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

04 October 2019

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 considered under the end of life medicine process:

**atezolizumab (Tecentriq®)** is not recommended for use within NHSScotland.

**Indication under review:** In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.

In a phase III study, the addition of atezolizumab to bevacizumab, carboplatin and paclitaxel was associated with an increase in median progression-free survival in patients with metastatic non-squamous NSCLC.

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

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

**Chairman**
**Scottish Medicines Consortium**
Indication
In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.¹

Dosing Information
During the induction phase, the recommended dose of atezolizumab is 1,200mg administered by intravenous infusion, followed by bevacizumab, paclitaxel, and then carboplatin every three weeks for four or six cycles. 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.

The induction phase is followed by a maintenance phase without chemotherapy in which 1,200mg atezolizumab followed by bevacizumab, is administered by intravenous infusion every three weeks. Please also refer to the full prescribing information for the other medicines in the regimen. It is recommended that patients are treated with atezolizumab until loss of clinical benefit or unmanageable toxicity.

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer. Further details are included in the summary of product characteristics (SPC).¹

Product availability date
5 March 2019
Atezolizumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 27 December 2018 (EAMS number 00031/0005). The indication was in combination with bevacizumab, paclitaxel and carboplatin for the treatment of adult patients with metastatic NSCLC with EGFR activating or ALK-positive tumour mutations after failure of appropriate targeted therapies.
Atezolizumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy
Atezolizumab is a humanised immunoglobulin G1 (IgG1) 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 stops PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity.¹ Atezolizumab has previously been accepted for restricted use by SMC as monotherapy in patients with locally advanced or metastatic NSCLC after prior chemotherapy. It
has now been licensed for use in metastatic non-squamous NSCLC when given in combination with bevacizumab, paclitaxel and carboplatin as first line treatment. In patients with epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC it can be used once appropriate targeted therapies have failed.

The submitting company has requested that SMC considers atezolizumab for use
- in patients whose tumours express PD-L1 tumour proportion score (TPS) between 0 and 49%, and/or
- patients with EGFR/ALK mutation positive disease and appropriate targeted therapies have failed.

Key evidence for this indication is from IMpower150, an open-label, active-controlled, randomised, phase III study. The study recruited adult patients with stage IV or recurrent metastatic non-squamous NSCLC, classified according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1), who had not previously been treated with chemotherapy. Patients were required to have a baseline Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients with any PD-L1 immunohistochemistry status were eligible. Those with EGFR/ALK genomic alterations were only included if they had disease progression or unacceptable adverse effects with at least one appropriate tyrosine kinase inhibitor.

Patients were randomised equally to receive intravenous infusions of atezolizumab plus carboplatin plus paclitaxel (n=402), atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (n=400, the atezolizumab licensed combination group), or bevacizumab plus carboplatin plus paclitaxel (n=400, known as the control group hereafter). Randomisation was stratified by sex, presence/absence of liver metastases at baseline, and PD-L1 tumour expression. Induction treatment with the combination regimens above was administered by intravenous infusion for four or six 21-day cycles (number of cycles determined by investigator before randomisation) at the following doses: atezolizumab 1,200mg, bevacizumab 15mg/kg, paclitaxel 200mg/m² body surface area (BSA), and carboplatin at an area under the concentration-time curve of 6mg/mL/minute. After the induction phase, patients continued to receive maintenance treatment with atezolizumab, bevacizumab or both. Treatment continued until disease progression or unacceptable toxicity however atezolizumab could be continued after progression if there was evidence of clinical benefit. No crossover was allowed. Atezolizumab plus carboplatin plus paclitaxel is not a licensed treatment and this group is not discussed further.

The first co-primary outcome was investigator assessed progression-free survival (PFS) according to RECIST v1.1 in patients in the intention-to-treat population (ITT) who had a wild-type (WT) genotype (patients with EGFR or ALK genomic alterations were excluded), and patients in the ITT-WT population who had high tumour expression of an effector T-cell (Teff) gene signature. The Teff gene signature is defined by the average mRNA expression of PD-L1, CXCL9, and IFN-γ genes, normalised to a reference gene. It is a surrogate for both PD-L1 expression and a pre-existing
immunity within the tumour microenvironment. Overall survival assessed in the ITT-WT population was the second co-primary outcome.\textsuperscript{2, 3}

At the time of the primary PFS analysis (15 September 2017, minimum duration of follow-up 9.5 months), in the ITT-WT population, 68% (241/356) of patients had disease progression or died in the atezolizumab licensed combination group compared with 82% (276/336) of the control group. Median PFS was significantly longer in the atezolizumab licensed combination group than in the control group.\textsuperscript{2} In the Teff-high WT population, 63% (97/155) of patients in the atezolizumab licensed combination group and 80% (103/129) of the control group had disease progression or died. Median PFS was also significantly longer in the atezolizumab licensed combination group than in the control group.\textsuperscript{2} See table 1 for results.

