# nivolumab concentrate for solution for infusion (Opdivo®)

## Bristol Myers Squibb Pharmaceuticals Ltd

05 December 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics 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:** in combination with ipilimumab for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following setting: first-line treatment of unresectable or metastatic colorectal cancer.

In a phase III study of patients with untreated mismatch repair deficient or microsatellite instability-high unresectable or metastatic colorectal cancer, nivolumab plus ipilimumab significantly improved progression-free survival compared with investigator's choice of chemotherapy.

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

**Vice Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

### 1.1. Medicine background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that targets the programmed death (PD)-1 receptor and blocks interaction with its ligands, PD-L1 and PD-L2 leading to potentiation of T-cell responses, including anti-tumour responses. Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4) leading to enhanced T-cell responses towards the tumour. Dual blockade of PD-1 and CTLA-4 is considered to have synergistic anti-tumour activity.[1]

For this indication, the recommended dose of nivolumab is 240 mg by intravenous infusion in combination with ipilimumab 1 mg/kg by intravenous infusion every 3 weeks for a maximum of four doses, followed by nivolumab monotherapy 240 mg by intravenous infusion every 2 weeks or 480 mg by intravenous infusion every 4 weeks. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.[1] Refer to the Summary of Product Characteristics (SPC) for further information.

Nivolumab in combination with ipilimumab has previously been accepted by SMC for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (SMC2394).

### 1.2. Disease background

Colorectal cancer is one of the most common cancer types in Scotland, accounting for 12% of all cancers.[2] Colorectal cancer is clinically defined by its tissue of origin in the colon or rectum but is heterogeneous in terms of genetic classification. Approximately 15% to 30% of patients present with metastases and 20% to 50% of patients initially diagnosed with localised disease will develop metastases.[3] DNA repair defects, defined as dMMR or MSI-H, occur in approximately 4% to 7% of metastatic colorectal cases.[4] Evidence suggests that patients with dMMR or MSI-H metastatic colorectal cancer demonstrate less favourable progression-free survival (PFS) and overall survival (OS) outcomes compared with patients who have microsatellite stable (MSS) tumours following treatment with first-line therapies.[5]

### 1.3. Treatment pathway and relevant comparators

The predominant first-line treatment in NHSScotland for the treatment of dMMR or MSI-H unresectable or metastatic colorectal cancer is pembrolizumab (SMC2375). A small proportion of patients may receive combination chemotherapy regimens such as capecitabine and oxaliplatin (CAPOX), 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX), or 5-fluorouracil, leucovorin and irinotecan (FOLFIRI); cetuximab (SMC1012/14) and bevacizumab (NCMAG123) may be used in combination with chemotherapy in some cases. These comparators were confirmed by clinical experts consulted by SMC and Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data.[6]

### 1.4. Category for decision-making process

Eligibility for a PACE meeting

Nivolumab meets SMC orphan equivalent criteria for this indication.

## 2. Summary of Clinical Evidence

### 2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of nivolumab in combination with ipilimumab for this indication comes from the first-line population of CheckMate 8HW.[4] Details are presented in Table 2.1.

