Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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nivolumab, 10mg/mL concentrate for solution for infusion (Opdivo®)

SMC No 1261/17

Bristol-Myers Squibb

4 August 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 assessed under the end of life and ultra-orphan medicine process

nivolumab (Opdivo®) is accepted for restricted use within NHS Scotland.

Indication under review: As monotherapy, for the treatment of squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.

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

A phase III randomised study demonstrated significantly improved overall survival in patients receiving nivolumab compared with investigator choice of treatment (taxane, folic acid antagonist or epidermal growth factor receptor monoclonal antibody) in adults with SCCHN who had progressed within six months after platinum-based therapy.

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

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy, for the treatment of squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.[1]

Dosing Information

The recommended dose of nivolumab as monotherapy is 3mg/kg nivolumab administered as an intravenous (IV) infusion over 60 minutes every two weeks. Treatment should be continued as long as clinical benefit is observed or until no longer tolerated by the patient. Atypical responses (ie, an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.[1]

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation, withholding of doses and management of immune-related adverse reactions are described in the summary of product characteristics (SPC). Patients treated with nivolumab must be informed about its risks and be given a patient alert card.[1]

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[1]

Product availability date

28 April 2017

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

Background

Nivolumab is a human monoclonal antibody that acts as an immune checkpoint inhibitor.[2] Patients with recurrent or metastatic SCCHN after platinum chemotherapy have a very poor prognosis and limited therapeutic options. Nivolumab is the first programmed death 1 ligand (PD-L1) inhibitor to be licensed for this indication.

Nivolumab has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

Most patients with SCCHN present with loco-regionally advanced disease, and have recurrence within three years. Patients with disease progression within six months after platinum-based chemotherapy for primary or recurrent disease have a median survival of up to six months.[2] Further platinum-based therapy may be an option for a small number of fitter patients who have progressed more than six months after prior platinum therapy. Clinical experts consulted by SMC

advised that if further platinum therapy or enrolment in a clinical study is not possible, palliative treatment with docetaxel monotherapy or methotrexate may be considered, however most patients receive supportive care only. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, as there are currently no satisfactory treatments. Nivolumab meets SMC end of life and ultra-orphan criteria for this indication.

A patient and clinician engagement (PACE) meeting was held to consider the added value of nivolumab in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the fact that these patients have very poor quality of life in their last few remaining weeks/months. Patients will have already received invasive, complex, toxic therapies and be living with pain, breathing difficulties, inability to speak and swallow as well as disfigurement of the face and neck. Being unable to speak and engage in meals and social situations can cause frustration, anger, depression and social withdrawal. The impact on family/friends is huge. Caring becomes extremely onerous as patients find it difficult to speak or swallow and their severe disfigurement can be very distressing. Patients can develop stridor which causes much anxiety for carers. Often carers are unable to work due to the high level and complexity of care required for the patient as a result of tracheostomy, insertion of a percutaneous endoscopic gastrostomy (PEG) tube, high symptom burden and declining performance status. PACE participants stressed how dying from progressive untreated head and neck cancer is something very distressing for family to witness.

Impact of new technology

Summary of evidence on comparative efficacy

The evidence supporting the marketing authorisation is from a phase III randomised, open-label study, CheckMate 141, which compared nivolumab with investigator choice of treatment in 361 patients with recurrent SCCHN whose disease had progressed on or within six months after platinum-based chemotherapy.[2] Patients were included if they were at least 18 years old and had histologically confirmed, recurrent or metastatic SCCHN of the oral cavity, pharynx, or larynx that was not amenable to curative treatment. Tumour progression or recurrence had to have occurred within six months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1; adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1.[2]

Prior to randomisation, investigators decided which comparator treatment (docetaxel, methotrexate or cetuximab) each patient would receive if allocated to the comparator arm of the study. Patients were then randomised in a 2:1 ratio, stratified according to prior cetuximab treatment (yes or no) to receive treatment with:

- nivolumab 3mg/kg body weight IV infusion every two weeks (n=240)

or with one of three investigator choices of treatment (n=121):

- docetaxel 30mg/m^2 to 40mg/m^2 body surface area IV infusion every week (45%; n=54)
- methotrexate 40mg/m^2 (may be increased to 60mg/m^2) IV infusion every week (43%; n=52)
- cetuximab 400mg/m^2 in week 1, then 250mg/m^2 IV infusion every subsequent week (12%; n=15)[2, 3]

