Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2397

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

Bristol-Myers Squibb Pharmaceuticals Limited

10 December 2021

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

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

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

Indication under review: in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

Nivolumab plus ipilimumab and 2 cycles of platinum-based chemotherapy significantly improved overall survival compared with platinum-based chemotherapy in patients with previously untreated stage IV or recurrent non-small cell lung cancer (NSCLC).

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

Chairman
Scottish Medicines Consortium

Indication

Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.[1, 2]

Dosing Information

The recommended dose is 360mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360mg nivolumab administered intravenously every 3 weeks in combination with 1mg/kg ipilimumab every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Dose adjustment is not recommended. Adverse effects should be managed through dosing delay or discontinuation. Please see individual Summary of Product Characteristics (SPCs) for further information.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[1, 2]

Product availability date

5 November 2020

Nivolumab meets SMC end of life criteria for this indication

Summary of evidence on comparative efficacy

Nivolumab is a monoclonal antibody that potentiates T-cell responses, including anti-tumour responses, by binding to programmed death-1 (PD1) receptor and blocking its interaction with PD-L1 and PD-L2 ligands. Ipilimumab is a CTLA-4 inhibitor that blocks T-cell inhibitory signals and increases the number of reactive T-effector cells, which mobilise to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Nivolumab and ipilimumab have been shown to have synergistic anti-tumour activity (in metastatic melanoma).[1, 2] The submitting company has requested that SMC considers this product when positioned for use in a subgroup of adults with untreated metastatic NSCLC who express PD-L1 at a level of <50%.

CheckMate 9LA is an international, randomised, open-label, phase III study that recruited adults with histologically confirmed stage IV or recurrent NSCLC. Eligible patients had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no prior treatment for advanced or

metastatic disease and no EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy.[3, 4]

Patients were randomised equally to receive nivolumab 360mg every 3 weeks with ipilimumab 1mg/kg every 6 weeks plus histology-based platinum doublet chemotherapy (PDC) every 3 weeks for two cycles (n=361) or histology-based PDC every 3 weeks for four cycles (n=358). All treatments were administered intravenously. The chemotherapy regimens were: carboplatin area under the concentration-time curve (AUC) 6 plus paclitaxel 200mg/m^2 (or 175mg/m^2 as per local institution practice) for squamous histology, and pemetrexed 500mg/m^2 plus investigator's choice of carboplatin AUC 5 or 6 or cisplatin 75mg/m^2 for non-squamous histology. Treatment with nivolumab and ipilimumab continued for up to 24 months, or until RECIST 1.1-defined disease progression or unacceptable toxicity. Treatment could continue beyond initial RECIST 1.1 defined progressive disease, at the discretion of the investigator if the patient was clinically stable and deriving clinical benefit (as per pre-specified criteria). If discontinuation criteria were met for ipilimumab but not for nivolumab, treatment with nivolumab could be continued. Treatment with ipilimumab could not continue alone. Patients in the chemotherapy group with non-squamous tumour histology could receive optional maintenance therapy with pemetrexed 500mg/m^2 every 3 weeks until disease progression or unacceptable toxicity. Randomisation was stratified according to PD-L1 level (≥1% versus < 1% or not quantifiable), histology (squamous versus non-squamous) and sex.[3, 4]

The primary outcome was overall survival (OS), defined as the time from randomisation to the date of death due to any cause, and assessed in all randomised patients. A planned interim analysis was conducted at the data cut-off 3 October 2019 after a median follow-up of 9.7 months. There was a statistically significant improvement in overall survival with nivolumab plus ipilimumab plus PDC compared with PDC. This was supported by significant increases in key secondary outcomes including progression-free survival (PFS) and objective response rate (ORR) and a longer duration of response. An updated exploratory analysis was conducted at the data cut-off 9 March 2020 with a longer median follow-up of 13.2 months. The results are presented in Table 1.[3, 4]

Table 1: Primary and key secondary outcomes from CheckMate 9LA in the ITT population.[3, 4]

