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Advising on new medicines for Scotland
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NHS SCOTLAND
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nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)

SMC No 1285/18

Bristol-Myers Squibb Pharmaceuticals Ltd

8 December 2017

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

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

nivolumab (Opdivo®) is not recommended for use within NHS Scotland.

Indication under review: Nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

In a single arm, phase II study of patients with metastatic, or surgically unresectable, urothelial carcinoma with progressive disease on or after platinum based chemotherapy, treatment with nivolumab resulted in an objective response in 20% of patients.

The submitting company did not present a sufficiently robust economic and clinical analysis to gain acceptance by SMC.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.[1]

Dosing Information

Nivolumab 3mg/kg administered intravenously over 60 minutes every two weeks. Treatment with nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[1]

Product availability date

2 June 2017

Nivolumab meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Nivolumab is a monoclonal antibody which binds to the programmed death-1 (PD-1) receptor found on T-cells. The PD-1 receptor is a negative regulator of T-cell activity which is involved in the control of T-cell immune responses. PD-ligand 1(L1) and PD-L2 are proteins produced by cancer cells that interact with the PD-1 receptor and switch off the activity of T-cells. Nivolumab blocks PD-L1 and PD-L2 from binding to the PD-1 receptor and prevents T-cell deactivation.[1]

Urothelial carcinoma (also called transitional cell carcinoma) accounts for 90% of bladder cancers and is three times more prevalent in men than women. At diagnosis around 50% of patients have non-muscle invasive urothelial carcinoma, 33% have localised muscle invasive urothelial carcinoma and the remainder have metastatic disease.[2]

Evidence of efficacy comes from CheckMate 275, an ongoing, phase II, single-arm, open-label multi-centre study designed to assess activity and safety of nivolumab monotherapy. Patients had metastatic or surgically unresectable urothelial carcinoma, measurable by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, and an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1. Patients were required to have progression or recurrence after treatment with at least one platinum-containing chemotherapy regimen for metastatic or surgically unresectable locally advanced urothelial cancer, or within 12 months of neoadjuvant or adjuvant treatment with a platinum agent in the setting of cystectomy for localised muscle-invasive urothelial cancer. Patients were also required to have serum creatinine ≤1.5 times upper limit of normal or creatinine clearance ≥30mL/min. PD-L1 expression was determined on screening but was not an inclusion criterion.[2, 3]

All patients received nivolumab 3mg/kg by intravenous infusion over one hour, every two weeks. Patients were treated until documented disease progression and clinical deterioration, unacceptable toxicity or other protocol-defined reasons. Dose reductions or escalations were not permitted but dose delays were permitted. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient experienced a clinical benefit, did not have rapid disease progression, and was tolerating study drug, based on investigator assessment.[3] The median number of nivolumab infusions received was seven (range 1 to 30) and median duration of treatment was 3.25 months (database lock, May 2016).[2]

The primary endpoint was objective response (best overall response of complete response or partial response) assessed by blinded-independent review committee (BIRC) in all-treated patients, patients with PD-L1 expression ≥5%, and in patients with PD-L1 expression ≥1%.

For the primary analysis in all-treated patients (database lock, May 2016), the primary endpoint of objective response was achieved in 20% (52/265) of patients (95% confidence interval [CI]: 15.0 to 24.9); six patients (2.3%) had a complete response and 46 patients (17%) had partial response. Objective response was higher in patients with PD-L1 expression ≥1% versus <1% (24% versus 16%) and in patients with PD-L1 expression ≥5% versus <5% (28% versus 16%). In an updated analysis (database lock, September 2016) objective response was achieved in 20% (54/270) of all-treated patients (95% CI: 15.4 to 25.3).[2, 3]

Secondary endpoints included overall survival (OS) and progression free survival (PFS), defined as time from first treatment to the date of the first documented tumour progression, based on BIRC assessments (using RECIST 1.1), or death due to any cause.[3] Results (database lock, September 2016 where median length of follow up was 11.5 months[1]) are presented in Table 1.

