Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2279

atezolizumab 1,200 mg concentrate for solution for infusion (Tecentriq®)

Hoffmann-La Roche Ltd

9 October 2020

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

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

atezolizumab (Tecentriq®) is accepted for use within NHSScotland.

Indication under review: Atezolizumab, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

In one randomised, double-blind phase III study, the combination of atezolizumab with carboplatin and etoposide was associated with modest significant improvements in progression free survival and overall survival compared with chemotherapy alone in adult patients with untreated ES-SCLC.

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

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

Vice Chairman
Scottish Medicines Consortium

Indication

In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Dosing Information

During the induction phase, atezolizumab is given as an intravenous infusion at a dose of 1,200mg, followed by carboplatin and then etoposide as intravenous infusion on day 1. Etoposide is also administered as an intravenous infusion on days 2 and 3. This regimen is administered every 3 weeks for four cycles.

The induction phase is followed by a maintenance phase without chemotherapy, in which atezolizumab 1,200mg is administered as an intravenous infusion every 3 weeks. It is recommended that patients are treated with atezolizumab until disease progression or unmanageable toxicity. Treatment beyond disease progression may be considered at the discretion of the physician.

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.

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer.

See the Summary of Product Characteristics for further details.[1]

Product availability date

6 September 2019.

Atezolizumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 7th June 2019 for the indication under review.

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

Summary of evidence on comparative efficacy

Atezolizumab is a humanised monoclonal antibody that binds to programmed death-ligand 1 (PD-L1) and blocks its interactions with the programmed death-1 (PD-1) and B7.1 receptors on tumour cells and/or tumour-infiltrating immune cells. This prevents PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab has received marketing authorisation for use in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).[1, 2]

The key evidence for atezolizumab in this indication comes from IMpower133, an international, multicentre, randomised, double-blind, parallel group phase III study which evaluated the efficacy

of atezolizumab plus carboplatin and etoposide compared with placebo plus carboplatin and etoposide in 403 previously untreated patients with ES-SCLC.[2, 3]

IMpower133 study recruited adult patients with histologically or cytologically confirmed ES-SCLC (as defined according to the Veterans Administration Lung Study Group staging system), measurable ES-SCLC according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 who had not received previous systemic treatment for ES-SCLC. Patients with treated asymptomatic central nervous system (CNS) metastases could participate.[2, 3]

During the induction phase, patients were randomised equally to receive atezolizumab (n=201) or placebo (n=202), each in addition to carboplatin plus etoposide for four, 21-day cycles. Atezolizumab 1,200mg or placebo was given on day 1 intravenously (IV) over 60 minutes. Carboplatin to reach area under the curve (AUC) 5mg/mL/min was administered on day 1 IV over 30-60 minutes, and etoposide 100mg/m^2 IV over 60 minutes was given on days 1, 2 and 3. A maintenance phase followed induction, during which patients continued to receive either atezolizumab or placebo (on day 1 of each 21-day cycle, according to the previous random assignment) until they had unacceptable toxic effects, disease progression according to RECIST, version 1.1, or no additional clinical benefit. No dose modification was allowed in the atezolizumab or placebo treatment but study treatment could be temporarily suspended due to toxicity. Dose modifications were allowed to manage toxicity of carboplatin and etoposide. Blinded study treatment could continue after disease progression until loss of clinical benefit in patients who met pre-specified criteria. Randomisation was stratified according to sex, ECOG performance status (0 or 1) and presence of brain metastases (yes or no).[2, 3]

The two co-primary outcomes were overall survival (defined as the time between date of randomisation and death due to any cause) and investigator-assessed progression-free survival (PFS, defined as the time between date of randomisation to the date of first progression using RECIST v1.1 criteria, or death due to any cause, whichever occurred first). Efficacy analyses were performed in the intent-to-treat (ITT) population, which included all patients who underwent randomisation.[2, 3]

At the time of the primary PFS and interim overall survival analysis (cut-off date April 2018), the two co-primary endpoints were met and the combination of atezolizumab with carboplatin and etoposide was associated with modest significant improvements in PFS and overall survival, compared with placebo plus carboplatin and etoposide. An updated overall survival analysis was performed (cut-off date January 2019) and results are considered exploratory and descriptive. Results for the ITT population are detailed in Table 1.[2, 3]