**Table 2.1. Overview of relevant study**

| Criteria | CheckMate 8HW [4, 7] |
|---|---|
| Study design | International, randomised, open-label, phase III study. |
| Eligible patients | • Adult patients ≥18 years of age.<br>• Histologically confirmed recurrent or metastatic colorectal cancer with no prior treatment history with chemotherapy or targeted agents for metastatic disease and not amenable to surgery. Participants treated with adjuvant chemotherapy were eligible if disease progression occurred later ≥6 months after completion of chemotherapy.<br>• Known tumour MSI-H or dMMR status per local standard of practice.<br>• Measurable disease by CT or MRI per RECIST 1.1 criteria.<br>• ECOG performance status ≤1. |
| Treatments | Patients were randomised to receive nivolumab 240 mg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 12 weeks followed by nivolumab 480 mg IV every 4 weeks;or, nivolumab 240 mg monotherapy IV every 2 weeks, followed by nivolumab 480 mg IV every 4 weeks; or, investigator's choice of chemotherapy (mFOLFOX6or FOLFIRI with or without bevacizumab or cetuximab every 2 weeks).<br><br>The nivolumab monotherapy group will not be discussed further.<br><br>Patients in the chemotherapy group were permitted to receive nivolumab plus ipilimumab if disease progression was confirmed by blinded review. Patients in the crossover group received nivolumab 240 mg IV every 2 weeks for the first 12 weeks plus ipilimumab 1 mg/kg IV every 6 weeks, followed by nivolumab 480 mg IV every 4 weeks plus ipilimumab 1 mg/kg IV every 6 weeks.<br><br>Treatment was to continue until disease progression, unacceptable toxicity, consent was withdrawn or for a maximum of 2 years in patients who received nivolumab plus ipilimumab except in patients with late response (during second year of treatment). In patients with late response, treatment could continue for an additional 12 months after onset of response. |
| Randomisation | Patients were randomised in a 2:2:1 ratio. Randomisation was stratified by tumour location (right versus left). |
| Primary outcome | PFS with nivolumab plus ipilimumab versus chemotherapy in patients with centrally confirmed MSI-H or dMMR status. Defined as the time between date of randomisation to the date of first progression (assessed by BICR using RECIST v1.1 criteria) or death due to any cause, whichever occurred first. MSI-H or dMMR status was confirmed by PCR or immunohistochemistry. |
| Secondary outcomes | • PFS assessed by BICR per RECIST v1.1 criteria in the ITT population (all randomised patients). |

| | |
|---|---|
| | • PFS2 in patients with centrally confirmed MSI-H or dMMR status was an exploratory secondary outcome. Defined as the time from randomisation to investigator defined disease progression per RECIST v1.1 criteria after the start of the next line of therapy, start of second next line therapy or death from any cause, whichever occurred first. |
| Statistical analysis | A hierarchical statistical testing strategy was applied with no formal testing of outcomes after the first non-significant outcome, however results for secondary outcomes included in the hierarchy, ORR and OS, were not available at the time of the interim analysis as the predetermined number of events had not been reached. |

Abbreviations: BICR = blinded independent central review; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; dMMR = deficient mismatch repair; FOLFIRI = 5-fluorouracil, leucovorin and irinotecan; mFOLFOX6= modified 5-fluorouracil, leucovorin and oxaliplatin; ITT = intention-to-treat; IV = intravenous; MRI = magnetic resonance imaging; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PCR = polymerase chain reaction; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours.

At the interim analysis (data cut-off 12 October 2023), after a median follow-up of 31.5 months, nivolumab plus ipilimumab demonstrated significant improvements in PFS compared with chemotherapy.[4] See Table 2.2 for details.

**Table 2.2: Primary and selected secondary outcomes from CheckMate 8HW in the first-line population (data cut-off 12 October 2023).[4, 7]**

| | Nivolumab plus ipilimumab | Chemotherapy |
|---|---|---|
| **Primary outcome: PFS assessed by BICR per RECIST v1.1 (centrally confirmed population)** | | |
| Number of patients | 171 | 84 |
| Events, n | 48 | 52 |
| Median PFS, months | NR | 5.9 |
| HR (95% CI), p-value | 0.21 (0.14 to 0.32), p<0.001 | |
| KM-estimated PFS at 12 months | 79% | 21% |
| **Secondary outcome: PFS assessed by BICR per RECIST v1.1 (ITT population)** | | |
| Number of patients | 202 | 101 |
| Events, n | 73 | 62 |
| Median PFS, months | NR | 6.2 |
| HR (95% CI) | 0.32 (0.23 to 0.46) | |
| **Secondary outcome: PFS2 assessed by investigator per RECIST v1.1 (centrally confirmed population)** | | |
| Number of patients | 171 | 84 |
| Events, n | 29 | 40 |
| Median PFS2, months | NR | 29.9 |
| HR (95% CI) | 0.27 (0.17 to 0.44) | |
| KM-estimated PFS2 at 12 months | 89% | 65% |

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; NR = not reached; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours.

At a later data cut-off (28 August 2024), with a minimum follow-up of 16.7 months, median PFS was 54.1 months versus 5.9 months (HR: 0.21, 95% CI: 0.14 to 0.31) in the centrally confirmed population assessed by BICR per RECIST v1.1.[8].

