SMC2677

durvalumab concentrate for solution for infusion (Imfinzi®)

AstraZeneca UK Ltd

08 November 2024

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

durvalumab (Imfinzi®) is not recommended for use within NHSScotland.

Indication under review: In combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known EGFR mutations or ALK rearrangements

In a randomised, double-blind, phase III study, the addition of neoadjuvant and adjuvant durvalumab compared with the addition of placebo to neoadjuvant chemotherapy significantly improved complete pathological response and event-free survival in patients with resectable NSCLC.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Durvalumab is a human monoclonal antibody which binds to programmed cell death ligand-1 (PD-L1) and inhibits the interaction of PD-L1 with PD-1 and CD80. This enhances anti-tumour immune responses and increases T-cell activation.[1]

The recommended dose of durvalumab is 1,500 mg by intravenous (IV) infusion in combination with platinum-based chemotherapy every 3 weeks for up to four cycles prior to surgery, followed by 1,500 mg monotherapy every 4 weeks for up to 12 cycles after surgery. In patients weighing ≤30 kg, the dose is weight-based. See the Summary of Product Characteristics (SPC) for details.[1]

1.2. Disease background

Lung cancer is the leading cause of cancer mortality worldwide and it is the most common type of cancer in Scotland, with 4,851 cases reported in 2022. In most cases, diagnosis is made at an advanced stage; in 2022, 2,189 cases (45%) at stage IV. Approximately 28% of patients were diagnosed at stages II to III (7.7% stage II and 21% stage III). Non-small cell lung cancer (NSCLC) is the most prevalent type accounting for approximately 85% of all lung cancer cases.[2, 3]

1.3. Treatment pathway and relevant comparators

For patients who present with early NSCLC, stage I to IIIA, surgery with curative intent may be an option for suitable patients. However, many patients experience recurrence within 5 years. Guidelines recommend adjuvant chemotherapy for patients with resected stage IIB 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 > 4cm. Despite the use of adjuvant chemotherapy, recurrence rates remain high and the survival benefits are modest. For patients with resectable stage IIIA NSCLC who can have surgery and are fit enough for multimodality therapy, neoadjuvant chemoradiotherapy can be considered with surgery. However, equivalence of neoadjuvant and adjuvant chemotherapy has been reported for overall survival. Post-operative radiotherapy is not recommended for patients with completely resected stage I to IIIA disease but should be considered for those with microscopic residual tumour (R1) resection.[4-7]

Recently, novel neoadjuvant and adjuvant treatments have been accepted for use in Scottish clinical practice for specific subgroups of early-stage resectable and resected NSCLC patients. These include nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC (SMC2619), adjuvant atezolizumab for stage II to IIIA NSCLC with PD-L1 expression on ≥50% of tumour cells (SMC2492), adjuvant pembrolizumab for NSCLC with PD-L1 expression on ≥50% of tumour cells and adjuvant osimertinib for stage IB to IIIA epidermal growth factor receptor (EGFR) mutation-positive NSCLC (SMC2383). Pembrolizumab has also recently received a marketing authorisation similar to the durvalumab indication under review and is under assessment by SMC (SMC2688).

The submitting company considered neoadjuvant nivolumab in combination with platinum-based chemotherapy, adjuvant chemotherapy and surgery alone as potential comparators. Clinical

experts consulted by SMC considered that neoadjuvant nivolumab in combination with platinum-based chemotherapy was the most relevant comparator.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements comes from the AEGEAN study.[4]

Table 2.1. Overview of relevant studies[4]