Table 1: Overall survival and progression free survival results of study IMpower133 (ITT population, n=403)[2, 3]

	Atezolizumab group[a] (n=201)	Placebo group (n=202)	Atezolizumab group (n=201)	Placebo group (n=202)
Data cut-off date	24 April 2018 (primary data cut)		24 January 2019 (exploratory)	
Median duration of follow-up (months)	13.9		22.9	
Overall survival				
Number of deaths	104	134	142	160
Median OS, months	12.3	10.3	12.3	10.3
Stratified HR (95% CI)	0.70 (0.54 to 0.91)		0.76 (0.60 to 0.95)	
p-value (log-rank)	0.007[b]		-	
1-year event-free rate	52%	38%	52%	39%
Progression-free survival				
Number of patients with event	171	189	NR	NR
Median PFS, months	5.2	4.3	NR	NR
Stratified HR (95%)	0.77 (0.62 to 0.96)		NR	NR
p-value (log-rank)	0.017		NR	NR

CI = confidence interval; HR = hazard ratio; NR = not reported; OS = overall survival; PFS = progression-free survival.

[a] Patients in all groups were assigned to receive carboplatin and etoposide in addition to atezolizumab or placebo.

[b] Interim Analysis OS was tested at two-sided α of 0.0193 (with 238 observed OS events at CCOD) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary.

Key secondary endpoints included investigator-assessed objective response rate (ORR, defined as the proportion of patients with either partial response or complete response when assessed using RECIST v1.1) and the duration of response (DoR, defined as the time from the first occurrence of a documented objective response to the time of disease progression or death from any cause on study, whichever occurs first). Confirmed ORR (exploratory endpoint) was numerically lower in patients in the atezolizumab group (60% [121/201]) compared with the placebo group (64% [130/202]) and so not supportive of the results from the primary endpoints. Overall, 2.5% (5/201) patients in the atezolizumab group and 1.0% (2/202) patients in the placebo group had a complete response. The median DoR was 4.2 months versus 3.9 months respectively.[2, 3]

The time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnoea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) was also assessed as secondary endpoint. No clinically meaningful consistent differences in TTD of lung cancer symptoms were observed between the treatment groups.[2, 3]

Summary of evidence on comparative safety

In the IMpower133 study at data cut-off 24 April 2018, the safety population comprised 198 patients who received at least one dose of atezolizumab and 196 patients who received placebo. The median duration of treatment in the atezolizumab group was 4.7 months and in the placebo group was 4.1 months. Treatment emergent adverse events (AEs) were reported in 100% (198/198) of atezolizumab and 96% (189/196) of placebo patients and treatment-related AEs (related to any component of the study regimen) were reported by 95% and 92% of patients respectively. In the atezolizumab and placebo groups respectively, patients reporting a grade 3 or 4 AE were 57% versus 56%, patients with a reported serious AE were 37% versus 35%, and the rate of patients discontinuing any treatment component due to an AE was 11% versus 3%.[3]

The most frequently reported AEs of any grade with a difference in incidence of at least 5% between the atezolizumab and placebo groups were: anaemia (43% versus 35%), nausea (38% versus 33%), decreased appetite (27% versus 18%), hypokalaemia (4% versus 9.2%) and hypothyroidism (10% versus 0.5%). Treatment-related AEs with a difference in incidence of at least 5% between groups were anaemia (39% versus 33%), neutrophil count decreased (18% versus 23%), and decreased appetite (21% versus 13%). There were three treatment-related deaths in each of the atezolizumab and placebo groups. Cause of death in patients treated with atezolizumab was neutropenia, pneumonia and unspecified, and for placebo-treated patients was pneumonia, septic shock and cardiopulmonary failure. [2, 3]

Overall, there were no new safety concerns associated with the use of atezolizumab in combination with carboplatin and etoposide in patients with ES-SCLC, although higher rates of immune-related AEs (40% versus 25%), with the most frequent being rash (19% versus 10%), hypothyroidism (13% versus 0.5%) and hepatitis (7% versus 5%), and treatment withdrawals due to AEs were observed when adding atezolizumab to standard chemotherapy.[2]

Summary of clinical effectiveness issues

Small cell lung cancer (SCLC) represents about 15% of all lung cancers and can be classified into two stages of disease: limited stage (LS) and extensive stage (ES). Of those patients diagnosed with SCLC, approximately 70% have ES-SCLC and survival is extremely poor in this group of patients.

