SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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atezolizumab 1,200mg concentrate for solution for infusion (Tecentriq®)

SMC No 1336/18

Roche Products Limited

8 June 2018

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

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

atezolizumab (Tecentriq®) is accepted for restricted use within NHS Scotland

Indication under review: As monotherapy for the treatment of adult patients with locally advanced or metastatic non‑small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*)‑positive tumour mutations should also have received targeted therapy before receiving atezolizumab.

SMC restriction: treatment with atezolizumab is subject to a two-year clinical stopping rule.

Atezolizumab, compared with a standard taxane monotherapy, significantly improved overall survival in adults with advanced NSCLC who had progressed after platinum-based chemotherapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of atezolizumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Vice Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*)-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.[1]

Dosing Information

The recommended dose of atezolizumab is 1,200mg administered intravenously every three weeks until loss of clinical benefit or unmanageable toxicity. The infusions must not be administered as an intravenous push or bolus. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.[1]

Treatment with atezolizumab must be initiated and supervised by a physician experienced in the treatment of cancer.[1]

See the summary of product characteristics (SPC) for further information.[1]

Product availability date

21 September 2017
Atezolizumab meets SMC orphan equivalent and end of life criteria for this indication.

Summary of evidence on comparative efficacy

Atezolizumab, an immune checkpoint inhibitor, is a humanised monoclonal antibody that binds to programmed death-ligand 1 (PD-L1) and blocks its interactions with both the programmed death-1 (PD-1) and B7.1 receptors. This removes PD-L1 / PD-1 mediated inhibition of the immune response, including reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity.[1]

Comparative clinical study evidence versus docetaxel is available from the pivotal phase III study, OAK.[2]

The OAK study was an international, multicentre, randomised, open-label study that recruited adult patients with histologically or cytologically documented locally advanced or metastatic NSCLC and investigator assessed measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and who were expected to live for at least 12 weeks. Tumour tissue specimens were required for PD-L1 expression evaluation. Patients had disease progression either during or following prior platinum containing chemotherapy for locally advanced, unresectable / inoperable or metastatic NSCLC or disease recurrence within six months of treatment with a platinum based adjuvant / neoadjuvant or combined modality regimen with curative intent. Patients with a sensitising *EGFR* mutation or *ALK* fusion oncogene must have experienced disease progression during or after treatment with an appropriate tyrosine kinase inhibitor (TKI). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate haematologic and end organ function.[3, 4]

A total of 1,225 patients were randomised to study treatment, however the published efficacy results (used by the regulatory agency) are from the primary population which consisted of the first 850 patients recruited into the study. These patients were randomised to receive intravenous atezolizumab 1,200mg (n=425) or intravenous docetaxel 75mg/m^2 (n=425) every three weeks. Study treatment was continued

until unacceptable toxicity or investigator assessed disease progression, however atezolizumab treatment was permitted beyond disease progression if the investigator deemed there was continued clinical benefit.[2] Randomisation was stratified by PD-L1 expression on immune cells determined by immunohistochemistry category (<1%, 1 to 5%, 5 to 50%, ≥50%); number of previous chemotherapy regimens (one versus two); and histology (non-squamous versus squamous).[2, 4]

There were two co-primary outcomes; overall survival (OS; time from randomisation until death from any cause) was assessed in two populations: the primary population (n=850) and in patients with ≥1% PD-L1 expression (n=463). OS was assessed at a median follow-up of 21 months after 67% of the primary population had died; data cut-off 07July 2016.[2] In the atezolizumab group 64% (271/425) of patients had died compared with 70% (298/425) of patients in the docetaxel group. Median OS (primary population) was 13.8 months in the atezolizumab group and 9.6 months in the docetaxel group; hazard ratio (HR): 0.73 (95% confidence interval [CI]: 0.62 to 0.87), p=0.0003.[2, 5] Median OS in the subgroup with ≥1% PD-L1 expression was 15.7 months and 10.3 months in the atezolizumab and docetaxel groups respectively; HR=0.74 (95% CI: 0.58 to 0.93), p=0.0102.[2, 4]