### 2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using two questionnaires: EQ-5D-3L and the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life

Questionnaire (QLQ-C30) version 3. EQ-5D-3L and EORTC QLQ-C30 data were collected prior to dosing on day 1 in cycles one, two and three and every other cycle thereafter.[4]

Both treatment groups had increases in EQ-5D-3L scores during treatment, but the improvements appeared greater in the nivolumab plus ipilimumab group. In the nivolumab plus ipilimumab group, the average changes from baseline met the minimum important difference thresholds for improvement at multiple timepoints throughout the treatment period up to week 101. The chemotherapy group did not reach the minimum important difference for improvement at any timepoint during the treatment period up to week 37.[7]

From week 13 onward, there was an apparent trend towards meaningful improvements in overall health and quality of life in the nivolumab plus ipilimumab group, as measured by the Global Health Status subscale of the EORTC QLQ-C30 questionnaire. The difference between the two treatment groups from week 13 onwards was clinically meaningful, indicating that nivolumab plus ipilimumab provided a HRQoL benefit compared with chemotherapy.[4]

### 2.3. Supportive study

CheckMate 142 was an international, open-label, single-arm, phase II study. The data presented are from cohort three of the study; patients with previously untreated MSI-H metastatic colorectal cancer. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks plus ipilimumab 1 mg/kg by intravenous infusion every 6 weeks until disease progression, discontinuation, death or end of study.[9]

A total of 45 patients were enrolled in CheckMate 142. The primary outcome was investigator assessed ORR per RECIST version 1.1. Exploratory endpoints included PFS and OS.[9] At 64.2 months follow-up, ORR was 71% (95% CI: 56 to 84), median PFS and OS were not reached and 60 month PFS and OS rates were 55% and 67% respectively.[10]

### 2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus pembrolizumab, the submitting company performed indirect treatment comparisons (ITCs). Further details are presented in Table 2.3.

**Table 2.3: Summary of indirect treatment comparison**

| Criteria | Overview |
|---|---|
| Design | Fractional polynomial NMA |
| Population | Adults ≥18 years, with untreated MSI-H or dMMR metastatic colorectal cancer |
| Comparators | • Nivolumab plus ipilimumab<br>• Pembrolizumab |
| Studies included | CheckMate 8HW (NCT04008030) for nivolumab plus ipilimumab (n=202) [4]<br>KEYNOTE-177 (NCT02563002) for pembrolizumab (n=153) [11] |
| Outcomes | PFS |
| Results | Nivolumab plus ipilimumab was associated with a statistically significant benefit in PFS versus pembrolizumab across all timepoints. |

Abbreviations: dMMR = mismatch repair deficient; MSI-H = microsatellite instability high; NMA = network meta-analysis; PFS = progression-free survival; SoC = standard of care.

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

## 3. Summary of Safety Evidence

Evidence from CheckMate 8HW supports the relative safety of nivolumab plus ipilimumab compared with chemotherapy for the treatment of patients with untreated MSI-H or dMMR metastatic colorectal cancer. Chemotherapy is a relevant comparator for a small number of patients in this setting; there are no comparative safety data versus the most relevant comparator, pembrolizumab. In the CheckMate 8HW study at data cut-off 12 October 2023, the median duration of treatment was 13.5 months in the nivolumab plus ipilimumab group and 4 months in the chemotherapy group.[4]

In the nivolumab plus ipilimumab and chemotherapy groups respectively, patients reporting a treatment-related grade 3 or higher adverse event (AE) were 23% (46/200) versus 48% (42/88), patients with a reported serious grade 3 or higher treatment-related AE were 16% in both groups and patients discontinuing therapy due to a treatment-related AE was 16% versus 32%.[4]

The most frequently reported treatment-related AEs of any grade with an incidence ≥10% in the nivolumab plus ipilimumab group were: pruritus (22% versus 5%), diarrhoea (21% versus 51%), hypothyroidism (16% versus 0%), asthenia (14% versus 35%) and fatigue (13% versus 14%). There were two (1%) treatment-related deaths in the nivolumab plus ipilimumab group from myocarditis and pneumonitis (one patient each) and zero in the chemotherapy group.[4]

The safety profile in CheckMate 8HW was consistent with the known safety profile of nivolumab plus ipilimumab and no new safety concerns were identified. Immune-mediated AEs are of special interest, most of these AEs were grade 1 or 2 in severity and overall are considered manageable.[7]

