 testing based on the possible costs of testing to identify a patient with (CPS)≥10.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The base case results for pembrolizumab were an incremental cost-effectiveness ratio (ICER) of £36,147 per quality adjusted life year (QALY) vs. gemcitabine / carboplatin with the PAS, based on an incremental cost of £56,491incremental life years gained of 2.11 and incremental QALYs of 1.56 . A key driver of the incremental cost of pembrolizumab is the additional medicine acquisition costs, with additional disease management costs in progressive disease also incurred. The majority of the QALY gain for pembrolizumab is associated with incremental life years and QALYs obtained in the progressive disease state, with a gain of 0.2 life years 0.14 QALYs in the pre-progression health state and 1.91 life years and 1.16 QALYs (all discounted) in the post-progression state.

One way sensitivity analysis indicated the ICER was sensitive to the predicted HR for OS from the STC and NMA for gemcitabine / carboplatin vs pembrolizumab (Table 3), and scenario analysis indicated the ICER was sensitive to the method of OS extrapolation, exploratory scenarios capping the OS treatment

benefit at 12 and 24 months, and the use of utilities based on progression free and progressed states compared to time-to-death state utilities (Table 3). Use of 44 weeks instead of 32 weeks as the cut for extrapolation of pembrolizumab OS results in improved ICERs (Table 3). The results were not highly sensitive to varying PFS, cost and relative AE disutility estimates.

Table 3: selected sensitivity analysis

	Scenario analysis	**ICER with PAS price**
1	HR for OS for Gem+ Carbo vs pembrolizumab (Upper – lower bound – scale parameter)	£32,391 - £62,324
2	HR for OS set to 1 beyond 24 months	£38,707
3	PFS equivalence between both arms	£35,823
4	2nd order Fractional Polynomial (FP) time varying HRs	£40,708
5	OS cut-off at 44 weeks	£28,129
6	Overall survival (from 0 weeks – fitted to whole KM curve) with log-normal function	£39,579
7	Overall survival (from 32 weeks) with exponential function	£55,156
8	Overall survival (from 32 weeks) with log logistic function	£39,835
9	Time horizon of 15 years	£37,561
10	Time horizon of 10 years	£41,383
11	Utilities – progression based	£43,477
12	Increased cost of PD-L1 test of £130	£36,557

There are several weaknesses and uncertainties with the economic analysis:

- Only single arm clinical evidence was available for pembrolizumab for use in the economic analysis, with limited patient follow-up time and immature survival data. In addition, the data used to support the economic analysis in the population of interest is based on a small patient subgroup (n=110 PD-L1 CPS ≥10%). Hence, there is further uncertainty associated with the results, given the HRs estimated for PFS and OS and applied in the analysis are from sub-group population data.
- In the economic analysis in patients with PD-L1 CPS ≥10% the pattern for the HRs over the 24 month follow-up was different than in the whole population and worsened over time for PFS (HR of 1.21 at 24 months) and for OS (from 0.35 at 3 months, better than in the whole population in earlier months, to 0.48 at 24 months), but after extrapolation beyond 24 months still demonstrated a maintained survival benefit over time for pembrolizumab. The different HR trend seen for the PD-L1 sub-population compared to the whole population pattern indicates there is uncertainty in the robustness of the HRs estimated for the sub-group, associated with the limitations in the pembrolizumab clinical data and the ITC/STC. Hence, assuming a HR for OS of 1 at 24 months (i.e., no benefit beyond 24 months) resulted in a slightly higher ICER of £38,707/QALY with PAS. The relatively low impact on the ICER could be associated with the declining trend in the HR estimated over the first 24 months, but as mentioned above there is uncertainty in the robustness of these estimates due to limitations in the clinical data and consequent STC/ITC. The scenario analysis using the upper – lower bound scale parameter credible intervals for the OS HRs resulted in an ICER range of £32,391 - £62,324/QALY with PAS.
- In addition, the ITC/STC for the updated economic analysis compares different patient populations as the data for pembrolizumab was in PD-L1 CPS ≥ 10% patients, whereas PD-L1 status was not known for the gemcitabine+carboplatin patients from the published studies used. Therefore, there could be bias potentially in favour of pembrolizumab associated with this (given PD-L1 CPS ≥ 10% patients are estimated to have better outcomes in the pembrolizumab group).

- There are uncertainties and ICER sensitivity associated with the approaches adopted for OS extrapolation, as shown in scenarios 7 and 8 in table 3. Fitting a function to the whole observed data overcomes the issue of the time point from which to extrapolate from with the piecewise approach, However the SMC Statistical Advisor has commented that using a piecewise approach may be appropriate to use in the economic analysis.
- The time horizon of 20 years in the base case is long given the observed median overall survival of just 11.0 months in the most recent data analysis. Long-term survival benefit (e.g. beyond 10 years) is highly uncertain. Reducing the time horizon increases the ICER; for a time horizon of 10 years the ICER was estimated at £41,383/QALY (Table 3).
- The economic model included a treatment stopping rule at two years, and it is uncertain whether a stopping rule would be applied in clinical practice.
- There is some uncertainty associated with the costs associated with PD-L1 testing, but as shown in table 4, using a higher price of £130 per test did not materially affect the ICER.

The Committee considered the benefits of pembrolizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as pembrolizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept pembrolizumab for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

All published guidelines predate the licensing of the immunotherapy checkpoint inhibitors.

