Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2153

nivolumab 10mg/ml concentrate for solution for dilution (Opdivo®)

Bristol-Myers Squibb Pharmaceuticals Ltd

10 May 2019

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

nivolumab (Opdivo®) is accepted for use within NHSScotland.

Indication under review: in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (RCC).

Overall survival was significantly longer in the nivolumab plus ipilimumab group compared with a multiple receptor tyrosine kinase inhibitor in a phase III study in treatment naïve patients with intermediate/poor-risk advanced RCC.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of nivolumab in combination with ipilimumab.

Chairman
Scottish Medicines Consortium

Indication

In combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor risk advanced RCC.[1, 2]

Dosing Information

The recommended dose is 3mg/kg nivolumab in combination with 1mg/kg ipilimumab administered intravenously (IV) every 3 weeks for the first four doses. This is followed by a second phase in which nivolumab monotherapy is administered IV at either 240mg every 2 weeks or at 480mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240mg every 2 weeks

  or

- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480mg every 4 weeks

Treatment should be continued as long as clinical benefit is observed or until the patient is unable to tolerate further treatment.

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

Product availability date

15 January 2019

Nivolumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is also a key regulator of T-cell activity. Ipilimumab is a CTLA-4 inhibitor that blocks T-cell inhibitory signals and increases the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Nivolumab and ipilimumab have been shown to have synergistic anti-tumour activity (in metastatic melanoma). Nivolumab monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.[1-4]

The evidence supporting the efficacy and safety of nivolumab plus ipilimumab comes from CheckMate 214, a multicentre, randomised, open-label, active-controlled phase III study which recruited adult patients with histologically confirmed RCC with a clear-cell component. Patients were required to have advanced (not amenable to curative surgery or radiation therapy) or metastatic (American Joint Committee on Cancer [AJCC] Stage IV) RCC, and measurable disease

according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients were treatment naïve before enrolment, and had a Karnofsky performance-status score of at least 70 (scale of 0 to 100 with lower scores signifying greater disability).[3, 4]

The International Metastatic RCC Database Consortium (IMDC) risk score, based on six risk factors, was used to classify patients as favourable, intermediate, or poor prognostic risk. Intermediate risk patients had one or two risk factors at baseline, and poor risk patients had three or more. Although patients of all risk categories were included in the study, the primary objectives of the study focused on intermediate and poor risk patients only. Results in the favourable risk group of patients are not relevant to the current submission and will not be discussed.[3, 4]

Patients were randomised to receive nivolumab plus ipilimumab (n=550) or sunitinib (n=546). In the nivolumab plus ipilimumab group, patients received nivolumab 3mg/kg IV combined with ipilimumab 1mg/kg IV every 3 weeks for four doses followed by nivolumab monotherapy 3mg/kg IV every two weeks. Patients in the sunitinib group were given 50mg orally once daily for four weeks, followed by two weeks off and repeated. Randomisation was stratified according to IMDC prognostic score (0 [favourable risk] or 1 to 2 [intermediate risk] or 3 to 6 [poor risk]) and region (US or Canada/Western Europe/Northern Europe or rest of world). Treatment was allowed to continue after initial investigator-assessed progression (using RECIST v1.1 criteria), provided that the investigator felt the treatment was providing clinical benefit and the patient was tolerating treatment. Dose modifications were not permitted for the nivolumab plus ipilimumab group but were permitted for patients treated with sunitinib.[3, 4]

CheckMate 214 had three co-primary outcomes: overall survival, progression free survival (PFS), and objective response rate (ORR), each assessed in all randomised patients in the intermediate and poor risk categories. ORR was defined as the proportion of patients who achieved a best response of complete response (CR) or partial response (PR) and PFS was defined as the time between date of randomisation and the date of first progression (both independently assessed using RECIST v1.1 criteria) or death due to any cause, whichever occurred first. Overall survival was defined as the time between date of randomisation and death due to any cause. Patients were censored if lost to follow-up, if death or progression were not observed, and in the case of the primary PFS analysis, if a patient commenced subsequent anti-cancer treatment.[3-5]

At a median follow up of 25.2 months, 140 / 425 (33%) patients had died in the nivolumab plus ipilimumab group and 188 /422 patients (45%) had died the sunitinib group. Nivolumab plus ipilimumab was associated with a significant improvement in overall survival compared with sunitinib in the intermediate/poor risk population (hazard ratio [HR] 0.63 (99.8% CI: 0.44 to 0.89; p<0.001). The 12-month survival rate in the nivolumab plus ipilimumab group was 80% versus 72% in the sunitinib group, and the respective 18-month survival rates were 75% and 60%.[3, 4] A numerical benefit in PFS, assessed by independent radiological review committee (IRRC) was observed in the nivolumab plus ipilimumab group, but failed to reach statistical significance. Similarly, IRRC assessed ORR was numerically superior, however, as no formal statistical tests were prespecified, the results could not be considered statistically significant. Details of the results of the co-primary endpoints are shown in Table 1.