## 4. Summary of Clinical Effectiveness Considerations

### 4.1. Key strengths

- At the interim analysis (12 October 2023) of the phase III study CheckMate 8HW, nivolumab in combination with ipilimumab was associated with a statistically significant and clinically meaningful improvement in PFS compared with investigator's choice of chemotherapy with or without targeted treatments. Investigator assessed PFS was consistent with the primary analysis, and the benefit was observed across all subgroups.[4] This was supported by data from a later cut-off (28 August 2024), which showed continued median PFS benefit of nivolumab in combination with ipilimumab with a median PFS gain of 48.2 months (54.1 months versus 5.9 months).[8]
- Nivolumab in combination with ipilimumab would be the first dual immunotherapy approved in NHSScotland for the first-line treatment of dMMR or MSI-H unresectable or metastatic colorectal cancer.

### 4.2. Key uncertainties

- In the absence of direct evidence versus pembrolizumab, the submitting company performed ITCs. There were limitations affecting the results of the ITCs, including differences in data maturity between the studies, lack of OS and patient reported outcome data, and only two included studies. The KEYNOTE-777 study only tested locally for dMMR

or MSI-H status, therefore the locally confirmed population of CheckMate 8HW was included. Despite these limitations, the results of the ITCs are considered reasonable.

- OS data from CheckMate 8HW are not available as the predetermined number of events have not been reached.[4] In the absence of OS data from CheckMate 8HW, the submitting company provided OS data from CheckMate 142 to support the submission. However, these data have several limitations, including small patient numbers within a non-randomised, non-comparative study, and there were differences in dosing and treatment duration compared with the licensed regimen.[9] PFS2 data are available as an exploratory outcome and were considered by the regulator to support the long-term benefit of nivolumab plus ipilimumab.[4]
- CheckMate 8HW is an open-label study which may introduce bias for subjective quality of life and safety outcomes. Quality of life outcomes reported from CheckMate 8HW should therefore be interpreted with caution.
- While the eligibility criteria included patients with unresectable MSI-H or dMMR colorectal cancer, CheckMate 8HW only enrolled patients with metastatic disease (stage IV) disease. The regulator considered that extrapolation of data to patients with unresectable disease was acceptable.[7]

### 4.3. Clinical expert input

Clinical experts consulted by SMC consider that nivolumab in combination with ipilimumab is a therapeutic advancement due to significant improvements in PFS demonstrated in the CheckMate 8HW study. Clinical experts considered that the place in therapy would be for patients who are fit enough to tolerate nivolumab in combination with ipilimumab.

### 4.4. Service implications

Clinical experts consulted by SMC consider that nivolumab plus ipilimumab may impact the service. Administration of nivolumab plus ipilimumab may initially require more time in chemotherapy day units and clinics, and monitoring and management of immune-related adverse reactions is also necessary.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

## 5. Summary of Patient and Carer Involvement

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

- We received a patient group submission from Bowel Cancer UK, which is a registered charity.
- Bowel Cancer UK has received 3.5-4% pharmaceutical company funding in the past two years, including from the submitting company.
- A bowel cancer diagnosis is life-changing and has a huge impact on people's day-to-day lives. It also affects the lives of their friends and family. It is even more acute for those

diagnosed in the later stages of the disease, when it is harder to treat and there are lower chances of survival.

- Existing treatments have a range of side effects, and in some instances can be debilitating, resulting in deep fatigue and anxiety. Access to more treatment options is preferable, with many patients in a survey conducted by the patient group requesting easier access to immunotherapy and testing being made a priority.

- Several respondents to the patient group's survey shared the positive impact nivolumab with ipilimumab had on their lives, saying how well it worked in such a short space of time, having nowhere near as severe side effects. The same respondents called for its wider roll out, with one sharing that it saved their life.