Table 1: results of some secondary endpoints from CheckMate 275 (database lock, September 2016)[2]

	All patients (n=270)	**PD-L1 ≥1% (n=124)**	**PD-L1 ≥5% (n=81)**	**PD-L1 <1% (n=146)**
Progression free survival				
Median, months (95% CI)	2.00 (1.87 to 2.63)	3.55 (1.94 to 3.71)	3.71 (1.91 to 5.55)	1.87 (1.77 to 2.04)
Overall survival				
Median, months (95% CI)	8.57 (6.05 to 11.27)	11.63 (9.10 to NR)	12.94 (9.63 to NR)	5.95 (4.37 to 8.08)

CI=confidence interval, NR=not reached

In all-treated patients, the OS rate was 57% at six months, 49% at nine months and 41% at 12 months. The proportion of patients who received subsequent therapy was 20% (54/270); 10% (28/270) of patients received systemic anti-cancer therapy (mostly chemotherapy) and 9.3% (25/270) of patients received radiotherapy (mostly palliative). Median OS in the 216 patients not receiving subsequent therapy was 6.47 months (95% CI: 4.76 to 9.99) and the 12-month OS rate was 41%.[2]

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and Euroqol-5D (EQ-5D) were exploratory outcomes and results were reported up to week 41. The mean EORTC QLC-C30 global health status score increased from baseline for each assessment up to week 41. The mean change from baseline remained stable but did not reach clinically meaningful changes. The mean visual analogue scale EQ-5D score improved from baseline (60.2) to week 41 (81.1).[3]

Supportive data come from CheckMate 032, an ongoing phase I / II single-arm, open-label multi-centre study of various advanced or metastatic tumour types. A total of 78 adult patients with histologically or cytologically confirmed urothelial carcinoma were treated with nivolumab monotherapy (regimen as for CheckMate 275). The primary endpoint was objective response (best overall response of complete response or partial response per RECIST), assessed by investigator. At the March 2016 database lock the proportion of patients with an objective response was 24% (19/78) (95% CI: 15.3 to 35.4). Secondary endpoints included PFS and OS. Median investigator-assessed PFS was 2.8 months (95% CI: 1.5 to 5.9) and the 12-month PFS rate was 21%. With a median follow up of 15.2 months, median OS was 9.7 months (95% CI: 7.3 to 16.2). Analyses of PFS and OS according to PD-L1 expression, which were exploratory endpoints, showed similar differences as observed in CheckMate 275. [2, 4]

Summary of evidence on comparative safety

No new safety concerns were identified with nivolumab monotherapy in CheckMate 275 and no comparative safety data are available.

Treatment-related adverse events occurred in 64% (174/270) of patients. Most adverse events were grade 1 or 2 (46%); grade 3 adverse events occurred in 16% (44/270) of patients and grade 4 in 1.5% (4/270) of patients. The proportion of patients discontinuing due to nivolumab adverse events was 4.8% (13/270). Treatment-related adverse events (any grade) included; fatigue (17%), pruritus (9.3%), diarrhoea (8.9%), decreased appetite (8.1%), hypothyroidism (7.8%), nausea (7.0%), rash (5.9%), asthenia (5.9%) and pyrexia (5.6%). The most common grade 3 adverse events were fatigue or diarrhoea (five patients each). Three deaths (not related to disease progression) were considered by the investigator to be related to treatment and all occurred in patients with metastatic disease. There was one death due to pneumonitis, one due to acute respiratory failure and one due to cardiovascular failure.[3]

Summary of clinical effectiveness issues

There is no standard of care for patients who progress during or after platinum-based combination chemotherapy.[2, 5] 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, or single-agent paclitaxel (off-label) or vinflunine (not recommended by SMC), best supportive care (BSC) or entry into a clinical study.[5-7] In a recent meta-analysis the pooled median overall survival of second line single-agent chemotherapy (paclitaxel, docetaxel or vinflunine) was 6.98 months.[8]

SMC clinical experts state that currently patients are treated with weekly paclitaxel or BSC. SMC clinical experts also advise that re-challenge with a platinum based therapy may be considered for a small proportion of patients with a previous good response and if the relapse occurs more than 6 months and ideally more than 12 months from prior platinum treatment. However platinum-based chemotherapy is not considered a comparator by the company and they note that no relevant data for re-treatment with platinum-based chemotherapy were identified to allow an indirect comparison to take place. While the submitting company state that they are not positioning nivolumab, it would appear that the proposed use of nivolumab is for patients who would otherwise receive paclitaxel or BSC.

Nivolumab meets SMC end of life and orphan equivalent criteria for this indication.