	Nivolumab+ ipilimumab+ PDC (n=361)	**PDC (n=358)**	**Nivolumab+ ipilimumab+ PDC (n=361)**	**PDC (n=358)**
Data cut-off	Planned interim analyses 3 October 2019		Exploratory analyses 9 March 2020	
Median follow-up	9.7 months		13.2 months	
Overall survival				
Deaths (n)	156	195	190	242
Median OS	14.1 months	10.7 months	15.6 months	10.9 months
Hazard ratio	0.69 (96.7% CI: 0.55 to 0.87), p<0.001		0.66 (95% CI: 0.55 to 0.80)	
KM estimated OS at 12 months	NR		63%	47%

PFS (BICR as per RECIST 1.1)				
PFS events (n)	232	249	249	265
Median PFS	6.8 months	5.0 months	6.7 months	5.0 months
Hazard ratio (95% CI)	0.72 (0.60 to 0.86), p<0.001		0.68 (0.57 to 0.82)	
KM estimated PFS at 12 months	NR		33%	18%

PDC= platinum doublet chemotherapy; OS= overall survival; CI=confidence interval; DOR=duration of response; ITT=intention to treat; KM=Kaplan-Meier; ORR = objective response rate; PFS= progression-free survival; BICR= blinded independent central review; RECIST = Response Evaluation Criteria in Solid Tumours.

Results from the most recent data cut (18 February 2021) were consistent with previous results; OS hazard ratio: 0.72 (95% CI: 0.61 to 0.86), PFS HR: 0.67 (95% CI: 0.56 to 0.79).[5]

Analysis of pre-specified subgroups were generally consistent with the primary analysis including subgroups according to gender, PD-L1 expression (including subgroups of PD-L1<1%, PD-L1≥1%, PD-L1 1 to 49% and PD-L1≥50%) and histology (squamous and non-squamous).[3, 4]

A subgroup of 497 patients (69% of the overall study population) with PD-L1 <50% represents the proposed positioning requested by the submitting company. OS and PFS results in this subgroup were consistent with the overall study population.[6]

Patient reported outcomes were assessed as exploratory outcomes using the Lung Cancer Symptom Scale average symptom burden index and 3- item global index (LCSS ASBI/3-IGI); health-related quality of life (HRQoL) was evaluated using European Quality of Life Five Dimension three levels (EQ-5D-3L) visual analog scale and utility index (EQ-5D-3L VAS/UI). A similar trend for improvement in mean LCSS ASBI and 3-IGI was observed in both treatment groups however, the minimally important difference (10 or more points) from baseline was not reached in either group. Mean EQ-5D-3L VAS scores in both groups approached UK population norm at approximately 30 weeks.[7]

Due to the limited follow-up time of patients at the interim analyses of CheckMate 9LA, the submitting company have used longer term follow-up data from CheckMate-227 to help inform predictions of effect beyond the available CheckMate 9LA data. CheckMate-227 was an open-label, multi-centre, randomised, phase III study in patients with stage IV or recurrent NSCLC, with no prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease and no known EGFR mutations or ALK translocation. CheckMate-227 part 1A included patients with PD-L1 ≥1% (n=1,189) and part 1B included patients with PD-L1 <1% (n=553). Both parts of the study included 3 treatment arms. None of these arms included the regimen under review; however, each part contained an arm with nivolumab in combination with ipilimumab and an arm with histology-based PDC. At the July 2019 data cut-off (minimum follow-up 29.3 months), in the overall study population (PD-L1 ≥1% and PD-L1<1%), median overall survival was 17.1 months in the nivolumab plus ipilimumab group and 13.9 months in the PDC group (HR: 0.73 [95% CI: 0.62 to 0.86]).[4, 8, 9]

In the absence of direct evidence against a key comparator, and due to varying hazard ratios over time, a fractional polynomial network meta-analysis (NMA) was conducted. The NMA compared

the efficacy of nivolumab plus ipilimumab and PDC [efficacy data from CheckMate-9LA[3] and CheckMate-227[8] studies] versus pembrolizumab plus PDC [efficacy data from KEYNOTE-189[10] and KEYNOTE-407[11] studies] in adults patients with advanced (stage IIIB or IV) or recurrent NSCLC treated with first-line anticancer therapy. The results indicate insufficient evidence of a difference between treatments for OS or PFS. However, the submitting company concluded that that there is a benefit in terms of OS for nivolumab plus ipilimumab plus PDC over pembrolizumab plus PDC.

