Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2247

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

Merck Sharp and Dohme Limited

7 August 2020

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life process:

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

Indication under review: in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma in adults.

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

In an open-label, phase III study, first-line treatment with pembrolizumab plus axitinib significantly improved progression-free and overall survival in adults with advanced renal cell carcinoma compared with a vascular endothelial growth factor (VEGF)-targeting tyrosine-kinase inhibitor (TKI).

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

Dosing Information

The recommended dose of pembrolizumab as part of combination therapy is 200mg every 3 weeks administered by an intravenous infusion over 30 minutes. Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (i.e., 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.

When used in combination with pembrolizumab, dose escalation of axitinib above the initial 5mg dose may be considered at intervals of six weeks or longer.

The SPC gives recommended treatment modifications for managing adverse events. Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[1]

Product availability date

26 August 2019

Pembrolizumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. It now has marketing authorisation in combination with axitinib (vascular endothelial growth factor [VEGF]-targeting tyrosine kinase inhibitor [TKI]) for the first-line treatment of adults with advanced renal cell carcinoma.[1, 2]

The evidence comes from the open-label, randomised, phase III KEYNOTE-426 study in 861 patients with histologically confirmed renal cell carcinoma with clear cell component. Eligible patients had locally advanced or metastatic disease (newly diagnosed or recurrent stage IV disease), measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and available tumour sample for biomarker assessment. They had received no previous treatment for advanced disease and had a Karnofsky performance status score of ≥70%. Patients were randomised equally to pembrolizumab (200mg intravenously every 3 weeks for up to 35 cycles) plus axitinib (orally 5mg twice daily continuously) or sunitinib (orally 50mg daily in 6-week cycles of 4 weeks on and 2 weeks off treatment). The axitinib dose could be adjusted

(upwards to 7mg and then 10mg twice daily according to safety criteria or downwards to 3mg and then 2mg twice daily to improve tolerability). The sunitinib dose could be reduced to 37.5mg daily and then 25mg to manage toxic effects. Study treatment was continued until disease progression, unacceptable toxicity or withdrawal by patient or investigator (or for up to 35 cycles of pembrolizumab). Randomisation was stratified by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups (favourable, intermediate or poor) and geographic area (North America, Western Europe or the rest of the world).[2, 3]

The study had two co-primary outcomes: overall survival (defined as the time from randomisation to death due to any cause) and progression-free survival (PFS, defined as the time from randomisation to first documented disease progression according to RECIST version 1.1 assessed by blinded independent central review, or death due to any cause). Analysis was performed in the intention to treat (ITT) population, which comprised all randomised patents. An interim analysis of PFS was planned after 305 PFS events and all patients had been followed up for ≥7 months. At this interim analysis (data cut-off August 2018) median PFS and overall survival were both significantly longer in the pembrolizumab plus axitinib group compared with the sunitinib group. Details are presented in table 1 below. The key secondary outcome was objective response rate (ORR) according to RECIST version 1.1 assessed by blinded independent central review. At the first interim analysis (data cut-off August 2018) ORR was significantly higher in the pembrolizumab plus axitinib group compared with the sunitinib group. The duration of response and disease control rate, both based on blinded independent central review, were other secondary outcomes and results favoured pembrolizumab plus axitinib group over sunitinib.[2, 3]

Table 1: Results of the co-primary and key secondary outcomes of KEYNOTE-426[1-3]

	Pembrolizumab plus axitinib (n=432)	Sunitinib (n=429)	Hazard ratio or difference (95% CI)
PFS			
Median follow-up for PFS analysis (data cut-off August 2018)	13.2 months	12.1 months	
PFS event (n)	183	213	
Median PFS	15.1 months	11.1 months	0.69 (0.57 to 0.84) P<0.001
Estimated PFS rate at 12 months	60%	46%	
Estimated PFS rate at 18 months	41%	33%	

Overall survival			
Median follow-up for overall survival analysis (data cut off August 2018)	13.2 months	12.1 months	
Deaths (n)	59	97	
Median overall survival	Not reached	Not reached	0.53 (0.38 to 0.74) P<0.001
Estimated survival at 12 months	90%	78%	
Estimated survival at 18 months	82%	72%	
Secondary outcome: ORR			
ORR	59% (256/432)	36% (153/429)	24% (17% to 30%), p<0.001
Complete response	5.8% (25/432)	1.9% (8/429)	
Partial response	53% (231/432)	34% (145/429)	