An updated analysis of OS in the primary population after a minimum follow-up of 26 months (data cut-off January 2017) reported a 2-year OS rate of 28% in the atezolizumab group compared with 18% in the docetaxel group. A total of 6.4% (27/425) of atezolizumab patients and 12% (49/425) of docetaxel patients were censored before the required minimum 24 months of follow-up and excluded from the analysis.[6] At the time of this analysis the following post study lung cancer treatments had been taken by patients in the atezolizumab and docetaxel groups: chemotherapy by 41% and 31%; targeted treatments (primarily erlotinib) by 15% and 16% and immunotherapy (primarily nivolumab) in 4.5% and 17%.[2, 6]

Key secondary outcomes of the OAK study were progression free survival (PFS), objective response rate (ORR) and duration of response [2, 4,] The results reported at the primary data cut-off of July 2016 for the primary population are presented in Table 1 below.

Table 1: Key secondary outcomes of the primary population in the OAK study, (July 2016 data cut) [2, 4]

		Atezolizumab (n=425)	**Docetaxel (n=425)**
Progression-free survival	Event rate	89% (n=380)	88% (n=375)
	Median	2.8 months	4.0 months
	HR (95% CI)	0.95 (0.82 to 1.10), p=0.49	
Objective response rate	Responders	14% (n=58)	13% (n=57)
	Complete response	1.4% (n=6)	0.2% (n=1)
	Partial response	12% (n=52)	13% (n=56)
	Stable disease	35% (n=150)	42% (n=177)
	Progressive disease	44% (n=187)	28% (n=117)
	Missing or not evaluable	7.1% (n=30)	17% (n=74)
Duration of response	Median	16.3 months	6.2 months
	HR (95% CI)	0.34 (0.21 to 0.55), p<0.0001	

HR = hazard ratio; CI = confidence interval

Health related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13). Prolonged time to deterioration of patient-reported pain in chest was observed with atezolizumab compared with docetaxel (HR=0.71, 95% CI: 0.49 to 1.05; median not reached in either group). The time to deterioration

in other lung cancer symptoms (i.e. cough, dyspnoea, and arm / shoulder pain) was similar between the atezolizumab and docetaxel groups.[4]

A systematic review and meta-analysis of randomised clinical studies of anti-PD-1 / anti-PD-L1 immunotherapy versus docetaxel in NSCLC was published in February 2018.[8] Analysis included 2,737 patients from four phase III studies: OAK (atezolizumab versus docetaxel)[2]; KEYNOTE-010 (pembrolizumab versus docetaxel)[9]; CheckMate 057 (nivolumab versus docetaxel in non-squamous NSCLC)[10] and CheckMate 017 (nivolumab versus docetaxel in squamous NSCLC).[8, 11] A random-effects model was used to determine the pooled HR for OS, PFS and duration of response. The inverse-variance method was used to calculate the pooled odds ratio for ORR and treatment-related AEs. Heterogeneity was assessed using the τ^2 and I^2 statistics. There was no evidence of significant statistical heterogeneity for the OS outcome, which was the primary outcome in all studies, or in duration of response; there was significant statistical heterogeneity for the PFS and ORR outcomes.
Treatment with anti-PD-1 / anti-PD-L1 medicines was associated with benefits compared with docetaxel for all measured outcomes:

- OS pooled HR: 0.69 (95% CI 0.63 to 0.75; p<0.00001)
- PFS pooled HR: 0.85 (95% CI 0.75 to 0.96; p=0.007)
- Duration of response pooled HR: 0.32 (95% CI 0.24 to 0.43; p<0.00001)
- ORR pooled odds ratio (OR): 1.77 (95% CI 1.26 to 2.50; p=0.001).
- Treatment-related AEs ≥ grade 3 OR: 0.19 (95% CI 0.12 to 0.30; p<0.00001)[8]

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

Summary of evidence on comparative safety

In the pivotal OAK study the safety analysis at the 07 July 2016 cut-off was conducted in patients from the entire ITT (n=1,225) population who had received at least one dose of study medication (n=1,187).[2] Median treatment duration was 3.4 months in the atezolizumab group and 2.1 months in the docetaxel group.