Table 1. Co-primary outcome results from CheckMate 214 in intermediate/poor risk patients.

	nivolumab plus ipilimumab n=425	**sunitinib n=422**
Median follow up of 25.2 months		
Median Overall Survival	Not reached	26.0 months
	HR 0.63 (99.8% CI: 0.44 to 0.89; p<0.001)	
IRRC assessed median PFS (following 456 PFS events)	11.6 months	8.4 months
	HR 0.82 (99.1% CI: 0.64 to 1.05; p = 0.03)	
IRRC assessed ORR[A] (using RECIST v1.1 criteria)	42%	27%
Confirmed best overall response		
Complete response	9%	1%
Partial response	32%	25%

IRRC = independent radiological review committee, PFS = progression free survival, ORR = objective response rate, RECIST = Response Evaluation Criteria in Solid Tumors, HR = hazard ratio, CI = confidence interval

A: ORR includes complete response and partial response.

Median time to response (TTR) was shorter in the nivolumab plus ipilimumab group compared with sunitinib in the intermediate/poor risk population (2.79 months versus 3.04 months). Furthermore, the median duration of response was not reached at the time of analysis in the nivolumab plus ipilimumab group compared with 18.17 months in the sunitinib group.[4]

Exploratory subgroup analyses were broadly supportive of nivolumab plus ipilimumab. The predefined subgroups included age, sex, race, region, baseline IMDC risk, Karnofsky performance status, previous nephrectomy, prior radiotherapy, and corrected calcium levels. All subgroup analyses favoured the combination for overall survival, whilst the majority of subgroups favoured nivolumab plus ipilimumab for PFS and ORR. Further exploratory analyses were conducted related to levels of PD-L1 expression, and showed that nivolumab plus ipilimumab was associated with longer overall survival across varying levels of PD-L1 expression.[3]

Health related quality of life (HRQoL) was assessed using three questionnaires: Functional Assessment of Cancer Therapy-General (FACT-G), the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-19) and the European Quality of Life 5 Dimensions questionnaire (EQ-5D).[5] All three questionnaires appeared to support the use of nivolumab plus ipilimumab over sunitinib. [4]

Summary of evidence on comparative safety

In the CheckMate 214 study, the median duration of treatment was 7.8 months in both treatment groups. Any treatment-related adverse event (AE) was reported by 93% of patients in the nivolumab plus ipilimumab group (n=547) and 97% in the sunitinib group (n=535). In the

nivolumab plus ipilimumab and sunitinib groups respectively, patients reporting a grade 3 or higher treatment-related AE were 46% versus 63%. The overall number of AEs (regardless of causality) that led to a dose delay or a dose reduction were 54% versus 43%, patients with a reported serious AE were 56% versus 40%, and patients discontinuing therapy due to an AE were 31% versus 21%.[3, 4]

The most commonly reported AEs in the nivolumab plus ipilimumab group (n=547) were fatigue (45%), diarrhoea (38%), pruritus (33%) and nausea (30%). In the sunitinib group (n=535), the most commonly reported AEs were diarrhoea (58%), fatigue (54%), palmar-plantar erythrodysesthesia syndrome (44%), hypertension (43%), nausea (43%) and dysgeusia (35%).[3] Immunotherapies such as nivolumab and ipilimumab have characteristically high incidences of immune-related AEs. In CheckMate 214, 80% (n=463) of patients treated with nivolumab plus ipilimumab (n=547) experienced a treatment-related immune-mediated AE. Of those 436 patients, 35% required treatment with high dose corticosteroids. The safety profiles observed for both treatments in the study were consistent with what has previously been reported in the literature. The EMA concluded that the safety profiles for the two treatments were very different, and that nivolumab plus ipilimumab appears to be less well tolerated than sunitinib.[3]

