



# nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)

Bristol-Myers Squibb Pharmaceuticals Limited

9 November 2018

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

**ADVICE:** following a full submission

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

**Indication under review:** As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Adjuvant treatment with nivolumab improved recurrence free survival compared with another immunotherapy in adults with melanoma with involvement of lymph nodes or metastatic disease who had undergone complete resection.

SMC advice takes account of the benefit of Patient Access Schemes (PAS) that improve the cost effectiveness of nivolumab and is contingent upon the continuing availability of this PAS in NHSScotland or a list price that is equivalent or lower.

**Chairman  
Scottish Medicines Consortium**

## Indication

As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.<sup>1</sup>

## Dosing Information

3mg/kg nivolumab administered by intravenous (IV) infusion over 60 minutes every two weeks for a maximum duration of 12 months.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.<sup>1</sup>

## Product availability date

01 August 2018

Nivolumab meets SMC 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 in 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. Programmed death ligands 1 and 2 (PD-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 the binding of PD-L1 and PD-L2 to the PD-1 receptor and prevents T-cell deactivation.<sup>1</sup> Nivolumab has previously been accepted by SMC for restricted use in unresectable or metastatic melanoma; SMC 1120/16 (monotherapy) and 1187/16 (in combination with ipilimumab).

The evidence supporting this indication is from an ongoing double-blind, randomised, phase III study, CheckMate 238, that recruited patients at least 15 years of age with histologically confirmed melanoma (stage IIIB, IIIC, or IV according to American Joint Committee on Cancer [AJCC] 7<sup>th</sup> edition), metastases to regional lymph nodes or distant (including brain) metastases that had been surgically resected, complete regional lymphadenectomy or resection within 12 weeks before randomisation and Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1.<sup>2</sup>

Patients were randomised to receive IV infusions of nivolumab 3mg/kg every two weeks (n=453) or ipilimumab 10mg/kg every three weeks for four doses and then every 12 weeks (n=453). Treatment was to continue for one year unless there was recurrence of disease, unacceptable toxicity or consent withdrawal. Randomisation was stratified according to disease stage (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c) and PD-L1 expression status of tumour cells (<5% or ≥5%).<sup>2</sup>

The primary outcome was recurrence free survival (RFS), defined as the time from randomisation until the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause. Recurrence was assessed by the investigator. The primary outcome was analysed at a pre-specified interim analysis at 18 months minimum follow up in the intention-to-

treat (ITT) population; median RFS had not been reached in either treatment group.<sup>2</sup> Tables 1 and 2 show the results of the primary outcome. Median RFS is not available due to low number of patients and censoring with 24 months of follow up.<sup>1</sup>

**Table 1: Recurrence free survival rates in CheckMate 238<sup>1, 2</sup>**

RFS rate (95% CI)	Nivolumab (n=453)	Ipilimumab (n=453)
<b>12 months</b>	70% (66 to 74)	60% (55 to 65)
<b>18 months</b>	66% (62 to 70)	53% (48 to 58)
<b>24 months</b>	63% (58 to 67)	50% (45 to 55)

RFS=recurrence free survival; CI=confidence interval; n=number

**Table 2: Recurrence and deaths in CheckMate 238 at 18 and 24 months<sup>2</sup>**

Recurrence or death	Nivolumab (n=453)	Ipilimumab (n=453)
<b>18 months</b>	34% (154/453)	46% (206/453)
	HR 0.65 (97.56% CI: 0.51 to 0.83; p<0.001)	
<b>24 months</b>	38% (171/453)	49% (221/453)
	HR 0.66; p<0.0001*	

n=number; HR=hazard ratio; CI=confidence interval; \*confidence intervals not reported

Overall survival (OS) was a secondary outcome; data are immature.