At the second interim analysis of overall survival (22 January 2018) in the ITT-WT population the minimum duration of follow-up was approximately 14 months. Death had occurred in 50% (179/359) of the atezolizumab licensed combination group compared with 58% (197/337) of the control group. Overall survival was significantly longer in the atezolizumab licensed combination group than in the control group.\textsuperscript{2, 3}

Key secondary outcomes included investigator assessed PFS and overall survival in the ITT population (all enrolled patients, including those with EGFR or ALK genomic alterations [the licensed indication]). In the ITT population, PFS was longer in the atezolizumab licensed combination group than the control group.\textsuperscript{2} At the time of the interim analysis of overall survival in the ITT population (22 January 2018), 48% (192/400) of patients in the atezolizumab licensed combination group and 58% (230/400) of patients in the control group had died. Overall survival was longer in the atezolizumab licensed combination group than in the control group. Patients are being followed up for the final analysis of overall survival.\textsuperscript{3}

For the subgroups of patients with low or negative PD-L1 expression (n=557) and the subgroup with EGFR or ALK genomic alterations (n=108), results were consistent with the ITT population for PFS and overall survival.\textsuperscript{2, 3}
Table 1: Selected outcomes from IMpower150.\textsuperscript{2,3}

<table>
<thead>
<tr>
<th></th>
<th>atezolizumab plus bevacizumab plus carboplatin plus paclitaxel</th>
<th>bevacizumab plus carboplatin plus paclitaxel</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median PFS (months) in WT-ITT population</td>
<td>8.3</td>
<td>6.8</td>
<td>0.62 (0.52 to 0.74)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Median PFS (months) in Teff-high population</td>
<td>11.3</td>
<td>6.8</td>
<td>0.51 (0.38 to 0.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Median overall survival (months) in WT-ITT population</td>
<td>19.2</td>
<td>14.7</td>
<td>0.78 (0.64 to 0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.02</td>
</tr>
<tr>
<td><strong>Selected key secondary outcome</strong></td>
<td></td>
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</tr>
<tr>
<td>Median PFS (months) in ITT population</td>
<td>8.3</td>
<td>6.8</td>
<td>0.61 (0.52 to 0.72)*</td>
</tr>
<tr>
<td>Median overall survival (months) in ITT population</td>
<td>19.8</td>
<td>14.9</td>
<td>0.76 (95% CI: 0.63 to 0.93)*</td>
</tr>
</tbody>
</table>

*provided for descriptive purpose only. CI = confidence interval, PFS = progression-free survival, WT = wild-type, ITT = intention-to-treat.

Health related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 and -LC13 questionnaires. At baseline, all groups reported moderately impaired HRQoL. The results suggest that mean scores return to baseline after chemotherapy and numerically improve after that. Similar results were observed across groups. A clinically meaningful worsening (≥10 point increase from baseline) was observed across groups for both patient-reported peripheral neuropathy and alopecia. Initially large increases were observed in all treatment groups and reduced over time at similar time points across groups.\textsuperscript{3}

A Bayesian network meta-analysis of five studies was conducted to compare atezolizumab plus bevacizumab plus carboplatin plus paclitaxel with pemetrexed plus platinum with or without pemetrexed maintenance in patients with metastatic NSCLC previously untreated with chemotherapy. Outcomes assessed were overall survival, PFS, objective response rate (ORR) and adverse events leading to discontinuation. The point estimates favoured atezolizumab plus bevacizumab plus carboplatin plus paclitaxel over pemetrexed plus platinum with or without pemetrexed maintenance for PFS, overall survival and ORR. However, the credible intervals were wide and, for overall survival, included zero suggesting no difference. The results for the outcome ‘adverse events leading to discontinuation’ favoured pemetrexed plus platinum with or without pemetrexed maintenance.
Summary of evidence on comparative safety

The European Medicines Agency (EMA) observed that atezolizumab plus bevacizumab plus carboplatin plus paclitaxel was tolerable but had a notably worse safety profile than the other treatment arms in IMpower150. The atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (atezolizumab licensed combination) group and the bevacizumab plus carboplatin plus paclitaxel (control) group only are discussed below.