In CheckMate 275 the proportion of patients with an objective response was 20%; the lower bound of the 95% CI was above 10%, the pre-specified threshold below which objective responses was not considered an improvement over historical control data for single-agent chemotherapy.[3] Median PFS was 2.0 months and OS was 8.57 months. Analysis of CheckMate 032 supports these results. Patients recruited to CheckMate 275 were considered to have a poor prognosis given the short treatment-free interval and high proportion of patients with visceral metastases (84%). Around two-thirds of patients had one or more Bellmunt risk factors, which include haemoglobin <100g/L, ECOG performance status ≥1 and presence of liver metastases. The patient population in CheckMate 032 was considered to be similar.[2]

The studies have limitations. There are no comparative data. The primary outcome in both studies was objective response (where most patients had partial responses); PFS and OS were secondary outcomes. In both studies OS was longer in patients with PD-L1 expression ≥1% (versus <1%); longer term follow up is required to ascertain whether these differences translate into longer term differences.[4]

Results from post-hoc, exploratory analyses indicate that in patients with low (e.g. <1%) to no tumour PD-L1 expression, other patient characteristics (e.g. liver metastases, visceral metastases, baseline haemoglobin <100g/L and ECOG performance status of 1) might contribute to the clinical outcome.[1]

OS data are limited to a median follow up of 11.5 months in CheckMate 275 and 15.2 months in CheckMate 032; updated analyses are awaited. In Checkmate 275, subsequent treatments were received by 20% (52/265) of patients and included gemcitabine, carboplatin, cyclophosphamide, docetaxel, paclitaxel and vinflunine and these may have impacted on OS. When patients who did not receive subsequent treatment were excluded from the analysis median OS was lower than the all-treated population (6.47 months and 8.57 months), however the 12-month OS rate was 41% in both analyses.[2]

Results for OS and objective response rate were poorer for patients with a shorter time from the most recent prior regimen (i.e. patients with rapidly progressing disease) compared with those patients with a longer time since prior treatment (patients with more indolent disease). Those with rapidly progressing disease may not have had sufficient time to respond to nivolumab. In studies of nivolumab for other indications a delay in the onset of response to nivolumab has been observed. However, due to the single-arm design of the study, it is not possible to know whether the survival curve of nivolumab would be below chemotherapy at the beginning of the treatment.[2]

There are no comparative data versus single-agent paclitaxel or BSC, the key comparators considered by the company in their submission. Consequently they undertook a simulated treatment comparison (STC) approach in order to estimate the relative efficacy of nivolumab with respect to paclitaxel and BSC. This used individual patient data from the pooled nivolumab studies described previously and baseline characteristics from the comparator studies to estimate how patients in each comparator study would have responded to nivolumab. A network analysis (NMA) was then used to synthesise the results, using a fixed effects model, across all comparator studies (one study each for paclitaxel and BSC).

Outcomes included objective response rate, PFS and OS. For objective response rate there was no evidence of a difference between nivolumab and paclitaxel; nivolumab was superior to BSC as would be expected. PFS and OS results were presented for a range of time intervals. For PFS, results favoured paclitaxel over nivolumab up to week 12, but favoured nivolumab over paclitaxel at weeks 20 to 24, 44 to 48 and 68 to 72. For weeks 92 to 96 there was no evidence of a difference between nivolumab and paclitaxel. A comparison of PFS for nivolumab versus BSC was not possible due to Kaplan Meier PFS data for BSC not being available. For OS, results favoured paclitaxel over nivolumab for weeks 0 to 4 and favoured nivolumab over paclitaxel at weeks 44 to 48 and 68 to 72. Results favoured nivolumab over BSC at all time points up to week 72. At all other time points there was no evidence of a difference between nivolumab and comparators.

There are limitations with the STC and NMA including pooling of nivolumab studies (which may not be appropriate given differences in study results), use of overly simplistic prediction models, inclusion of some small and single-arm studies, and no comparison available for PFS versus BSC. Results from the random effects model were considered by the SMC statistician to be preferable and were provided by the company on request. The credible intervals included one for all time intervals reported for the PFS and OS results and also for objective response rate for nivolumab versus paclitaxel.

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 nivolumab, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- The prognosis for patients with advanced unresectable or metastatic urothelial carcinoma is very poor. There have been no new effective treatments which are well tolerated for advanced or metastatic urothelial carcinoma for decades.

- There is substantial unmet need in locally advanced unresectable or metastatic urothelial carcinoma as there are no proven treatments currently available in Scotland following first-line platinum-containing treatment regimens.

- Nivolumab appears to be well tolerated with the potential for improved quality and quantity of life, and side effects which are manageable. Nivolumab treatment may allow patients to live a close to 'normal' life. Patients who respond to treatment may have considerably extended overall survival.

- While nivolumab is administered by intravenous infusion every two weeks, it may be preferable to patients and families, compared with chemotherapy administration and its associated side effects which requires additional hospital visits.

- Although use of nivolumab is expected to have an impact on chemotherapy units, the number of patients eligible for treatment is expected to be low.

