SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND

pembrolizumab 25mg/mL concentrate for solution for infusion and 50mg powder for concentrate for solution for infusion (Keytruda®)

SMC No 1291/18

Merck Sharp and Dohme Limited

12 January 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 assessed under the end of life and orphan medicine process

pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland.

Indication under review: as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

SMC restriction: treatment with pembrolizumab is subject to a two-year clinical stopping rule.

In a phase III study of patients with measurable urothelial carcinoma with progressive disease on or after platinum-based chemotherapy, treatment with pembrolizumab was associated with a statistically significant improvement in overall survival when compared with investigator's choice of single-agent chemotherapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pembrolizumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

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Indication

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.[1, 2]

Dosing Information

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

The recommended dose of pembrolizumab for urothelial carcinoma is 200mg administered as an intravenous infusion over 30 minutes every 3 weeks.

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.[1, 2]

Product availability date

24 August 2017

Pembrolizumab meets SMC end-of-life and orphan-equivalent criteria.

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 received prior platinum-containing chemotherapy. The pembrolizumab licence also permits use in adults who are not eligible for cisplatin-containing regimens. The submitting company has advised that this will be covered in a separate submission to SMC.

The pivotal evidence in patients who have received prior platinum-containing chemotherapy is KEYNOTE-045, a multi-centre, open-label, randomised, controlled, phase III study.[4]

The study recruited adults (≥18 years of age) with urothelial carcinoma of the bladder, urethra, renal pelvis or ureter (cytologically or histologically confirmed). Histology was to be predominantly transitional cell carcinoma. Patients had measurable disease, based on Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1. Patients had either disease progression following platinum-based regimen for advanced disease, or had disease recurrence less than 12 months following completion of platinum-based neoadjuvant / adjuvant therapy. No more than two prior lines of systemic chemotherapy were permitted in the advanced disease setting. Patients had adequate coagulation and renal, hepatic, and haematological function, and Eastern Co-operative Oncology Group (ECOG) performance status

of 0, 1 or 2. Patients with ECOG performance status of 2 were excluded if they also had another adverse prognostic factor, one of: haemoglobin <100g/L, liver metastases, or had most recent chemotherapy in prior three months.[4]

All study treatments were administered every three weeks intravenously. Patients were randomised 1:1 to receive open-label pembrolizumab 200mg, or investigator's pre-selected choice of chemotherapy (paclitaxel 175mg/m^2, docetaxel 75mg/m^2, or vinflunine 320mg/m^2). Randomisation was stratified by the following prognostic factors: ECOG performance status (0 or 1 versus 2), haemoglobin (<100g/L versus ≥100g/L), presence of liver metastases, and time since last dose of chemotherapy (<3 months versus ≥3 months). Treatment was continued until RECIST-defined progression, unacceptable toxicity, withdrawal of consent, physician decision, or after two years of pembrolizumab therapy. Patients who were clinically stable with radiographic progression could continue treatment at the investigator's discretion. Early discontinuation of pembrolizumab was permitted for patients with a complete response who had received at least 24 weeks of treatment and at least two doses after initial complete response.[4]

The study had two co-primary endpoints (progression-free survival [PFS] and overall survival) which were to be analysed, intention-to-treat (ITT) in three cohorts: all patients, those with PD-L1 expression ≥1%, and in patients with PD-L1 expression ≥10%. PD-L1 progression was categorised with the combined score; the percentage of PD-L1 expressing tumour and infiltrating immune cells relative to the total number of tumour cells. Progression free survival (PFS) was the time from randomisation to disease progression (according to RECIST 1.1, assessed by blinded, independent radiological review) or death from any cause. Two interim analyses were planned.[4]

The study was stopped early following review of the second interim analysis by the data and safety monitoring committee. At the data cut-off in September 2016, the median duration of follow-up was 14.1 months. In the all-patient cohort, pembrolizumab was associated with a statistically significant improvement in overall survival, see Table 1. In the cohort of patients with PD-L1 expression ≥10%, the overall survival event rate was 63% (104/164), and the hazard ratio was 0.57 (95% confidence interval [CI]: 0.37 to 0.88), p=0.005. Median survival was 8.0 months and 5.2 months in the pembrolizumab and control groups, respectively. Analysis of survival in the cohort of patients with PD-L1 expression ≥1%, was not formally part of the analysis plan for the second interim analysis; the hazard ratio for this cohort also favoured pembrolizumab at this data cut-off, 0.61 (95% CI: 0.43 to 0.86).[1, 2, 4]

No statistically significant difference in PFS was demonstrated in the all-patient cohort (see Table 1), or the cohort with PD-L1 expression ≥10%.[4]