Treatment-related adverse events (as determined by the investigator) occurred in 94% of the patients in the atezolizumab licensed combination group and in 95% of the control group. Serious treatment-related adverse events were reported in 25% of the patients in the atezolizumab licensed combination group and in 19% of the control group. Adverse events leading to dose modification/interruption and leading to treatment withdrawal occurred in 63% and 34% of the atezolizumab licensed combination group and 48% and 25% of the control group. The most commonly reported treatment related adverse events were alopecia, peripheral neuropathy, nausea, fatigue, anaemia, decreased appetite, diarrhoea and neutropenia. The most common grade 3 or 4 treatment related adverse events were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension.

Treatment related adverse events that occurred more commonly in the atezolizumab licensed combination group included rash, stomatitis, febrile neutropenia, and haemoptysis. The most common immune related adverse events were rash (29% and 13%), hepatitis (12% and 7.4%), hypothyroidism (13% and 3.8%), hyperthyroidism (4.1% and 1.3%), pneumonitis (2.8% and 1.3%) and colitis (2.3% and 0.5%). Patients with NSCLC that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the IMpower150 after several cases of fatal pulmonary haemorrhage were observed.

Summary of clinical effectiveness issues

First-line treatment for patients with metastatic NSCLC, without EGFR mutations or ALK translocation, can include platinum-based chemotherapy and pemetrexed, followed by pemetrexed maintenance therapy if appropriate. Pembrolizumab as monotherapy is also accepted for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with ≥50% TPS with no EGFR or ALK positive tumour mutations. Approximately 10 to 15% of patients with NSCLC have an EGFR mutation and 2% to 6% have ALK translocation, both mutations are oncogenic drivers in NSCLC. These patients receive initial treatment with targeted therapies such as afatinib, erlotinib (EGFR mutation), crizotinib or alectinib (ALK translocation), and usually second line treatment with platinum-based chemotherapy. Overall survival for patients with metastatic NSCLC treated with platinum based chemotherapy plus pemetrexed followed by pemetrexed maintenance has been reported as 10.5 to 14 months. Atezolizumab for this indication meets SMC end of life criteria.
In the key IMpower150 study, the addition of atezolizumab to bevacizumab, carboplatin and paclitaxel was associated with a significantly longer median PFS in the ITT-WT population of patients with metastatic non-squamous NSCLC. The EMA suggest that this difference of 1.5 months is clinically relevant. Similar results for PFS were observed in the full ITT population, including patients with EGFR mutations or ALK translocations, relevant to the licensed indication. Addition of atezolizumab was associated with an increased median PFS in the EGFR mutations or ALK translocations subgroup and the subgroup of patients with low or negative PD-L1 expression, relevant to the proposed positioning. The subgroup of patients with EGFR/ALK mutations was small and the study was not stratified by EGFR/ALK status.

Overall survival was included as a co-primary outcome and is a direct health outcome. A statistically significant difference favouring the atezolizumab licensed combination group was observed in the ITT-WT primary outcome populations but when considering the full study period (the whole Kaplan Meier curve, not just the median) the EMA considered that difference between groups was not clinically relevant. Treatments received after progression could confound overall survival results. Statistical significance in the ITT population could not be provided due to a non-significant difference for a preceding comparison the hierarchical multiple testing sequence. In the subgroups of patients with low or negative PD-L1 expression and those with EGFR/ALK genomic alterations the results suggest an overall survival advantage in the atezolizumab licensed combination group compared with the control group. 

The study had an open-label design which could bias patient reported outcomes such as HRQoL outcomes and adverse events. Patients with significant cardiovascular disease, inadequately controlled hypertension and those taking clopidogrel were excluded from the study. Patients were required to have an ECOG performance status of 0 or 1; there is no information about the efficacy or tolerability in patients with a poorer performance status. There was a limited numbers of patients aged ≥75 years included in the study and treatment effect size in this group is uncertain.

