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SMC2619

nivolumab concentrate for solution for infusion (Opdivo®)

Bristol Myers Squibb

11 December 2023

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: in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable (tumours ≥4 cm or node positive) non-small cell lung cancer in adults.

In an open-label, randomised, phase III study, the addition of nivolumab to platinum-based chemotherapy as neoadjuvant treatment was associated with significant benefits in event-free survival and pathological complete response in patients with stage IB to IIIA resectable non-small cell lung cancer.

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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Nivolumab is a human immunoglobulin G4 monoclonal antibody that targets the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. This potentiates T-cell responses, including antitumour responses.[1]

Nivolumab is the first immunotherapy to be licensed for neoadjuvant use in resectable (tumours ≥4 cm or node positive) non-small cell lung cancer (NSCLC) in adults.

The recommended dose is 360 mg nivolumab administered intravenously (IV) in combination with platinum-based chemotherapy every 3 weeks for three cycles. [1]

1.2. Disease background

Lung cancer is the most common type of cancer in Scotland and it is the leading cause of cancer mortality worldwide. NSCLC accounts for approximately 85 % of cases. In Scotland in 2021, nearly half of lung cancer cases were diagnosed at stage IV (metastatic), while a fifth were diagnosed at stage III (locally advanced); and only about 30 % of patients were diagnosed at an early stage (I or II).[2-5]

1.3. Treatment pathway and relevant comparators

For patients who present with early NSCLC, surgery with curative intent may be an option for suitable patients who are well enough. Guidelines recommend adjuvant chemotherapy for patients with resected stage II and III NSCLC, taking account of performance status, comorbidities, time from surgery and recovery; for patients with stage IIA disease, adjuvant chemotherapy can be considered for those whose resected tumours were >4 cm. The role of adjuvant chemotherapy in stage IB tumours is not clear and should be decided on individual basis and depending on the size of the tumour among other factors. Three or four cycles with cisplatin-based combination chemotherapy (or carboplatin if cisplatin not suitable) mainly with vinorelbine (non-squamous) or with gemcitabine (squamous histology), but also docetaxel or pemetrexed (non-squamous, only for adenocarcinomas) is recommended. Despite the use of adjuvant chemotherapy, recurrence rates remain high and the survival benefits are modest. The 5-year survival rates for resected NSCLC vary between 70 % of patients with stage I, to 25 % with stage III. For patients with resectable stage IIIA NSCLC who can have surgery and are well enough for multimodality therapy, neoadjuvant chemoradiotherapy can be considered with surgery. Equivalence of neoadjuvant and adjuvant chemotherapy has been reported for overall survival; however, the use of chemotherapy in the adjuvant setting is currently the preferred and recommended approach.[3-7]

The PD-L1 inhibitor, atezolizumab, is accepted for use within NHSScotland as monotherapy as adjuvant treatment following complete resection for adult patients with stage II to IIIA NSCLC whose tumours have PD-L1 expression on ≥50 % of tumour cells and whose disease has not progressed following platinum-based adjuvant chemotherapy (SMC2492).

The epidermal growth factor receptor (EGFR) inhibitor, osimertinib, is also accepted for restricted use (subject to a three-year clinical stopping rule) as adjuvant treatment after complete resection, for adult patients with stage IB to IIIA NSCLC whose tumours have *EGFR* exon 19 deletions or exon