The National Institute for Health and Care Excellence (NICE) published national guideline 2; Bladder cancer: diagnosis and management, in February 2015. In patients with locally advanced or metastatic muscle-invasive bladder cancer, first-line chemotherapy is cisplatin-based. For patients with locally advanced or metastatic urothelial bladder cancer and an ECOG performance status of 0 to 2 who are unsuitable for cisplatin-based chemotherapy due to poor performance status, inadequate renal function or co-morbidities, carboplatin plus gemcitabine is recommended.[14]

The European Society for Medical Oncology (ESMO) published Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up, in 2014. This recommends cisplatin-based chemotherapy as standard first-line treatment for patients with advanced surgically unresectable and metastatic patients who are fit enough to tolerate cisplatin. The guideline suggests that approximately half of patients are unfit for cisplatin-based chemotherapy due to poor performance status, impaired renal function or co-morbidities. It is recommended that these patients may be palliated with carboplatin-based chemotherapy (carboplatin plus gemcitabine or methotrexate plus carboplatin plus vinblastine [M-CAVI]). These regimens are active for patients unfit for cisplatin but do not offer a statistically significant advantage in PFS or overall survival. Since toxicity is slightly higher with M-CAVI, carboplatin plus gemcitabine is the preferred treatment for unfit patients.[8]

The European Association of Urology (EAU) updated their guideline on muscle-invasive and metastatic bladder cancer, in 2017. Cisplatin-based chemotherapy is recommended as standard of care for fit patients with metastatic bladder cancer. However more than half of patients are unfit for cisplatin. Carboplatin-based chemotherapy (carboplatin plus gemcitabine or M-CAVI) was inferior to

cisplatin-based regimens but provided limited benefit in patients with performance status of 2 and impaired renal function who were unfit for cisplatin.[15]

Additional information: comparators

Carboplatin-based regimen, or best supportive care.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
pembrolizumab	**3-week cycle** **200mg by IV infusion on day 1**	**5,260**
carboplatin plus gemcitabine	3-week cycle carboplatin AUC 4.5 by IV infusion on day 1 gemcitabine 1,000mg/m^2 by IV infusion on days 1 and 8	172

IV = intravenous; AUC = area under the curve. Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 05 March 2018. Costs calculated using the full cost of vials / ampoules assuming wastage and based on body surface area of 1.8m^2 and creatinine clearance of 50mL/min. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 19 patients eligible for treatment with pembrolizumab in year 1, rising to 20 patients in year 5 to which confidential estimates of treatment uptake were applied.

Without PAS

The gross impact on the medicines budget was estimated to be £986k in year 1 rising to £1.04m in year 5. As other medicines were expected to be displaced the net budget impact was £979k in year 1 rising to £1.035m in year 5. Taking into account additional costs associated with PDL-1 testing, the overall impact was estimated at £985k in year 1 rising to £1.04m in year 5.

*Other data were also assessed but remain commercially confidential.**

References

1. Electronic Medicines Compendium. KEYTRUDA 25 mg/mL concentrate for solution for infusion. 2018 [cited 2018 Jul 13]; Available from: http://www.medicines.org.uk/emc/medicine/33162.

2. Electronic Medicines Compendium. KEYTRUDA 50 mg powder for concentrate for solution for infusion. 2018 [cited 2018 Jul 13]; Available from: http://www.medicines.org.uk/emc/medicine/30602.

3. European Medicines Agency. European Public Assessment Report; EMA/512404/2017. 2017.

4. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T*, et al.* First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. The Lancet Oncology. 2017;18(11):1483-92.

5. NCT02335424: study of pembrolizumab (MK-3475) in participants with advanced urothelial cancer (MK-3475-053 / KEYNOTE-52). 12 February 2018 [cited 20 February 2018]; Available from: www.clinicaltrials.gov.

6. *Commercial in Confidence**

7. O'Donnell P BP, Bellmunt J, . Biomarker findings and mature clinical results form KEYNOTE-052: first-line pembrolizumab in cisplatin ineligible advanced urothelial cancer. American Society of Clinical Oncology 2017

8. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25 Suppl 3:iii40-8. Epub 2014/08/07.

9. Bristol-Myers Squibb Pharmaceuticals limited. Opdivo 10mg/mL concentrate for solution for infusion - summary of product characteristics. 12 January 2018 [cited 05 March 2018]; Available from: www.medicines.org.uk.

10. Roche Products Limited. Tecentriq 1,200mg concentrate for solution for infusion - summary of product characteristics. 10 November 2017 [cited 05 March 2018]; Available from: www.medicines.org.uk.

11. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P*, et al.* Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30:191-9.

12. Powles T, Gschwend JE, Loriot Y, Bellmunt J, Geczi L, Vulsteke C*, et al.* Phase 3 KEYNOTE-361 trial: Pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer. Journal of Clinical Oncology. 2017;35(15 Supplement 1).

13. Study of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy alone in urothelial carcinoma (MK-3475-361/KEYNOTE-361): NCT02853305. 2018 02 March 2018 [cited 05 March 2018]; Available from: www.clinicaltrials.gov.

14. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management (NG2). 2015 [cited; Available from: https://www.nice.org.uk/guidance/NG2.

15. Alfred Witjes J, Lebret T, Comperat EM, Cowan NC, De Santis M, Bruins HM*, et al.* Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017;71(3):462-75. Epub 2016/07/05.

This assessment is based on data submitted by the applicant company up to and including 11 June 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.