NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using atezolizumab with carboplatin and etoposide in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2019

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using atezolizumab with carboplatin and etoposide in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 28 January 2020

Second appraisal committee meeting: 18 February 2020

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Atezolizumab with carboplatin and etoposide is not recommended, within its marketing authorisation, for untreated extensive-stage small-cell lung cancer in adults.

1.2 This recommendation is not intended to affect treatment with atezolizumab, with carboplatin and etoposide, that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with untreated extensive-stage small-cell lung cancer have carboplatin and etoposide chemotherapy as their first treatment. Clinical trial evidence is in people with good performance status (they are more able to do daily tasks and ordinary activities than those with poorer performance status). It suggests that atezolizumab with chemotherapy could help people to live longer without their disease progressing, and to live for longer compared with chemotherapy alone. However, people in the NHS in England are likely to have poorer performance status than people in the trial.

There are uncertainties about how long people having atezolizumab live. These include how well the modelled curves fit the trial data and how well they predict long-term survival, with more flexible models fitting the trial data better. So, the cost-effectiveness estimates comparing atezolizumab and chemotherapy with chemotherapy alone are highly uncertain.

Atezolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. Even so, the cost-effectiveness estimates for atezolizumab with chemotherapy are higher than what is considered a cost-effective use of NHS resources. So, atezolizumab with carboplatin

and etoposide is not recommended for untreated extensive-stage small-cell lung cancer.

2 Information about atezolizumab with carboplatin and etoposide

Marketing authorisation indication

2.1 Atezolizumab (Tecentriq, Roche) with carboplatin (generic) and etoposide (generic) is indicated for 'the first-line treatment of adult patients with extensive-stage small-cell lung cancer (ES-SCLC)'.

Atezolizumab received a promising innovative medicine (PIM) designation in November 2018 and a positive opinion from the early access to medicines scheme (EAMS) in June 2019.

Dosage

2.2 Induction phase, every 3 weeks for 4 cycles:

- atezolizumab: 1,200 mg, intravenously administered, day 1 of each cycle
- carboplatin: (area under the curve 5 mg/ml/min), intravenously administered, day 1 of each cycle
- etoposide: 100 mg/m^2, intravenously administered, on days 1 to 3 of each cycle.

Maintenance phase after the induction phase, every 3 weeks until loss of clinical benefit or unmanageable toxicity:

- atezolizumab monotherapy without chemotherapy, 1,200 mg administered intravenously on day 1 of each cycle.

Price

2.3 The list price of atezolizumab: £3,807.69 per 1,200 mg vial (excluding VAT; BNF online, assessed December 2019). The mean treatment cost of

a course of treatment for a patient with ES-SCLC is £32,798.39 for atezolizumab (at list price), £76.18 for carboplatin and £30.89 for etoposide.

The company has an existing commercial arrangement with the NHS. This makes atezolizumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and the technical report developed by the NICE team through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- Carboplatin with etoposide is the most relevant comparator for this appraisal (issue 1, see technical report page 11).
- Because carboplatin with etoposide is the most relevant comparator for this appraisal, clinical data from the IMpower133 trial is acceptable for decision making (issue 2, see technical report page 12).
- The company's approach of using time-to-death to estimate utility values, using the ERG's preferred model, is acceptable for decision making (see section 3.5; issue 3, see technical report page 16).
- It is appropriate for disutilities associated with adverse events to be incorporated in the model (issue 4, see technical report page 18).

The committee recognised that there was remaining uncertainty associated with the analyses presented (see technical report, page 19), and took this into account in its decision making. It discussed the issue of long-term survival estimates (issue 5, see

technical report page 18), which was outstanding after the technical engagement stage. This included uncertainty about how long people having atezolizumab live, and how well the model fitted the trial data and predicted long-term survival. At the first appraisal committee meeting, the committee recommended that NICE request further clarification and analyses from the company for the second meeting. It requested that this should include a revised cost-effectiveness model with further methods of estimating overall survival for both atezolizumab and comparator groups. After receiving new analyses and information from the company, the committee discussed the long-term survival estimates again. It also discussed treatment effect duration and end of life, which were outstanding issues after the first committee meeting.

Clinical need and comparator

There is an unmet need for treatment options in this disease

3.1 A patient expert highlighted that people diagnosed with extensive-stage small-cell lung cancer (ES-SCLC) are often dismayed at their lack of treatment options, particularly compared with non-small-cell lung cancer (NSCLC). Treatment options have not changed for decades, and patients are aware of the success of immunotherapy for treating other cancers. After starting chemotherapy, people often feel better at first, but this may only last for a few months before their condition deteriorates. Any treatment that could extend life, even only for a short period, would allow more time for advanced care planning. The patient expert commented that many people with this condition spend their last days in a hospital bed, meaning a worse quality of life for them and their family. More time to plan for end of life care could help to reduce the incidence of this. The committee noted that ES-SCLC progresses rapidly, and the impact that this has on patients and their friends and family. It agreed that an additional more effective treatment option would benefit people with untreated ES-SCLC, and concluded that atezolizumab with carboplatin and etoposide would be a welcome treatment option.