Current guidelines recommend conventional chemotherapy for the first-line treatment of ES-SCLC, generally as a platinum agent plus etoposide for three to six cycles and clinical experts consulted by SMC noted that the combination of carboplatin plus etoposide was mainly used in practice for up to six cycles.[4-6] However, it was accepted that in Scotland the number of cycles of chemotherapy generally given to patients with ES-SCLC is four. Atezolizumab, in combination with carboplatin and etoposide, is the first immunotherapy to be licensed in the EU for the treatment of untreated ES-SCLC. Clinical experts consulted by SMC considered that the combination of atezolizumab plus carboplatin and etoposide fills an unmet need for more effective treatment for ES-SCLC, which is associated with a poor prognosis.

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

Evidence to support the licensed indication for atezolizumab comes from the key study IMpower133, which compared the efficacy and safety of atezolizumab plus carboplatin and etoposide, with placebo plus carboplatin and etoposide as first-line treatment in patients with ES-SCLC. The study met its two co-primary efficacy endpoints (overall survival and PFS) and the combination of atezolizumab with carboplatin and etoposide was associated with a gain of 2 months in overall survival and 0.9 months in PFS compared with chemotherapy alone. The EMA considered the gains to be modest but clinically meaningful given the high unmet medical need.[2, 3]

It is unclear if the effects associated with the addition of atezolizumab to carboplatin and etoposide were related to the induction (four cycles) or maintenance phase. The effects and tolerability of using atezolizumab in combination with carboplatin and etoposide for more than four cycles are unknown.

Clinical experts consulted by SMC suggested that, in practice, patients who respond to carboplatin and etoposide may be treated with consolidation thoracic radiotherapy and prophylactic cranial radiotherapy. During the maintenance phase of study IMpower133, prophylactic cranial radiotherapy and palliative thoracic radiotherapy were permitted (per local standard-of-care). Thoracic radiation with curative intent or the intent to eliminate residual disease was not permitted.[2] One clinical expert consulted by SMC noted that consolidation thoracic radiotherapy would be omitted if atezolizumab was given, because of the risk of pneumonitis. The number of patients in study IMpower133 treated with these radiotherapies was limited, thus, the effects of treating patients with both atezolizumab and these remain unknown.

At the final overall survival analysis (data cut-off 24 January 2019), the median follow-up time was 22.9 months. The Kaplan-Meier survival curves appear to converge after approximately 26 months and therefore the long-term benefit of atezolizumab on overall survival is uncertain.[2] In IMpower133, treatment could continue beyond disease progression until loss of clinical benefit, provided pre-specified criteria (including evidence of clinical benefit and no decline in ECOG performance status) were met. Patients received a median of seven cycles of atezolizumab (range 1 to 30). The benefit of treating patients beyond disease progression is also unclear. A substantial proportion of patients in both treatment groups received subsequent anti-cancer therapy (52% and 57% at April 2018 cut-off) which may have confounded the results. The secondary endpoint of ORR was numerically higher in patients in the placebo group and did not support the results from the primary endpoints.[2, 3] IMpower133 excluded patients with ECOG performance status ≥2 and it is therefore unclear if the results are generalizable to patients with poorer ECOG performance status (≥2) in clinical practice. The study also provided limited evidence for people with brain metastases therefore conclusions cannot be drawn in this population.

Exploratory subgroup analyses of overall survival and PFS were generally consistent with the primary analysis. The EMA noted that conclusions were difficult to draw for some small subgroups of patients, such as patients with brain metastases and with anti-drug antibodies. A retrospective analysis by PD-L1 status in 42% of the ITT population was also conducted, but it did not permit to draw conclusions by PD-L1 immunohistochemistry status.[2]

The available quality of life data from IMpower133 suggested that the addition of atezolizumab to carboplatin and etoposide did not seem to make treatment less tolerable or significantly increase the risk. However, there was a higher incidence of immune-related AEs in the atezolizumab group and more patients discontinued due to AEs.