Summary of clinical effectiveness issues

RCC is the most common type of kidney cancer accounting for approximately 90% of kidney neoplasms. It most commonly occurs between the ages of 60 and 70 years. Clear-cell RCC accounts for approximately 80% of RCC cases.[6] At the time of diagnosis approximately 25 to 30% of patients have metastatic disease with a 10% chance of 5-year survival.[7] Surgical resection is most commonly used in localised disease and targeted therapies are most commonly recommended in metastatic disease.[3] Median overall survival ranges from 8 months in patients with poor risk to 4 years in patients with a favourable IMDC risk score. Morbidity of advanced RCC is significantly affected by the extent and location of metastases.[6] SMC clinical experts advised that the tyrosine kinase inhibitors, pazopanib and sunitinib, are currently the first-line systemic treatment options for patients in all risk categories with advanced or metastatic RCC in Scotland. Tivozanib is also used in the same setting and has recently been accepted by SMC. The combination of nivolumab with ipilimumab is the first immunotherapy treatment licensed for use in first-line advanced RCC. Nivolumab monotherapy is accepted for use in Scotland for the treatment of advanced RCC in patients who have received prior therapy (SMC1188/16). Nivolumab plus ipilimumab meets SMC end of life criteria in this setting.

Nivolumab with ipilimumab was associated with a statistically significant advantage over sunitinib for median overall survival in treatment naïve patients with intermediate/poor-risk advanced RCC. The overall survival data are immature; 51% of patients had died at the point of the interim analysis and interpretation may be confounded by subsequent anti-cancer treatments (which was received by 39% and 54% of the nivolumab plus ipilimumab and sunitinib groups respectively).[3] Median PFS was found to be only partially supportive of the overall survival results.[3-5]

The inclusion and exclusion criteria of the CheckMate 214 study reduce the generalisability to the Scottish population, particularly to patients with cardiovascular disease, central nervous system (CNS) metastases, or patients with non-clear cell RCC. The study included RCC patients with a clear cell component only, a subtype that approximately 80% of all RCC patients have. Therefore, there is uncertainty about the applicability of the results to patients with less common subtypes. However, the EMA state that the efficacy is not anticipated to be worse for patients with non-clear cell RCC. Nivolumab monotherapy has previously been shown to be effective in non-clear cell RCC.[3, 6, 8, 9]

CheckMate 214 was of open-label design, which may have biased assessment and reporting of efficacy, safety, and patient reported outcomes. The risk of assessment bias was mitigated by the use of independent review for all subjective co-primary endpoints. Sensitivity analyses of some efficacy outcomes were also conducted to provide further reassurance. There were further limitations of the Health Related Quality of Life (HRQoL) data, namely low response rates to questionnaires after one year, limited data presented for the intermediate/poor risk subpopulation, and the lack of specificity in the FKSI-19 instrument to detect immunotherapy-related AEs.[3]

In the absence of direct comparative evidence with pazopanib, a relevant comparator in Scottish practice, the submitting company presented a Bucher indirect treatment comparison to compare nivolumab plus ipilimumab with pazopanib in patients with previously untreated, metastatic or advanced renal cell carcinoma. The indirect comparison was anchored by sunitinib, the common comparator in the CheckMate 214 and COMPARZ studies. Outcomes that were assessed included overall survival in intermediate/poor risk patients, and PFS in the intermediate risk subgroup, defined as the time between the date of randomisation and the first date of documented progression, as determined by independent review (as per RECIST), or death due to any cause, whichever occurred first. ORR, safety outcomes and quality of life outcomes were not included in the indirect comparison. For overall survival, nivolumab plus ipilimumab was superior to pazopanib and there was no significant difference in PFS between the two treatments. There were some limitations to the Bucher indirect treatment comparison. The two studies used different prognostic scoring tools. Although both studies had similar numbers of “intermediate” risk patients using different definitions, it is uncertain that baseline prognostic risk would have been the same had both studies used the same scoring tool. In addition, baseline characteristics differed between the two studies, as the number of Asian patients was proportionally greater in the COMPARZ study compared with the CheckMate 214 study.[4, 10] A further limitation of the ITC, was that the COMPARZ study was not powered to detect differences in overall survival or differences amongst the intermediate and poor risk subpopulations. The overall survival data from both studies used to conduct the ITC were immature. Lastly, the PFS analysis presented in the ITC only investigated intermediate risk patients for COMPARZ, and uncertainty remains for poor risk patients. Despite these limitations, the submitting company’s conclusion of statistically significant overall survival benefit with nivolumab plus ipilimumab compared to pazopanib seems reasonable.