# 6. Summary of Comparative Health Economic Evidence

### 6.1. Economic case

An overview of the economic analysis is presented in Table 6.1

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost-utility analysis |
| Time horizon | Lifetime (40 years) |
| Population | First-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) colorectal cancer (CRC). |
| Comparators | Nivolumab in combination with ipilimumab versus pembrolizumab; chemotherapy |
| Model description | A five-state semi-Markov model was used. The Markov component consisted of three health states representing progression-free, progressed disease and death. An additional two health states were included for patients receiving surgery consisting of post-surgery progression-free and post-surgery progressed disease states. A partitioned survival modelling approach was used for estimating PFS and OS for the post-surgery component. Model cycle length was 28 days. |
| Clinical data | ITT data from the phase 3 CM8HW clinical study was used to estimate transition probabilities for progression-free (PF) to progressed disease (PD) for nivolumab plus ipilimumab and chemotherapy, based on time to progression (TTP) estimates.[8] Estimates for pembrolizumab were derived from the ITCs of study KN-177 with CM8HW, with a fractional polynomial NMA used in the base case and MAIC in scenario analysis.[12] Only PFS estimates were available for pembrolizumab which were converted to TTP estimates and transition probabilities for inclusion in the economic model.<br><br>Due to lack of longer term data from study CM8HW, the phase 2 CM142 study was used to provide post progression data for estimating transitions from progressed disease to death for nivolumab plus ipilimumab, and the same estimates were applied for pembrolizumab.[9] For the chemotherapy comparator post progression CM142 data was applied but also data from published studies to reflect the use of second line subsequent treatment predominantly with immunotherapy, or further chemotherapy.[13, 14] Scotland general population mortality rates were used to estimate progression-free to death transitions, assumed the same for all interventions.<br>A simple fixed effects NMA of study CM8HW and KN-177 was performed to estimate the odds of surgery for both chemotherapy and pembrolizumab and for nivolumab for inclusion in the economic analysis. PFS and OS estimates for the post-surgery health state outcomes were |

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| | derived from a published study for a cure model survival analysis after hepatic resection for colorectal liver metastases.[15]<br><br>AEs of grade 3+ and ≥5% incidence and AEs of special interest to immunotherapies were included in the economic analysis, derived from CM8HW for nivolumab plus ipilimumab and chemotherapy, and KN-177 for pembrolizumab. |
| Extrapolation | Extrapolation of TTP outcomes for nivolumab plus ipilimumab and for chemotherapy from study CM8HW were performed by fitting the generalised gamma function in the base case, with hazard ratios applied for pembrolizumab vs nivolumab plus ipilimumab estimated from the FP NMA.<br><br>Post progression survival (PPS) after first-line nivolumab plus ipilimumab, and assumed equivalent for pembrolizumab, was extrapolated using the log logistic function in the base case assuming the use of chemotherapy as the subsequent 2nd line therapy, and for chemotherapy the exponential function was applied to extrapolate PPS post 1st line chemotherapy accounting for the use of subsequent 2nd line therapies (IO's or chemotherapy). For post-surgery PFS and OS extrapolation the generalised gamma was selected in the base case.<br><br>Time to treatment discontinuation (TTD) was estimated for nivolumab plus ipilimumab and chemotherapy using CM8HW observed data , without any further extrapolation. Pembrolizumab was assumed to have the same TTD as nivolumab plus ipilimumab but capped by pembrolizumab TTP. |
| Quality of life | Analysis of EQ-5D-3L data collected in the CM8HW study was used to estimate treatment specific health state utilities for PF and PD. PF utility estimates for nivolumab plus ipilimumab were assumed to also apply to pembrolizumab. The same PF and PD utilities were applied for the post surgery states.<br><br>Disutilities were also included for selected AEs, with these applied only in a scenario analysis in which non-treatment specific PF utilities were applied (in the base case it was assumed the impact of AEs was captured within the analysis of treatment specific utilities). |
| Costs and resource use | Drug acquisition costs were included for all medicines included in the economic analysis, and drug administration costs were estimated for IV or oral administration of nivolumab, ipilimumab, and the chemotherapy regimens. The pembrolizumab dose included in the economic analysis was 400mg Q6W. No vial sharing was assumed and relative dose intensity was not considered.<br><br>For the chemotherapy comparator, the estimated cost was for a basket of therapies, with this predominantly consisting of FOLFOX, FOLFIRI and CAPOX regimens based on clinical expert opinion. Subsequent therapies used second line post progression estimated to be used in 54% of patients (from prior NICE and SMC technology appraisals) were assumed to consist of chemotherapy (FOLFOX and FOLFIRI) after nivolumab plus ipilimumab or pembrolizumab, and predominantly nivolumab plus ipilimumab or pembrolizumab immunotherapy (with a small proportion of patients receiving further chemotherapy) after progression with 1st line chemotherapy. The duration of subsequent treatments was estimated from CM8HW or prior technology appraisals.<br><br>Costs were also included for disease monitoring in PF and PD states with resource use estimates based on those used in prior technology appraisals.[16, 17] Other costs were AE costs, costs for surgery, post-surgery monitoring and end of life best supportive care. |
| PAS | A Patient Access Scheme (PAS) was submitted by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of nivolumab and ipilimumab respectively. A PAS discount is in place for pembrolizumab. Nivolumab plus |