The network meta-analysis comparing atezolizumab plus bevacizumab plus carboplatin plus paclitaxel to pemetrexed plus platinum with or without pemetrexed maintenance was associated with a number of limitations. The indirect comparison was conducted in the population of patients that matched the licensed indication, not the positioning proposed by the company. Although the efficacy results PFS and ORR favour atezolizumab plus bevacizumab plus carboplatin plus paclitaxel over pemetrexed plus platinum with or without pemetrexed maintenance, the inclusion of small underpowered studies at increased risk of bias and the variation in results in the common control arms of included studies, reflecting clinical and methodological differences, suggest the results of the indirect comparison are highly uncertain. Adverse events leading to discontinuation were more likely in the atezolizumab plus bevacizumab plus carboplatin plus paclitaxel group.

The introduction of atezolizumab in combination with bevacizumab, carboplatin and paclitaxel may provide an additional treatment option for patients with metastatic NSCLC, who usually
undergo rapid clinical deterioration during disease progression, with many not receiving second line treatment.³

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 medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic NSCLC is a devastating, life-limiting illness. Symptoms can include cough, breathlessness, weight loss, chest pain, and fatigue. A diagnosis of metastatic NSCLC may also have a significant psychological impact on patients.

- There is unmet need in patients with metastatic NSCLC as outlook is poor and those with disease as described by the company’s proposed positioning currently do not have access to immunotherapy. Patients are likely to receive pemetrexed and carboplatin, potentially followed by pemetrexed maintenance therapy.

- If this treatment improved time without progression it may give patients more time without further symptoms. This could also have a psychological benefit and improve their quality of life. It would give patients an additional treatment option and access to immunotherapy at this stage in their treatment pathway which may be particularly relevant for patients with EGFR mutation positive NSCLC.

- The introduction of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin would have significant service implications and patients would need to spend more time in hospital to receive their treatment.

- Atezolizumab is given in combination with a regimen that is not the current standard of care in Scotland and would therefore be a change in practice. The complexity of this four-medicine regimen should also be considered. This treatment is associated with significant toxicity but patients may feel that potential adverse events are manageable.

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 7.5% 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, including 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.
The submitting company presented a cost-utility analysis comparing the atezolizumab licensed combination group versus pemetrexed plus platinum with pemetrexed maintenance therapy. Pemetrexed plus platinum without maintenance was also considered. The analysis was based on subgroup-specific analyses of the atezolizumab licensed combination group in patients with low or negative PD-L1 tumour burden (TPS between 0 and 49%), and/or ALK/EGFR positive mutations who have failed appropriate targeted therapies.

In each analysis a standard three-state partitioned survival model was employed, with states of PFS, post-progression, and death, over a lifetime (20 years) time horizon.

A two-year stopping rule was applied in the model, with treatment effects assumed to apply for a maximum of five years in the base case. Patients entering the analysis were assumed to be 63 years of age with average body surface area of 1.81m² and weight 71.9kg based on the clinical study.

The choice of base case distribution for the OS, PFS, and time to treatment discontinuation (TTD) endpoints was based on goodness of fit and corroboration of extrapolation with external data. The submitting company drew on UK National Lung Cancer Audit data and the United States Flatiron retrospective study’s 5-year survival estimates of 8-12% in selecting the base case OS distribution. The log-logistic was preferred as the base case in both the low/negative PD-L1 and EGFR/ALK positive groups based on agreement of estimates in the overall study population with the estimate from the UK audit data for the pemetrexed based arm, and clinical advice for the atezolizumab licensed combination arm. The log-logistic was favoured on similar grounds for PFS, however, parametric extrapolation was applied only in modelling the tail (≤20% PFS) in the PD-L1 group. In the EGFR/ALK positive analysis parametric analysis was employed over the whole time horizon because of the smaller sample size in this group. For TTD an exponential extrapolation was attached to KM data for the atezolizumab licensed combination. Duration of chemotherapy components in the atezolizumab licensed combination were based directly on IMpower150 KM data. Time on treatment was proxied in the chemotherapy arm by modelled PFS.