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

Summary of evidence on comparative safety

In CheckMate 9LA, the safety profile of nivolumab plus ipilimumab and chemotherapy was reflective of the known safety profile of the immunotherapy and chemotherapy components in first-line NSCLC and no new safety signals or toxicities were identified. At the data cut-off 9 March 2020, the median duration of treatment in the nivolumab plus ipilimumab with chemotherapy group was 6.1 months and in the chemotherapy group was 2.4 months. Any treatment-related adverse event (TRAE) was reported by 91% (327/358) of patients in the nivolumab plus ipilimumab with chemotherapy group and 87% (303/349) in the chemotherapy group. In each group respectively, patients reporting a grade 3 or higher TRAE were 47% versus 38%, patients with a reported serious TRAE were 30% versus 18%, and patients discontinuing therapy due to a TRAE was 19% versus 7%.[3, 4]

The most frequently reported treatment-related AEs of any grade with an incidence >15% in either the nivolumab plus ipilimumab with chemotherapy group or the chemotherapy group were: nausea (27% versus 36%), anaemia (23% versus 38%), asthenia (21% versus 18%), pruritus (21% versus 1.7%), diarrhoea (21% versus 12%), rash (19% versus 3.2%), hypothyroidism (16% versus 0.3%), fatigue (17% versus 11%), neutropenia (10% versus 17%), decreased appetite (16% in both groups) and vomiting (14% versus 15%).[3]

Immunotherapies such as nivolumab and ipilimumab have characteristically high incidences of immune-related AEs. The most commonly reported grade 3 or 4 treatment-related AEs with potential immunological cause in the immunochemotherapy group compared with the chemotherapy group were gastrointestinal (5.6% versus 0.6%), skin (4.0% versus 0.3%), and hepatic (4.4% versus 0.9%), most of which resolved. Grade 3 or 4 toxicity typically associated with chemotherapy occurred less frequently in the immunochemotherapy group compared with the chemotherapy group; anaemia (5.9% versus 14%), neutropenia (6.7% versus 9.2%), febrile neutropenia (3.9% versus 2.9%), and thrombocytopenia (2.8% versus 2.6%).[3]

Summary of clinical effectiveness issues

Lung cancer is the most common cancer worldwide and the most prevalent type is NSCLC, accounting for approximately 85% of all cases. NSCLC can be subdivided into non-squamous cell carcinoma (including adenocarcinoma, large-cell carcinoma, and other less common subtypes) and

squamous cell carcinoma. The submitting company has requested that SMC considers nivolumab when positioned for use in adults with untreated metastatic NSCLC who express PD-L1 at a level of <50%. First-line treatment options for metastatic disease in tumours with <50% PD-L1 expression differ depending on histological subtype. For squamous cell NSCLC, pembrolizumab in combination with carboplatin and paclitaxel has been accepted for restricted use by SMC (SMC2187). For non-squamous NSCLC, pembrolizumab in combination with pemetrexed and platinum chemotherapy followed by pemetrexed maintenance has been accepted for restricted use by SMC (SMC2207). [4, 12] Most patients present with advanced stage unresectable disease where prognosis is poor; the 5 year survival for metastatic NSCLC is <5%, although recent immunotherapy treatments have improved survival. Nivolumab meets SMC end of life criteria for this indication.

In CheckMate 9LA, at the planned interim analysis, treatment with nivolumab plus ipilimumab and two cycles of chemotherapy was associated with a statistically significant improvement in OS of 3.4 months compared with chemotherapy. At the exploratory analysis (after an additional 4.6 months follow-up) a numerical improvement of 4.7 months was observed. This was considered clinically relevant by the European Medicines Agency. The Kaplan-Meier OS curves showed an immediate improvement favouring the immunochemotherapy combination. The survival benefit was observed across subgroups based on tumour histology and PDL1 expression and secondary outcomes including PFS and ORR were supportive.[3, 4]

CheckMate-9LA is ongoing and study data are not fully mature; longer follow-up will provide further characterisation of the efficacy and safety profile of nivolumab plus ipilimumab in combination with chemotherapy for this indication. The evidence to support the proposed positioning is from an unplanned subgroup analysis, in this type of analysis the risk of detecting a false positive result has not been controlled for, however the subgroup was large (n=497 patients, 69% of the total study population) and the result was consistent with the overall study population which is reassuring. CheckMate 9LA had an open-label study design because of differences in the treatment regimens and toxicity profiles.[4] This may have introduced assessment bias for subjective outcomes such as quality of life outcomes, adverse events, PFS and ORR. This risk was mitigated for PFS and ORR by assessment by blinded independent central review.