Criteria	AEGEAN
Study design	International, randomised, double-blind, phase III study.
Eligible patients	• Adults aged ≥18 years with previously untreated, histologically or cytologically confirmed, resectable (stage II, IIIA, or IIIB [N2] according to the AJCC staging system, 8th edition) NSCLC • Suitable for surgery with lobectomy, sleeve resection, or bilobectomy. • At least one lesion, not previously irradiated, that qualified as a RECIST version 1.1 target lesion at baseline. • ECOG performance status of 0 or 1. • Confirmation of tumour PD-L1 status by central laboratory. • Patients with EGFR or ALK alterations were excluded following a protocol update
Treatments	Neoadjuvant durvalumab 1,500 mg or placebo IV on day 1 of a 3-week cycle in combination with neoadjuvant platinum-based doublet chemotherapy for up to 4 cycles or until unacceptable toxicity, withdrawal of consent, or another discontinuation criterion. Chemotherapy regimen was based on tumour histology and investigator's discretion from the following options. For squamous tumours: • carboplatin (AUC 6) plus paclitaxel (200mg/m^2 BSA) on day 1 of a 3-week cycle • or either cisplatin (75mg/m^2 BSA) or carboplatin (AUC 5) on day 1 plus gemcitabine (1,250mg/m^2 BSA) on days 1 and 8 of a 3-week cycle For non-squamous tumours: • pemetrexed (500mg/m^2 BSA) plus either cisplatin (75mg/m^2 BSA) or carboplatin (AUC 5) on day 1 of a 3-week cycle. Surgery was performed within 40 days of the last dose of neoadjuvant treatment. Post-operative radiotherapy was allowed according to local guidance and had to start within 8 weeks of surgery. After surgery, patients continued to receive durvalumab 1,500 mg or placebo IV every 4 weeks for up to 12 cycles or until local or distant recurrence, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion. Adjuvant treatment started as soon as clinically possible and within 10 weeks from surgery (or within 3 weeks of completing radiotherapy).
Randomisation	Randomised equally to the durvalumab or placebo groups. Randomisation was stratified according to disease stage (II or III) and PD-L1 expression (<1% or ≥1%).
Primary outcome	The co-primary outcomes were:

	• pCR, defined as the proportion of patients with absence of any viable tumour cells on complete evaluation of the resected lung cancer and all sampled regional lymph nodes by BCPR. • EFS, defined as the time from randomisation to progressive disease that precluded surgery, progressive disease that was discovered and reported by the investigator when attempting surgery and prevented completion of surgery, local or distant recurrence (based on BICR assessment according to RECIST 1.1) or death from any cause.
Secondary outcomes	• MPR, defined as ≤10% viable tumour cells in resected primary tumour and lymph nodes. • DFS, defined as the time from the date of surgery until the first date of disease recurrence (local or distant, determined by BICR using RECIST v1.1) or death due to any cause (analysed in the modified resected population). • Overall survival, defined as the time from randomisation to death from any cause.
Statistical analysis	A hierarchical testing strategy was applied for the co-primary and listed secondary outcomes with alpha allocation and recycling between outcomes and interim and final analyses. Unless otherwise stated, efficacy analyses were performed in the mITT population, which included all patients who underwent randomisation and had no known EGFR or ALK alterations.

AJCC = American Joint Committee on Cancer; AUC: area under the curve; BCPR = blinded central pathology review; BICR = blinded independent central review; BSA = body surface area; DFS = disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS = event-free survival; IV: intravenously; mITT = modified intention-to-treat; MPR = major pathological response; NSCLC: non-small cell lung cancer; pCR = pathological complete response; PD-L1: programmed death ligand-1; RECIST = Response Evaluation Criteria in Solid Tumors.

At the planned interim analysis of pathological complete response (pCR) and first interim analysis of event-free survival (EFS), the addition of durvalumab to platinum-based chemotherapy showed statistically significant improvements for pCR, major pathological response (MPC) and EFS. There was no significant improvement in disease-free survival (DFS) between durvalumab and placebo and further formal statistical testing was not performed. However, descriptive results for overall survival were provided. Details are presented in Table 2.2.

Table 2.2: Results for the AEGEAN study (data cut-off 10 November 2022; mITT population)[1, 4, 8]

	Durvalumab plus chemotherapy (n=366)	**Placebo plus chemotherapy (n=374)**
pCR by BCPR		
pCR, % (n/N)	17% (63/366)	4.3% (16/374)
Difference (95% CI)	13% (8.7% to 18%)[A]	
EFS by BICR		
Median duration of follow-up, months	11.7	
Number of EFS events	98	138
Median EFS, months	NR	25.9
HR (95% CI), p-value	0.68 (0.53 to 0.88), p=0.004	
KM EFS estimate at 12 months	73%	64%
KM EFS estimate at 24 months	63%	52%

MPC by BCPR		
MPC, % (n/N)	33% (122/366)	12% (46/374)
Difference (95% CI)	21% (15% to 27%)[A]	
Overall survival		
Median follow-up in censored patients	15.90	
Number of deaths	81	82
Median overall survival, months (95% CI)	NR (NR to NR)	NR (NR to NR)
HR (95% CI)	1.02 (0.75 to 1.39)	

BCPR = blinded central pathologic review; BIPR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; KM=Kaplan Meier; mITT = modified intention-to-treat; MPC = major pathological response; NR = not reached; RECIST = Response Evaluation Criteria in Solid Tumours; pCR=pathological complete response.