The introduction of atezolizumab in addition to carboplatin and etoposide would offer patients with previously untreated ES-SCLC an immunotherapy option that has been associated with improved overall survival and PFS.

Clinical experts consulted by SMC generally considered that the combination of atezolizumab plus carboplatin and etoposide was a therapeutic advancement offering improved overall survival. They considered that its place in therapy was in-line with the licensed indication and that there would be service implications to manage immune-related adverse events and due to increased outpatient appointment attendance in chemotherapy units.

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 end of life and orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Extensive-stage small cell lung cancer (ES-SCLC) is an aggressive malignancy with a dismal prognosis. It is severely debilitating with multiple distressing symptoms including breathlessness, chest pain, weight loss and fatigue.
- There is a high unmet need for a more effective first-line treatment option for ES-SCLC. There has been no significant advancement in the treatment for ES-SCLC for over 20 years. First-line standard chemotherapy with carboplatin and etoposide has good response rates, but early relapse is common and response to second-line chemotherapy is poor.
- The addition of atezolizumab to carboplatin and etoposide may offer significantly improved overall survival and progression-free survival compared with carboplatin and etoposide alone. ES-SCLC progression tends to cause a very high burden of symptoms, thus delaying progression with the addition of atezolizumab may have a major impact on quality of life and help maintain patients' independence for longer.
- The addition of atezolizumab to standard chemotherapy may reduce the number of chemotherapy cycles for some patients from up to six to four. There would also be reduced administration of prophylactic cranial radiotherapy and chest radiotherapy, reducing toxicity to the patient, improving quality of life, as well as reducing associated service delivery.
- Although atezolizumab is associated with autoimmune related side effects, immunotherapy is already routinely used in the first (in combination with chemotherapy) and second-line setting for NSCLC, thus clinicians have experience in dealing with these.

Additional Patient and Carer Involvement

We received a patient group submission from the Roy Castle Lung Cancer Foundation, which is a registered charity. The Roy Castle Lung Cancer Foundation has received 7.5% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from the Roy Castle Lung Cancer Foundation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis, which assessed the cost effectiveness of the addition of atezolizumab to carboplatin and etoposide combination therapy compared with carboplatin and etoposide combination therapy alone for the first-line treatment of ES-SCLC. SMC clinical experts indicated that the choice of comparator treatment was appropriate.

The economic model was based on a partitioned survival model structure, comprising of three model health states: PFS, progressed disease (PD) and death. The cycle length assumed in the model was one week, with half cycle correction applied and the time horizon used in the submitting company's base-case analysis was 20 years.

The key clinical data used in the model was PFS and overall survival, obtained from the IMpower133 trial. PFS and overall survival Kaplan-Meier (KM) data from IMpower133 were used to inform independent standard parametric extrapolations to estimate the percentage of patients occupying the PFS and death health states over the time horizon of the model. The submitting company's approach to curve selection was based on statistical goodness of fit, visual inspection of the curves against the observed data and clinical plausibility of long-term survival predications.

Occupation of the PD health state was calculated as the difference between extrapolated overall survival and PFS per model cycle. Time on treatment (ToT) based on data from IMpower133 was included in the model to estimate the proportion of patients on or off atezolizumab treatment in any given model cycle. In IMpower133, treatment with atezolizumab was permitted beyond disease progression if there was evidence of clinical benefit. Treatment with carboplatin and etoposide in either arm of the model was restricted to four cycles.

For the base case analysis, extrapolation of PFS was based on KM data and an extrapolated tail using the log-logistic distribution from the point at which 10% of patients are at risk. For overall survival, KM data was also used directly up to month 20 and then a log-logistic extrapolation was implemented for the remainder of the time-horizon. Survival estimates at 60 months for the overall survival were 2.18% for the comparator and 4.70% for the intervention arm.

The submitting company included an assumption about the duration of treatment effect for atezolizumab, by implementing a treatment effect cap of 60 months. ToT was extrapolated using a hybrid of KM data and the generalised gamma distribution from the point at which 10% of patients remain at risk.

Health benefits were measured in quality adjusted life years (QALYs) and utilities were based on EQ-5D-5L data obtained directly from IMpower133 and converted into EQ-5D-3L values using the crosswalk algorithm. In the economic model, a time to death approach was used to estimate the decline in health-related quality of life over time as a patient neared death and were further stratified by being on or off treatment. The submitting company also included disutilities associated with treatment-related grade 3-5 AEs.