There were no clinically significant changes from baseline in quality-of-life in either treatment group as assessed with the European Organisation for Research and Treatment of Cancer (EORTC) quality of life 30 item questionnaire (QLQ-C30) and European Quality of Life 5 Dimension (EQ-5D) tools.<sup>2</sup>

## Summary of evidence on comparative safety

In the CheckMate 238 study treatment related grade 3 or 4 adverse events (AEs) occurred in 14% of patients in the nivolumab group and in 46% in the ipilimumab group and led to study medicine discontinuation in 7.7% and 42% of the respective groups.<sup>2</sup>

The summary of product characteristics notes that, in the dataset of nivolumab 3mg/kg as monotherapy for the adjuvant treatment of melanoma (n=452), the most frequent treatment-related AEs (≥10%) were fatigue (46%), rash (29%), diarrhoea (24%), pruritus (23%), nausea (15%), arthralgia (13%), musculoskeletal pain (11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The overall safety profile was consistent with that established across tumour types for nivolumab monotherapy.<sup>1</sup>

## Summary of clinical effectiveness issues

The global incidence of melanoma is increasing.<sup>3</sup> It has a relatively young age distribution and often affects people of working age. Some melanoma patients with lymph node involvement and even metastatic spread, may be able to have complete surgical resection of the tumour. Despite

this, there is a high recurrence rate.<sup>4</sup> Clinical experts consulted by SMC have advised that, in Scotland, these patients are currently managed by routine surveillance. Interferon alfa is the only other licensed medicine for the treatment of resected melanoma in the adjuvant setting, but it is not recommended for this use by the Scottish Intercollegiate Guidelines Network other than in a clinical trial setting.<sup>5</sup> Nivolumab meets SMC orphan equivalent criteria for this indication.

Clinical experts consulted by SMC considered that nivolumab fills an unmet need in this therapeutic area, namely providing an adjuvant treatment option post tumour resection.

CheckMate 238 demonstrated the superiority of 12 months treatment with nivolumab over ipilimumab in prolonging RFS in a large study of patients with complete resection of melanoma. Ipilimumab is not a relevant comparator but is licensed in the US for the indication under review. RFS was assessed when all patients had been followed up for at least 18 months. This is a relatively short time period and median RFS had not been reached in either treatment group.<sup>2</sup> The European Medicines Agency guideline on the evaluation of anticancer medicinal products in man states that, in the adjuvant setting, the ultimate therapeutic aim is to increase cure rate. It goes on to state that, as the use of adjuvant therapy may limit therapeutic options at time of recurrence, OS data should be reported.<sup>6</sup> OS data for nivolumab are currently immature.<sup>1</sup>

The summary of product characteristics for nivolumab notes that the CheckMate 238 study population had stage IIIB/C or stage IV AJCC, 7th edition, histologically confirmed melanoma (which was completely surgically resected) and that this corresponds to patients with lymph node involvement or metastases per the AJCC 8th edition.<sup>1</sup>

Most (90%) study patients had ECOG performance status of 0;<sup>1</sup> it is not clear if the study results would apply to less fit patients.

There is no direct comparative evidence versus routine surveillance, which is the relevant comparator for NHSScotland. The submitting company indirectly compared nivolumab with placebo, as a proxy for routine surveillance, using patient level data meta-regression in a parametric survival analysis (used in the economics base case) and also via a Bucher comparison (used in a scenario analysis in the economic case). Both indirect treatment comparisons (ITCs) included two studies: the pivotal CheckMate 238 study, comparing nivolumab with ipilimumab in patients with completely resected stage IIIB, IIIC, or IV melanoma and CA 184-029, an international, double-blind, randomised, phase III study comparing adjuvant ipilimumab therapy with placebo in 951 patients with completely resected stage III melanoma at high risk of recurrence.<sup>2,4</sup> The only outcome of the ITCs was RFS. For the patient level data meta-regression ITC, the results of the long-term extrapolation using a log-logistic model indicated improved RFS for nivolumab over both ipilimumab and placebo, and improved RFS for ipilimumab over placebo. This result was supported by Bucher ITC that included several consistent analyses, the most robust of which was the ITT analysis adjusted for age, disease stage and sex which indicated longer RFS for nivolumab compared with placebo. Limitations of the ITCs include differences between the two studies in the definition of RFS, in treatment duration and in disease staging; RFS data from CheckMate 238 were immature; no comparative data are available for OS, safety or patient reported outcomes.

The impact of the use of nivolumab as adjuvant therapy on subsequent treatment in the metastatic setting is not known. The best treatment sequencing is not known.