Adverse events (AEs) (any grade) were reported by 94% (573/609) and 96% (555/578) of patients in the atezolizumab and docetaxel groups and these were of grade 3 or 4 severity in 37% and 54%, and were fatal in 1.6% and 2.4% of patients in the respective groups.[2] Serious AEs were reported in 32% of patients in the atezolizumab group and 31% in the docetaxel group.[2, 4] As a result of AEs, treatment withdrawal occurred in 7.6% and 19% of patients in the atezolizumab and docetaxel groups and dose modification, delay, or interruption of study medication occurred in 25% and 36% of patients in the respective groups.[2]

Treatment related grade 3 or 4 AEs were reported in 15% and 43% of patients randomised to atezolizumab and docetaxel respectively. There was one treatment related death, in the docetaxel group.[2] Treatment related serious AEs were reported by 10% of patients in the atezolizumab group and by 18% in the docetaxel group.[4] The most frequently reported treatment related AEs, (any grade), in the atezolizumab group were fatigue (14%), nausea (8.7%), decreased appetite (8.5%), and asthenia (8.4%).[2,] The most frequently reported AEs of special interest (incidence ≥5% in either group) were rash (in both groups), peripheral neuropathy (docetaxel group), and increased aspartate aminotransferase and alanine aminotransferase levels (atezolizumab).[4]

The European Public Assessment Report (EPAR) specifically noted the higher rates (atezolizumab group versus docetaxel group) of musculoskeletal pain (11% versus 4.3%) and immune-mediated events (13% versus 9.5%).[4] Immune-mediated AEs in the atezolizumab group included pneumonitis

(any grade in 1.0% of patients; grade 3 in 0.7%), hepatitis (grade 3 in 0.3%), and colitis (grade 2 in 0.3%).[2]

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

Summary of clinical effectiveness issues

Most patients with NSCLC are diagnosed with distant metastatic disease, leading to poor prognosis.[4] Median OS to date is less than 13 months.[2, 9-12] The immune checkpoint inhibitor PD-1 antibodies nivolumab and pembrolizumab are licensed for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults (pembrolizumab only if tumours express PD-L1).[13, 14] SMC has accepted both medicines for use (SMC advice 1204/17, 1180/16 and 1144/16). Pembrolizumab is also licensed as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score with no *EGFR* or *ALK* positive tumour mutations; and this has been accepted for use (SMC advice 1239/17).[13] Patients with *EGFR* positive or *ALK* positive mutations receive targeted treatment and chemotherapy before nivolumab or pembrolizumab. Both medicines have demonstrated OS benefit compared with docetaxel which has now been superseded as the principal established treatment option.[8] SMC oncology expert advice is that nivolumab is now the main treatment used in Scotland for relapsed metastatic NSCLC after prior chemotherapy.

Atezolizumab meets SMC orphan equivalent and end of life criteria for this indication.

The pivotal OAK study demonstrated a statistically and clinically significant improvement of more than four months in median OS for atezolizumab compared with docetaxel in adults with stage IIIB or IV NSCLC who had received prior platinum based chemotherapy.[2] Treatment with atezolizumab also produced a significant benefit in duration of response.[2, 5] The clinical benefit of atezolizumab is further strengthened as it appears to be better tolerated than docetaxel. Atezolizumab was effective in patients without PD-L1 expression, however subgroup analyses suggest increased benefit in patients with strongly positive PD-L1 expression.[3] The effectiveness of atezolizumab may also be affected by histology and the number of prior therapies.[4] Patient crossover / treatment switching was not permitted in the OAK study until the pre-specified primary analysis.[2, 5] However substantial numbers of patients received subsequent therapies after discontinuing study treatment, with imbalances between treatment groups; the docetaxel group used less chemotherapy, and more immunotherapy, especially nivolumab. This may have confounded OS results at the updated analysis in January 2017.

The OAK study had a number of limitations: It was open label and treatment allocation was not blinded, posing a risk of bias for outcomes involving assessment of response and also patient reported outcomes. This may also have contributed to the imbalance in withdrawal from the study prior to the first dose; a higher proportion of patients in the docetaxel group did not receive any study treatment. Another limitation is that the efficacy outcome results for the full ITT population and the health related quality of life outcome results for QLQ-C30 and EQ-5D have not been published.