Tumour responses were secondary outcomes. In the all-patient ITT population, the objective response rate (ORR) was 21% in the pembrolizumab group and 11% in the control group, p=0.001. Complete responses were achieved in 7.0% and 3.3% of patients, respectively. The median duration of response had not yet been reached in the pembrolizumab group, and was estimated to be 4.3 months in the control group. At data cut-off (median follow up 14.1 months), 72% (41/57) of responders to pembrolizumab had maintained their response, as did 35% (11/31) of control group responders.[4]

At a later data cut-off in May 2017, with median duration of follow-up of 22.5 months, pembrolizumab continued to demonstrate statistically significant overall survival benefit versus control. According to Kaplan-Meyer estimates, 18-month overall survival rates were 33.2% (95% CI: 27.5 to 38.9) for pembrolizumab versus 19.7% (95% CI: 14.7 to 24.8) for chemotherapy. The median duration of tumour response had not yet been reached in the pembrolizumab group versus 4.4 months in the control group.[11]

Table 1: Co-primary outcomes in the second interim analysis of KEYNOTE-045 (all-patient, ITT population)[1, 2, 4]

Outcome		pembrolizumab (n=270)	control group (n=272)
Overall survival	Events, number (%)	155 (57%)	179 (66%)
	Median	10.3 months	7.4 months
	12-month rate	44%	31%
	Hazard ratio (95% CI)	0.73 (0.59 to 0.91), p=0.002	
PFS	Events, number (%)	218 (81%)	219 (81%)
	Median	2.1 months	3.3 months
	12-month rate	17%	6.2%
	Hazard ratio (95% CI)	0.98 (95% CI: 0.81 to 1.19), p=0.42	

ITT = intention-to-treat, CI = confidence interval, PFS = progression-free survival

Patient-reported outcomes were exploratory outcomes of KEYNOTE-045; the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and Euroqol-5D (EQ-5D) tools were used.[4] The time to deterioration of global health status measured by EORTC QLQ-C30 (change of 10 points) was delayed in patients treated with pembrolizumab versus control; hazard ratio 0.70 (95% CI: 0.55 to 0.90).[1, 2] Analysis of change in global health from baseline to week 15 suggests global health status was stable with pembrolizumab, but declined with control treatment.[1, 2]

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

Summary of evidence on comparative safety

Treatment-related adverse events (AEs) were reported in 61% of pembrolizumab-treated patients and 90% of patients in the control group. They were at least grade 3 in severity in 15% and 49% of patients respectively. Discontinuation due to treatment-related AEs occurred in 5.6% and 11% of patients respectively.[4]

Treatment-related pruritus was more frequently reported in patients in the pembrolizumab group (20%) versus control (2.7%). Treatment-related AEs reported less frequently in the pembrolizumab group than the control group were: alopecia (no pembrolizumab patients versus 38% of control patients), fatigue (14% versus 28% respectively), anaemia (3.4% versus 25%), nausea (11% versus 24%), constipation (2.3% versus 20%), decreased appetite (8.6% versus 16%), neutropenia (nil versus 15%), decreased neutrophil count (nil versus 14%), asthenia (5.6% versus 14%), diarrhoea (9.0% versus 13%), peripheral sensory neuropathy (nil versus 11%), and peripheral neuropathy (0.4% versus 11%).[4]

Immune-mediated AEs of interest were reported in 17% of pembrolizumab and 7.5% of control group patients; they were at least grade 3 severity in 4.5% and 1.6% of patients respectively. Events of interest of at least grade 3 severity reported in at least 1% of pembrolizumab patients were pneumonitis (2.3% versus no control patients), and colitis (1.1% versus no patients).[4]

Four patients in each treatment group died from a treatment-related AE. In the pembrolizumab group, the deaths were due to pneumonitis (n=1), urinary tract obstruction (n=1), malignant neoplasm progression (n=1) and unspecified cause (n=1); in the control group, deaths were due to sepsis (n=2), septic shock (n=1) and unspecified cause (n=1).[4]

Summary of clinical effectiveness issues

Pembrolizumab is the third PD-1 targeted antibody to be licensed for use in patients with urothelial carcinoma.