In CheckMate 9LA, the median age was 66 years, this is younger than the median age of patients with NSCLC which is 71 years and may affect generalisability of results. The sample size for patients aged ≥75 years is small (n=70) therefore efficacy and safety data for this patient population is limited. A proportion of patients in the immunochemotherapy group received subsequent treatment with immunotherapy or targeted therapy which is not representative of standard care in Scotland.[3, 4]

When CheckMate 9LA was designed, standard first-line treatment for metastatic NSCLC without a driver mutation was histology-based PDC. Since then, pembrolizumab in combination with histology-based PDC has been licensed and accepted for use by SMC for NSCLC. There is no direct evidence comparing nivolumab plus ipilimumab and chemotherapy with pembrolizumab and chemotherapy which is the most relevant comparator in Scottish clinical practice.

There were some limitations associated with the NMA. These included; clinical and methodological differences across studies in terms of study design, baseline histology, PD-L1 level at baseline, severity of the condition and median duration of treatment, in addition, no measures of heterogeneity were presented. The target population was broader than the population within the proposed positioning, the population included in the base-case analysis was comprised of PD-L1 all-comers input data from the included studies, instead of PD-L1<50%. While the submitting company justified this, use of PD-L1 all-comers data adds uncertainty to the results. Given the differences between the KEYNOTE and CheckMate studies, it is difficult to make clear conclusions.

Companion diagnostic required: contact local laboratory for information**.**

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

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **nivolumab**, as an **end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced NSCLC is an incurable disease with a poor prognosis. Patients often experience multiple debilitating and distressing symptoms including breathlessness, weight loss, fatigue and chest pain which can be difficult to treat and have a significant impact on quality of life.
- Current first-line standard of care for fit patients with metastatic NSCLC whose tumours express PD-L1 at <50% is pembrolizumab in combination with histology-based PDC. Chemotherapy is generally continued for four cycles with associated risk of neutropenic sepsis and other complications with each cycle.
- Nivolumab plus ipilimumab in combination with two cycles of chemotherapy reduces the amount of chemotherapy given which could be desirable for some patients who wish to limit their exposure to this type of treatment. This might improve tolerability due to a reduction in chemotherapy-related side effects e.g. neuropathy and hair loss. However, there may be an increased risk of immune related toxicities associated with dual immunotherapy.
- PACE participants considered that an additional immunotherapy treatment option that potentially offers increased survival in comparison to chemotherapy could give patients a psychological boost at a time when they may feel options are limited. PACE participants also noted that immunotherapy might improve distressing symptoms such as breathlessness and cough. This could have a positive impact on quality of life for patients and their family and may allow a return to normal life, the ability take part in social events and potentially return to work.
- Nivolumab plus ipilimumab in combination with chemotherapy is the first dual immunotherapy licensed for NSCLC. This treatment combination would provide an alternative

first-line option to pembrolizumab plus chemotherapy.

Additional Patient and Carer Involvement

We received patient group submissions from the Roy Castle Lung Cancer Foundation, and the Scottish Lung Cancer Nurses Forum. Roy Castle Lung Cancer Foundation is a registered charity and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation. Roy Castle Lung Cancer Foundation has received 12.5% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has received 100% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum participated in the PACE meeting. The key points of the submissions from both organisations have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing nivolumab plus ipilimumab and 2 cycles of PDC against PDC (4 cycles) and pembrolizumab in combination with 4 cycles of PDC for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation. The submitting company has requested that SMC considers nivolumab plus ipilimumab with chemotherapy when positioned for use in patients with PD-L1<50%. The current treatment pathway in Scotland for patients with untreated metastatic NSCLC is determined by both PD-L1 expression and histology. As such, the cost-effectiveness results for the proposed position are presented by histology (squamous NSCLC PD-L1 <50% and non-squamous NSCLC PD-L1 <50%).