There is no direct clinical evidence versus nivolumab or pembrolizumab which are more relevant comparators. The submitting company presented a Bayesian network meta-analysis (NMA) to compare atezolizumab with nivolumab and pembrolizumab in patients who had received prior systemic treatment for locally advanced or metastatic NSCLC. The NMA included 31 studies and three outcomes were measured: OS, PFS and adverse events (any grade). Fractional polynomial methodology was used for the efficacy outcomes as this does not rely on the assumption of proportional hazards.

The results suggest that the PD-1 targeted therapies have similar effectiveness to each other for OS, PFS and similar incidence of any grade of AE. The submitting company concluded that results of the ITC demonstrated that atezolizumab is non-inferior in efficacy compared with nivolumab and pembrolizumab and that it has a similar safety profile and used this to support a cost-minimisation analysis.

Key limitations of the NMA: it was not designed to detect non-inferiority; there was substantial heterogeneity and some missing statistical detail concerning the methodology and presentation of results.

The conclusion of the published meta-analysis of four phase III studies was that, in patients with progressive advanced NSCLC, PD-1 targeted therapies were significantly better than docetaxel in terms of OS, PFS, DOR and ORR.[8] There is some uncertainty concerning the precision of the pooled effect sizes due to reported substantial heterogeneity, noted above, especially for the PFS and ORR outcomes and the lack of direct comparative data.

Clinical experts consulted by SMC considered that the introduction of atezolizumab, which is administered every three weeks, would provide a more convenient option for patients and the service than nivolumab which is administered every two weeks.[1, 13, 14]

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 atezolizumab, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced NSCLC is a devastating incurable disease with progressive symptoms including breathlessness, weight loss and chest pain that can be very difficult to manage. Patients are often elderly and/or have co-morbidity. There is a high negative physical and psychological impact on patients due to a reduced ability to look after themselves and be involved in family or work activities.
- Atezolizumab's 3-weekly administration schedule, compared with the current standard 2-weekly nivolumab, would improve the quality of life of the patient and family as it is more convenient, less restricting and less expensive.
- The 33% reduction in hospital visits would also benefit the service in terms of out-patient staffing and capacity.
- There is a potential advantage in patients with non-squamous NSCLC and no or low PD-L1 expression as there is evidence of benefit in this patient group for atezolizumab over docetaxel, but not for nivolumab over docetaxel.
- Atezolizumab is the only immunotherapy with evidence of efficacy in patients with treated asymptomatic supratentorial central nervous system metastases as the nivolumab and pembrolizumab studies excluded these patients.

Additional Patient and Carer Involvement

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 6.1% pharmaceutical company funding in the past two years with none from the submitting company. The Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the past two years with none from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The economic analysis submitted by the company was for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Atezolizumab was compared against docetaxel in a cost-utility analysis (CUA) and against pembrolizumab and nivolumab in a cost minimisation analysis (CMA). SMC clinical expert feedback for this review indicated that nivolumab is the primary comparator relevant for analysis, and that comparisons against pembrolizumab and docetaxel are helpful but of less relevance for the decision context in Scotland.

Clinical evidence for the company's CUA was based on the phase III OAK trial, which is used as the data source for clinical outcomes (OS, PFS), adverse events, health related quality of life (utilities), treatment dose and treatment duration (time to treatment discontinuation [TTD]) in the model. A partitioned survival analysis was undertaken, modifying the typical three state oncology model (progression-free, post-progression, and death) to one based on on-treatment, off-treatment, and death. This on/off treatment approach was justified by the company as the progression free endpoint may be unsuitable for immunotherapies such as atezolizumab where there may be benefits to continuing treatment beyond progression. The CUA model used a patient mean age of 63 years and adopted a 25 year time horizon by which time less than 1% of the atezolizumab patients were alive. Alternative shorter time horizons (5, 10 and 20 years) were explored in scenario analyses.

The OAK study had relatively mature OS data (survival probability of 0.30 for atezolizumab and 0.10 for docetaxel) at the end of the study follow-up (approximately two years), however the long term extrapolation beyond the study period is subject to uncertainty. Proportional hazards was rejected so lifetime extrapolation was undertaken by separately fitting survivor functions to each study arm in OAK. A log-logistic mix-cure model with cure fraction of 0% was adopted for atezolizumab, while a generalised gamma mix-cure model was selected for docetaxel. These models provide a very close fit to Kaplan Meier (KM) data on visual inspection. Based on goodness of fit statistics, visual inspection and clinical plausibility the Weibull distribution was considered to be the most appropriate functional form for TTD and the generalised gamma distribution was considered most appropriate for the PFS extrapolation. Scenario analyses were conducted to explore alternative OS, PFS and TTD extrapolations.