PFS: progression-free survival; CI: confidence interval; ORR: objective response rate

Results at a later, unplanned analysis (data cut-off January 2019) after a median follow-up of 17.4 months in the pembrolizumab plus axitinib group and 15.7 months in the sunitinib group, also found significantly longer overall survival in the combination group; hazard ratio 0.59 (95% confidence interval [CI]: 0.45 to 0.78), although median overall survival was still not reached in either group. In an abstract report of a later analysis (data cut-off January 2020, after a median follow up of 27 months), median overall survival was not reached in the pembrolizumab plus axitinib group compared with 35.7 months in the sunitinib group; hazard ratio 0.68 (95% CI: 0.55 to 0.85).[2, 4]

At the interim analysis (data cut-off August 2018), subgroup analyses for both PFS and overall survival indicated that the treatment effects were consistent with the overall population. Subgroup analyses included age, sex, geographic region, IMDC risk category, Karnofsky performance status score, PD-L1 status and number of organs with metastases.[2, 3]

Two patient reported outcomes were assessed during the study: time to true deterioration and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) score. At the interim analysis (data cut-off August 2018) the time to true deterioration (defined as the time to first onset of ≥3 decrease from baseline in the Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms [FKSI-DRS]) favoured sunitinib over pembrolizumab plus axitinib; hazard ratio 1.44 (95% CI: 1.14 to 1.82). At this time, the EORTC QLQ-C30 score found no clinically meaningful differences from baseline to week 30 in the EORTC QLQ-C30 global health status score for patients in both groups.[2]

The submitting company presented indirect treatment comparisons with pazopanib, sunitinib and tivozanib in treatment-naïve adult patients with advanced or metastatic renal cell carcinoma (four studies) and with nivolumab plus ipilimumab in the subgroup of patients with intermediate- or poor-risk disease (two studies). These were Bayesian network meta-analyses (NMAs) using fixed effects models and assessed PFS and overall survival. The NMAs were performed using constant and time-varying hazard ratio analyses and, although there was evidence that the proportional hazards assumptions had been violated, the NMA results using time-varying hazard ratios were more uncertain and the NMA results using constant hazard ratios which had narrower credible intervals were considered more appropriate by the company. In the overall population, the NMA results indicated that pembrolizumab plus axitinib improved PFS compared with pazopanib, sunitinib and tivozanib and overall survival compared with pazopanib and sunitinib. Results of the NMA in the intermediate- or poor-risk subgroup found no evidence of a significant difference between pembrolizumab plus axitinib and nivolumab plus ipilimumab in PFS and overall survival, although the results numerically favoured pembrolizumab plus axitinib. The time-varying hazard ratio NMA results varied at different timepoints.

Summary of evidence on comparative safety

Safety was assessed in the treated population of KEYNOTE-426, which comprised all randomised patients who had received at least one dose of study medication: pembrolizumab plus axitinib (n=429) or sunitinib (n=425) and reported from the first interim analysis (data cut-off August 2018). An adverse event was reported in 98% of pembrolizumab plus axitinib patients and 99% of sunitinib patients and were considered related to study treatment in 96% and 98% of patients respectively. Adverse events of grade 3 or higher were reported in 76% of pembrolizumab plus axitinib patients and 71% of sunitinib patients and were considered to be related to study treatment in 63% and 58% of patients respectively. Adverse events led to discontinuation of either pembrolizumab or axitinib in 30% of patients and sunitinib in 14% of patients.[3]

The most frequently reported treatment-related adverse events in the pembrolizumab plus axitinib and sunitinib groups respectively were: diarrhoea (49% versus 41%), hypertension (42% versus 43%), hypothyroidism (31% versus 28%), fatigue (30% versus 33%), palmar-plantar erythrodysesthesia (28% versus 40%), increased alanine aminotransferase (24% versus 13%), dysphonia (23% versus 2.8%), increased aspartate aminotransferase (23% versus 14%), decreased appetite (22% versus 25%), nausea (21% versus 26%), proteinuria (15% versus 9.2%), stomatitis (14% versus 20%), mucosal inflammation (13% versus 21%), pruritus (12% versus 4.2%), arthralgia (12% versus 3.5%), hyperthyroidism (12% versus 3.3%), asthenia (12% versus 13%), rash (11% versus 8.9%) and dysgeusia (9.3% versus 30%).[3]