For the squamous NSCLC PD-L1 <50% subgroup, comparators include pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel, and PDC, including docetaxel, gemcitabine, paclitaxel or vinorelbine with platinum-based chemotherapy. For the non-squamous NSCLC PD-L1 <50% subgroup, comparators include pembrolizumab in combination with pemetrexed and platinum-based chemotherapy, and PDC, defined as cisplatin with pemetrexed. Clinical experts considered that PDC and pembrolizumab in combination with PDC are the predominant treatments for the proposed population in Scottish clinical practice.

In CheckMate-9LA, treatment with nivolumab and ipilimumab was capped to 24 months and as such the submitting company has included a 2-year stopping rule in its base case, which is appropriate.[3] A 2-year stopping rule has also been included for pembrolizumab as per the recommendations in SMC2187 and SMC2207. For non-squamous patients who have not progressed after 4 cycles of PDC, pemetrexed maintenance treatment is an option, but was not included in the base case.

A three-state partitioned survival model was used, with health states consisting of PFS, post-progression, and death. The time horizon of the model was 25 years. The primary source of PFS and OS data for nivolumab plus ipilimumab with PDC and platinum doublet chemotherapy was

from CheckMate-9LA and CheckMate-227.[3, 8] A piecewise modelling approach was adopted for both OS and PFS, where Kaplan-Meier (KM) data from CheckMate-9LA was implemented for the first 24 months of the model and thereafter, extrapolated data from CheckMate-227 were used. For the comparison with pembrolizumab in combination with PDC, time dependent HRs predicted from the fractional polynomial NMA were applied to the baseline nivolumab plus ipilimumab with PDC survival curves for PFS and OS. The submitting company has assumed that there is an ongoing treatment effect with nivolumab plus ipilimumab with PDC.

Health benefits were measured in quality adjusted life years (QALYs) and were estimated from utility data collected directly from patients in CheckMate-9LA, using the EQ-5D-3L questionnaire. In the base case, a time to death approach was used to estimate the decline in health-related quality of life over time as a patient neared death. Pooled time to death utility values were used in the base case. Scenarios were explored using treatment-specific time to death utilities and utilities based on progression status. Disutilities were included for grade 3 or 4 AEs with a ≥5% incidence in either treatment are from CheckMate-9LA.[3]

In the base-case analysis, medicines acquisition and administration costs of the intervention and comparators, cost of subsequent treatment, adverse event costs and the costs of disease management for the progression-free and progressed disease health states were included. The submitting company also included a one-off terminal care cost in the model.

Only one line of subsequent treatment was included in the model due to the advanced nature of the disease and lack of data on multiple lines of treatment. Subsequent treatment proportions were based on data from CheckMate-227 as these were considered more representative of the proportions receiving subsequent therapy in Scotland. This results in 45% of patients on nivolumab plus ipilimumab with PDC and 61% of patients on PDC assumed to go on to subsequent treatment.[8] For patients on pembrolizumab in combination with PDC the proportion who go on to subsequent treatment is assumed to be the same as patients on nivolumab plus ipilimumab with PDC (45%). Subsequent treatment for patients on immunotherapy was assumed to be docetaxel. For patients on PDC, subsequent therapy was split between nivolumab (15%), pembrolizumab (25%) and atezolizumab (60%).

Duration of treatment for each subgroup was informed directly from KM data from CheckMate-9LA for nivolumab plus ipilimumab with PDC and PDC.[3] For pembrolizumab in combination with PDC for each subgroup, PFS was used as a proxy for duration of treatment.

A Patient Access Scheme (PAS) was submitted by the 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. A PAS is also included for ipilimumab.

The results presented do not take account of the PAS for pembrolizumab or atezolizumab, or the PAS for nivolumab or ipilimumab, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for these medicines due to commercial confidentiality and competition law issues. As such, all results are presented at list prices.

Error! Reference source not found.2 present the submitting company's base case results and Table 3 presents the key scenarios.