The investigator choice treatments were to continue until unacceptable drug-related toxicity or disease progression, however treatment with nivolumab was allowed to continue after disease

progression (assessed clinically or radiographically) if the investigator determined that the patient was gaining clinical benefit. Patients were followed for overall survival every three months until death, loss to follow-up, or withdrawal of consent.[2]

The primary outcome was overall survival, defined as the time from randomisation to date of death from any cause, and this was analysed in all randomised patients (intention-to-treat [ITT]).[2] On the advice of the Independent Data Monitoring Committee, the study was stopped at the interim analysis which was planned after 195 deaths had occurred.[2] At the interim analysis data cut-off on 18 December 2015, median duration of follow-up was 5.1 months (range 0 to 16.8). At this time 55% (133/240) of patients in the nivolumab group and 70% (85/121) of patients in the investigator choice group had died. Median overall survival was significantly longer in patients receiving nivolumab compared with investigator choice of treatment: 7.5 months (95% confidence interval [CI]: 5.5 to 9.1) versus 5.1 months (95% CI: 4.0 to 6.0); hazard ratio (HR) for death 0.70 (97.73% CI: 0.51 to 0.96), p=0.01). There was a delayed separation of the Kaplan-Meier survival curves; survival rates at one year for nivolumab versus investigator choice were estimated to be 36% versus 17%.[2, 3]

Updated overall survival data are available from a database lock on 20 September 2016, representing a minimum follow-up of 11.4 months. At this point 6.7% (16/240) of patients in the nivolumab group and 0.8% (1/121) of patients in the investigator choice group were still receiving treatment. A total of 77% (184/240) of patients in the nivolumab group had died compared with 87% (105/121) of patients in the investigator choice group; (stratified Cox proportional hazard model) HR 0.71 (95% CI: 0.55 to 0.90; p<0.05). Median overall survival for nivolumab versus investigator choice groups: 7.72 months versus 5.06 months. Estimated survival rates at 6, 12 and 18 months in the respective groups were 56% versus 43%; 34% versus 20% and 22% versus 8.3%.[4, 12]

Median overall survival was also reported for the three patient subgroups receiving each investigator choice treatment; with each subgroup being compared with the corresponding subgroup in the nivolumab arm according to pre-randomisation assignment. See Table 1 below.

Table 1: Analysis of median overall survival according to each component of investigator choice of therapy (18 December 2015 data cut) [2, 3, 5]

	Nivolumab	**Docetaxel**	**Nivolumab**	**Methotrexate**	**Nivolumab**	**Cetuximab**
No of patients	88	54	119	52	33	15
Median OS in months	*	5.8	*	4.6	*	4.1
HR (for death) (nivolumab versus comparator)	0.82 (95% CI: 0.53 to 1.28)		0.64 (95% CI: 0.43 to 0.96)		0.47 (95% CI: 0.22 to 1.01)	

OS=overall survival; HR=hazard ratio; CI=confidence interval. Nivolumab subgroups comprise patients who had been assigned to corresponding comparator therapy before randomisation.
*Commercial in Confidence**

Other subgroup analyses performed included gender, region, PD-L1 expression and human papilloma virus protein 16 (HPV p16) status. The nivolumab treatment effect was more pronounced in men versus women; in non-European Union versus European Union countries; in patients with PD-L1 expression ≥1% versus <1% (pre-specified analysis); and in patients with positive versus negative HPV p16 status (post hoc analysis).[6]

Key secondary outcomes were progression free survival (PFS), defined as time from randomisation to date of disease progression or death; and rate of objective response, assessed by the investigator every six weeks from week 9, according to RECIST version 1.1.[2]