[A] Since p<0.001 at the interim analysis, there was no formal statistical testing at the final analysis of pCR.

Results of further unplanned, updated overall survival analyses provided by the company to the FDA at data cut-off 14 August 2023 found median overall survival had not been reached in either group, hazard ratio 0.91 (95% confidence interval 0.69 to 1.19) and at data cut-off 10 May 2024 found median overall survival had not been reached in the durvalumab group versus 53.2 months in the placebo group, hazard ratio 0.89 (95% confidence interval 0.70 to 1.14).[9] Results for OS remain immature.

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30), version 3, the EORTC 13-item Lung Cancer Quality of Life Questionnaire (QLQ-LC13), the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) and the EuroQoL 5-Dimension, 5-Level health state utility index (EQ-5D-5L). Available results indicate that outcomes were generally similar between treatment groups throughout the neoadjuvant period.[1, 4]

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

In the absence of direct evidence comparing perioperative durvalumab plus neoadjuvant platinum-based doublet chemotherapy (PDC) with neoadjuvant nivolumab plus neoadjuvant PDC, adjuvant PDC and surgery alone, the submitting company presented a number of indirect comparisons. This included a matching adjusted indirect comparison (MAIC) versus neoadjuvant nivolumab plus neoadjuvant PDC and network meta-analyses (NMAs) versus adjuvant PDC and surgery alone. Comparisons were based on the outcome EFS. The results indicated that there was no evidence of a difference in EFS between perioperative durvalumab plus neoadjuvant PDC with comparators. Details are presented in Table 2.3. Results from each analysis were used to inform the economic analysis.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Anchored MAIC, piecewise ≥3 months[A] Random effects, piecewise NMA, ≥3 months[A]

Population	Adults (≥18 years) with resectable stage I to III NSCLC
Comparators	Perioperative durvalumab plus neoadjuvant PDC versus: MAIC: neoadjuvant nivolumab plus neoadjuvant PDC anchored via neoadjuvant PDC NMA: adjuvant PDC and surgery alone were compared via neoadjuvant PDC
Studies included	MAIC: two studies (AEGEAN [4] and CheckMate-816 [10]) NMA: seven studies (AEGEAN, [4] CHEST, [11] Gilligan 2007, [12] Li 2009, [13] NATCH, [14, 15] Pisters 2010, [16] and Rosell 1994 [17, 18])
Outcomes	EFS
Results	The central estimates of the comparisons with neoadjuvant nivolumab plus PDC, PDC and surgery alone all favoured the durvalumab regimen, however the confidence and credible intervals were wide and similar EFS could not be excluded. Results for indirect comparisons were considered confidential by the company

Abbreviations: EFS, event-free survival; HR, hazard ratio; MAIC, matching-adjusted indirect comparisons; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; PDC, platinum-based doublet chemotherapy. The piecewise approach divided AEGEAN EFS data into 0 to 3 months and 3 months onwards intervals.

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

3. Summary of Safety Evidence

In the AEGEAN study at data cut-off 10 November 2022, the median duration of treatment in the durvalumab group was 32.0 weeks and in the placebo group was 28.4 weeks. The median duration of neoadjuvant chemotherapy was 12.1 weeks in both groups. In the durvalumab and placebo groups respectively, patients reporting a grade 3 or higher adverse events (AE) were 42% versus 43%, a serious AE were 38% versus 31% and the proportion of patients discontinuing durvalumab or placebo therapy due to an AE was 12% versus 6.0%.[4, 8]

The most frequently reported AEs of any grade were mainly considered to be related to the neoadjuvant chemotherapy were mostly similar in both treatment groups.[4] There was also a higher incidence of immune-related AEs (any grade) in the durvalumab compared with the placebo group (24% versus 9.3%). These included hypothyroid events (9.2% versus 2.3%), dermatitis/rash (5.5% versus 1.8%), pneumonitis (3.7% versus 1.8%), hepatic events (3.2% versus 0.8%), hyperthyroid events (1.7% versus 1.0%) and diarrhoea/colitis (0.7% versus 1.3%). The SPC provides recommendations for the management of immune-related reactions.[1, 4]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Results from the AEGEAN study demonstrate significant improvements in both primary outcomes, pCR and EFS, with durvalumab compared with placebo when added to neoadjuvant chemotherapy. Event-free survival is considered an appropriate surrogate outcome for overall survival in the neoadjuvant setting.