Clinical experts consulted by SMC considered that nivolumab in combination with ipilimumab is a therapeutic advancement due to significant improvements in overall survival, and numerical

improvements in objective response rate compared with current available treatments. They considered that the place in therapy for nivolumab plus ipilimumab would be as per the licensed indication, and would serve as an alternative to existing first-line treatment options for intermediate/poor risk advanced RCC patients. The introduction of nivolumab plus ipilimumab for this indication would have an impact on both the service and patient, as current standard of care involves the use of oral anti-cancer medications. Extra chair time at oncology units would be required as immunotherapy treatments are administered intravenously and would require close monitoring for AEs. For the patient, it would result in frequent hospital visits for administration.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis to evaluate nivolumab plus ipilimumab versus both sunitinib and pazopanib for intermediate/poor-risk patients with advanced renal cell carcinoma. SMC clinical experts confirmed the comparators are appropriate. The time horizon for the analysis was 40 years, which may be long given the study population. It was reduced in a scenario analysis to 25 years.

A cohort-level partitioned survival model was used, with six states including end of life and death, along with progression-free survival and post-progression survival both on and off-treatment. The cycle length was one week.

Clinical data were taken from the CheckMate 214 study for overall survival, progression-free survival (for which there were multiple different definitions) and time to treatment discontinuation. These data were modelled beyond the median trial follow up period of 25.2 months, in each case informed by statistical fit but predominantly chosen based on clinical expert input. In addition, it was assumed that over the longer term, those receiving a durable response with therapy would experience a 0.5 probability of receiving a long-term immunotherapy survival benefit. The appropriateness of this assumption is not clear.

Utility data were modelled based on EQ-5D-3L data collected in the study. The submitting company provided details from the CheckMate 214 study on the baseline utility score for each treatment, as well as the numbers of intermediate/poor-risk participants who provided data at each time point. A review of the wider evidence base was also conducted and the utility values appear consistent with the ranges reported in other published studies, but the difference between progression-free and post-progression states in the model seems underestimated compared to literature values, and the assumptions that informed the use of utility values on and off each treatment in the model (including the stepwise modelling process that led to the selection of these values) remain unclear and may be counter-intuitive. Nevertheless, the utility values used were not found to disproportionately affect the results in sensitivity analyses.

Disutilities associated with adverse events in the base case were assumed to be incorporated in these elicited utilities from the CheckMate 214 study. However, a scenario analysis considered the impact of applying disutilities separately based on the frequency of grade 3 and 4 treatment-

related adverse events affecting 15% or more of the study population, and the estimated duration of each type of these events. This scenario analysis offers a conservative estimate of utilities by potentially double-counting disutilities associated with adverse events. Utilities used in the model are provided in table 2.

Table 2: Utility values used in the model

	Nivolumab plus ipilimumab	**Sunitinib/ Pazopanib**
Progression Free Survival - On 1st Line Treatment	0.793	0.751
Progression Free Survival - Off 1st Line Treatment	0.719	0.699
Post-Progression Survival - On 1st Line Treatment	0.793	0.751
Post-Progression Survival - Off 1st Line Treatment	0.719	0.699
Post-Progression Survival On 2nd line treatment with nivolumab	0.798	0.798
Post-Progression Survival On 2nd line treatment with TKI/mTOR	0.762	0.762

Aside from medicines costs and their administration, costs included GP visits in both the progression-free and post-progression states. In addition, CT scanning costs and blood tests were included for those in the progression-free state whereas specialist nurse visits and analgesics were included once participants reached the post-progression state. The cost of treating treatment-related grade 3 and 4 adverse events were included and the cost of end-of-life treatment was applied when patients reached this state. The submitting company believes the items included in the costs associated with the progression-free and post-progression states are comprehensive for this population. The costs associated with second-line treatments were incorporated in the base case informed by clinical advice on the proportion of patients receiving each subsequent therapy. The impact of using study data was considered in scenario analysis but was not a key driver of the results.

Patient Access Schemes (PAS) for nivolumab and ipilimumab were proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. PASs are in place for sunitinib and pazopanib and these were included in the analysis by using an estimate of the PAS prices of sunitinib and pazopanib based on information that is in the public domain. The base case results are provided below.