At the 18 December 2015 data cut, there was no significant difference between treatment groups in PFS; events had occurred in 79% (190/240) versus 85% (103/121) of patients in the nivolumab and investigator choice groups, HR for disease progression or death, 0.89 (95% CI: 0.70 to 1.13, p=0.32). Median PFS was 2.0 months (95% CI: 1.9 to 2.1) in the nivolumab group versus 2.3 months (95% C: 1.9 to 3.1) in the investigator choice group. The PFS rate at six months was 20% in the nivolumab group versus 9.9% in the investigator choice group.[2] At the 20 September 2016 data cut, PFS events had occurred in 85% (204/240) and 86% (104/121) of patients in the nivolumab and investigator choice groups; HR 0.87 (95% CI: 0.69 to 1.11). Median PFS was 2.04 months (95% CI: 1.91 to 2.14) versus 2.33 months (95% CI: 1.97 to 3.12), stratified log-rank test p-value 0.260. Kaplan-Meier estimates for the respective groups of rates at six months were 21% (95% CI: 15.9 to 26.6) versus 11% (95% CI: 5.9 to 18.3); and at 12 months were 9.5% (95% CI 6.0 to 13.9) versus 2.5% (95% CI: 0.5 to 7.8).[4, 12]

Data on rate of response were based on a database lock on 5 May 2016.[2] The hierarchical testing procedure of the study precluded the formal testing of response rates due to non-significant results in the PFS outcome. The objective response rate (ORR=complete and partial responses) was 13% in the nivolumab group versus 5.8% in the investigator choice group.[2] Median time to response was similar in each group; 2.1 (range 1.8 to 7.4) and 2.0 months (range 1.9 to 4.6). Median duration of response was 9.7 months (range 2.8 to 20.3+) and 4.0 months (range 1.5+ to 8.5+). Clinical benefit rate, (response or stable disease) was 36% versus 41%.[1]

Table 2: Response rates according to treatment groups[1]

	Nivolumab group	**IC group**
Complete response	2.5% (6/240)	0.8% (1/121)
Partial response	11% (26/240)	5.0% (6/121)
Stable disease	23% (55/240)	36% (43/121)

IC=investigator choice

Health related quality of life assessments were exploratory and yielded valid results up to 15 weeks only, due to the low response rate in the investigator choice group.[7, 8] The following outcomes remained stable in the nivolumab group, but worsened in the investigator choice group: physical, role, social functioning and symptoms (fatigue, dyspnoea, appetite loss) (assessed with the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [QLQ-C30] module); pain, sensory, social contact (assessed with the head and neck specific QLQ-H&N35); and health status (assessed with the European Quality of Life–5 Dimensions (EQ-5D-3L).[2, 8]

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

Summary of evidence on comparative safety

In CheckMate 141 treatment-related adverse events were reported in 59% (139/236) of patients in the nivolumab group compared with 77% (86/111) of patients in the investigator choice group; and were grade 3 or 4 in 13% and 35% of the respective groups. The most frequent treatment-related adverse events in the nivolumab versus investigator choice groups were fatigue (14% versus 17%), nausea (8.5% versus 21%), rash (7.6% versus 4.5%), decreased appetite (7.2% versus 7.2%), pruritus (7.2% versus 0) and diarrhoea (6.8% versus 14%).[2] Adverse events of the endocrine system (mainly hypothyroidism) were reported in 7.6% versus 0.9% of the respective groups. Pneumonitis was observed in 2.1% of patients treated with nivolumab.[2] Two treatment-related deaths were reported in the nivolumab group (pneumonitis and hypercalcaemia in one patient each), and one patient in the investigator choice group died from a treatment-related lung infection.[2]

Patients receiving nivolumab should be monitored continuously (at least up to five months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of therapy. They should be provided with a patient alert card. The SPC includes details of immune-related toxicity and infusion reactions caused by nivolumab.[1]

The SPC notes that physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease.[1]

Summary of clinical effectiveness issues

CheckMate 141 was a well conducted study that demonstrated significantly improved overall survival (median extended by 2.4 months) in patients receiving nivolumab compared with investigator choice of treatment (docetaxel, methotrexate or cetuximab) in adults with SCCHN who had progressed within six months after platinum-based therapy. There was no significant difference between treatment groups in the secondary outcome of PFS.[2] Treatment with nivolumab increased response rates but not clinical benefit rate, which also included patients whose disease has remained stable.[1] Nivolumab was associated with stable health related quality of life from baseline to week 15 of the study.[8] A pre-specified subgroup analysis suggested greater overall survival benefit with nivolumab over investigator choice in patients with tumour PD-L1 expression ≥1% than <1%. A post hoc subgroup analysis suggested greater overall survival benefit with nivolumab over investigator choice in patients with positive than negative tumour HPV p16 status. However the published study report noted that for both PD-L1 expression and HPV p16 status, the interactions between the corresponding subgroups were not significant and were not corrected for multiple comparisons.[2]

There are recognised limitations in using RECIST 1.1 to assess tumour response as it may not fully capture the benefits of nivolumab which is an immune mediated medicine, as some patients may initially have pseudo-progression that subsequently responds to treatment. PFS and tumour response data are therefore difficult to interpret. Another limitation of the study was an imbalance, in favour of nivolumab, in the proportions of patients in the ITT population who did not receive any study treatment: 1.7% of patients in the nivolumab group and 8.3% of patients in the comparator group.[2] In addition, the open-label nature of the study may have affected patient reported outcome completion rates in the comparator group; and may have contributed to performance bias.