Survival in the comparator arm was modelled based on application of time dependent hazard ratios to the atezolizumab licensed combination hazards. These hazard ratios were based on the network meta-analysis, which excluded the PARAMOUNT study that compared outcomes in the pemetrexed maintenance phase only. The analysis was based on the overall IMpower150 population (there were no significant subgroup effects in IMpower150 and the EGFR/ALK sample size was small). Hazard ratios for PFS favoured atezolizumab licensed combination over all time points and were significant. As noted above for OS, point estimates favoured atezolizumab licensed combination but were not significant. Treatment effects were applied for up to 5 years; beyond this period hazards from the comparator arm were adopted (that is, HR-1.00).
Health state utilities for the model were based on IMpower150 EuroQol EQ-5D data, with estimates derived according to time to death. Estimates were pooled across arms for the base case based on the absence of statistically significant differences between arms. Time intervals (before death) were ≤5 weeks, >5 & ≤15 weeks, >15 & ≤30 weeks and >30 weeks (health state utility range 0.52-0.73). Alternative estimates based on progression (using IMpower150 data and secondary sources), and alternative time to death estimates sourced from a previous SMC assessment were also considered. No adjustment for general population age-related quality of life was applied. An average utility decrement due to adverse events was estimated from the IMpower150 data and applied in the model base case.

Costs included medicine acquisition and administration costs, including those related to subsequent therapies, monitoring and management of disease, adverse events and terminal care. The model base case assumed equal proportions of patients would receive subsequent therapies following progression, but with the composition of these depending on initial treatment arm. Following atezolizumab licensed combination all subsequent therapy was assumed to be docetaxel, whereas following pemetrexed based regimens approximately 25% and 55% was assumed to be nivolumab and pembrolizumab respectively (the remainder docetaxel). Monitoring and disease management costs were based on NICE guidelines and previous technology appraisals with separate estimates of resource use for the pre- and post- progression disease stages.

Patient Access Schemes (PAS) were submitted by the company for both atezolizumab and bevacizumab and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. PAS discounts are also in place for nivolumab and pembrolizumab, which, due to the different compositions of subsequent therapies, may impact the cost-effectiveness analyses and as such were included in the results used for decision-making by using estimates of the comparator PAS discounts. However, the results presented in table 2 do not take account of the PAS for nivolumab or pembrolizumab. 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.

Table 2: Results base-case: Atezolizumab licensed combination versus pemetrexed with maintenance (with all relevant PAS discounts, and excluding subsequent therapy PAS discounts)

<table>
<thead>
<tr>
<th>Atezolizumab licensed combination versus Pemetrexed+platinum+ maintenance:</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low or negative PD-L1 tumour burden population</td>
<td>17,995</td>
</tr>
<tr>
<td>ALK/ EGFR positive mutations population</td>
<td>23,528</td>
</tr>
</tbody>
</table>

The company also presented results for the overall population, which were broadly consistent with the subgroup results reported in Table 2. A range of sensitivity analyses and scenario analyses were provided and some key results are noted in table 3.
**Table 3: Scenario analyses (with all relevant PAS discounts, and excluding subsequent therapy PAS discounts)**

<table>
<thead>
<tr>
<th></th>
<th>ICER (£/QALY)</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low/negative PD-L1</td>
<td>EGFR/ALK</td>
</tr>
<tr>
<td>Base case</td>
<td>17,955</td>
<td>23,528</td>
</tr>
<tr>
<td>PFS exponential</td>
<td>20,698</td>
<td>25,392</td>
</tr>
<tr>
<td>OS exponential</td>
<td>22,260</td>
<td>29,682</td>
</tr>
<tr>
<td>Nafees utilities</td>
<td>21,168</td>
<td>28,433</td>
</tr>
<tr>
<td>Treat until progression</td>
<td>21,937</td>
<td>26,337</td>
</tr>
<tr>
<td>Pemtrexed without</td>
<td>25,000</td>
<td>24,464</td>
</tr>
<tr>
<td>maintenance</td>
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</tbody>
</table>

Scenario analyses were also provided to reflect the inclusion of generic chemotherapies at eMIT prices. These results were provided for information only as SMC process requires results based on list prices or accepted PAS prices.

There were a number of weaknesses associated with the analysis:
- As noted above, there were a range of weaknesses associated with the indirect comparison. In particular, it is noted that the overall survival estimate was very uncertain with the credible interval including one. Sensitivity analysis indicated that there was sensitivity in the ICER to changes in the predicted overall survival benefits of treatment.
- The economic analyses were based on subgroups of the IMpower150 study population.
- With regard to the ALK/EGFR subgroup, while the group was pre-specified it should be noted that the sample size in this subgroup is small.