Table 3: Base case results

nivolumab plus ipilimumab vs sunitinib	**Costs**	**LYs**	**QALYs**	**ICER**
nivolumab plus ipilimumab	£98,746	7.83	4.36	
sunitinib	£61,195	4.48	2.67	
Incremental	£37,552	3.35	1.69	£22,210
nivolumab plus ipilimumab vs pazopanib				
nivolumab plus ipilimumab	£98,746	7.83	4.36	
pazopanib	£61,799	4.48	2.67	
Incremental	£36,948	3.35	1.69	£21,855

LY= life-year, QALY = quality-adjusted life-year, ICER=incremental cost-effectiveness ratio

One-way, probabilistic and scenario sensitivity analyses were undertaken. The one-way sensitivity analysis found that the model was sensitive to the choice of model used to extrapolate time to treatment discontinuation in the nivolumab plus ipilimumab group.

The scenario analyses found the ICER was lowered by changing a number of assumptions, most notably reducing the treatment stopping rule to 3 years, or assuming 100% of patients with a durable response would receive a long-term immunotherapy survival benefit. Conversely, changing modelling assumptions regarding the longer-term extrapolation of overall survival data, time to treatment discontinuation data, or excluding the probability that durable responders will receive a long-term immunotherapy survival benefit, raises the ICER. Key scenario analyses are provided in table 4.

Table 4: Scenario Analyses

	Nivolumab plus ipilimumab versus sunitinib	**Nivolumab plus ipilimumab versus pazopanib**
Base case	£22,210	£21,855
Overall survival proportional hazards assumption fitting dependent log logistic model	£25,851	£25,418
Time to treatment discontinuation fitted curve choice altered	£24,653	£24,279
Probability of durable responders on nivolumab plus ipilimumab receiving long term immunotherapy benefit reduced from 50% to 0%	£25,734	£25,335
Probability of durable responders on nivolumab plus ipilimumab receiving long term immunotherapy benefit raised from 50% to 100%	£19,990	£19,668
Dosing method changed from 480 every 4 weeks for nivolumab to weight based 240 every 2 weeks.	£25,792	£25,438
Treatment stopping rule changed from 5 years to 3 years	£19,051	£18,694
Treatment stopping rule removed	£23,723	£23,370
Time horizon of 25 years and the probability of durable responders on nivolumab plus ipilimumab receiving long-term immunotherapy survival benefit is 0	£26,647	£26,234
Time horizon of 25 years and overall survival proportional hazards assumption being dependent, log-logistic	£27,022	£26,570
Time horizon of 25 years and the probability of durable responders on nivolumab plus ipilimumab	£34,952	£34,379

receiving long-term immunotherapy survival benefit to 0 and overall survival proportional hazards assumption being dependent, log-logistic.		
The probability of durable responders on nivolumab plus ipilimumab receiving long-term immunotherapy survival benefit to 0 and overall survival proportional hazards assumption being dependent, log-logistic	£33,906	£33,350
Time horizon of 25 years and log normal distribution is used for sunitinib overall survival but Gompertz is used for nivolumab plus ipilimumab	£35,293	£34,667

The main limitations with the analysis were:

- It was assumed in the model that 30.1% of patients treated with nivolumab plus ipilimumab would have a durable response and a probability of 0.5 of experiencing life expectancy similar to the general population. Given the immaturity of the overall survival data that informed the economic model and that these assumptions were largely based on clinical expert opinion, the results based on this are uncertain. However, further scenario analyses were provided showing the impact on the ICER of varying this assumption (to a zero rather than 0.5 probability) in combination with changes to other assumptions simultaneously.
- The length of the time horizon (40 years) may be unrealistic for an end-of-life treatment but this was reduced in the scenario analysis to 25 years. However, median survival in the intervention group had not been reached at the time of the analysis, and it is notable that previous submissions for this medicine have also considered time horizons of 40 years. Further scenario analyses were also provided showing the impact on the ICER of reducing the time horizon to 25 years in combination with changes to other assumptions simultaneously.
- Extrapolations appear to rely more predominantly on clinical expert input rather than statistical fit for each of the clinical outcomes included in the model and may not always be best when quantifying longer-term outcomes. However, alternative statistical fits were tested in scenario analysis, including in combination with changes to other assumptions and the results were not overly sensitive to alternative curves.
- There was a lack of detail provided about the utilities data from the CheckMate 214 study and underlying assumptions about progression-free and post-progression utility are not available. However, the values were tested in sensitivity analyses and did not have a significant impact on the ICER.
- The list of resources used in the progression-free and post-progression states appears scant, but the submitting company has reiterated that they consider it to be comprehensive for this population.