21 (L858R) substitution mutations (SMC2383); however, it is not considered a relevant comparator.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Nivolumab received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency (MHRA) Innovative Licensing and Access Pathway.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of nivolumab for this indication comes from the ongoing study, CheckMate 816. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	CheckMate 816 [3, 8]
Study design	International, open-label, randomised, active-controlled, phase III study.
Eligible patients	• Males and females ≥18 years or age of majority. • Eastern Cooperative Group (ECOG) Performance Status: 0 to 1. • Histologically confirmed stage IB (≥4 cm), II, IIIA (N2) NSCLC (per the 7th International Association for the Study of Lung Cancer) with disease that is considered resectable. • Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. • Must have a tumour tissue sample available for PD-L1 IHC testing. • Absence of major associated pathologies that increase the surgery risk to an unacceptable level and pulmonary function capacity capable of tolerating the proposed lung resection according to the surgeon. • No known ALK translocations or EGFR mutations
Treatments	Nivolumab (360 mg IV every 3 weeks for up to three cycles) plus IV neoadjuvant platinum-based doublet chemotherapy or neoadjuvant platinum-based doublet chemotherapy alone. Selection of a chemotherapy regimen was based on investigator's choice, and was performed after each patient had been randomised. The platinum-based doublet chemotherapy options available for patients treated in both the nivolumab arm and control arm were: ○ Cisplatin (75 mg/m^2 body surface area [BSA] on Day 1 of a 3-week cycle for up to three cycles) and one of the following: ▪ Gemcitabine (1,000 mg/m^2 BSA or 1,250 mg/m^2 BSA [per local prescribing information] on Days 1 and 8 of a 3-week cycle for up to three cycles) (squamous histology) ▪ or pemetrexed (500 mg/m^2 BSA on Day 1 of a 3-week cycle for up to three cycles) (non-squamous histology) ○ or carboplatin (area under the plasma drug concentration-time curve [AUC] 5-6 on Day 1 of a 3-week cycle for up to three cycles) and paclitaxel (175 or 200 mg/m^2 BSA on Day 1 of a 3-week cycle for up to three cycles) (any histology) • The control arm had the following additional options: ○ Cisplatin (75 mg/m^2 BSA on Day 1 of a 3-week cycle for up to three cycles) and one of the following: ▪ Vinorelbine (25 mg/m^2 or 30 mg/m^2 BSA [per local prescribing information] on Days 1 and 8 of a 3-week cycle for up to three cycles) ▪ Or docetaxel (60 mg/m^2 or 75 mg/m^2 BSA [per local prescribing

	information] on Day 1 of a 3-week cycle for up to three cycles) Surgery was planned to occur within 6 weeks after the completion of neoadjuvant treatment, after which patients in both groups could receive up to four cycles of adjuvant chemotherapy, radiotherapy or both at the discretion of the investigator. CheckMate 816 also had a nivolumab plus ipilimumab treatment arm but enrolment in this arm was later stopped and it is not relevant to this submission, so it is not discussed.
Randomisation	Patients were randomised equally and stratified according to: PD-L1 status (≥1 % and <1 % or not evaluable/indeterminate), disease stage (IB/II versus IIIA) and gender.
Coprimary outcomes	• Event-free survival (EFS) by blinded independent central review (BICR), defined as the length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression or disease recurrence (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Patients who do not undergo surgery for reasons other than progression were considered to have an event at RECIST 1.1 progression (based on BICR) or death. • Pathological complete response (pCR) rate by blinded independent pathology review (BIPR), defined as number of randomised patients with absence of residual tumour in lung resected tissue and lymph nodes, divided by the number of randomised patients for each treatment group.
Selected secondary outcomes	• Overall survival, defined as the time between the date of randomisation and the date of death due to any cause. Overall survival was censored on the last date a patient was known to be alive. • Time to Death or Distant Metastasis (TDDM), defined as the time between the date of randomisation and the first date of distant metastasis or the date of death in the absence of distant metastasis. A distant metastasis was defined as any new lesion outside of the thorax using BICR and RECIST 1.1 criteria. Patients who had not developed distant metastasis or died at the time of the analysis were censored on the date of their last evaluable tumour assessment.
Statistical analysis	Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation. A hierarchical statistical testing strategy was applied in the study for the coprimary outcomes and secondary outcome of overall survival with no formal testing of outcomes after the first non-significant outcome in the hierarchy (in order: pCR, EFS, overall survival). Results reported for other outcomes are descriptive only.