In the base-case analysis, the costs of medicine acquisition and administration costs, subsequent treatment, adverse event treatments and terminal care costs were included in the model. Etoposide in the intervention arm was costed as an IV intervention, in line with how it was administered in IMpower133. However, for the comparator arm, etoposide has been costed as an oral intervention as per Scottish clinical practice.

The cost of prophylactic cranial irradiation (PCI) was included in the economic model for patients who are in the PFS health state, irrespective of treatment arm. Furthermore, the costs of outpatient visits, GP visits, nurse visits and monitoring associated with patients being on treatment with atezolizumab plus carboplatin and etoposide, carboplatin and etoposide or atezolizumab monotherapy and routine surveillance only were also included in the model.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount is offered on the list price of the medicine.

The results of the base case analysis and key scenario analyses are shown below.

Table 2: Company's deterministic base case results with atezolizumab PAS

Treatment	Incremental LYG	ICER (£/QALY)
Atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide	0.36	£31,910
ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years		

Table 3: Key scenario analyses with PAS

Scenario	Base case setting	Scenario setting		ICER (PAS price)
Base case	N/A	N/A		£31,910
Survival extrapolation	PFS – KM + log-logistic extrapolation (10% at risk)	1	PFS - Log-logistic extrapolation for entire time horizon	£31,899
	OS – KM + log-logistic extrapolation (20-month cut-off)	2	OS - Log-logistic extrapolation for entire time horizon	£36,228
		3	OS - Restricted cubic spline model one knot odds	£38,571
Treatment effect cap	60 months	4	36 months	£33,695
Utilities	Time to death categories: ≤ 5 weeks before death > 5 & ≤ 15 weeks before death > 15 weeks & ≤ 30 weeks before death > 30 weeks before death	5	One week earlier for each category	£32,791
		6	One week later for each category	£32,692
Administration of etoposide for intervention arm	IV etoposide	7	Oral etoposide	£25,910
Vial sharing	Yes	8	No	£31,920
Treatment cycles of carboplatin and etoposide	4 cycles	9	6 cycles	£31,839
Combined analysis	- OS – KM + log-logistic extrapolation (20-month cut-off) - Treatment cap of 60 months - IV etoposide for intervention arm	10	Combination of scenarios 2, 4, 7	£31,394

ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; N/A = not applicable; OS = overall survival; PAS = patient access scheme; PFS = progression free survival.

The submission was subject to the following limitations:

- As noted in the clinical effectiveness section above, IMpower133 included only patients with good performance status (ECOG score of 0 or 1). As such, the results of the cost-effectiveness analysis may not be applicable to patients with poorer performance status (ECOG scores greater than 1).
- In IMpower133, carboplatin and etoposide was given for a maximum of four cycles. According to SIGN guidelines, carboplatin and etoposide can be given for a maximum of six cycles and one SMC clinical expert stated that this would happen in Scottish clinical practice if the patient is responding to treatment.[4] However, local data suggests a median of 4 cycles is likely to reflect the company's base case regimen and can be considered reflective of current clinical practice. The submitting company did explore a scenario implementing the costs of six cycles of treatment with carboplatin-etoposide in the model, but this had a minimal impact on the ICER (scenario 9).
- For PFS and overall survival, implementation of the log-logistic extrapolation for the entire model duration instead of a hybrid of KM data and log-logistic tail is considered more appropriate in terms of best practice. Given the OS data are relatively mature the hybrid approach in the base case is not unreasonable, but it is helpful to see the effect of applying the extrapolation over the entire model period. This is not a significant issue for PFS, as changes to the assumptions do not produce any substantial changes to the ICER. However, switching to the log-logistic extrapolation for overall survival for the entire model duration increases the ICER by approximately £4,000 (table 3 scenario 2).
- The company's assumption of a treatment cap is considered reasonable and in line with other immunotherapy appraisals. However, the cut-off point of 60 months is uncertain as no long-term data exist on the duration of treatment effect. Instead capping the treatment effect to the end of trial follow up may be appropriate, especially as the IMpower133 KM curves for overall survival presented in the company submission appear to converge towards the end of follow up. However the company note that the convergence of the KM overall survival curves should be interpreted with caution as there is a high degree of censoring. The submitting company explored different cut-off points in scenario analyses and found that assuming a treatment cap of 36 months (the closest scenario to the trial follow up) increased the ICER by approximately £2,000 (table 3 scenario 4). While this may be conservative, it is helpful in showing the impact of the uncertainty associated with the treatment cap assumption.
- In IMpower133, etoposide was administered as an IV treatment and was costed as such in the atezolizumab arm of the base case model. However, in Scottish clinical practice, etoposide would be given as an oral treatment for patient convenience. The submitting company provided a scenario where oral etoposide is used for both arms of the model for days 2 and 3, which resulted in the ICER reducing by £6,000 (table 3 scenario 7).
- Use of vial sharing is likely to be limited in Scottish clinical practice. However, a scenario removing the vial sharing assumption had minimal impact on the ICER (table 3 scenario 8).