Eleven patients in the pembrolizumab plus axitinib group and 15 patients in the sunitinib group died due to an adverse event. There were four deaths in the pembrolizumab plus axitinib group due to adverse events considered to be related to study treatment: one each due to myasthenia gravis, myocarditis, necrotizing fasciitis and pneumonitis. There were seven deaths in the sunitinib

group due to adverse events considered to be related to study treatment: one each due to acute myocardial infarction, cardiac arrest, gastrointestinal haemorrhage, intracranial haemorrhage, hepatitis fulminant, progression of malignant neoplasm and pneumonia.[3]

Summary of clinical effectiveness issues

Standard first-line treatment of advanced renal cell carcinoma has been based on monotherapy with VEGF-targeting TKIs, including sunitinib, pazopanib and tivozanib. However, first-line treatment is evolving to include immunotherapy and some European clinical guidelines have recently been updated.[5, 6] The combination of pembrolizumab (PD-L1 inhibitor) plus axitinib (TKI) is one of three immunotherapy combination regimens recently licensed for the first-line treatment of advanced renal cell carcinoma. Nivolumab (PD-L1 inhibitor) plus ipilimumab (CTLA-4 immune checkpoint inhibitor) is only licensed for the treatment of adult patients with intermediate or poor-risk disease and has been accepted for use by SMC. Avelumab (PD-L1 inhibitor) and axitinib (TKI) has also been licensed for the first-line treatment of adult patients with advanced renal cell carcinoma of any risk category; this combination is currently being assessed by SMC. The key studies for relevant comparators, either immunotherapy or VEGF-targeted therapy, for first-line treatment of advanced renal cell carcinoma would indicate median overall survival of 2 to 2.5 years. Pembrolizumab plus axitinib was considered to meet SMC end of life criteria for this indication.

The results from the interim analysis of the key study (KEYNOTE-426) have shown that PFS and overall survival were significantly longer with pembrolizumab plus axitinib compared with sunitinib for the first-line treatment of advanced renal cell carcinoma. This was supported by results of the key secondary outcome of ORR. The absolute improvement in median PFS was 4.1 months. Although results found a significant improvement in overall survival with pembrolizumab plus axitinib, the number of deaths in both treatment groups was small and median overall survival had not been reached. The results are therefore immature and final overall survival results are awaited. The subsequent use of anticancer treatment, including a higher frequency of PD-L1 or PD-1 inhibitor after disease progression in the sunitinib group compared with the pembrolizumab plus axitinib group (21% versus 1.9%, respectively), may confound future overall survival results.[2, 3]

KEYNOTE-426 was of open-label design but assessment of PFS and response was based on blinded independent committee review, which would minimise potential bias for these outcomes but not for safety or quality of life. PFS was also assessed by the investigator and in approximately 20% of assessments there was disagreement between the independent review and the investigator. Investigator-assessed PFS found no significant difference between pembrolizumab plus axitinib and sunitinib (absolute difference of 2.6 months). [2]

KEYNOTE-426 excluded patients with symptomatic central nervous system (CNS) metastases and with poor performance status (Karnofsky score <70). Therefore the study results may not be generalisable to these patients in clinical practice.[2, 3]

The median duration of study treatment was longer in the pembrolizumab plus axitinib group (10.4 months) compared with the sunitinib group (7.8 months) and after adjustment for the difference, the safety profile was considered less favourable with pembrolizumab plus axitinib than with sunitinib, although the EMA considered it to be overall manageable. The EMA notes that the safety assessment of pembrolizumab plus axitinib is partially hampered by the lack of a direct comparison with axitinib but that indirect comparison with monotherapies suggests a clearly worse safety profile. There was a higher than expected incidence of hepatic adverse events in the pembrolizumab plus axitinib group of KEYNOTE-426 and the SPC recommends that liver enzymes should be monitored before the initiation of and periodically throughout treatment and recommendations are given for dose adjustment, interruption or discontinuation. A higher frequency of cardiac arrhythmias / atrial fibrillation was also observed in the pembrolizumab plus axitinib group of KEYNOTE-426 compared to the sunitinib group and a causal relationship with pembrolizumab cannot be ruled out.[1, 2]