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 met.

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

*Other data were also assessed but remain confidential.*

**Additional information: guidelines and protocols**

The National Institute for Health and Care Excellence (NICE) published Lung cancer: diagnosis and management (NG 122) in March 2019. The guidance makes recommendations for patients with non-squamous non-small-cell lung cancer, stages IIIB and IV. It advises initial treatment with tyrosine kinase inhibitors (TKIs) for patients with EGFR tyrosine kinase mutations (afatinib, erlotinib and gefitinib) or ALK-positive gene rearrangement (crizotinib, ceritinib and alectinib).
After progression on first line TKI, second line TKIs are recommended for some EGFR mutations (osimertinib) and ALK mutations (ceritinib and brigatinib). On progression following treatment with TKIs (or treatment of those without EGFR or ALK mutations), treatment options include pemetrexed plus carboplatin or other platinum doublet with or without pemetrexed maintenance therapy. Pembrolizumab, with pemetrexed and platinum chemotherapy is recommended for use within the Cancer Drugs Fund, as a first-line option for in patients without EGFR/ALK mutations. Atezolizumab, nivolumab, pembrolizumab, nintedanib plus docetaxel or docetaxel monotherapy are treatment options following progression after first-line chemotherapy.

The European Society for Medical Oncology (EMSO) published a clinical practice guideline for the diagnosis, treatment and follow-up of metastatic NSCLC in 2018. These were broadly in line with the NICE guidelines.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 137, Management of lung cancer in February 2014. The guidance recommends that patients who have advanced NSCLC and who have a sensitising EGFR mutation, first line single agent tyrosine kinase inhibitors should be offered. For patients with advanced non-squamous NSCLC, are performance status 0 to 1, and are EGFR mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed. All other patients with NSCLC should be offered combination systemic anticancer therapy with cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine). A Second line treatment with pemetrexed should be considered for patients with advanced non-squamous NSCLC who have been previously treated with first line chemotherapy for advanced disease.

### Additional information: comparators

Platinum-based chemotherapy and pemetrexed, followed by pemetrexed maintenance therapy if appropriate.

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atezolizumab</td>
<td>1,200mg by IV infusion</td>
<td>6,083 to 7,250</td>
</tr>
<tr>
<td>+ bevacizumab</td>
<td>7.5mg/kg or 15mg/kg of body weight by IV infusion</td>
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<tr>
<td>+ paclitaxel</td>
<td>175mg/m$^2$ IV infusion</td>
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<tr>
<td>+ carboplatin</td>
<td>Target area under the curve (AUC) 6, by IV infusion</td>
<td></td>
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<tr>
<td></td>
<td>All doses administered on day 1 of 3 week cycle for 4 cycles</td>
<td></td>
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<tr>
<td>pemetrexed</td>
<td>500mg/m$^2$ by IV infusion</td>
<td>1,332 to 1,418</td>
</tr>
<tr>
<td>+ cisplatin</td>
<td>75mg/m$^2$ by IV infusion</td>
<td></td>
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</tbody>
</table>
or carboplatin Target area under the curve (AUC) 5, by IV infusion
All doses administered on day 1 of 3 week cycle for 4 cycles

Maintenance regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Details</th>
<th>Cost Range</th>
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<tbody>
<tr>
<td>atezolizumab bevacizumab</td>
<td>1,200mg by IV infusion 7.5mg/kg or 15mg/kg of body weight by IV infusion Both administered on day 1 of 3 week cycle, continued until loss of clinical benefit/intolerance</td>
<td>5,217 to 6,384</td>
</tr>
<tr>
<td>pemetrexed</td>
<td>500mg/m² by IV infusion, administered on day 1 of 3 week cycle, continued until progression/intolerance</td>
<td>1,260</td>
</tr>
</tbody>
</table>

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 8 July 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Doses were calculated assuming adult weighing 70kg, body surface area of 1.8m² and glomerular filtration rate of 60ml/min. IV: intravenous*

Additional information: budget impact

The submitting company estimated there would be 466 patients eligible for treatment with atezolizumab in year 1, rising to 478 by year 5 to which confidential estimates of treatment uptake were applied.

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

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


This assessment is based on data submitted by the applicant company up to and including 16 August 2019.

*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.