There is no standard of care for patients who progress during or after platinum-based combination chemotherapy. In the second-line setting, UK and European guidance recommend use of cisplatin (or carboplatin in patients not eligible / unable to tolerate cisplatin) in combination with gemcitabine, taxane-based regimen, vinflunine (not recommended by SMC), best supportive care (BSC) or entry into a clinical study.[6-8]

SMC clinical experts consider that there is unmet need in this therapeutic area; often patients are not fit enough for aggressive chemotherapy, and the effectiveness of treatment is limited. In a recent meta-analysis the pooled median overall survival of second-line single-agent chemotherapy (paclitaxel, docetaxel or vinflunine) was 6.98 months.[9] SMC clinical experts also advise that active treatment options offered to patients include: platinum re-challenge if eligible (eg good response, progression-free interval of at least six months and fit enough), or single-agent paclitaxel (off-label).

Pembrolizumab meets SMC end-of-life and orphan-equivalent criteria.

The KEYNOTE-045 study found that pembrolizumab treatment was associated with a statistically significant improvement in overall survival when compared with investigator's pre-selected single-agent chemotherapy; there was no advantage in terms of PFS.

While the overall survival treatment effect was modest in the full study population (unadjusted extension of median survival of 2.9 months in all patients), this is in the context of limited survival following standard second-line chemotherapy. The extension of median survival tended to increase in cohorts selected by PD-L1 expression, although no formal interaction tests for treatment effect by PD-L1 expression were presented to confirm this observation and there is some uncertainty on the predictive value of PD-L1 expression. Since the study was stopped early at the point of interim analysis, survival curves were not yet mature to characterise the size of any long-term survivor cohort; two- or three-year survival rates were not able to be estimated at the cut-off and future results from subsequent data cut-offs may be confounded by treatment switching / crossover.

The survival curves for overall survival suggested an early favourable effect for the control with a crossover around month three to four. The European Medicines Agency reported that there was a higher rate of censoring in the control group in the first two months. Factors associated with early death were presence of liver metastases and time from most recent prior therapy <3 months.[10]

KEYNOTE-045 did not demonstrate a significant treatment effect for the co-primary outcome of PFS. A different pattern of response is associated with immunotherapies, including the initial appearance of pseudo-progression on radiological imaging; PFS (assessed by RECIST) may not fully capture their clinical benefits.

The magnitude of clinical benefit is enhanced when the comparative tolerability of pembrolizumab (versus chemotherapy) is also considered.

The open-label design may have contributed to an imbalance in patient drop-out. A higher proportion of patients discontinued study medication due to withdrawal of patient consent or due to physician decision in the control arm (n=56) compared to the pembrolizumab arm (n=9).[10] This drop-out (and censoring of patient data) may have contributed to the early benefit in overall survival observed with control in the study and described above.

Baseline characteristics between the treatment groups in the all-patient population were generally well balanced for important Bellmunt prognostic factors with the exception of ECOG performance status; a greater proportion of pembrolizumab patients compared with control were performance status 0 (44% versus 39% respectively). In addition, a greater proportion of pembrolizumab patients were participating in the study in the second- or later-line for advanced disease, when compared with control treatment (88% versus 80%); where a corresponding 8% more control patients were participating following receipt of neoadjuvant / adjuvant platinum-therapy.

At the time of interim analysis, crossover was not permitted, however 13% of patients in the control group had subsequently been treated with immunotherapy.[4] The company provided analyses taking into account the potential confounding from treatment switching in its submission and this had a small effect on the hazard ratio for overall survival (HR ranging from 0.68 to 0.70 versus 0.73).

Of the patients in the control group, paclitaxel was given to 31%, docetaxel to 31% and vinflunine to 32%. 6.3% of patients dropped-out before receiving chemotherapy. In sub-group analysis, the treatment effect of pembrolizumab was similar regardless of chemotherapy agent administered.[4] As previously noted, vinflunine is not routinely used in NHS Scotland. The company conducted a *post-hoc* subgroup analysis in which patients whose investigator had selected vinflunine pre-randomisation were excluded. Overall survival was corrected for treatment switching using various statistical approaches. Results of these analyses were used in the economic modelling.

Although KEYNOTE-045 permitted recruitment of patients with ECOG performance status 2 (in certain circumstances), only 1.1% (6/542) patients were categorised ECOG performance status 2.[4]

No comparative data for pembrolizumab and platinum re-challenge, or best supportive care were presented. This was because there were insufficient data to conduct indirect treatment comparisons with platinum re-challenge and best supportive care was not considered to be an appropriate comparator for patients with reasonable performance status (ECOG 0 to 2) eligible for active treatment.

The optimal duration of treatment with pembrolizumab is uncertain. While patients in the KEYNOTE-045 study could continue to receive pembrolizumab for a maximum duration of two years, it is unclear whether treatment of the small proportion of long-term responders would be stopped at two years in clinical practice.

Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to the improvement in overall survival coupled with favourable tolerability and suitability for a broader range of patients when compared with current treatment options. They considered that the place in therapy was in accordance with pembrolizumab's licensed indication.

Paclitaxel is often administered on a weekly schedule. Pembrolizumab would offer an advantage for patients with less frequent attendance at three-weekly intervals. Furthermore, in contrast to other options, pembrolizumab does not require pre-medication (unless infusion-related reactions occur)[1, 2] and may have a shorter infusion time.

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

Summary of patient and clinician engagement

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 / end-of-life medicine, in the context of treatments currently available in NHS Scotland.
The key points expressed by the group were:

- A diagnosis of metastatic urothelial cancer is devastating to patients and carers. The prognosis for patients is very poor, with little opportunity for patients to spend quality time with their loved ones.

- There is no current standard of care for patients following treatment with a platinum-based regimen. Treatment options are cytotoxic medicines (with limited evidence of survival benefit) and are poorly tolerated in this elderly patient group.

- Pembrolizumab appears to be a well-tolerated treatment which offers improved quality of life alongside the opportunity of prolonged survival, especially in the cohort of patients who achieve durable tumour responses (around one in five patients). Pembrolizumab treatment may therefore allow patients to continue a highly valued active, independent lifestyle for longer.

- The burden of treatment with pembrolizumab is expected to be lower than second-line chemotherapy with less frequent and shorter hospital visits for administration (30-minute infusion every three weeks) as well as fewer attendances to manage adverse events. Clinicians noted that ongoing treatment of the small proportion of long-term responders would have some impact on outpatient clinics.

- Clinicians noted developing expertise in managing immune-mediated adverse events associated with immunotherapies such as pembrolizumab.

- PACE participants stressed that pembrolizumab addresses an unmet need by providing an effective well tolerated treatment in this patient group.

Additional Patient and Carer Involvement
We received a patient group submission from Fight Bladder Cancer, which is a registered charity. Fight Bladder Cancer has received 5.3% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Fight Bladder Cancer 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 submitting company presented a cost-utility analysis that evaluated pembrolizumab as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Pembrolizumab was compared against standard of care (SOC), which was defined as a weighted average of paclitaxel (49%) and docetaxel (51%).

The economic evaluation used a partitioned survival cost-effectiveness model, consisting of three states (pre-progression, post progression, and dead). Post-progression state occupancy is determined as the difference between progression free and overall survival (OS) where these endpoints are modelled directly. The time horizon for the analysis was 35 years.

The model was based on data from KEYNOTE-045 (post hoc analyses excluding vinflunine, though there was no statistically significant interaction effect by individual agent in the control group), and estimated time to progression and death using observed Kaplan-Meier (KM) data up to 21 and 40 weeks respectively, and then longer term outcomes extrapolated using parametric functions fitted to the study data. For both endpoints separate parametric functions were fitted to each arm based on rejection of proportional hazards. Due to treatment switching following progression, both the KM data and parametric functions in the pembrolizumab arm were adjusted based on a simplified two-stage method. The choice of appropriate time to event distribution for OS (lognormal) was based on proximity to Cancer UK 5-year relative survival in stage IV bladder cancer.

Adverse events were included based on incidence in KEYNOTE-045 (grade 3+ of any adverse event occurring in 5% or more of patients in either treatment arm). Nine adverse event types were included in the model, and in each case incidence was higher in the SOC arm.

Health related quality of life weights (utilities) were estimated from study data based on time to death rather than model states (though the latter was addressed in sensitivity analyses). At greater than 360 days to death, the pooled utility estimate across both arms was 0.78, declining to 0.69 (days 180 to 360), 0.59 (90 to 180), 0.45 (30 to 90), and ultimately 0.33 (<30 days). Disutilities for adverse events were also included in the analysis.

The model's total costs for pembrolizumab depend on a stopping rule for pembrolizumab (at 24 months) which follows from the trial protocol. Resource use largely reflected assumptions in a previous UK HTA submission for urothelial cancer, supplemented with published estimates for resource use at point of terminal care in a range of cancers.

A complex Patient Access Scheme proposed by the submitting company was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case results and selected sensitivity analyses including the pembrolizumab PAS are presented in the tables below.