The Committee also considered the benefits of nivolumab plus ipilimumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee accepted nivolumab plus ipilimumab for use in NHSScotland.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Kidney Research UK, the Kidney Cancer Support Network (KCSN) and Kidney Cancer Scotland. All three organisations are registered charities.

- Kidney Research UK has received 15.5% pharmaceutical company funding in the past two years, including from the submitting company. KCSN has received 34% pharmaceutical company funding in the past two years, including from the submitting company. Kidney Cancer Scotland has received 11.5% pharmaceutical company funding in the past two years, including from the submitting company.

- Advanced RCC is a devastating incurable disease. Diagnosis can be delayed or missed because some symptoms are similar to the symptoms of other conditions, which can leave patients confused, angry and frustrated. Symptoms can include: extreme tiredness, weight loss, back pain, high temperatures, night sweats, anaemia and high blood pressure, all of which make daily living difficult. The majority of patients are forced to give up work. This can bring with it enormous financial pressures and precipitate psychological problems; depression, and loss of confidence and self-worth.

- There are few effective treatment options for this rare cancer. Current treatments are extending life but can have severe side effects which affect quality of life for patients and carers.

- Any new treatment that offers an improved response rate, offers patients with RCC hope for the future. The side-effect profile of the new treatment is described as manageable and the patient groups report that patients are willing to accept more adverse events for a greater survival benefit. Additionally, the administration of the new treatment may reduce impact on carers as they don’t have to oversee the alternative oral medication. Although patients have to travel to hospital for infusion every two weeks, this means they can be monitored and have the opportunity to meet other patients.

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO) produced a clinical practice guideline in 2016 titled 'Renal cell carcinoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up' which was updated in 2017. The guideline advises partial or radical nephrectomy for patients with local or locoregional RCC. Radiofrequency ablation, cryoablation and active surveillance are alternative options for some patient groups. Radical nephrectomy is suggested for patients with locally advanced disease. For the management of patients with metastatic disease the guideline notes that the recommendations primarily relate to patients with clear cell histology, as most studies were conducted in this group of patients. For patients with metastatic disease and good or intermediate prognosis; sunitinib or pazopanib monotherapy (most commonly used), or bevacizumab with interferon are recommended first line treatments. High dose interleukin-2, sorafenib and low dose interferon with bevacizumab are listed as alternative first line treatment options. For patients with a poor prognosis temsirolimus is the preferred option with sunitinib, pazopanib and sorafenib as alternative options. Best supportive care is also a management option in patients with poor prognosis.[11] These recommendations pre-date the licensing of nivolumab plus ipilimumab or cabozantinib for use in treatment naïve patients with advanced RCC.

The European Association of Urology (EAU) guidelines on renal cell carcinoma were most recently updated in 2018. The recommendations in this guideline for the first line treatment of metastatic clear cell RCC are more recent than in the ESMO recommendations above. This guideline advises the use of ipilimumab plus nivolumab in treatment-naïve patients with clear-cell metastatic RCC of IMDC intermediate and poor risk, stating that this combination leads to superior survival compared to sunitinib (the evidence to support this recommendation is considered strong). It also recommends cabozantinib and sunitinib for this patient group (evidence considered weak) and pazopanib is recommended to use it patients with IMDC intermediate risk only (evidence considered weak). Sunitinib and pazopanib are recommended for IMDC favorable risk disease (evidence considered strong). Sunitinib is recommended for patients requiring treatment for non-clear cell RCC.[12]

Additional information: comparators

Sunitinib and pazopanib are the relevant comparators for treatment-naïve advanced RCC patients with intermediate or poor risk as per IMDC in Scottish practice.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
nivolumab plus ipilimumab	**3mg/kg nivolumab intravenously and 1mg/kg ipilimumab intravenously every 3 weeks for the first 4 doses.** **This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks.**	**93,192**
pazopanib	800mg orally daily	27,203
sunitinib	50mg orally daily for four weeks followed by a 2-week treatment free period to complete a six week cycle	27,203

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 28 February 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Doses are based on body weight of 70kg.

Additional information: budget impact

The number of patients assumed to be eligible was 106 in year 1 rising to 120 by 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 confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 April 2019.

**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.