At the final pCR analysis (data cut-off 16 September 2020) and first prespecified interim EFS analysis (data cut-off 20 October 2021; median follow-up: 29.5 months), a statistically significant improvement was demonstrated for both coprimary outcomes with nivolumab plus chemotherapy compared with chemotherapy alone. Due to the data immaturity, no conclusions could be drawn on the effect of nivolumab plus chemotherapy on overall survival at the first (data cut-off 20 October 2021) and second interim (data cut-off 14 October 2022; median follow-up: 41.4 months) analyses. See Table 2.2 for details.[3, 8, 9]

Table 2.2. Primary and selected secondary outcomes of CheckMate 816.[3, 8-10]

	nivolumab + chemotherapy (n=179)	chemotherapy (n=179)	nivolumab + chemotherapy (n=179)	chemotherapy (n=179)
Coprimary outcome: pCR per BIPR				
	primary pCR analysis – data cut-off 16 September 2020			
Responses, %	24 %	2.2 %	-	
95 % CI	18 to 31	0.6 to 5.6		
Difference (95 % CI)	22 % (15 to 28)			
Odds ratio	13.9			
95 % CI	4.86 to 40.02			
Stratified p-value	<0.001			
Coprimary outcome: EFS per BICR				
	IA1 - data cut-off 20 October 2021		**IA2 - data cut-off 14 October 2022**	
Event, n (%)	64 (36 %)	87 (49 %)	69 (38 %)	88 (49 %)
Median EFS, months (95 % CI)	31.57 (30.16 to NR)	20.80 (14.03 to 26.71)	NR (31.57 to NR)	21.06 (14.75 to 42.09)
HR (IA1: 97.38 % CI / IA2: 95 % CI)	0.63 (0.43 to 0.91)		0.68 (0.49 to 0.93)	
Stratified p-value	p=0.0052		-	
1-year EFS, %	-		77 %	64 %
2-year EFS, %			65 %	47 %
3-year EFS, %			57 %	43 %
Key secondary outcome: Overall survival				
	IA1 - data cut-off 20 October 2021		**IA2 - data cut-off 14 October 2022**	
Deaths, n (%)	35 (20 %)	59 (33 %)	44 (25 %)	67 (37 %)
Median overall survival, months (95 % CI)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (46.78 to NR)
HR (IA1: 99.67 % CI / IA2: 99.34 % CI)	0.57 (0.30 to 1.07)		0.62 (0.36, 1.05)	
p-value	NS[a]		NS[a]	
1-year overall survival, %	-		90 %	90 %
2-year overall survival, %			83 %	70 %
3-year overall survival, %			78 %	64 %
Secondary outcome: TTDM per BICR				
			IA2 - data cut-off 14 October 2022	
Median TTDM, months (95 % CI)	-		NR (48.6 to NR)	34.3 (23.6 to NR)
HR (95 % CI)			0.55 (0.39 to 0.78)	
1-year TTDM, %			86 %	76 %
2-year TTDM, %			77 %	58 %
3-year TTDM, %			71 %	50 %

[a] The difference between treatment groups did not reach the prespecified cut-off for statistical significance.
Abbreviations: BICR = blinded independent central review; BIPR = blinded independent pathological review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; IA = interim analysis; NR = not reached; NS = not significant; pCR = pathological complete response; TTDM = time to death or distant metastases.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the instrument, EQ-5D-3L index score and visual analogue scale (VAS), as exploratory outcomes. During the neoadjuvant period (week 4, week 7 and postneoadjuvant visit 1), scores were generally similar to baseline for both treatment groups and there were no clinically meaningful differences between the two groups.[11]