The most appropriate comparator is carboplatin and etoposide chemotherapy

3.2 The company submitted cost-effectiveness analyses comparing atezolizumab with carboplatin and etoposide, with carboplatin and etoposide chemotherapy. This used Kaplan-Meier data from Impower133 (see section 3.3). In response to technical engagement, it also provided an exploratory comparison with cisplatin and etoposide, but clinical experts explained that less than 5% of people with untreated ES-SCLC would be offered this. The committee agreed that the most appropriate comparator for this appraisal was chemotherapy consisting of carboplatin and etoposide.

Clinical trial evidence

Atezolizumab with chemotherapy improves overall and progression-free survival compared with chemotherapy but the long-term benefit is uncertain

3.3 The clinical evidence for atezolizumab with carboplatin and etoposide came from IMpower133, a randomised placebo-controlled trial. It compared atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide in adults with untreated ES-SCLC with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. At the April 2018 data-cut, median progression-free survival was 5.2 months for atezolizumab combination therapy and 4.3 months for standard chemotherapy (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.62 to 0.96). Overall survival data were provided from a later data-cut (January 2019). Median overall survival was 12.3 months for atezolizumab combination therapy and 10.3 months for standard chemotherapy (HR 0.76, 95% CI 0.60 to 0.95). The committee considered a Kaplan-Meier plot of overall survival from the January 2019 data-cut. It noted that the atezolizumab and placebo arms had almost come together by about 30 months, which could show that there is little overall survival benefit for the atezolizumab arm after this. The committee concluded that the trial data showed that atezolizumab with carboplatin and etoposide

improves overall and progression-free survival compared with standard chemotherapy, but the long-term benefit on overall survival is uncertain.

Data from IMpower133 are not generalisable to people with an ECOG performance status score of 2 or higher which is likely in clinical practice in England

3.4 IMpower133 only included people with a good ECOG performance status of 0 or 1. Clinical experts commented that many people with untreated ES-SCLC in the NHS in England are likely to have an ECOG performance status of 2 or higher, that is, a worse performance status. They stated that IMpower133 data should not be extrapolated to people with worse performance status because treatment effects can be very different for people with a larger disease burden. Lower effectiveness of immunotherapies in general have been seen in people with a different disease (NSCLC) and an ECOG performance status of 2 or higher. The committee agreed that the treatment effect of atezolizumab with carboplatin and etoposide seen in IMpower133 should not be used to estimate the effectiveness of the treatment for people with worse performance status and are not generalisable to people in clinical practice in England.

Economic model

The company's time-to-death approach for estimating utility values in the model is accepted for this appraisal

3.5 The company used a time-to-death approach to get utility values for their base-case economic model. The committee had concerns about this approach. After new analysis was provided at technical engagement, the technical team preferred the ERG's preferred approach of using the ERG-requested utility model with 'time-to-death categories 1 week earlier' to estimate utility values. The company stated that disease progression had little effect on quality-of-life data from IMpower133. However, clinical experts commented that they would expect a patient's quality of life to

decrease after disease progression. The committee were concerned that EQ-5D data for patients whose disease had progressed could be biased because of informative censoring (that is, when quality of life after progression is measured before there is any decrease in quality of life caused by progression, or if people whose disease has progressed are less likely to complete quality-of-life questionnaires). Also, during the trial, quality-of-life data might no longer have been reliably collected once a patient's disease had progressed or they had stopped having treatment. The company commented that their updated time-to-death statistical model for estimating utility based on trial EQ-5D data did include progression status. However, the committee considered that the problems around informative censoring remain. The company also highlighted that previous appraisals used this approach to estimate utility. However, the committee was aware that recent NICE technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer preferred using progression-based utility values instead of a time-to-death based approach. The committee concluded that the company's time-to-death approach to estimate utilities was acceptable for this appraisal, given the specific circumstances but this should not be considered the usual methodology for this disease.