Table 2: Base case results (with PAS)

Comparator	Incremental cost	Incremental QALY*	ICER(£)**
SOC	£39,115	0.85	45,833

*Quality adjusted life year

**Incremental cost effectiveness ratio

Table 3: Selected sensitivity analysis (with PAS)

Scenario	ICER (£)
Switchover – ITT (no adjustment)	64,101
Switchover- RPSFT adjustment	31,509
OS cut-off – 24 weeks	34,168
UK SOC as for UK market shares	45,940
Utilities – progression based (per arm)	42,738
Utilities - time to death (per arm)	49,555
Utilities - progression (pooled arms)	54,665
Common post 24-month OS hazards	58,104

Weibull OS	89,337
No stopping rule	£52,806

Issues relating to the modelled cost-effectiveness analysis include:

- The analysis is predicated on a 24 month stopping rule based on the KEYNOTE-045 study protocol; it is uncertain whether in clinical practice treatment would cease at 24 months. Sensitivity analyses with on-going acquisition and administration costs for pembrolizumab beyond 24 months increased the ICER (see Table 3 above).
- The parametric function adopted produced very long tails in the survival curve estimated by the model, and alternative, less favourable assumptions as to long term survival (in both pembrolizumab and SOC arms) can increase the ICER substantially. For example the company provided a sensitivity analysis where patients in the pembrolizumab arm switched to the risk of death for SOC patients at 24 months. The results of this analysis are presented in Table 3 above.

The Committee also 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 a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and a substantial improvement in quality of life. In addition, as pembrolizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

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

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

Additional information: guidelines and protocols

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, second-line chemotherapy options include gemcitabine plus cisplatin, or accelerated (high-dose) MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) in combination with granulocyte-colony stimulating factor for people with incurable locally advanced or metastatic urothelial bladder cancer who have progressed after first-line chemotherapy in patients with adequate renal function (glomerular filtration rate ≥60mL/min/1.73m^2) and are physically fit (ECOG performance status 0 or 1).
- In patients with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it, then second-line chemotherapy options include carboplatin plus paclitaxel or gemcitabine plus paclitaxel.[10]

The European Society for Medical Oncology (ESMO) published "Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up", in 2014. In patients with progression <12 months after first-line chemotherapy treatment with vinflunine, taxane-based regimen or clinical trial is recommended and in patients who progressed >12 months, re-challenge with platinum-based regimen is recommended. The guideline notes that in patients with advanced or metastatic disease results of second-line chemotherapy treatments from phase II data are highly variable with results depending on patient selection. Prognostic factors have been developed (haemoglobin, presence of liver metastases and ECOG performance status) and risk increases as number of these present increases. Phase III data indicate that vinflunine plus best supportive care has modest activity versus best supportive care.[7]

The European Association of Urology (EAU) updated their guideline on "Muscle-invasive and metastatic bladder cancer", in 2017. In patients progressing at least six to twelve months after first-line cisplatin-based combination chemotherapy then re-challenge with cisplatin-containing regimen is suggested. Otherwise, in patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine or entry into a clinical trial are options.[8]

Additional information: comparators

Paclitaxel, gemcitabine plus cisplatin or carboplatin. The PD-L1 inhibitors nivolumab and atezolizumab are also licenced for the treatment of locally advanced or metastatic urothelial cancer.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
pembrolizumab	**3-week cycle** **200mg IV on day 1**	**5,260**
Nivolumab	2-week cycle 3mg/kg IV on day 1	2,633
Atezolizumab	3-Week cycle 1,200mg IV on day 1	3,808
paclitaxel	4-week cycle 80mg/m^2 IV on days 1, 8 and 15	902
paclitaxel	3-week cycle 175mg/m^2 IV on day 1	668
carboplatin plus gemcitabine	3-week cycle carboplatin AUC 4.5* IV on day 1 gemcitabine 1,000mg/m^2 IV on days 1 and 8	192
cisplatin plus gemcitabine	4-week cycle cisplatin 70mg/m^2 IV on day 2 of 28-day cycle gemcitabine 1,250mg/m^2 IV on days 1, 8 and 15	185

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS on 03 October 2017 and BNF online on 11 October 2017. Costs calculated using 1.8m^2 body surface area and using the full cost of vials / ampoules assuming wastage. Costs do not take any patient access schemes into consideration. assumes creatinine clearance 60mL/min resulting in dose of 400mg.

Additional information: budget impact

The submitting company estimated there would be 51 patients eligible for treatment with pembrolizumab in year 1 rising to 54 patients in year 5 to which confidential uptake rates were applied

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

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11. De Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ *et al*. Pembrolizumab versus paclitaxel, docetaxel, or vinflunine for recurrent, advanced urothelial cancer: mature results from the phase 3 KEYNOTE-045 trial. Abstract presented at: 2017 ESMO Congress; September 8-12; Madrid, Spain. Abstract LBA37

This assessment is based on data submitted by the applicant company up to and including 28 November 2017.

*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 medicine 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.