Evidence for the CMA is based upon the NMA indirect treatment comparison (ITC), as there is no direct study evidence comparing atezolizumab with pembrolizumab or nivolumab. The company based the CMA on a claim of non-inferiority from this ITC, however, the NMA was not designed to detect non-inferiority. For the CMA, the CUA model was adapted. OS for pembrolizumab and nivolumab was assumed to be the same as atezolizumab so the CMA removed OS differences and health related quality of life from the CUA model. To inform duration of treatment, the study TTD data were used for atezolizumab, however, since TTD data were not available for pembrolizumab and nivolumab, PFS was used as a proxy to determine treatment duration and supportive care costs. The PFS curves for pembrolizumab and nivolumab were based on the PFS network meta-analysis. Proportional hazards was rejected and a fractional polynomial approach to accommodate non constant hazard ratios was

employed. The analysis shows a hazard ratio of greater than 1.00 for atezolizumab versus nivolumab and less than 1.00 vs pembrolizumab. The magnitude of the HRs increase over time. Therefore the company assumed equivalence (based only on claimed non-inferiority, with no associated margin being specified), but at the same time fit time dependent treatment effects. For the CMA the company provided a sensitivity analysis in which the treatment duration for nivolumab and pembrolizumab was assumed to be equal to that of atezolizumab. A further scenario analysis was provided upon request in which all outcome related parameters (OS, PFS, TTD, subsequent therapies) are assumed to be equal, in line with SMC guidance. The results of this analysis are presented in table 2 below.

For the CUA utilities were derived from the OAK study using the Euroqol 5 dimension 3 level at baseline, during treatment and for atezolizumab at follow-up 6,12 and 24 weeks post progression. The model applies utilities to the 'on treatment' and 'off treatment' states then incorporates a time to death approach whereby various weekly categories are assigned utilities dependent on proximity to death.

The main costs are treatment and administration costs, supportive care, management of adverse events and subsequent treatment costs. In the CUA treatment with atezolizumab is until loss of clinical benefit or unmanageable toxicity, and is modelled to continue as per the study's TTD with parametric extrapolation of the tail. In the CMA atezolizumab, pembrolizumab and nivolumab (non-squamous NSCLC only) are subject to the two year treatment stopping rule.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price for atezolizumab. A PAS is in place for pembrolizumab and nivolumab and these were included in the results used for decision-making by using an estimate of the PAS prices for pembrolizumab and nivolumab.

The base case results using the list price for all medicines, are presented in the tables below, with key sensitivity analyses. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

CMA (atezolizumab versus pembrolizumab and nivolumab)

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

Table 2: SMC preferred base case - CMA assuming all outcome parameters equal for atezolizumab vs pembrolizumab and nivolumab for squamous and non-squamous disease at list price for all medicines

Scenario	Atezolizumab (2 year stopping rule)	Pembrolizumab (2 year stopping rule)	Nivolumab Non-squamous (2 year stopping rule)	Nivolumab Squamous
Assume all outcome parameters equal (OS, PFS, TTD)	£66,102	£67,654	£67,064	£72,971

CUA (atezolizumab versus docetaxel)

The base case analysis estimated an incremental cost effectiveness ratio (ICER) of £74,951 per QALY for atezolizumab (without PAS) compared to docetaxel. Incremental life years and QALY gains were 0.88 and 0.64 respectively with atezolizumab.

Table 3: CUA base case and scenario analyses results atezolizumab versus docetaxel

	Base case / scenario	ICER vs. docetaxel (without PAS for atezolizumab)
B	Base case	£74,951
S1	Treatment switching: RPSFT	£67,643
S2	Docetaxel list price	£68,817
S3	OS mix cure rate:1% cure atezolizumab	£69,863
S4	OS mix cure rate:5% cure atezolizumab	£55,196
S5	OS : log-logistic	£92,464
S6	OS : GenGamma	£111,437
S7	OS : Weibull	£143,366
S8	TTD Weibull	£75,738
S9	TTD KM + GenGamma	£75,182
S10	TTD GenGamma	£75,716
S11	TTD KM + Log-logistic	£77,466
S12	TTD Log-logistic	£79,861
S13	Clinical efficacy vs. doc: FP NMA	£74,148
S14	Utilities: On/Off treatment only	£76,981
S15	Time horizon 20	£76,336
S16	Time horizon 15	£79,590
S17	Time horizon 10	£88,151

Amongst one-way sensitivity analyses undertaken, the principal parameters driving the model results were medicine costs, supportive care costs on and off treatment.