The duration of treatment benefit from the start of treatment is uncertain, but varying this duration has a small effect on the cost-effectiveness results

3.6 The committee requested investigation of the effect of reducing the duration of treatment benefit on model results. This is because, based on a Kaplan-Meier data plot of overall survival from IMpower133, there may be no treatment benefit from approximately 30 months (see section 3.3). The company presented scenario analyses for no treatment effect cut-off, as well as 36, 48 and 60 months from the start of treatment, choosing to use a 60-month effect cut-off in their base case. The ERG did a further analysis that showed the incremental cost-effectiveness ratio (ICER) might be as high as £52,646 per quality-adjusted life year (QALY) gained if the cut-off was as low as 30 months. This was approximately the

maximum follow up in the trial. However, varying the treatment effect duration did not have a large impact on the ICER overall. The company's preferred 60-month treatment effect duration from starting treatment was plausible but uncertain because follow up was still short.

Flexible methods of estimating overall survival were explored to identify the most appropriate model assumptions for decision making

3.7 In its original submission, the company used log-logistic extrapolations in its base-case model and stated that the Weibull extrapolations were not appropriate for overall survival (the ERG's preferred approach at the time). This was because it predicted that all people with ES-SCLC did not survive past about 40 months. The company commented that several studies showed that people having standard care are alive after this time, and that it expected to see prolonged survival for people having atezolizumab, consistent with immunotherapeutic effects seen in other indications. Clinical experts commented that while there is some evidence that immunotherapy causes prolonged remission for NSCLC, it is too early to see if this is the case for SCLC. The committee did not accept that observing a longer-term treatment effect in 1 disease would necessarily translate to another disease. Confirmatory long-term data are needed. The experts also explained that while some people with SCLC do survive for 5 years, this is mostly people with early-stage SCLC. Not everyone with ES-SCLC would die from the condition by 5 years, but the proportion surviving by that point was likely to be less than 1%. The committee commented that neither the Weibull or log-logistic models fitted the IMpower133 data very well and were the least poor fitting of the parametric survival extrapolations used by the company. Also, looking at the hazard over time, there was a complex pattern which would have been clearer if a plot of hazard function over time had been provided. The committee concluded that the Weibull extrapolation for overall survival may be too pessimistic to reflect the chemotherapy-only group outcome, and the log-logistic may be too optimistic. It did not consider either approach suitable for decision making at the first appraisal committee

meeting, and requested that the company provide new analyses exploring further methods for estimating mean overall survival. The committee considered that alternative, more flexible models may allow better representation of the available survival data and would provide a more robust basis for decision making.

Restricted spline models may provide the best method for modelling atezolizumab with chemotherapy long-term overall survival

3.8 In response to the committee's request for new analyses with alternative models, the company provided plots of the hazard function over time, commenting that long-term hazards were decreasing, and that both groups in Impower133 had different shaped curves before and after approximately 5 months. The company validated the new models with 8 consultant oncologists to understand how well the extrapolations reflected long-term overall survival in clinical practice. It presented a new base-case model with changed curve-fitting and extrapolation of overall survival. This was a hybrid model using Kaplan-Meier data then switching at 20 months to a log-logistic extrapolation for both the atezolizumab and the chemotherapy groups. The ERG stated that there was no compelling reason to choose a hybrid model of Kaplan-Meier data followed by extrapolation instead of a parametric curve extrapolation alone. The ERG preferred a log-logistic model for the chemotherapy group because it was the most plausible based on statistical fit, visual fit, decreasing hazards and 2.5% survival at 5 years. The ERG further commented that fitting different models to each of the Kaplan-Meier group data may be appropriate, because of the different shapes of the curves and behaviour of the hazards over time. The committee agreed to use a log-logistic method for the chemotherapy arm, with a more flexible curve-fitting approach for the atezolizumab arm in its decision making. It considered that the chemotherapy group hazard reduced over time, but this was not reflected in the company's preferred hybrid model. The committee also considered that visual fit alone should not be the basis for selecting a preferred model. It was concerned that the company's hybrid modelling

was inappropriate, because the event hazard rate had been applied for the whole model duration, rather than a hazard rate related to a specific cut-point in time. The committee concluded that the most appropriate overall survival model for the atezolizumab arm was one that not only fitted to the whole curve (rather than just a section of it), but also took into account the changing hazard profile over time. Therefore, the committee agreed that some of the spline-based models for the atezolizumab arm were most appropriate, but statistical criteria did not show that any one was a better choice than any other. It also noted that when using the 60-month treatment effect duration (see section 3.6), the ICER generated with a log-logistic model for the chemotherapy arm and 1 of the preferred spline models for the atezolizumab arm would give an ICER that was over £50,000 per QALY gained, and could be as high as £75,544 per QALY gained.