Table 2. Submitting company's deterministic incremental base case results – list price

Technologies	**ICER (£/ QALY)**
Squamous NSCLC PD-L1 <50%	
PDC	-
Pembrolizumab+PDC	Extendedly dominated
Nivolumab+ipilimumab+PDC	96,922
Non-squamous NSCLC PD-L1 <50%	
PDC	-
Nivolumab+ipilimumab+PDC	82,130
Pembrolizumab+PDC	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer; PDC, platinum doublet chemotherapy; QALY, quality-adjusted life-year. Extended dominance - The ICER for a given treatment alternative is higher than that of the next, more effective, alternative Dominated – less costly and more effective	

Table 3. Submitting company pairwise scenario analyses – list prices

Scenario	Comparator	Pairwise ICER – nivo+ipi vs. comparator (£/QALY)
Squamous NSCLC PD-L1 <50%		
Base case	PDC	96,922
	Pembro+PDC	22,995
CheckMate-9LA only extrapolation for OS	PDC	82,542
	Pembro+PDC	22,432
CheckMate-9LA only extrapolation for PFS	PDC	97,950
	Pembro+PDC	31,699
Progression-based utility values	PDC	107,718
	Pembro+PDC	24,315
Equal PFS and OS for nivo+ipi+PDC and pembro+PDC	PDC	96,922
	Pembro+PDC	121,419
Treatment waning after 3 years for nivo+ipi+PDC and pembro+PDC	PDC	142,361
	Pembro+PDC	65,803
Treatment waning after 5 years for nivo+ipi+PDC and pembro+PDC	PDC	116,955
	Pembro+PDC	35,334
Subsequent treatment proportions from CheckMate-227 (TA724 preferred assumption)	PDC	85,402
	Pembro+PDC	23,338

Non-squamous NSCLC PD-L1 <50%		
Base case	PDC	82,130
	Pembro+PDC	Dominant
CheckMate-9LA only extrapolation for OS	PDC	156,702
	Pembro+PDC	Dominant
CheckMate-9LA only extrapolation for PFS	PDC	83,427
	Pembro+PDC	Dominant
Progression-based utility values	PDC	88,974
	Pembro+PDC	Dominant
Equal PFS and OS for nivo+ipi+PDC and pembro+PDC	PDC	82,130
	Pembro+PDC	104,949
Treatment waning after 3 years for nivo+ipi+PDC and pembro+PDC	PDC	111,864
	Pembro+PDC	92,430
Treatment waning after 5 years for nivo+ipi+PDC and pembro+PDC	PDC	90,460
	Pembro+PDC	Dominant
Subsequent treatment proportions from CheckMate-227 (TA724 preferred assumption)	PDC	73,176
	Pembro+PDC	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; LY, life-year; nivo, nivolumab; NSCLC, non-small cell lung cancer; PDC, platinum doublet chemotherapy; pembro, pembrolizumab; QALY, quality-adjusted life-year.		

The submission was subject to the following limitations:

- The submitting company considered that clinical data from CheckMate-9LA are relatively immature and that long-term extrapolations based on data with a relatively short follow-up would be uncertain. More recent data cuts from CheckMate-9LA and CheckMate-227 were used to update the submitting company's economic model, but the piecewise modelling approach was maintained. Extrapolations based entirely on the more mature data from CheckMate-9LA would have been more appropriate, especially as data from the February 2021 data cut are relatively mature.
- The submitting company's comparison with pembrolizumab in combination with PDC is highly uncertain and potentially biased in favour of nivolumab plus ipilimumab with PDC.
    - Fractional polynomial NMA results for nivolumab plus ipilimumab with PDC versus pembrolizumab in combination with PDC do not provide evidence of a difference between the two treatments.
    - While mean PFS and OS for the non-squamous NSCLC PD-L1 <50% population are in favour of nivolumab plus ipilimumab with PDC, median results in the model favour pembrolizumab in combination with PDC. As such, the benefit of nivolumab plus ipilimumab with PDC over pembrolizumab in combination with PDC is estimated in the long-term extrapolation of the clinical data, which is the most uncertain aspect of the model.

- Based on the results of the fractional polynomial NMA, assuming clinical equivalence between the two treatments is an appropriate assumption to reduce uncertainty and should be considered as part of a plausible base case. It is noted that assuming clinical equivalence between the two combination treatments is potentially optimistic given that the nivolumab combination includes an additional immunotherapy (ipilimumab), but a reduced number of chemotherapy cycles (2 versus 4 for pembrolizumab combination treatment).
- Using PFS as a proxy for duration of treatment for pembrolizumab in combination with platinum doublet chemotherapy may not be reasonable as it potentially overestimates costs as patients may discontinue treatment for reasons other than progression of disease. However, as a 2-year stopping rule is in place for pembrolizumab, the impact of this assumption is minimised but the bias is still in favour of nivolumab plus ipilimumab with PDC.