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

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus relevant comparators, the submitting company performed a Bayesian network meta-analysis (NMA), which compared neoadjuvant nivolumab plus platinum chemotherapy with neoadjuvant chemotherapy, adjuvant platinum chemotherapy (including surgery) and surgery alone for the treatment of resectable NSCLC. The "core" NMA, which is referred to as the "base case" analysis in the company submission, included studies with potentially resectable patients (using data from five studies). On clarification, the company explained that an NMA sensitivity analysis including potentially resectable and completely resected patients informed the main cost-effectiveness analysis. This was to allow comparison with adjuvant platinum chemotherapy for the key outcomes used in the economic analysis, namely time to distant metastases (TTDM) and time to locoregional recurrence (TTLR). A separate indirect treatment comparison (ITC) was conducted for atezolizumab, as the company considered that differences in study design (as patients in IMpower010 were enrolled after surgery and platinum-based adjuvant chemotherapy) may bias the results; this ITC was used to justify the cost-minimisation analysis against atezolizumab.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian NMA
Population	Adults with resectable, non-metastatic (stages I-III) NSCLC.
Comparators	The NMA comparators were: neoadjuvant chemotherapy, surgery followed by adjuvant chemotherapy and surgery alone. Adjuvant atezolizumab was also included in a separate ITC.
Studies included	In total, the NMAs ("core" and sensitivity analyses) included 14 studies. The separate atezolizumab ITC included three studies.
Outcomes	Event-free survival (EFS); overall survival; time to locoregional recurrence (TTLR); time to distant metastases (TTDM).
Results	For the majority of outcomes, the evidence suggests that nivolumab plus platinum chemotherapy is likely to be superior to the comparators.
Abbreviations: CI = confidence interval; Crl=credible interval; EFS=event-free survival; HR=hazard ratio; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; TTDM=time to distant metastases; TTLR=time to locoregional recurrence.	

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

3. Summary of Safety Evidence

In the CheckMate 816 study at data cut-off 14 October 2022, the median follow-up was 41.4 months. Any treatment-emergent adverse event (AE) was reported by 94 % (165/176) of patients in the nivolumab plus chemotherapy group and 98 % (173/176) in the chemotherapy group and these were considered treatment-related in 84 % and 90 % respectively. In the nivolumab plus chemotherapy and chemotherapy groups respectively, patients reporting a grade 3 or 4 AEs were 43 % versus 45 %, patients with a reported serious AE were 17 % versus 14 %, and patients discontinuing due to an AE was 10 % versus 11 %.[9, 10]

The most frequently reported treatment-related AEs of any grade with an incidence ≥15 % in the nivolumab plus chemotherapy group versus the chemotherapy group were: nausea (33 % versus 42 %), anaemia (23 % versus 23 %), constipation (21 % versus 20 %), decreased appetite (17 % versus 21 %), neutropenia (17 % versus 17 %) and decreased neutrophil count (14 % versus 22 %).[9, 10]

Immune-mediated AEs that occurred in ≥2 % of patients in the nivolumab plus chemotherapy arm were rash (8 %), hyperthyroidism (4 %) and hypothyroidism/thyroiditis (3 %).[9, 10]

Overall, adding nivolumab to chemotherapy in the neoadjuvant setting did not appear to result in a significantly worse toxicity profile. Importantly, it did not cause substantially more surgery delays, cancellations or complications. AEs observed align with the known safety profile of nivolumab and chemotherapy and no new safety concerns were identified. The key study did not assess immunogenicity and further investigations will be performed to address this uncertainty.[3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In a randomised, phase III study, CheckMate 816, the addition of three cycles of nivolumab to platinum-based chemotherapy showed statistically significant improvements in both pCR and EFS as neoadjuvant treatment in patients with resectable NSCLC.[3, 8, 9]
- Secondary outcomes were supportive. A positive trend in overall survival was observed for nivolumab plus chemotherapy, which was considered encouraging by regulators.[3, 8, 9]

4.2. Key uncertainties

- The control group in CheckMate 816 (neoadjuvant platinum-based chemotherapy) is not commonly prescribed in Scottish practice and may not be a relevant comparator. Patients in this setting in Scotland commonly receive surgery only or surgery followed by adjuvant platinum-based chemotherapy; a subset may go on to receive atezolizumab after adjuvant platinum-based chemotherapy though numbers are expected to be low. No direct data are available against any potentially relevant comparators. Of note, it was considered reassuring that neo-adjuvant and adjuvant chemotherapy options are generally considered equivalent. [4, 5]
- The indirect comparisons have several limitations including heterogeneity across studies, generalisability to the Scottish population and some of the studies were conducted several years ago and some were stopped early and underpowered. The NMA sensitivity analysis that

informed the main cost-effectiveness analysis included both neoadjuvant and adjuvant patients, key differences between these groups may bias the results. Due to differences in study design and patient populations in the trials of atezolizumab after adjuvant chemotherapy and CheckMate 816 and associated potential for bias, atezolizumab was included in a separate ITC. However, this separate comparison was also associated with several limitations, including the ad hoc methods used. Though clinical experts consulted by SMC seemed to find the assumption of clinical equivalence of neoadjuvant nivolumab plus platinum-based chemotherapy followed by surgery with surgery followed by adjuvant platinum-based chemotherapy and then atezolizumab reasonable. However, despite the identified limitations, the results were considered acceptable for decision-making by NDC.