Cost-effectiveness results

The curve-fitting and extrapolation of overall survival has a large impact on the ICER

3.9 The company's new deterministic base case showed that the ICER for atezolizumab and chemotherapy compared with chemotherapy alone was £41,894 per QALY gained. All analyses included the patient access scheme for atezolizumab. The ERG preferred to use a log-logistic extrapolation for long-term survival for the chemotherapy arm. It considered several different plausible extrapolations for the atezolizumab arm, giving ICERs between £39,710 and £75,544 per QALY gained. The committee agreed that a log-logistic extrapolation was appropriate for the chemotherapy arm (see section 3.8). Also, it found that some of the flexible curves considered plausible fits to the trial data by the ERG and technical team for the atezolizumab group were more appropriate, particularly the spline-based models. This increased the most plausible ICER to between just over £50,000 per QALY gained and £75,544 per QALY gained.

End of life

Restricted mean analysis of overall survival data from Impower133 may support atezolizumab with chemotherapy meeting NICE's end-of-life criteria

3.10 A restricted mean analysis of the overall survival data from IMpower133 may help estimate the extent that atezolizumab with chemotherapy extends life compared with chemotherapy alone. The company explained that the restricted mean survival time increases with further data cuts and gets closer to NICE's end-of-life extension-to-life criterion. With the company's updated base case, the mean difference in overall survival was 4.93 months, which is above the 3 months threshold needed to meet the end-of-life criteria. The ERG explained that the restricted mean analysis indicated that 1 of the end-of-life criteria might not be met if the difference in mean survival based on the trial data only is used to estimate increase in life expectancy. However, the difference in means is larger the later the cut-off, and the model predicts a gain in life expectancy of over 3 months using any of the log-logistic based models. The committee used the evidence on restricted mean analysis to discuss whether or not all end-of-life criteria were met (see section 3.11).

Atezolizumab with carboplatin and etoposide for ES-SCLC meets NICE's end-of-life criteria

3.11 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. Based on evidence from IMpower133 and clinical expert opinion, the committee concluded that the life expectancy of people with untreated ES-SCLC would be under 24 months with current NHS treatment. The company's preferred economic model was a hybrid model using Kaplan-Meier data with log-logistic extrapolation from 20 months. This predicted a mean increase in survival of 4.93 months for atezolizumab with carboplatin and etoposide. The increase in median overall survival from IMpower133 was 2.0 months for atezolizumab compared with placebo (12.3 months compared with 10.3 months). This is

less than what is normally considered appropriate for the extension-to-life criterion to be met (usually 3 months or more). The committee had concluded that there was uncertainty about the most appropriate method for estimating mean overall survival in this appraisal (see section 3.8). However, almost all the models for overall survival that it considered plausible gave a survival gain of 3 months or more for atezolizumab and chemotherapy compared with chemotherapy alone. So, the committee accepted that this criterion was met in this circumstance. It concluded that, on balance, with trial and modelled evidence and taking both mean and median survival into account, the NICE criteria for a treatment at the end of life were met.

Cancer Drugs Fund

Atezolizumab with carboplatin and etoposide is not recommended for use in the Cancer Drugs Fund

3.12 Having concluded that atezolizumab with carboplatin and etoposide could not be recommended for routine use, the committee considered if it could be recommended for untreated ES-SCLC within the Cancer Drugs Fund. The company did not express an interest in the treatment being considered for funding through the Cancer Drugs Fund. The committee considered that the Impower133 evidence was fairly mature. So, uncertainties about treatment effect duration and overall survival were unlikely to be resolved through further data collection. Therefore, the committee did not recommend atezolizumab with carboplatin and etoposide for use in the Cancer Drugs Fund.

Other factors

There are no equalities issues and all relevant benefits of the treatment are captured in the QALY

3.13 No relevant equalities issues were identified that could be addressed by the recommendations in this guidance. Atezolizumab with carboplatin and

etoposide may be innovative. However, all relevant benefits of the technology were captured in the QALY.

Conclusion

Atezolizumab with carboplatin and etoposide is not recommended for untreated ES-SCLC

3.14 Although the company provided multiple models of overall survival at the request of the committee and updated their base case, the committee still found some remaining uncertainty around which of the more flexible models of overall survival was most appropriate. However, based on the various models with different fits to the atezolizumab and chemotherapy arms that the committee found plausible (see section 3.8), the ICER was over £50,000 per QALY gained. This is higher than is usually considered a cost-effective use of NHS resources, even when applying the NICE end-of-life criteria. The committee concluded not to recommend atezolizumab with carboplatin and etoposide for untreated ES-SCLC.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
December 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Amy Crossley, Thomas Walker
Technical leads

Sally Doss
Technical adviser

Louise Jafferally
Project manager

ISBN: [to be added at publication]