KEYNOTE-426 compared pembrolizumab plus axitinib with sunitinib which is currently one of a number of relevant comparators for the first-line treatment of advanced renal cell carcinoma in Scotland. However, there are no directly comparative data versus the other TKIs used in Scotland (pazopanib or tivozanib) or with nivolumab plus ipilimumab in patients with intermediate or poor risk disease. The company has presented results of indirect comparisons with pazopanib, sunitinib and tivozanib in the overall population and although results indicated that pembrolizumab plus axitinib may improve PFS compared with pazopanib and tivozanib and overall survival compared with pazopanib, due to weaknesses in the use of constant hazard ratios (which narrowed the credible intervals), the limited overall survival data and the weak linking of tivozanib to the network, the NMA results were not used in the economic case. Instead, clinical equivalence between sunitinib, pazopanib and tivozanib was assumed. A direct comparison of pazopanib and sunitinib as first-line treatment found similar efficacy and provides some reassurance on this assumption.[7] The NMA results in the intermediate- or poor-risk subgroup, suggesting no or varying differences between pembrolizumab plus axitinib and nivolumab plus ipilimumab, should be interpreted with caution due to the immaturity of the evidence used.

The introduction of pembrolizumab plus axitinib for the first-line treatment of patients with advanced renal cell carcinoma would offer an immunotherapy option for patients with all risk groups of disease. Initial results indicate that the combination improved PFS and overall survival compared with sunitinib. Treatment with this combination would require an intravenous infusion of pembrolizumab every 3 weeks for up to 2 years which has implications for the patients and service compared with the first-line use of orally administered TKIs.

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 end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced renal cell carcinoma is an incurable, heterogeneous cancer and not all patients respond to treatment. The disease symptoms have a negative impact on the quality of life of patients and make daily living difficult. Anecdotal evidence suggests an increasing number of younger patients have been diagnosed in recent years and symptoms may also affect their ability to look after family and/or work.

- There is an unmet need for a greater choice of treatment options and since approximately 50% of patients will not go on to receive second-line treatment, effective first-line treatments are particularly needed.

- The combination of pembrolizumab plus axitinib has almost doubled response rate and significantly improved overall survival compared with other treatment, making it the preferred first-line treatment for the majority of patients.

- The improved response rate and potential for durable disease control with immunotherapy may improve the quality of life of patients and allow them to return to normal daily and family activities and work. Durable disease control is a feature for a proportion of kidney cancer patients, and this proportion has been greatly increased with immunotherapies.

- Although adverse events are associated with immunotherapy and TKIs, they are familiar to clinicians and are considered to be manageable.

Additional Patient and Carer Involvement

We received patient group submissions from Kidney Cancer Scotland and the Kidney Cancer Support Network. Both organisations are registered charities. Kidney Cancer Scotland has received 14% pharmaceutical company funding in the past two years, including from the submitting company. Kidney Cancer Support Network has received 47% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions 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 in combination with axitinib for the first-line treatment of advanced renal cell carcinoma (RCC) against sunitinib and also against tivozanib and pazopanib. The base case analysis was provided for the entire disease population and a sub-group analysis was provided for the intermediate and poor risk sub-population against nivolumab in combination with ipilimumab.

A partitioned survival cohort simulation model was used. The model consisted of three mutually exclusive health states: pre-progression (starting health state), post-progression and death. The cycle length was one week with patients either remaining in state, transitioning to post-progression or death at the end of each weekly cycle. The model projected two primary outcomes: overall survival and PFS. An NHS perspective and a 40-year time horizon were selected in the base case of the economic model.