- Overall survival results from CheckMate 816 are still immature and did not meet predefined statistical significance criteria. At the last presented interim analysis, after a median follow-up of 41.4 months, 78 % of patients in the nivolumab chemotherapy group and 64 % in the chemotherapy alone group were alive.[9] The study is ongoing and further analysis may help better define effect on overall survival.
- The study population of CheckMate 816 is heterogeneous and treatment effect of nivolumab plus platinum-based chemotherapy may not be consistent across all subgroups. Although not powered to detect differences (and therefore should be interpreted cautiously), subgroup analyses suggest that efficacy may be reduced in earlier disease stages (IB/II), and in patients with PD L1 tumour expression <1 %. [3] Results for the overall study population were considered acceptable for decision making by NDC.
- The choice of chemotherapy regimens was made after randomisation, which could have introduced bias. Additionally, there were differences in allowed chemotherapy regimens between treatment groups. Notably, cisplatin plus vinorelbine, commonly used in practice, was only allowed in the neoadjuvant chemotherapy arm.[3]
- Adjuvant therapy was allowed by protocol, with 15 % of patients in the nivolumab group and 25 % in the chemotherapy group receiving it. This is a potential source of heterogeneity and bias, given the possible influence on time-to-event outcomes of adjuvant therapy, although regulators noted it should reflect current clinical practice.[3]

4.3. Ongoing studies

Updated results from CheckMate 816 with a longer follow-up may address some of the key uncertainties relating to overall survival.

4.4. Clinical expert input

Based on observed efficacy, clinical experts consulted by SMC considered that this medicine fills an unmet need in this therapeutic area, and is a therapeutic advancement.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the service delivery including the time required to assess patient suitability for neoadjuvant treatment and for treatment administration.

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 the Roy Castle Lung Cancer Foundation which is a registered charity.
- Roy Castle Lung Cancer Foundation has received 8% pharmaceutical company funding in the past two years, including from the submitting company.
- Living with lung cancer can have a huge impact on the person's quality of life, symptoms such as persistent cough, fatigue, and breathlessness affect their normal day to day activities. Personal care can become exhausting, the person may also be unable to work which can put financial strain on them and their loved ones. There is huge emotional stress caring for and living with someone who has lung cancer, it changes and affects the lives of the person's loved ones.
- Surgery is offered for those lung cancer tumours that are resectable and the patient is often given a choice to have adjuvant chemotherapy after their surgery; which may be followed up by atezolizumab. Not everyone chooses to have adjuvant chemotherapy, as they are still recovering from surgery and reluctant to follow-up with this treatment, as they often feel it would further impact on their quality of life.
- This treatment has the potential to have an enormous benefit psychologically in coping with the cancer and provide a more hopeful and positive treatment journey not just for the patient but for their loved ones also. It can potentially reduce the size of the tumour, giving better surgery options, recovery and outcomes. It has the potential to allow the person to plan their life better, knowing that there is a specific timeline for the treatment and then the surgery, which could give them a bit more control as they can plan around the treatment regime.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis and an additional cost-minimisation analysis.
Time horizon	**Cost-utility analysis:** 35 years **Cost-minimisation analysis:** Duration of neoadjuvant or adjuvant treatment
Population	The submitting company requested SMC consider nivolumab in combination with platinum-based doublet chemotherapy (PDC) for the neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) NSCLC in adults.
Comparators	**Cost-utility analysis:** Surgery only (patients proceed immediately to surgery and no neoadjuvant or adjuvant therapy is received) and adjuvant PDC (patients proceed immediately to surgery, and subsequently receive a course of adjuvant PDC). **Cost-minimisation analysis:** Atezolizumab (patients proceed immediately to surgery, subsequently receive a course of adjuvant PDC, and then receive atezolizumab).