The CheckMate 141 study population consisted only of patients with disease progression within six months of prior platinum therapy, which is narrower than the eligible population for the licensed indication under review. In patients with good performance status whose disease had progressed more than six months after prior platinum therapy, further platinum therapy may be an option. No comparative data with platinum therapy were presented.

Factors that may affect generalisability of the study results to the Scottish population include that patients in CheckMate 141 were required to have a performance status of 0 or 1 and the benefit from nivolumab may not be applicable to less fit patients. In patients with poor performance status, fast progressive disease on prior platinum therapy or high tumour burden, there were more deaths in the first three months in patients treated with nivolumab compared with docetaxel.[1] The study population also included a higher proportion of men (83%) than the UK population with SCCHN (69%).[9]

The comparator group in CheckMate 141 (docetaxel [45%], methotrexate [43%] and cetuximab [12%]) did not reflect current treatment in Scotland.). Docetaxel monotherapy and methotrexate may be used, but cetuximab is not used, for this indication. The economic case included a comparison with paclitaxel monotherapy, however this is not considered to be a relevant comparator.

Some patients previously not considered fit enough for chemotherapy may be considered for nivolumab due to better tolerability. The submitting company presented an economic case versus best supportive care (BSC) using a naive indirect comparison, which is generally considered to be useful as a sense check only. In the base case they compared overall survival data for nivolumab in the pivotal CheckMate 141 study with data from a subgroup (n=68) of a retrospective, non-randomised study (Leon 2005).[10] This involved the analysis of the clinical records of 151 patients treated between 1990 and 2000 at seven centres in Europe. Patients had recurrent and/or metastatic SCCHN with disease progression within 30 days of platinum-based chemotherapy and subsequently received either BSC (45%), chemotherapy (28%), radiotherapy (17%) or chemoradiotherapy (10%). Differences that could be identified between the full study populations in Leon 2005 and CheckMate 141 included proportion of males (92% versus 83%); proportion of Caucasians (100% versus 83%); primary tumour site, (pharynx, 58% versus 36%), (larynx, 24% versus 14%), (other, 18% versus 50%). Information on number of previous lines of systemic anticancer therapy, performance status or cigarette use in Leon 2005 patients was not available. In the BSC subgroup of Leon 2005, median overall survival was 56 days and all patients had died by 12 months.[10] The submitting company estimated that mean overall survival in this subgroup was 2.9 months. Current UK guidance notes that patients receiving only palliative care have an average overall survival of four months after diagnosis.[11] The submitting company also presented a scenario analysis using the relative efficacy of BSC versus chemotherapy (n=58) from the Leon 2005 study to adjust the efficacy of the investigator choice of therapy group in the pivotal CheckMate 141 study. Limitations of using data from Leon 2005 include small patient numbers, lack of randomisation, retrospective analysis and differences between the chemotherapy group and the investigator choice of therapy group in CheckMate 141. BSC was not defined, may have varied between treatment centres and may not reflect current practice in Scotland.

Clinical experts consulted by SMC considered that nivolumab is a therapeutic advancement due to a small increase in overall survival and to improvements in quality of life and tolerability of treatment compared with cytotoxic chemotherapy.

At the PACE meeting, it was noted that estimated survival rates from the CheckMate 141 study, 36% at 12 months and 22% at 18 months, are considered to be highly beneficial and the first significant improvement in the treatment of SCCHN for many years. The increase in median overall survival of 2.4 months was felt to be very meaningful as it constitutes a large proportion of remaining life. However a key benefit is that nivolumab has been shown to be well tolerated and would allow patients significantly more time with their families and loved ones while maintaining

a good quality of life. Clinicians emphasised that a small proportion of patients treated with nivolumab are likely to be long-term survivors.

Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- Patients with SCCHN that has progressed post platinum treatment generally live for less than six months. Quality of life is extremely poor as a result of pain, breathing difficulties, inability to speak and swallow as well as disfigurement of the face and neck.

- SCCHN places a major burden on families/carers who have to deal with complex care needs which are exacerbated by the patient's difficulties in communication and eating. This cancer type is disproportionately more common in people from low socio-economic groups and causes high levels of psychological, emotional and financial stress.

- Whilst a small proportion of patients receive second-line chemotherapy, this is associated with low response rates and high toxicity and there is no currently available treatment that provides meaningful survival or quality of life benefit in this group of patients.

- Nivolumab not only significantly increases survival rates compared with current standard of care, but it also has less treatment related toxicity than chemotherapy and has the potential to maintain quality of life during the limited remaining weeks/months of a patient's life. This may enable patients to live and function more independently and would be of considerable benefit for patients and their families/carers.

- Common with the response to immunotherapy in other tumour types, a small subgroup of patients receiving nivolumab are anticipated to be long-term survivors (overall survival rates of 36% at 12 months and 22% at 18 months).

Addition of Patient and Carer Involvement
SMC received patient group submissions from Let's Talk About Mouth Cancer and TRACTion Cancer Support. Let's Talk about Mouth Cancer is a Scottish Charitable Incorporated Organisation (SCIO) and TRACTion Cancer Support is a charitable trust. Neither organisation has received any pharmaceutical company funding in the past two years. Representatives from Let's Talk About Mouth Cancer participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Value for money

The company presented a cost-utility analysis which compared nivolumab against docetaxel, paclitaxel, and BSC in adults with SCCHN who have progressed on or after platinum-based therapy.

A cohort-based partitioned survival model was used to assess the cost-effectiveness of nivolumab versus the comparators using a time horizon of 20 years. In terms of model structure the model consisted of three health states: progression-free (PF), progressed disease (PD) and death. Patients entered the model in the progression-free health state and patients could either progress to a worse health state or die. Treatment duration for nivolumab, docetaxel and paclitaxel was based on estimated time to treatment discontinuation (TTD) and patients who discontinued treatment received supportive care. Estimating TTD did not apply to patients who received BSC and therefore patients were treated with BSC until death. The base case economic model included a two year stopping rule for patients who received nivolumab.

The sources of the clinical data included the CheckMate 141 study and Leon (2005)[12]. The CheckMate141 study was used to generate OS, PFS and TTD estimates for nivolumab, docetaxel and paclitaxel. CheckMate 141 compared nivolumab against investigator choice and the economic evaluation used data from the investigator choice arm of the study to proxy outcomes for docetaxel and paclitaxel. In order to generate survival estimates beyond the study period for nivolumab and the active comparators (i.e. docetaxel and paclitaxel) the data were extrapolated using the lognormal function for OS, and the generalised gamma function for both PFS and TTD. Leon study data were used to inform the efficacy of BSC in the economic model. OS estimates for BSC were derived from the Kaplan-Meier plot presented in the Leon publication. PFS was estimated by generating an exponential function with the same median PFS value as the median time to progression (TTP) estimate reported in Leon (2005).

Utility values for nivolumab in the progression-free and progressed disease health states were taken from EQ-5D data collected in the CheckMate 141 study. The company also applied the values for investigator choice from the CheckMate 141 study to the docetaxel, paclitaxel and BSC arms of the analysis. The base case analysis did not include adverse event disutilities although they were added to the model as sensitivity analysis.

Medicines costs were included in the analysis as well as administration, monitoring, disease management, terminal care, and adverse event costs.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case results and selected sensitivity analyses without the nivolumab PAS are presented below.