The clinical effectiveness parameters for pembrolizumab with axitinib and sunitinib were estimated from an interim analysis of the KEYNOTE-426 study. This included parameters for overall survival, PFS, incidence of adverse events, treatment discontinuation, subsequent therapies and patient utilities. The model assumed clinical equivalency between sunitinib, pazopanib and tivozanib using the study data. For the intermediate/poor risk subgroup, the results of the network meta-analyses described above were used to estimate clinical effectiveness against nivolumab plus ipilimumab.

Extrapolation of overall survival and PFS was required. Parametric models were fitted to the KEYNOTE-426 Kaplan-Meier data using fully fitted parametric curves for overall survival, and a piecewise approach for PFS based on observed data up to week 13, followed by parametric models fitted to the post-week 13 data. The most appropriate distributions for overall survival and PFS were selected based on internal validity and clinical plausibility. The base case estimates are displayed in Table 2.

Table 2 – Modelled overall survival and PFS base case estimates at different time points

	Pembrolizumab + axitinib		Sunitinib	
	Overall survival	PFS	Overall survival	PFS
Distribution	*Log-logistic*	*Exponential*	*Exponential*	*Exponential*
1 year	88.5%	57.1%	79.9%	45.8%
2 year	76.8%	32.8%	63.9%	22.2%
3 year	66.7%	18.7%	50.9%	10.6%
5 year	51.9%	6.2%	32.5%	2.5%
10 year	31.6%	0.4%	10.6%	0.1%

PFS=progression free survival

The base case assumed that pembrolizumab would be administered until disease progression or for a maximum of 35 cycles (i.e. 24 months), after which axitinib monotherapy would continue until confirmation of disease progression. This was consistent with the trial protocol. An alternate scenario was explored where a stopping rule of 2 years was applied to axitinib. The base case analysis also assumed a continuous treatment effect without any waning.

After adjustment for the different durations of study treatment, safety data suggests that the tolerability of pembrolizumab plus axitinib is poorer than sunitinib with a higher rate of treatment discontinuation due to adverse events and drug-related serious adverse events. Grade 3-5 adverse events with incidence ≥5% in one or more treatment groups were therefore included in the economic model.

Utility values were based on EQ-5D-3L data from the KEYNOTE-426 study. In the base case analysis, utilities were estimated based on time-to-death. This approach categorized time-to-death into discrete groups (360+ days to death; 180-360 days to death; 30-180 days to death; under 30 days to death). EQ-5D scores collected within each time category were used to estimate mean utility associated with that category. Mean EQ-5D utility scores by health status were also estimated per treatment arm and pooled for both arms as an alternative approach. Disutilities associated with grade 3+ adverse events were included.

Acquisition and administration costs for pembrolizumab, axitinib and all comparators were included in the analysis, as were the costs associated with any subsequent second line chemotherapies. Unit costs for managing adverse events, disease management, and a one-off cost for terminal care were also accounted for.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price for pembrolizumab. PAS are also in place for axitinib, and all comparator medicines.

The base case analysis presented by the submitting company produced an ICER of £60,994 at list prices against sunitinib. This results from an estimated quality adjusted life year (QALY) gain of 2.32 and an estimated difference in costs of £141,485. The company also presented incremental cost-effectiveness ratios (ICERs) against tivozanib (£58,350 at list prices), pazopanib (£59,242 at list prices) and nivolumab in combination with ipilimumab in the intermediate and poor risk subgroup (£80,529 at list prices).

Table 3 – Base case cost-effectiveness results at list prices

Treatment	Total LYs	Incremental costs pembrolizumab with axitinib versus comparator	Incremental QALYs pembrolizumab with axitinib versus comparator	ICER
Whole population				
Pembrolizumab with axitinib	6.88	-	-	-
Sunitinib	3.86	£141,485	2.32	£60,994
Pazopanib	3.86	£137,420	2.32	£59,242
Tivozanib	3.86	£135,350	2.32	£58,350
Intermediate / poor risk subpopulation				
Pembrolizumab with axitinib	5.878	-	-	
Nivolumab with Ipilimumab	4.95	£56,656	0.70	£80,529
Sunitinib	2.936	£137,652	2.275	£60,215
pazopanib	2.936	£134,432	2.275	£59,096
Tivozanib	2.936	£132,750	2.275	£58,357
QALYs= quality adjusted life years ICER= incremental cost-effectiveness ratio LY= life years				

The results presented do not take account of the PAS for sunitinib, tivozanib, pazopanib, nivolumab or ipilimumab or the PAS for pembrolizumab and axitinib but estimates of the PAS were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for comparator medicines and medicines used in combination with pembrolizumab due to commercial confidentiality and competition law issues.