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|---|---|
| | ipilimumab and pembrolizumab were also included as subsequent therapies. Account of these were included in the results used for decision-making by using estimates of the comparator/ subsequent therapies PAS price. |

### 6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

The life year and QALY benefits over pembrolizumab and chemotherapy were driven by extra time in the progression-free state for nivolumab plus ipilimumab. The QALYs estimated for chemotherapy were similar to those for pembrolizumab due to a proportion of patients receiving immunotherapies (IOs) as a second line treatment with higher post-progression survival. Estimated incremental costs were driven by higher drug acquisition costs for nivolumab plus ipilimumab versus comparators. There are high cost-offsets associated for the comparison with chemotherapy due to the use of IOs as a subsequent 2$^{nd}$ line therapy after chemotherapy.

### 6.3. Sensitivity analyses

Deterministic sensitivity analysis demonstrated modest sensitivity in the ICER for the comparison with pembrolizumab relating to varying treatment specific utilities and the proportion of patients receiving subsequent therapies after pembrolizumab. For the comparison with chemotherapy, the most ICER sensitive parameters were also the proportion of patients receiving subsequent therapies, and varying the mean duration of subsequent IO therapy.

Various scenario analyses were performed by the submitting company or requested. Key selected scenarios are described in Table 6.3. In addition, a subgroup analysis was performed in patients in CM8HW with centrally confirmed dMMR or MSI-H status (Scenario 9, Table 6.3).

**Table 6.2: Selected scenario analyses with PAS's applied**

| | **Parameter** | **Base Case** | **Scenarios** |
|---|---|---|---|
| 1 | ITC methods for pembrolizumab PF to PD transitions | Fractional Polynomial NMA | (a)Anchored MAIC |
| | | | (b)Unanchored MAIC |
| 2 | Pembrolizumab PF to PD transitions. | ITC used–FP NMA | (a) Apply PFS HR for nivolumab +ipilimumab vs nivolumab from CM8HW (HR=0.64) |
| | | | (b) CM8HW nivolumab monotherapy TTP extrapolation (generalised gamma) to represent pembrolizumab TTP |
| 3 | Pembrolizumab TTD | Pembrolizumab maximum of nivolumab + ipilimumab TTD or pembrolizumab TTP | Pembrolizumab TTD is the same as nivolumab monotherapy for all lines of therapy |

| | | | |
|---|---|---|---|
| 4 | Extrapolation of TTP (PF-PD) for nivolumab +ipilimumab in CM8HW | Generalised gamma | (a) Log normal |
| | | | (b) Log logistic |
| 5 | Extrapolation of TTP (PF-PD) for chemotherapy in CM8HW | Generalised gamma | (a) Log normal |
| | | | (b) Log logistic |
| 6 | Time horizon | 40 years | 20 years |
| 7 | Health state utilities | Treatment specific PF utilities based on CM8HW | Applying CM8HW non-treatment specific utilities (with AE disutilities separately applied) |
| 8 | Post-surgery health states | Model structure includes post surgery states with surgery probability informed by a simple NMA | Post surgery health states removed |
| 9 | Subgroup analysis: patient population | ITT population in CM8HW | Centrally confirmed dMMR/MSI-H status population in CM8HW |

Abbreviations ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality adjusted life years; TTD=time to treatment discontinuation; HR=Hazard ratio; ITC=indirect treatment comparison; FP NMA = fractional polynomial network meta-analysis; N/A=not applicable

### 6.4. Key strengths

- An appropriate economic model structure was utilised.
- The choice of comparators were considered appropriate.
- The availability of EQ 5D data from the CM8HW study for estimation of health state utilities.
- A good range of scenarios were explored.