- For the base case, an on-going treatment effect with nivolumab plus ipilimumab with platinum doublet chemotherapy was assumed. In recent appraisals for immune-oncology medicines, in particular for untreated NSCLC, treatment waning scenarios of 3 to 5 years have been explored and accepted by SMC as plausible. Requested scenarios exploring treatment waning have a substantial impact on the ICER and should be considered as part of a plausible base case.
- Progression-based utility values are preferred in economic evaluations where the health states in the model are based on progression status, as it maintain consistency with the estimation of QALYs and costs. The number of observations informing the ≤4 weeks category is low (114) compared with number of observations informing post-progression (1,004). It is, however, noted that SMC has accepted submissions in the past where a time to death approach to utilities has been used (for example, pembrolizumab).

The Committee considered the benefits of nivolumab plus ipilimumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios. After considering all the available evidence and the output from the PACE process, the Committee was unable to accept nivolumab plus ipilimumab for use in NHSScotland.

Additional information: guidelines and protocols

European Society for Medical Oncology (ESMO) published clinical practice guidelines on 18 September 2019: Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[12] These guidelines make the following recommendations for patients with EGFR- and ALK-negative NSCLC:

- Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥50% who do not otherwise have contraindications to use of immunotherapy.
- Pembrolizumab in combination with pemetrexed and a platinum-based chemotherapy

should be considered a standard option in metastatic non-squamous NSCLC, regardless of PD-L1 expression.

- Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel is a standard first-line treatment in patients with metastatic squamous NSCLC, regardless of PD-L1 expression.
- Atezolizumab in combination with carboplatin and nab-paclitaxel offers a new standard first-line treatment opportunity for patients with stage IV non-squamous NSCLC. (SMC2254, not recommended due to non-submission)
- Chemotherapy with platinum doublets should be considered for first-line treatment in all stage IV NSCLC patients without an actionable oncogenic driver, with contraindications to use of immunotherapy and without major co-morbidities. Several platinum-based regimens with third-generation cytotoxics (paclitaxel, gemcitabine, docetaxel, vinorelbine) have shown comparable efficacy.

National Institute for Health and Care Excellence (NICE) published NICE guideline [122]: Lung cancer: diagnosis and management on 28 March 2019.[13] These guidelines these guidelines make similar recommendations to the more recent ESMO guidelines.

Additional information: comparators

Squamous NSCLC and PD-L1<50%: pembrolizumab in combination with carboplatin and paclitaxel.

Non-squamous NSCLC and PD-L1 <50%: pembrolizumab in combination with pemetrexed and platinum chemotherapy (cisplatin or carboplatin) followed by pemetrexed maintenance.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
Non-squamous NSCLC		
Nivolumab Ipilimumab Carboplatin Pemetrexed or	360mg IV every 3 weeks 1mg/kg IV every 6 weeks AUC 5 IV every 3 weeks* 500mg/m^2 IV every 3 weeks*	Initial 6 week cycle £18,506
Nivolumab Ipilimumab Cisplatin Pemetrexed	360mg IV every 3 weeks 1mg/kg IV every 6 weeks 75mg/m^2 IV every 3 weeks* 500mg/m^2 IV every 3 weeks*	Initial 6 week cycle £18,288 Subsequent 6 week cycles £15,838

Squamous NSCLC		
Nivolumab Ipilimumab Carboplatin Paclitaxel	360mg IV every 3 weeks 1mg/kg IV every 6 weeks AUC 6 IV every 3 weeks* 175mg/m^2 every 3 weeks*	Initial 6 week cycle £17,885 Subsequent 6 week cycles £15,838

Costs from BNF online on 6 September 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs calculated using a body surface area (BSA) of 1.8m^2 glomerular filtration rate of 60mL/min *and a weight of 70kg. *only for initial 6 week cycle. Costs do not take patient access schemes into consideration.*

Additional information: budget impact

The submitting company estimated there would be 318 patients eligible for treatment with nivolumab plus ipilimumab and chemotherapy in each year, to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

*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 15 October 2021.

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

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

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

Advice context:

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

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