- The availability of an additional treatment option after failure of first-line platinum-containing chemotherapy is very important to patients and provides optimism for the future.

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.

Summary of comparative health economic evidence

The company presented a cost-utility analysis which compared nivolumab against paclitaxel and BSC in patients with locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing chemotherapy.

A cohort-based partitioned survival model was used to assess the cost-effectiveness of nivolumab versus the comparators. In terms of model structure, the model consisted of three health states progression-free (PF), post-progression (PP) and death. Patients entered the model in the PF health state and patients could either progress to a worse health state or die. Patients were initiated to nivolumab, paclitaxel and BSC in the PF health state and treatment duration for nivolumab was based on estimated time to treatment discontinuation (TTD). Treatment duration for paclitaxel was informed

by expert opinion and patients received a maximum of 6 cycles of treatment. The analysis assumed that patients treated with BSC received BSC indefinitely until death. The base case economic model also included a two year stopping rule for patients who received nivolumab. The stopping rule assumed that 75% of patients who were still receiving treatment at the end of two years would discontinue, while the remaining 25% of patients would remain on treatment until the estimated TTD or death.

The sources of the clinical data included using pooled data from the CheckMate 032 and CheckMate 275 studies and the STC/NMA. The pooled CheckMate 032 and CheckMate 275 studies were used to estimate PFS, OS and TTD for nivolumab in the economic model. In terms of modelling PFS and OS the submitting company used landmark analysis where separate survival curves for responders and non-responders were plotted for each outcome using data from week 8 onwards. The generalised gamma distribution was used to extrapolate the available PFS and OS data for responders and non-responders over the lifetime horizon of the economic model. The submitting company combined the extrapolated responder and non-responder functions for PFS and OS respectively, using a weighted average of the proportion of responders and non-responders from week 8 of the CheckMate 032 andCheckMate 275 studies. This approach therefore generated a single survival function for nivolumab for PFS weighted by response to treatment and a single survival function for OS, also weighted by response to treatment. In order to model the efficacy of paclitaxel and BSC in the analysis, hazard ratios derived from the STC were applied to the nivolumab weighted average survival functions for PFS and OS respectively. In the absence of a hazard ratio for BSC vs. nivolumab in terms of PFS, the analysis used a hazard ratio for BSC vs. vinflunine and applied this to the paclitaxel arm of the analysis. TTD was estimated for nivolumab by extrapolating the available data using the generalised gamma function.

Utility values for nivolumab, paclitaxel and BSC in the PF and PP health states were taken from EQ-5D data collected in the CheckMate 275 study. A utility value of 0.713 was used for the PF health state and 0.652 for the PP health state in the economic model. Disutilities due to adverse events were also captured in the base case analysis.

Medicine costs were included in the analysis as well as administration, monitoring, supportive care, radiotherapy and surgery, terminal care, and adverse event costs.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case results and selected sensitivity analyses including the PAS for nivolumab are presented in Table 2 below.

Table 2: base case analysis and selected sensitivity analysis (with nivolumab PAS)

Analysis	**Paclitaxel**	**BSC**
Results with 2 year stopping rule		
Base case analysis	£27,200	£33,459
8 week landmark analysis: Weibull extrapolation	£65,428	£73,893
26 week landmark analysis: exponential extrapolation	£40,250	£51,099
Standard survival modelling: Generalised gamma	£41,296	£52,955
Standard survival modelling: exponential extrapolation	£117,832	£99,228
Remove differences between nivolumab and comparator if credible interval crossed 1	£41,369	£37,288

TTD modelling Gompertz extrapolation	£60,928	£63,491
Stopping rule of 100% discontinuation at 2 years	£25,249	£31,722
Results without 2 year stopping rule		
Base case analysis	£33,051	£38,669
8 week landmark analysis: Weibull extrapolation	£81,112	£86,381
26 week landmark analysis: exponential extrapolation	£49,634	£59,512
Standard survival modelling: Generalised gamma	£50,854	£61,707
Standard survival modelling: exponential extrapolation	£142,130	£113,112
Remove differences between nivolumab and comparator if credible interval crossed 1	£50,889	£43,107
TTD modelling Gompertz extrapolation	£113,243	£110,071

The main weaknesses were

- In order to model PFS and OS for nivolumab in the economic evaluation the company used landmark analysis. However landmark analysis is not often presented in health technology assessments reviewed by the SMC and this is the first time landmark analysis has been presented in a nivolumab SMC appraisal. In addition it is unclear if adequate justification was provided regarding the application of landmark analysis, the use of strong assumptions, and whether uncertainty was adequately explored or tested.