### 6.5. Key uncertainties

- Based on SMC clinical expert feedback the key comparator was pembrolizumab. As the comparison against pembrolizumab was reliant on an indirect treatment comparison with some limitations, and the need to convert PFS estimates in the ITC to TTP for use in the economic analysis, there was some uncertainty over the cost-effectiveness results related to this.
- There was limited evidence for estimating post progression survival which, because of the immaturity of OS data in CM8HW, was based on a phase 2 study for nivolumab plus

ipilimumab (CM142) with low post progressed patient numbers. PD to death transitions were assumed to be the same as those for pembrolizumab.

- The magnitude of the survival benefit (life years gained) for nivolumab plus ipilimumab over pembrolizumab was uncertain. A later CMH8W datacut appeared to be available (August 2024) for PFS, but the submitting company stated updated OS results from the CM8HW were not available. One scenario extrapolated nivolumab monotherapy TTP extrapolation (generalised gamma) to represent pembrolizumab TTP produced much smaller incremental QALY gains for nivolumab plus ipilimumab producing a higher upper limit ICER estimate (Scenario 2b, Table 6.2).
- A further uncertainty for the comparison with pembrolizumab related to the estimates of relative time to treatment discontinuation (TTD). Whilst the estimation of TTD for nivolumab plus ipilimumab was based on observed CM8HW data and so appeared reasonably robust, the estimate for pembrolizumab which was capped at pembrolizumab TTP was uncertain. A scenario analysis that assumed the same TTD as nivolumab monotherapy improved the ICER (Scenario 3, Table 6.2). However, overall TTD was an area of uncertainty with unclear impact on the ICER.
- In the base case the impact of AEs on on-treatment PF utilities was implicitly assumed to be the same for doublet nivolumab plus ipilimumab and monotherapy pembrolizumab. Applying separate AE disutilities with non-treatment specific PF utilities was explored (Scenario 7, Table 6.2).
- The estimates of a difference in surgery probabilities between nivolumab plus ipilimumab vs comparators in the economic analysis were uncertain and based on the results of a fixed effects NMA with wide credible intervals for the comparisons versus pembrolizumab and chemotherapy. Scenario analysis removing the surgery component from the model (leaving a three-state model) was performed with a small impact on the ICER (Scenario 8, Table 6.2).
- There were limitations in the economic analysis versus chemotherapy including uncertainties over the transferability of the chemotherapy arm outcomes from CM8HW to the chemotherapy treatment mix assumed for Scottish clinical practice in the economic analysis, and assumptions regarding the use of subsequent 2$^{nd}$ line immunotherapies and impact on post progression survival and costs for the chemotherapy comparator. However, scenario analyses were performed to explore uncertainties versus chemotherapy, with modest impacts on the ICER (Scenarios 4-8, Table 6.2). Also, this did not appear to be an important comparator for Scottish clinical practice based on SMC clinical expert feedback.

## 7. Conclusion

After considering all the available evidence, the Committee accepted nivolumab in combination with ipilimumab for use in NHSScotland.

## 8. Guidelines and Protocols

The European Society for Medical Oncology (ESMO) published a clinical practice guideline for diagnosis, treatment and follow-up of metastatic colorectal cancer in 2023.[3]

The National Institute for Health and Care Excellence (NICE) updated NICE guideline 151 on colorectal cancer in 2021.[18]

The Scottish Intercollegiate Guidelines Network (SIGN) revised guideline 126 on the diagnosis and management of colorectal cancer in 2016.[19]

## 9. Additional Information

### 9.1. Product availability date

4 April 2025

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per year (£) |
|---|---|---|
| **nivolumab (in combination with ipilimumab)** | **240 mg IV (in combination with ipilimumab** 1 mg/kg IV every 3 weeks for a maximum of four doses**) every 3 weeks for a maximum of four doses followed by nivolumab monotherapy 240 mg IV every 2 weeks or 480 mg IV every 4 weeks for up to 24 months in patients without disease progression** | **93,192 (year one)**<br>**68,458 (subsequent year)** |

*Costs from BNF online on 26 November 2025. Costs calculated using the full cost of vials assuming wastage. Ipilimumab cost calculated based on 70 kg body weight. Costs do not take any patient access schemes into consideration.*

## 10. Company Estimate of Eligible Population and Estimated Budget Impact

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

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This assessment is based on data submitted by the applicant company up to and including **19 November 2025.**

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.