Most of the scenario analyses had relatively little effect on the ICER, but a key area of uncertainty is the extrapolation of OS, PFS and TTD for the lifetime analyses. Alternative assumptions regarding lifetime extrapolation of the OS and TTD curves significantly increase the with PAS ICERs.

The key points of weakness are:

- Clinical expert consensus was that nivolumab is the key comparator for atezolizumab in Scotland and therefore the CMA is the relevant analysis for decision-making. However, there is no direct study evidence comparing atezolizumab with nivolumab, and the NMA using indirect treatment comparisons is subject to methodological issues and considerable uncertainty.

- The suitability of the CMA approach is dependent on acceptance of the company's conclusion as to clinical equivalence or non-inferiority based on the company's ITC. For the CMA analyses equivalence and non-inferiority between the comparators was uncertain. However, on balance, SMC considered that despite the limitations of the ITC it was reasonable to conclude atezolizumab was non-inferior to nivolumab and pembrolizumab.
- The CUA comparing atezolizumab with docetaxel is of interest yet both pembrolizumab and nivolumab have demonstrated OS benefit compared with docetaxel and have now superseded docetaxel as the principal established treatment options.[8] Therefore it should be highlighted that the CUA comparison with docetaxel is of little relevance to the decision making context in Scotland.
- In the CUA the use of the log-logistic model in the base case produces a long tail in the OS for atezolizumab. The OS extrapolation is also based on separate functions for each arm. The implied benefit from treatment in the study period therefore continues to be extrapolated without the treatment effect being explicitly modelled, but continuing indefinitely
- The CUA scenario analyses indicate that the cost per QALY versus docetaxel is extremely sensitive to the choice of distribution for the lifetime extrapolation with alternatives significantly increasing the ICERs.
- The CUA uses the eMIT price for docetaxel as opposed to a published list price. Table 3, details the sensitivity analysis which used the docetaxel list price and is therefore the appropriate base case figure.

The Committee considered the benefits of atezolizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as atezolizumab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted atezolizumab for use in NHS Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 137, management of lung cancer in February 2014.[15]

The National Institute for Health and Care Excellence (NICE) published clinical guideline number 121, Lung cancer: diagnosis and management in April 2011.[16]

Both these guidelines predate the licensing of any checkpoint inhibitor (nivolumab, pembrolizumab or atezolizumab) for the treatment of advanced or metastatic NSCLC and do not reflect current therapy.

The European Society of Medical Oncology published Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2016 and these were updated in 2017. They include recommendations for the PD-1 targeted treatments, nivolumab and pembrolizumab. Nivolumab is recommended in pre-treated patients with advanced squamous cell carcinoma and it is a treatment option in pre-treated patients with advanced non-squamous cell carcinoma. Pembrolizumab is recommended in pre-treated patients with platinum-pre-treated, advanced (squamous or non-squamous cell) NSCLC with PD-L1 expression.[17]

Additional information: comparators

Relevant comparators are nivolumab and pembrolizumab (if tumours express PD-L1).

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Atezolizumab	**1,200mg by IV infusion every three weeks**	**3,808**
Pembrolizumab*	2mg/kg by IV infusion every three weeks	3,945
Nivolumab	3mg/kg by IV infusion every two weeks	2,633

IV=intravenous. Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 28 February 2018. Costs calculated using the full cost of vials/ampoules assuming wastage, and based on 70kg. Costs do not take any patient access schemes into consideration.
**programmed death-ligand 1 expression.*

Additional information: budget impact

The submitting company estimated there would be 1575 patients eligible for treatment with atezolizumab each year from years 1 to year 5.

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.

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This assessment is based on data submitted by the applicant company up to and including 13 April 2018.

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

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 drug 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 NHS Scotland 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 NHS Scotland 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.