- The treatment effect on pCR and EFS was generally consistent across predefined subgroups including stage of disease, histology and level of PD-L1 expression, although appeared smaller in female patients (n=210).[4]
- The randomised AEGEAN study is at low risk of bias, as it was double-blind and both outcomes were assessed independently by blinded central review and EFS according to standardised criteria (RECIST v1.1).[4]

4.2. Key uncertainties

- Pathological complete response has not been validated as a surrogate outcome for NSCLC since correlation with long-term patient outcomes is lacking. However, pCR is considered to provide useful information for assessing immediate treatment response. Overall survival data remains immature.[4, 19]
- The AEGEAN study did not compare the durvalumab regimen with some of the most relevant comparators, including the neoadjuvant nivolumab regimen. In the absence of direct evidence for these comparisons, the company presented indirect evidence. However, there were several limitations meaning the results were highly uncertain. These included heterogeneity across the studies, small sample sizes, piecewise approach used, wide credible and confidence intervals and that EFS was the only outcome considered.
- The treatment effect of durvalumab was assessed across the overall study period and use in the neoadjuvant and adjuvant settings was not considered separately making it difficult to determine the relative contribution of each.[4]
- Detailed quality of life data have only been reported during the neoadjuvant period when patients were also receiving chemotherapy. The effect on quality of life when durvalumab was continued as monotherapy after surgery in the adjuvant setting is unclear.[1]
- Study patients had a median age of 65 years and a baseline ECOG performance score <2, which may affect the generalisability of study results to an older patient population and those with poorer performance status.[4]

4.3. Clinical expert input

Clinical experts consulted by SMC did not identify any unmet need.

4.4. Service implications

Although significant service implications are not anticipated, additional capacity may be required in clinical, pharmacy and day unit settings to accommodate the neoadjuvant and adjuvant dosing regimen.

5. Summary of Patient and Carer Involvement

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

- We received patient group submissions from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum. The Roy Castle Lung Cancer Foundation is a registered charity, and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation.

- The Roy Castle Lung Cancer Foundation has received 7.6% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has not received any pharmaceutical company funding in the past two years.
- Living with lung cancer can be challenging with symptoms that are difficult to control, for example breathlessness, continuous cough and fatigue. Overall quality of life is impacted by not being able to do daily tasks, work, care for children and this can create an enormous stress on people with lung cancer and their loved ones.
- There are a few current options in Scotland for the treatment of resectable lung cancer. These treatments can be restricted due to specific biomarkers being present or not present. Having access to this proposed treatment of durvalumab with chemotherapy before surgery and continuing durvalumab after surgery may give the patient more confidence in a good outcome and ease the emotional strain on them and their loved ones.
- Durvalumab potentially adds benefits for both patients and society in preventing or delaying recurrence following surgery to resect their lung cancer.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	36 years, based on an assumed starting age of 64 years
Population	Patients with resectable NSCLC and no known EGFR mutations or ALK rearrangements.
Comparators	Durvalumab was compared against 5 alternative treatment regimens: • Neoadjuvant PDC • Neoadjuvant nivolumab plus PDC • Surgery alone • Adjuvant PDC • Adjuvant atezolizumab
Model description	The economic analysis employed a 4 state semi-Markov model. The included states were event free (EF), locoregional recurrence (LRR), distant metastatic (DM), and death. Patients started the model in the EF state and could progress in a forward direction to the more severe health states and then death. The model cycle length was one month, and a half cycle correction was used.
Clinical data	The central clinical data in the model came from the AEGEAN study, which compared the outcomes of patients receiving durvalumab in combination with PDC as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, with neoadjuvant PDC.[4] These data were used to inform the occupancy of the EF state. The AEGEAN study did not include the other comparators used within the economics, and so the modelling also utilised results from the MAIC and NMA described in Section 2.3.