Clinical experts consulted by SMC considered that nivolumab is a therapeutic advancement due to the potential for improved survival for patients with high risk melanoma and that place in therapy would reflect the licensed indication. They considered that the introduction of this medicine would impact on service delivery as treatment for 12 months would have implications for chemotherapy day units. Additional oncology clinic capacity for on treatment reviews and follow-up on completion of treatment would also be required. Overall patient numbers would be small and likely to be manageable.

Other data were also assessed but remain confidential.\*

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing nivolumab with routine surveillance for the adjuvant treatment of patients with stage III-IV melanoma post tumour resection. SMC clinical experts confirmed the comparator was appropriate for this stage of melanoma.

The model used consisted of a partitioned survival model with three states of recurrence-free and post-recurrence, and death. Patients with stage III-IV melanoma and an age range of 18-86 years started in a post resection state. The time horizon was lifetime (60 years) with a maximum age of 100 years, and the model cycle length was 28 days. Alternative Markov model structures were also developed and used in scenario analyses.

Clinical data used in the economic analysis were derived from the ITC described above consisting of a patient-level data meta-regression and parametric survival analysis comparing nivolumab with placebo (with placebo assumed to represent the routine surveillance comparator) via the CheckMate 238 study of nivolumab versus ipilimumab and the CA 184-029 study of ipilimumab versus placebo. This provided estimates of RFS for nivolumab and routine surveillance at 24 months data cut and OS estimates for routine surveillance. RFS for both arms was extrapolated by fitting parametric functions to the data, with the log logistic function representing the best fit in the meta-regression model. OS in the routine surveillance arm was extrapolated using the best fitting generalised gamma function. As nivolumab OS data were immature, a published predictive equation which estimated OS treatment effect based on RFS, was used in combination with the ITC.<sup>2,4</sup> This analysis generated a HR for nivolumab versus placebo/routine surveillance which was applied to the routine surveillance arm to estimate the survival benefit for nivolumab. Long term survival for both arms was estimated using 15 year follow-up data from the 8<sup>th</sup> edition of the AJCC registry in stage III melanoma patients,<sup>7</sup> applied at year 10 in the economic analysis on the grounds that this reflects the time point at which long term melanoma survival rates appear to plateau based on published evidence and expert opinion. Long run RFS was also adjusted to take account of applying the long term survival data.

Health-related quality of life data using the EQ-5D-3L were collected in the CheckMate 238 study, and a regression analysis performed in order to estimate pre and post recurrence utilities. Disutilities derived from a published study in adjuvant melanoma<sup>8</sup> were estimated for immune related, grade  $\geq 2$  diarrhoea and grade  $\geq 3$  adverse events and applied to estimates of the frequency and duration of the AEs from CheckMate 238.

Treatment duration for nivolumab was based on actual time on treatment (ToT) data from the CheckMate 238 study. There was no need for extrapolation of ToT as the maximum duration of nivolumab treatment is 12 months in the clinical study and in clinical practice.

Medicine acquisition and administration costs were included in the economic analysis. The dose for nivolumab was 3mg/kg and the use of the 40mg and 100mg vials was based on a methods of moments analysis of vial use in the CheckMate 238 study, and so took account of medicines wastage. Post recurrence subsequent medicine and radiotherapy / surgery costs were based on the proportion of patients by type of recurrence (loco-regional or distant) receiving these therapies in the CheckMate 238 study, with the post-ipilimumab medicines assumed to represent routine surveillance post recurrence therapies received. Health state resource use for disease monitoring was estimated through a clinical expert survey with 6 UK oncologists. Inpatient and outpatient adverse event management and end of life care costs were also included.

A Patient Access Scheme (PAS) was proposed by the submitting company and considered acceptable for implementation by the Patient Access Scheme Assessment Group (PASAG). The base case result and selected sensitivity analyses including the nivolumab PAS are available in Table 3 below.