Model description	**Cost-utility analysis:** A four state semi-Markov model was used with the health states of event-free (EF), locoregional recurrence (LR), distant metastasis (DM) and dead. All patients enter the model in the EF health state and could either progress to LR or DM health states, or enter the dead state. Patients in the LR health state may progress to DM, or enter the dead state. Patients in the DM health state were not subject to explicit transitions to the dead state, as this was implicitly captured through the application of one-off cost, QALY, and life-year values representing the outcomes of a subsequent treatment mix. A cure assumption was included in the model, starting from Year 5 and completing at Year 7, assuming a 95% cure for patients in the EF health state. **Cost-minimisation analysis:** A comparison of treatment acquisition costs only.
Clinical data	**Cost-utility analysis:** Clinical data from both arms of the CheckMate 816 study were used in the model. Although neoadjuvant PDC was not a comparator, clinical inputs for surgery only and adjuvant PDC were taken from the NMA, with hazard ratios applied to the neoadjuvant PDC data from CheckMate 816. **Cost-minimisation analysis:** The company conducted a separate ITC comparing neoadjuvant nivolumab plus PDC with atezolizumab. However due to limitations in the ITC, the company opted for an assumption of equal efficacy between the treatments.
Extrapolation	**Cost-utility analysis:** CheckMate 816 data for TTLR, time to any progression, event-free mortality, and LR mortality were extrapolated. For neoadjuvant nivolumab plus PDC, the EF to LR transition used time to LR data from the neoadjuvant nivolumab plus PDC arm and fitted a joint log-normal distribution. The EF to DM transition was derived from a constructed curve by taking the difference between extrapolated time to any progression (fitted with a joint log-normal distribution) and time to LR, using data from the neoadjuvant nivolumab plus PDC arm. For the comparators, the EF to LR and EF to DM transitions applied TTLR and TTDM hazard ratios, respectively, to the extrapolated neoadjuvant PDC outcomes from CheckMate 816. Mortality and LR to DM transitions were treatment independent. The EF to Dead transition fitted an exponential distribution to pooled event-free mortality data from both CheckMate 816 treatment arms. The LR to Dead transition fitted a spline (DF = 4, hazard) function to pooled locoregional recurrence mortality data from both CheckMate 816 treatment arms. The LR to DM transition relied on clinician opinion. The DM to dead transition was not explicitly modelled, and was implicitly captured by the one-off life years, QALYs and costs applied in the health state. **Cost-minimisation analysis:** None
Quality of life	**Cost-utility analysis:** Utility values were derived from CheckMate 816 EQ-5D data, capped at general population levels and adjusted by age and sex[21]. An AE disutility was applied in the first model cycle. **Cost-minimisation analysis:** Not applicable
Costs and resource use	**Cost-utility analysis:** The model included medicine acquisition, administration, surgery, adjuvant treatments (for patients who received neoadjuvant treatment), LR treatment, DM treatment, resource use, terminal care, and adverse event costs. Resource use frequency was based on estimates from the literature[22] and clinician input. **Cost-minimisation analysis:** Treatment acquisition costs only.
PAS	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 simple discount was offered on the list price. The cost-minimisation results presented do not take account of the PAS for nivolumab or the PAS for atezolizumab but these were considered in the results used for decision-making. SMC is unable to present the cost-minimisation results provided by the company which used an estimate of the PAS price for nivolumab due to commercial confidentiality and competition law issues.

6.2 Results

The base case results of the cost-utility analysis indicated that nivolumab plus platinum-based doublet chemotherapy was associated with an increased number of quality-adjusted life years (QALYs) over adjuvant platinum-based doublet chemotherapy and surgery, but at an increased cost to NHSScotland. Inclusive of the PAS discount on nivolumab the incremental cost effectiveness ratio (ICER) was £5,137 using adjuvant platinum-based doublet chemotherapy as the comparator and £6,090 using surgery as the comparator.

In both cases the majority of the incremental QALY gain for nivolumab were in the EF health state, with the majority of incremental costs attributed to nivolumab acquisition and resource use in the EF health state.