Extrapolation	The company presented evidence which they interpreted as highlighting a change in the hazard of non-death events (ie progression to LRR or DM) around the 3-month mark of the AEGEAN study in the neoadjuvant PDC arm. On this basis, the company adopted a piecewise approach, using the directly observed non-death event Kaplan Meier (KM) data up to 3 months and then a parametric tail thereafter. The log normal curve was used for the extrapolation, based on a combination of visual fit, statistical fit and clinical opinion. The company used the neoadjuvant PDC non-death EFS as a reference curve upon which the non-death EFS of all other comparators, including durvalumab, was based. All treatments were assumed to have the same EFS over the first 3 months, tracing the observed KM data in the neoadjuvant PDC arm. The company justified this stating that there was minimal separation between the arms in the AEGEAN study, and that consistent approach across all model arms was desirable. The post-3-month extrapolations for the non-neoadjuvant PDC comparators was estimated by applying the hazard functions estimated in the MAIC and NMA. Despite the presence of observed data from the AEGEAN study, the disaggregation of non-death events between movements to the LRR and DM states was based on clinical opinion. This split between LRR and DM was assumed equal across treatments and held constant across time. Due to the small number of events in each arm, to model death in the EF state the company pooled data across both arms of the AEGEAN study. This was extrapolated using the log-normal curve based on statistical and visual fit. The model utilised a cure assumption, where 95% of patients who remained in the EF state at 5 years were assumed cured. Cured patients had no chance of progression to either the LRR or DM state and had a mortality rate equal to the general population. The AEGEAN study was unable to supply data which could be used to inform the occupancy of the LRR and DM states. The company estimated survival in those states by drawing on external sources. The survival in each state was dependent upon treatment choice, with treatment-level survival functions weighted into composite survival functions based on the treatment proportions. Rechallenge with immunotherapies could take place in both the LRR and DM states if the patient progressed 6 months after the completion of a previous round of immunotherapy.
Quality of life	Health related quality of life data was collected in the AEGEAN study using the EQ-5D-5L instrument. This was cross walked to the 3L values before being used to estimate utility values in the EF and LRR states. The utility values in the DM state (which were stratified across progression free and progressed DM) came from external sources. The values used in the model for DM health states were 0.759 (progression-free) and 0.662 (progressed). Other utility values were considered academic in confidence by the submitting company. The model included disutilities from AEs experienced from treatment received in the EF state.
Costs and resource use	Medicine costs included in the model were for drug acquisition, administration, radiotherapy and AE management.

	Other NHS costs included in the model were surgery costs (for patients who undergo surgery after neoadjuvant treatment), monitoring costs, clinic visits, hospitalisation costs and an end-of-life cost.
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 discount was offered on the list price. PASs discounts are in place for nivolumab and atezolizumab and these were included in the results used for decision-making by including estimates of the comparator PAS prices.

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence and competition law concerns regarding the PAS, SMC is unable to publish these results. The company considers all results confidential and so they are not presented here. The base case analysis suggested that durvalumab was associated with higher costs, driven by the acquisition cost of durvalumab in the EF state. The analysis also suggested that durvalumab would be associated with better health outcomes from greater length of occupancy of the EF state.

6.3. Sensitivity analyses

The company conducted one-way sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore areas of uncertainty in the model. This analysis indicated that the model was stable across most parameters, however the results of the ITCs were found to have a large impact on the estimated cost-effectiveness.

A selection of scenarios considered by the SMC Committee are presented in Table 6.3.

Table 6.3 Scenario analysis results

#	Parameter	Base case	Scenario	Neoadj PDC	Neoadj nivo + PDC	Surgery alone	Adj. PDC	Adj. atez.
-	Base case	-	-	*	*	*	*	*
1	Time horizon	36 years	30 years	*	*	*	*	*
2			20 years	*	*	*	*	*
3	Proportion of EFS non-death events being EF→LRR	Clinical opinion received by company	Value observed in AEGEAN study	*	*	*	*	*
4	EFS distribution for neoadjuvant PDC arm	Log-normal	Log-logistic	*	*	*	*	*
5			Generalised gamma	*	*	*	*	*
6			Weibull	*	*	*	*	*
7	EFS extrapolation	Piecewise extrapolation (lognormal)	Single-piece extrapolation (lognormal)	*	*	*	*	*
8	Efficacy	Mean HR values from ITC used to model EFS	No EFS advantage of durvalumab over ITC comparators	**Requested from submitting company, but not provided**				