Table 4– Selected scenario analysis versus all comparators at list prices

	Scenario	**ICER vs sunitinib**	**ICER vs pazopanib**	**ICER vs tivozanib**
	Base Case	***£60,994***	***£59,242***	***£58,350***
1	OS/PFS fully exponential fit	£75,217	£73,032	£71,919
2	OS/PFS best statistical fit	£788,639	£764,709	£752,520
3	OS best statistical fit; PFS exponential	£792,057	£768,127	£755,938

4	PFS best statistical fit; OS base case	£60,743	£58,990	£58,098
5	Landmark Modelling approach	£63,107	£61,290	£60,365
6	Time-varying HR from NMA for sunitinib	£88,216	£85,638	£84,325
7	Treatment waning after 10 years	£89,251	£86,638	£85,306
8	PFS best statistical fit with time on treatment modelling	£80,320	£78,567	£77,675
9	20 year time Horizon	£70,759	£68,701	£67,652
10	Health-state based utilities (pooled, no response adjustment)	£65,220	£63,346	£62,392
11	Health-state based utilities (treatment specific)	£62,624	£60,825	£59,908
OS=overall survival; PFS=progression free survival; QALY= quality adjusted life year; ICER= incremental cost-effectiveness ratio; HR= hazard ratio; NMA=network meta-analysis.				

There were a number of limitations with the analysis which include the following:

- The sole source of data for clinical effectiveness is the ongoing KEYNOTE-426 study which is yet to reach median overall survival. The results from the interim analysis were therefore immature, which led to an over reliance on predicted outcomes to inform the economic model.
- The comparison against nivolumab with ipilimumab, restricted to the intermediate /poor risk subgroup, was based on indirect evidence that suggested no difference in comparative effectiveness. However, the model still predicted an incremental QALY gain of 0.70 for pembrolizumab. Whilst it is plausible that a clinically relevant difference may exist despite the non-significant hazard ratio, it is difficult to externally validate this through an indirect comparison. A cost-minimisation analysis against this comparator might have been more appropriate.
- Due to the immaturity of data, extrapolation of overall survival and PFS was required and parametric models were fitted to the KEYNOTE-426 Kaplan-Meier data using fully fitted parametric curves for overall survival and a piecewise approach for PFS. The most appropriate distributions for overall survival and PFS were selected based on internal validity and clinical plausibility. The choice of parametric distribution applied to overall survival is a key driver of the ICER. For pembrolizumab and axitinib, the log-logistic curve was selected for the base case

analysis due to a good visual fit to Kaplan-Meier data and because clinical experts considered the tail of the curve to be more credible based on the belief that a percentage of patients would derive a long-term survival benefit. The exponential curve had the best statistical fit but represented a constant hazard ratio over time, which was deemed unrealistic. For sunitinib, the exponential curve was selected for the base case because the best fitting log-normal curve was thought to have implausibly high 5- and 10-year survival. Clinical experts consulted by the company expected 5-year overall survival for sunitinib to be in the 20-25% range, and all of the parametric distributions predicted much higher levels of overall survival. However, small changes to the 5-year overall survival rates can lead to disproportionately large changes in the ICER. This uncertainty can only be resolved through availability of observed long-term data.

- There is uncertainty regarding the assumed absence of any treatment waning associated with pembrolizumab and axitinib. Sensitivity analysis showed that the removal of treatment effect at 10 years, at which point pembrolizumab with axitinib has the same hazard as the sunitinib arm, led to a substantial increase in ICER (table 4 scenario 7). The company also provided some additional sensitivity analysis assuming treatment waning by year 10 in a proportion of patients (16.2% of patients corresponding to those with progressive disease or who were not evaluable in the pembrolizumab arm of KEYNOTE- 426) and this resulted in an ICER of £64,707 at list prices.
- There is additional uncertainty around a suitable stopping rule for axitinib. Introducing an earlier stopping rule lowers the ICER due to reduction in ongoing medication costs, but it is unclear if this would have any impact on disease progression or overall survival.