- Subsequent therapy data was obtained from IMpower133 and use of second-line immunotherapy was recorded in both arms of the trial (approximately 3% and 9% for the intervention and comparator arm, respectively). SMC clinical experts have indicated that in Scottish clinical practice, it is unlikely second-line immunotherapy would be given after atezolizumab combination therapy or carboplatin-etoposide. However, as the analysis is based on data from IMpower133, efficacy and costs are appropriately balanced. Furthermore, scenario analyses supplied by the company demonstrated that the economic model was not sensitive to changes in subsequent treatment costs.
- The combined scenario presented in Table 3, which incorporates the overall survival log-logistic extrapolation for the entire time horizon, treatment effect cap of 36 months and oral etoposide costs for both arms of the model, may represent the most plausible ICER at £31,394 per QALY.

The Committee also 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 the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as atezolizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

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

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

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 137 Management of lung cancer in February 2014. The guideline recommends a regimen containing a platinum agent and etoposide for first-line treatment of patients with SCLC for three to six cycles. Combination systemic anti-cancer therapy should be considered for patients with SCLC over 70 years with performance status of 0 to 2. Maintenance systemic anticancer therapy following first-line treatment is not recommended.[4]

The National Institute for Health and Care Excellence (NICE) published NICE NG122 - Lung cancer: diagnosis and management in March 2019. This recommends platinum-based combination chemotherapy for up to six cycles to people with ES-SCLC if they are fit enough, and that maintenance treatment should only be offered to people with SCLC in the context of a clinical trial.[5]

The European Society for Medical Oncology (ESMO) also published in 2013 guidelines for SCLC recommending four to six cycles of etoposide plus cisplatin or carboplatin as first-line treatment of ES-SCLC.[6]

In March 2020, the National Comprehensive Cancer Network (NCCN) published an updated version of its SCLC clinical practice guideline. This recommends as the first preferred regimen for the primary or adjuvant treatment of patients with ES-SCLCL, the combination of atezolizumab with carboplatin and etoposide, for a maximum of four to six cycles, followed by maintenance with atezolizumab. Other preferred options include carboplatin/cisplatin and etoposide alone or in combination with durvalumab.[7]

Additional information: comparators

Atezolizumab is used in combination in addition to current standard of care (which is up to six cycles of etoposide plus platinum) and can be continued as monotherapy in maintenance.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
Atezolizumab	**1,200mg administered by intravenous infusion every 3 weeks (four-cycle induction phase, followed by maintenance phase).**	**3,808**

Costs from BNF online on 2 June 2020. Costs calculated using the full cost of vials. The duration of a cycle is 3 weeks. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 15 patients estimated to receive treatment in year one rising to 159 patients in year five. Responses from SMC clinical experts suggested there is variation in the expected size of the patient population.

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.

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

References

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6. Früh M, De Ruysscher D, Popat S, Crinò L, Peters S, Felip E. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi99-105. Epub 2013/07/03.

7. Network NCC. NCCN Guideline with NCCN Evidence Blocks™ - Small Cell Lung Cancer Version 3.2020. 2020 [cited 2020 Feb 10]; Available from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/sclc_blocks.pdf.

This assessment is based on data submitted by the applicant company up to and including 14 August 2020**.**

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

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises

NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

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

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