Using cost-minimisation analysis, neoadjuvant nivolumab was estimated as being cost-saving compared to neoadjuvant atezolizumab, when list prices were used for both medicines. Cost-minimisation analysis using the PAS prices cannot be reported as it would directly infer the confidential discounts available on those products.

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

The company conducted deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore areas of uncertainty in the model.

A selection of the conducted scenario analyses for the cost-utility analysis are summarised in Table 6.3. These results include the PAS discount for nivolumab.

Table 6.3 Scenario analysis results – (PAS)

	Scenario	Base case value	Scenario value	ICER – Adjuvant PDC	ICER - Surgery
	Base case	-	-	**£6,090**	**£5,137**
1	Cure	Include	Exclude	£6,899	£5,714
2	DM QALY outcome	Base case	5 QALYS	£10,261	£9,691
3	DM cost outcome	Base case	No cost applied	£13,591	£13,809
4	TTLR extrapolation	Log-normal	Generalised Gamma	£5,632	£4,411
5	Any progression extrapolation	Log-normal	Generalised Gamma	£8,579	£9,741
6	Event-free mortality extrapolation	Exponential	Gamma	£6,091	£5,159
7	Locoregional recurrence mortality extrapolation	Spline DF = 4	Log-normal	£5,699	£5,985
8	Utility	Base case utility values	Literature utility values[22]	£7,260	£6,192

Abbreviations: DM = Distant Metastasis; DR = Distant Recurrence; EF = Event-free; HR = Hazard ratio; ICER = Incremental cost effectiveness ratio; LR = Locoregional Recurrence; PDC = platinum doublet chemotherapy; QALY = quality-adjusted life-year; TTLR = time to locoregional recurrence.

6.2. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for resectable (tumours ≥ 4 cm or node positive) NSCLC.
- Key clinical data used in the model were from a phase III randomised controlled trial, CheckMate 816.
- A comprehensive selection of variables were considered in one-way deterministic sensitivity analysis.

6.3. Key uncertainties

- The company used the hazard ratio, generated through an NMA, to model outcomes in the comparator arms of the cost-utility analysis. There were several limitations in NMA and the generated hazard ratios had wide confidence intervals. Exploratory scenarios using the extremes of the confidence intervals led to large changes in the ICER, however these scenarios cannot be presented as the results of the NMA are considered academic in confidence by the company.
- The separate ITC used to inform the use of a cost-minimisation analysis against atezolizumab was subject to limitations. Although uncertainties were present, SMC clinical experts viewed the similar efficacy of neoadjuvant nivolumab and adjuvant atezolizumab as a reasonable assumption. The cost-minimisation analysis only included medicine acquisition costs, although the inclusion of further costs would have been unlikely to have materially changed the conclusions. Furthermore, SMC clinical experts noted this atezolizumab was a relevant comparator, but the expected patient numbers were small.
- The distant metastasis health state was a source of potential uncertainty, as one-off life-year, QALY and cost outcomes were applied based on the output of previous health technology assessments. It was recognised that the submitting company sought a pragmatic approach, although due to its simplicity uncertainty remained. However, conservative scenario analyses on this health state were conducted which provided indicative evidence that ICER increases would not be substantial (Scenarios 2 and 3).
- The base case extrapolation curves were subject to uncertainty as there was limited clinical validation and the patient characteristics of external data sets used to validate the extrapolations in the model did not fully align with those of CheckMate 816. However, alternative plausible extrapolations did not show substantial ICER increases (Scenarios 4 to 7).

7. Conclusion

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

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published "Management of lung cancer: A national clinical guideline (SIGN 137)" in February 2014.[6]

The National Institute for Health and Care Excellence (NICE) published "Lung cancer: diagnosis and management" in 2019, which was updated in July 2023.[7]

The European Society for Medical Oncology (ESMO) published "Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2017 and the guidance was subsequently updated in 2021.[4, 5]

9. Additional Information

9.1. Product availability date

16 August 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 3-week cycle (£)
nivolumab	**360 mg nivolumab intravenously every 3 weeks for three cycles**	**3,950**

Costs from BNF online on 01 September 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 638 patients eligible for treatment with nivolumab in each year.

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 16 October 2023.

**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.