Table 3: Base case results without PAS for nivolumab

Comparator	Incremental Cost	Incremental QALY	Incremental LY	ICER
Docetaxel	£25,457	0.40	0.52	£63,834
Paclitaxel	£25,407	0.40	0.52	£63,708
BSC	£29,083	0.67	0.99	£43,328

Table 4: Selected sensitivity analysis without PAS for nivolumab

Analysis	Docetaxel	Paclitaxel	BSC
Nivolumab utility for PD reduced by 20%	£84,658	£84,491	£50,744
2-spline model for OS	£80,840	£80,679	£47,027
Remove treatment specific utilities from the analysis	£80,202	£80,044	£49,080
Use health state values from the overall study population	£74,367	£74,221	£45,050
No stopping rule	£68,603	£68,477	£46,162
Subgroup analysis versus docetaxel included in the inv. choice arm of CheckMate 141	£86,407	-	-
Use investigator choice arm efficacy for BSC	-	-	£66,315
Use investigator choice arm efficacy for BSC and same utility in PD for all comparators.	-	-	£81,056

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The main weaknesses were

- The economic evaluation compared nivolumab against docetaxel, paclitaxel and BSC; however BSC was identified as the primary comparator in the economic evaluation and paclitaxel was not considered to be a relevant comparator. The base case analysis versus BSC was based on a naive comparison of the data which was associated with a number of weaknesses and limitations. The company has subsequently provided a sensitivity analysis using data from the investigator choice arm of CheckMate 141 to inform the efficacy of BSC and the results are presented in Table 4 above.
- There were additional weaknesses with the clinical data used in the economic evaluation such as using data from the investigator choice arm of CheckMate 141 to proxy/estimate OS, PFS

and TTD for docetaxel and paclitaxel although data were available for a subgroup of patients in the investigator choice arm who received docetaxel. The company has subsequently provided a sensitivity analysis versus docetaxel using data from the docetaxel subgroup of CheckMate 141 and the results are presented in Table 4 above.

- The company assumed treatment specific utility values from the pivotal study for nivolumab versus investigator choice were applicable to docetaxel, paclitaxel and BSC. In addition, the utility value for progressed disease appeared high for nivolumab when compared against other sources. The company has provided a sensitivity analysis which used a more conservative estimate for progressed disease utility for both nivolumab and BSC combined with using the investigator choice arm of CheckMate 141 to inform the efficacy of BSC. The results are available in Table 4 above.

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

Impact beyond direct health benefits and on specialist services

At the PACE meeting it was highlighted that an extension of good quality life for the patient would have an extremely beneficial impact on the family or carers. Nivolumab's different toxicity profile, compared with chemotherapy, would allow patients to spend their limited life expectancy with less treatment-related morbidity and to function at a higher level, reducing the impact on carers as well as on the wider health service. It was noted that for younger patients of working age, nivolumab could potentially reduce the impact of SCCHN on work productivity and employment status.

Currently most SCCHN patients with progression after platinum-based treatment receive palliative care only. While the number of patients eligible for nivolumab is low, there may be a small impact on the oncology day case service (chair time, plus nursing, pharmacy and medical input) to deliver fortnightly intravenous infusions. In addition, a minority of patients may continue on treatment for a long time and patient numbers are likely to increase over time. In comparison with the more intense daily regimens associated with current chemo/radiotherapy options for fit patients, nivolumab's fortnightly treatment schedule reduces the number of hospital visits, benefitting both patients and carers due to reduction in stress and in time and cost implications of receiving treatment.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 63 patients eligible for treatment with nivolumab in all years to which confidential uptake rate were applied.

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

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

Conclusion

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 that the criterion for a substantial improvement in quality of life was satisfied. In addition, as nivolumab is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

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

Additional information: guidelines and protocols

Recurrent head and neck cancer: United Kingdom national multidisciplinary guidelines[11], was published in 2016. However these guidelines are not widely used in Scotland.

Additional information: comparators

The main active comparator in Scottish practice (if further platinum treatment is not an option) is best supportive care; docetaxel, or methotrexate have been used rarely.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 24 weeks (£)
Nivolumab	**3mg/kg by intravenous infusion every two weeks**	**31,596**
Docetaxel*	30 to 40mg/m^2 by intravenous infusion every week	11,520 to 12,720
Docetaxel**	75mg to 100mg/m^2 by intravenous infusion every three weeks	7,200 to 9,836
Methotrexate**	40 to 60mg/m^2 by intravenous infusion every week	240

Doses are for general comparison and do not imply therapeutic equivalence. Costs were accessed on 03.05.17 from MIMS online for nivolumab and docetaxel and from Dictionary of Medicines and Devices for methotrexate. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Docetaxel is used off-label for this indication. *CheckMate 141 regimen; **regimens cited in UK guidelines.[11]

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This assessment is based on data submitted by the applicant company up to and including 16 June 2017.

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

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

Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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

Advice context:

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

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