- The analysis is not a standard landmark analysis; it is a combination of piecewise modelling, landmark analysis and weighted averages. In addition, the use of weighted averages may be a source of bias as the number of patients at risk in the responder and non-responder groups will be different throughout the analysis. Alternative functions may also represent a plausible fit to the data when extrapolating the responder and non-responder curves in the landmark analysis. The company provided a sensitivity analysis using the Weibull function for the extrapolation and the results are available in Table 2 above. In addition, the company presented sensitivity analyses using standard survival modelling and the results are also available in Table 2.

- The indirect comparison was associated with uncertainty and a PFS hazard ratio for BSC vs. nivolumab was not presented. Therefore the company used a hazard ratio for BSC vs. vinflunine and applied this to the paclitaxel arm of the analysis. Whether this produces valid PFS results for BSC in the context of this nivolumab appraisal is uncertain.

- The economic analysis included numerical differences in efficacy from the indirect comparison for results where the credible interval crossed 1. A sensitivity analysis has been provided by the company which removed these differences in the base case analysis (see Table 2 above). However it is worth noting the results of the random effects NMA, where credible intervals for all results presented included 1.

- In terms of treatment costs, alternative TTD functions were available which represented a similar fit to the data according to the goodness of fit statistics. The definition of the stopping rule (i.e. 75% of patients who remain on treatment discontinue at 2 years) was not considered clinically plausible according to SMC clinical experts. However the company provided a sensitivity analysis where the

stopping rule reflected 100% of patients still on treatment would discontinue at 2 years. The results are available in Table 2 above.

The Committee also considered the benefits of nivolumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed as nivolumab 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 was unable to accept nivolumab for 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 in combination with G-CSF for people with incurable locally advanced or metastatic urothelial bladder cancer who have progressed after first-line chemotherapy in patients with adequate renal function (GFR ≥60mL/min/1.73m^2) and are physically fit (ECOG PS 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.[6]

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 PS) and risk increases as number of these present increases. Phase III data indicate that vinflunine plus BSC has modest activity versus BSC.[5]

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.[7]

Additional information: comparators

Paclitaxel (weekly), carboplatin + gemcitabine, cisplatin + gemcitabine or BSC.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Nivolumab	**3mg/kg IV every two weeks**	£2,633 (2-week cycle)
Paclitaxel	80mg/m^2 IV on days 1, 8 and 15 of 4-week cycle	£902 (4-week cycle)
Carboplatin + gemcitabine	AUC 4.5* IV on day 1 1,000mg/m^2 IV on days 1 and 8 of 3-week cycle	£192 (3-week cycle)
Cisplatin + gemcitabine	70mg/m^2 IV on day 2 of 28-day cycle 1,250mg/m^2 IV on days 1, 8 and 15 of 4-week cycle	£186 (4-week cycle)

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs and DM&D on 5 September 2017. Costs calculated using the full cost of vials/ampoules assuming wastage, a body weight of 70kg and body surface area of 1.8m^2. Costs do not take any patient access schemes into consideration.*assumes creatinine clearance 60mL/min resulting in dose of 400mg. IV=intravenous; AUC=area under curve.*

Additional information: budget impact

The submitting company estimated there would be 61 patients eligible for treatment with nivolumab in all years to which confidential uptake rates were applied.

SMC is unable to publish the without PAS budget impact due to commercial in confidence issues

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

References

1. Bristol-Myers Squibb Pharmaceuticals L. Nivolumab (OPDIVO) 10 mg/mL concentrate for solution for infusion. Summary of Product Characteristics. 2017. Available at: https://www.medicines.org.uk/emc/medicine/30476 [Accessed 20 June 17].

2. European Medicines Agency. European Pubic Assessment Report; EMA/CHMP/172720/2017. 2017.

3. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J*, et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. The Lancet Oncology. 2017;18(3):312-22.

4. Sharma P, Callahan MK, Bono P, Kim J, Spiliopoulou P, Calvo E*, et al.* Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. The Lancet Oncology. 2016;17(11):1590-8.

5. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2014;25(suppl 3):iii40-iii8.

6. National Institute for Health and Care Excellence. [NG2]: Bladder cancer: diagnosis and management. Available: https://www.nice.org.uk/guidance/NG2 [Accessed 3 Feb 2017]. [cited.

7. European Association of Urology. Muscle-invasive and Metastatic Bladder Cancer Guidelines. Available at: http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/#1 [Accessed 3 Feb 2017]. 2016 [cited.

This assessment is based on data submitted by the applicant company up to and including 13 October 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 drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

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

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