NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
Published: 1 July 2020

www.nice.org.uk/guidance/ta638

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Atezolizumab with carboplatin and etoposide is recommended as an option for untreated extensive-stage small-cell lung cancer in adults, only if:

- they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and
- the company provides atezolizumab according to the commercial arrangement.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 These recommendations are not intended to affect treatment with atezolizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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 extensive-stage small-cell lung cancer have carboplatin and etoposide chemotherapy as their first treatment. Clinical trial evidence is in people with an ECOG status of 0 or 1 (that is, they are more able to do daily tasks and ordinary activities than those with poorer ECOG 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.

Atezolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. The cost-effectiveness estimates comparing atezolizumab and chemotherapy with chemotherapy alone are uncertain, but they are within what NICE normally considers an acceptable use of NHS resources. Because the clinical evidence is for people with an ECOG status of 0 or 1, atezolizumab with carboplatin and etoposide is only recommended

for this group.

2 Information about atezolizumab with carboplatin and etoposide

Marketing authorisation indication

2.1 Atezolizumab (Tecentriq, Roche) received a promising innovative medicine designation in November 2018 and a positive opinion from the Early Access to Medicines Scheme in June 2019.

Having received a marketing authorisation in other cancer indications in 2017, on 26 July 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product atezolizumab. The CHMP adopted a new indication as follows: 'Tecentriq, 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)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of atezolizumab is £3,807.69 per 1,200 mg vial (excluding VAT; BNF online, accessed April 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 a commercial arrangement. This makes atezolizumab available to the NHS with a discount. 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 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 (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 requested 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. During consultation, the company updated the confidential discount. This altered the incremental cost-effectiveness ratios (ICERs) from

the overall survival models for the atezolizumab arm, which the committee considered plausible. The committee considered these updated analyses in its final decision making.

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 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 plus carboplatin and etoposide with carboplatin and etoposide This used Kaplan–Meier data from IMpower133 (see section 3.3). The company also provided an exploratory comparison with cisplatin and etoposide, but the clinical experts explained that fewer 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 (atezolizumab combination therapy) with placebo plus carboplatin and etoposide (standard chemotherapy) 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 plots for 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 combination therapy improves overall and progression-free survival compared with standard chemotherapy, but the long-term benefit on overall survival was uncertain.

Data from IMpower133 are not generalisable to people with an ECOG performance status score of 2 or higher

3.4 IMpower133 only included people with a good ECOG performance status (0 or 1). The clinical experts commented that some 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. The clinical experts explained that a lower effectiveness of immunotherapies in general has 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 is not generalisable to people with this status in clinical practice in England. Therefore, the committee concluded that its decision should reflect the trial evidence.

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 its base-case economic model. The committee had concerns about this approach. After new analyses was provided at technical engagement, the technical team favoured the ERG's preferred approach of using the ERG-requested utility model with 'time-to-death categories 1 week earlier' to estimate utility values. Analysis done by the company during technical engagement showed that disease progression had little effect on the quality-of-life data from IMpower133. However, the clinical experts commented that they would expect a patient's quality of life to decrease after disease progression. The committee was concerned that EQ-5D data for patients whose disease had progressed could be biased. This was 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 its 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 remained. The company also highlighted that previous appraisals used this approach to estimate utility. However, the committee was aware that 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 particular 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 about 30 months (see section 3.3). The company presented scenario analyses for no treatment effect cut-off, as well as for 36, 48 and 60 months from the start of treatment. It chose to use a 60-month effect cut-off in its base case. The ERG carried out an illustrative scenario with a cut-off of 30 months, which was about the maximum follow up in the trial. However, varying the treatment effect duration did not have a large effect on the ICER overall. The committee concluded that 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 are 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. It stated that the Weibull extrapolations were not appropriate for overall survival (the ERG's preferred approach at the time). This was because the company 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 were alive after this time. It expected to see prolonged survival for people having atezolizumab, consistent with immunotherapeutic effects seen in other indications. The 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 clinical 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 fewer than 1%. The committee commented that neither the Weibull nor log-logistic models fitted the IMpower133 data very well, but 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. It requested that the company provided 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. It commented that long-term hazards were decreasing, and that both groups in IMpower133 had different shaped curves before and after about 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 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 modelling. 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 fitted to the whole curve (rather than just a section of it) and 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 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 one of the preferred spline models for the atezolizumab arm would give an ICER of between £32,433 per quality-adjusted life year (QALY) gained and £48,770 per QALY gained when the revised patient access scheme was applied.

The curve-fitting and extrapolation of overall survival has a large effect 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 £26,998 per QALY gained. All analyses included the revised 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 of between £25,567 and £48,770 per QALY gained for atezolizumab and chemotherapy compared with chemotherapy alone. 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. These spline models gave a

plausible ICER of between £32,433 per QALY gained and £48,770 per QALY gained for atezolizumab and chemotherapy compared with chemotherapy alone.

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 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. 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 showed that one 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 predicted 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.

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

3.11 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). 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, taking both mean and median survival into account, the NICE criteria for a treatment at the end of life were met.

Other factors

Healthcare professionals should consider ECOG performance status when implementing the recommendations

3.12 The committee considered whether its recommendations were associated with any potential issues related to equality. It concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

All relevant benefits of the treatment are captured in the QALY

3.13 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 recommended for untreated ES-SCLC in adults

3.14 The company provided multiple models of overall survival at the request of the committee and updated its base case, but the committee still found some remaining uncertainty around which of the more flexible models of overall survival was most appropriate. However, having considered the various models with different fits to the atezolizumab and chemotherapy arms that it found plausible (see section 3.8), the committee concluded that the range of plausible ICERs with the confidential discount was within the range considered cost effective for end-of-life treatments. The trial only included people with an ECOG performance status of 0 to 1, and the committee agreed that its recommendations should reflect the population in the trial. Therefore, it recommended atezolizumab with carboplatin and etoposide as an option for untreated ES-SCLC in adults, only if they have an ECOG performance status of 0 or 1.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because atezolizumab has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated extensive-stage small-cell lung cancer and the healthcare professional responsible for their care thinks that atezolizumab with carboplatin and etoposide is the right treatment, it should be available for use, in line with NICE's recommendations.

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: 978-1-4731-3796-7