After considering all the available evidence and the output from the PACE process, the Committee accepted pembrolizumab in combination with axitinib for restricted use in NHSScotland.

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

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO) produced a clinical practice guideline in 2019 titled Renal cell carcinoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up.[5] For the management of patients with advanced or metastatic disease the guideline recommends cytoreductive nephrectomy in patients with good performance status except in intermediate- and poor-risk patients with asymptomatic primary tumours when medical treatment is required. Radiotherapy can be used to treat unresectable local or recurrent disease and in patients unsuitable for surgery due to poor performance status or unsuitable clinical condition. Radiotherapy is an alternative if radioablation is not appropriate. Radiotherapy is an effective treatment for palliation of local and symptomatic metastatic RCC disease or to prevent the progression of metastatic disease in critical sites such as bones or brain. For first-line systemic treatment, VEGF-targeted agents and TKIs are recommended options for good- and intermediate-risk patients. The combination of nivolumab and ipilimumab is recommended for intermediate- and poor-risk patients but not for the good-risk group. Cabozantinib is EMA-approved for intermediate- and poor-risk groups. For second-line treatment, following TKIs, nivolumab or

cabozantinib is recommended. The combination of lenvatinib and everolimus following TKIs is FDA- and EMA-approved and is recommended after the nivolumab/ipilimumab combination. If none of these drugs is available, either everolimus or axitinib can be used. In patients already treated with two TKIs, either nivolumab or cabozantinib is recommended.

The European Association of Urology (EAU) guidelines on renal cell carcinoma were updated in 2019.[6] The recommendations in this guideline for the first line treatment of metastatic clear cell RCC are more recent than the ESMO recommendations above and have been updated based on recent evidence which is considered strong. This guideline recommends the use of pembrolizumab plus axitinib for the first-line treatment of patients with any IMDC risk metastatic clear-cell RCC and the use of ipilimumab plus nivolumab for patients with IMDC intermediate- and poor-risk disease. For patients who cannot receive or tolerate immune checkpoint inhibition, sunitinib or pazopanib are recommended as first-line treatment options for patients with any IMDC risk metastatic clear-cell RCC and first-line cabozantinib for those with IMDC intermediate- and poor-risk disease. The impact of front-line immune-checkpoint inhibition on subsequent therapies is unclear and the guideline notes that, after immunotherapy, it is not possible to recommend one vascular endothelial growth factor–targeted tyrosine kinase inhibitor above another. There are also no data on sequencing of immune checkpoint inhibitors after failure of immune checkpoint inhibitors and this is not currently recommended. Therefore, after progression on combination therapy with immune checkpoint inhibition, subsequent treatment should be offered with any vascular endothelial growth factor–targeted therapy that has not previously been used.

Additional information: comparators

Sunitinib, pazopanib, tivozanib, cabozantinib (not recommended for use by SMC) and nivolumab plus ipilimumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Pembrolizumab plus axitinib	**200mg intravenously every 3 weeks plus 5mg orally twice daily**	**136,894**

Costs from eVadis and eMC Dictionary of Medicines and Devices Browser on 4 December 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be an estimated 197 patients eligible for treatment with pembrolizumab plus axitinib in year 1 rising to 218 patients in year 5, and 25 patients treated in year 1 rising to 79 by year 5.

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 confidential.**

References

1. Merck Sharp & Dohme Ltd. Pembrolizumab 50mg powder for concentrate and 25mg/mL concentrate for solution for infusion (Keytruda), summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 4 September 2019.
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4. Plimock ER, Rini BI, Stus V, Gatanov R, Waddell T et al. Pembrolizumab plus axitinib versus sunitinib as first line therapy for advanced renal cell carcinoma (RCC); updated analysis of KEYNOTE-426 [astract 5001]. J Clin Oncol 2020; 38 (suppl)
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This assessment is based on data submitted by the applicant company up to and including 13 February 2020.

**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*

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 NHSScotland 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 NHSScotland 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.