**Table 3: Base case result and selected sensitivity/scenario analyses**

<b>Analysis</b>	<b>ICER with PAS</b>
Base case	£9,611
0-6% QALY discount rate	£5,334 - £13,270
Markov model structure	£9,244
30 year time horizon	£10,753
Upper bound OS HR for ipilimumab versus placebo used in the ITC	£12,683
Upper bound RFS HR for nivolumab versus ipilimumab used in ITC	£12,000
Applying long term survival data using 7 <sup>th</sup> edition AJCC registry data <sup>9</sup>	£10,998
5 years for application of long term survival data	£11,848
Applying 7 <sup>th</sup> edition registry data from 5 years	£15,731
Using upper 95% CI estimated for HR for OS derived from the predictive equation	£14,448
Applying lower utility values for recurrence free and post-recurrence states	£10,198
No differences in subsequent therapy costs post recurrence after nivolumab and routine surveillance	£9,863
Alternative survival analysis using CheckMate 238 study 24 month OS analysis: matching nivolumab OS from the predictive equation to the OS estimates from CheckMate 238 follow-up	£19,963

ICER= incremental cost-effectiveness ratio

The main uncertainty was associated with the estimation of the OS benefit for nivolumab versus routine surveillance:

- The estimation of OS benefit for nivolumab was based on a predictive equation using the RFS surrogate applied to an ITC which had limitations. The studies used to estimate the RFS – OS relationship were prior to the use of immune checkpoint inhibitors as standard treatments for post recurrence advanced melanoma, and so the HR for OS versus routine surveillance may be pessimistic.
- Analysis using the OS data from the unplanned 24 month OS analysis of CheckMate 238 produced lower estimates of life years and QALYs gained than in the base case and therefore a higher ICER. In addition, a weakness with this analysis is that it is based on extremely immature survival data. However, the company also provided a threshold analysis which demonstrates the HR for OS would need to exceed 0.88 for the ICER to exceed £30,000/QALY which was considered helpful for decision making at the SMC meeting.

The Committee also considered the benefits of nivolumab in the context of the SMC decision modifiers that can be applied and agreed that as nivolumab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

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

## Summary of patient and carer involvement

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

- We received patient group submissions from Melanoma UK, and Melanoma Action and Support Scotland (MASScot). Both are registered charities.
- Melanoma UK has received 8% of its funding from the pharmaceutical industry in the last two years, with none from the submitting company. MASScot has not received any pharmaceutical company funding in the past two years.
- Most people diagnosed with melanoma can be supported to continue working with a reasonable quality of life but always with the worry of what will happen next. This psychological effect is considerable, causing sleep loss or poor sleep quality which may be debilitating. If patients have to give up work, it can have an enormous impact on the whole family.
- Watch and wait is currently used with physical examination and scans at regular intervals. This approach can bring heightened tension which affects the family life and work, as well

as impacting on relationships and financial decisions. Quality of life may be improved if there is a further treatment option available at this stage.

- IV treatment on alternate weeks may cause difficulties for some patients and carers, especially those who live a distance away from the providing centres and/ or have children or other responsibilities. However this is considered well worth the added burden for the opportunity of increased survival.

### Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 146, Cutaneous melanoma in 2017.<sup>5</sup>

The European Dermatology Forum, the European Association of Dermato-Oncology and the European Organisation for Research and Treatment of Cancer published a joint guideline in 2016: Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline e Update 2016.<sup>3</sup>

The European Society for Medical Oncology published Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, in 2015.<sup>10</sup>

All the above guidelines pre-date the availability of nivolumab as adjuvant treatment for resected melanoma, and none provide recommendations on its use.

### Additional information: comparators

There are no relevant comparators. Patients are currently managed with routine surveillance.

### Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
<b>Nivolumab</b>	<b>3mg/kg nivolumab administered by intravenous infusion every 2 weeks for up to 12 months.</b>	<b>£68,458</b>

Cost of nivolumab from the BNF online on 06 August 2018. Cost based on 70kg body weight. Cost calculated using the full cost of vials/ampoules assuming wastage. Cost does not take any patient access schemes into consideration.

## Additional information: budget impact

The submitting company estimated there would be 134 patients eligible for treatment with nivolumab in year 1 rising to 150 patients in year 5 to which confidential uptake rates were applied

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

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

## References

1. Nivolumab 10mg/mL concentrate for solution for infusion (OPDIVO®). Summary of product characteristics. Bristol-Myers Squibb Pharmaceuticals Limited. Electronic Medicines Compendium [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/) Last updated 01 August 2018.
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This assessment is based on data submitted by the applicant company up to and including 12 September 2018.

*\*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](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.*