9		Reference curve = Neoadjuvant PDC	Reference curve = Durvalumab	**Requested from submitting company, but not provided**				
10	Transitions from LRR and DM states	Parametric distribution chosen based on "best fit"	Exponential function	*	*	*	*	*
11	No IO re-treatment	Yes	No	*	*	*	*	*
12	Waiting period before IO retreatment	6	12	*	*	*	*	*
13	EF utility capped at UK general population norm	*	0.829	*	*	*	*	*

Abbreviations: Neoadj., neoadjuvant; PDC, platinum-doublet chemotherapy; nivo, nivolumab, Adj, adjuvant; atez, atezolizumab; EF, event free; LRR, locoregional recurrence; DM, distant metastasise, HR, hazard ratio; ITC, indirect treatment comparison; IO, immune-oncology

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

6.4. Key strengths

- The comparators within the modelling were appropriate. These included neoadjuvant nivolumab plus PDC, which was the treatment that experts consulted by SMC suggested was the most likely to be displaced by durvalumab in Scottish practice.
- The model structure appeared to be appropriate and was similar to the structure seen in submissions within the same disease area and indication.
- The model used data from a phase III randomized, blinded study which compared perioperative durvalumab with neoadjuvant chemotherapy.

6.5. Key uncertainties

- The modelling drew on the results of two ITCs, an NMA and a MAIC. The results of these analyses were highly uncertain and suggested no statistical difference between durvalumab and the non-study comparators in terms of EFS. Despite this, the economic analysis estimated improvements in EFS in the durvalumab arm over those comparators through the application of the hazard ratio point estimates. It was unclear whether those EFS benefits would materialize in Scottish practice, and the realised economic case may be different from that presented. The company was asked to supply a scenario where no EFS advantage of durvalumab was assumed. They declined to do so, arguing that this would be overly conservative and inappropriate. While they did cite supportive evidence that durvalumab would be more effective than surgery alone and adjuvant PDC, a remaining concern was the uncertainty in the efficacy of durvalumab relative to neoadjuvant nivolumab plus PDC. The Committee felt that a scenario matching the efficacy between durvalumab and nivolumab was important to decision making. Setting EFS outcomes as the

same between nivolumab and durvalumab would lead to durvalumab being dominated by nivolumab meaning it would result in higher costs and worse health outcomes for patients.

- The company chose to use neoadjuvant chemotherapy as the reference curve in the model. The company reported having done so as it represented the common comparator across the ITCs and made the projections easier to validate. However, it also meant that the observed data for durvalumab patients was not directly used, which adds uncertainty in other ways and may impact the robustness of conclusions. The company was invited to explore this uncertainty by providing scenarios using durvalumab as the reference curve, however it declined to do so.
- The approach to modelling transitions in the LRR and DM states was seen as uncertain. To model those transitions the company used parametric distributions where the hazard changes over time (for example the log-logistic function). This function may have appropriately captured the changing risk of progression over time for a static population, but was applied to a dynamic population, with patients entering the LRR and DM states at different times. An alternative was to use the exponential function, which has a constant hazard. A scenario using the exponential function to model all transitions in the LRR and DM state increased the ICERs slightly (Scenario 10).
- The EF state utility value estimated from the data in the AEGEAN study sat above the value which would be expected in an age and sex matched general population sample. The company utilized the study value in the base case, which lacked face validity. A scenario using a value capped at the general population level led to a small increase in the ICERs (Scenario 13).

7. Conclusion

After considering all the available evidence, the Committee was unable to accept durvalumab for use in NHSScotland.

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published "Lung cancer: diagnosis and management" in 2019, which was updated in March 2024.[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.[5, 6]

The Scottish Intercollegiate Guidelines Network (SIGN) published "Management of lung cancer: A national clinical guideline (SIGN 137)" in February 2014.[20]

9. Additional Information

9.1. Product availability date

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
durvalumab	**Neoadjuvant durvalumab 1,500 mg intravenously every 3 weeks in combination with chemotherapy for up to four cycles or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with durvalumab 1,500 mg intravenously every 4 weeks as monotherapy for up to 12 cycles or until disease recurrence or unacceptable toxicity.**	**Up to 118,368**

Costs from BNF online on 22 August 2024. 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 134 patients eligible for treatment with durvalumab in each year.

SMC is unable to publish the 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 11 October 2024.

**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.