NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using atezolizumab 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?

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 determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using atezolizumab 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: 23 August 2017

Second appraisal committee meeting: 30 August 2017

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

1 Recommendations

1.1 Atezolizumab is not recommended for treating locally advanced or metastatic urothelial carcinoma in adults after prior platinum-containing chemotherapy.

1.2 The committee is minded not to recommend atezolizumab as an option for untreated locally advanced or metastatic urothelial carcinoma in adults for whom cisplatin-based chemotherapy is unsuitable. The company is invited to submit a proposal for including atezolizumab in the Cancer Drugs Fund for this population. This proposal should:

- demonstrate plausible potential for cost effectiveness
- detail how data collection will address the key clinical uncertainties described in section 3
- state the likelihood that additional research will reduce uncertainty enough to support positive guidance in the future
- state the proposed data collection approach and current status
- state the timeframe for availability of results
- if appropriate data collection is ongoing, summarise the study protocol
- if appropriate data collection is not going, and therefore data collection should be started to address the key areas of uncertainty, summarise the proposed data collection protocol, specifying:
  - methodology
  - study governance details (information governance, patient consent, ethical approval)
  - analysis plans
  - data access and accountability for disseminating results
  - accountability for monitoring and validation
  - any funding arrangements.

1.3 This recommendation is not intended to affect treatment with atezolizumab 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

Atezolizumab has been studied in a clinical trial, but it has not been directly compared with other treatments. Clinical experts explained that the trial results compare favourably with their experience of current treatments for the disease. The committee agreed that atezolizumab appears to be an effective treatment but the results are very uncertain.

Atezolizumab met NICE's criteria to be considered a life-extending treatment at the end of life. Life expectancy for people with locally advanced or metastatic urothelial carcinoma is less than 24 months. Atezolizumab is also likely to extend people's lives by more than 3 months, but the lack of evidence comparing atezolizumab with other treatments means that this is uncertain.

The most likely estimates of cost effectiveness are very uncertain because of the limited clinical evidence. They are higher than what NICE normally considers acceptable for end-of-life treatments.

For people with untreated disease for whom cisplatin is unsuitable, atezolizumab has the potential to be cost effective, but more evidence is needed. The IMvigor 130 trial is ongoing and could help to address some of the uncertainties, as it is directly comparing atezolizumab with other treatments. The company is invited to submit a proposal for including atezolizumab in the Cancer Drugs Fund for people with untreated disease for whom cisplatin is unsuitable.

Atezolizumab is not recommended for people who have had previous chemotherapy, because the cost-effectiveness estimates were much higher and it does not have the potential to be cost effective.

2 The technology

Atezolizumab (Tecentriq, Roche)	
Marketing authorisation/anticipated marketing authorisation	On 20 July 2017 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for atezolizumab, for treating adults with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.
Recommended dose and schedule	1,200 mg by intravenous infusion every 3 weeks.
Price	The proposed list price is £3,807.69 per 1,200 mg vial. The company has not yet confirmed this price with the Department of Health. The company has agreed a patient access scheme with the Department of Health. If atezolizumab had been recommended, this scheme would provide a simple discount to the list price of atezolizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence. The committee was not presented with evidence from the IMvigor 211 trial in people with previously treated locally advanced or metastatic urothelial carcinoma, which reported results in May 2017.

The condition

Metastatic urothelial carcinoma substantially decreases quality of life

3.1 Urothelial carcinoma causes a number of symptoms, including haematuria (blood in the urine) and increased frequency, urgency and pain associated with urination. Surgical treatments such as urostomy can have a substantial impact on quality of life and restrict daily activities. The patient experts explained that chemotherapy is associated with unpleasant side

effects such as fatigue, nausea and vomiting and places people at a greater risk of infection. The committee was aware that many people with locally advanced or metastatic urothelial carcinoma are older and may have comorbidities, which can affect treatment decisions. The committee recognised that locally advanced or metastatic urothelial carcinoma has a significant impact on quality of life.

Current treatments

There is unmet need for effective treatment options

3.2 Initial treatment is usually with a cisplatin-containing chemotherapy regimen. However, cisplatin can be damaging to the kidneys, so is not suitable for some people with impaired kidney function or a poor performance status. People who have had no previous chemotherapy and for whom cisplatin is unsuitable will usually be offered carboplatin plus gemcitabine or, if they are not well enough to tolerate this or they choose not to have it, best supportive care. Treatment options for people with disease progression after platinum-based chemotherapy include docetaxel, paclitaxel or best supportive care. The clinical experts explained that none of the current treatments offer lasting benefit and that prognosis is poor even for people having their first therapy. The patient experts explained that the side effects of chemotherapy can have a major negative impact on quality of life and that regular hospital visits for treatment disrupt usual activities. The clinical experts noted that there have been no new treatments for locally advanced or metastatic urothelial carcinoma for a number of years and that, unlike for other cancers, there is no targeted or personalised treatment. The committee concluded that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial carcinoma.

Comparators

Carboplatin plus gemcitabine and best supportive care are relevant comparators in untreated disease when cisplatin is unsuitable

3.3 The proposed marketing authorisation for atezolizumab includes people who have had no previous chemotherapy and for whom cisplatin is unsuitable and people who have had previous platinum-based chemotherapy. For the population with untreated disease, the company submitted clinical and cost-effectiveness analyses comparing atezolizumab with carboplatin plus gemcitabine (see section 3.2). Although it was included in the NICE scope, the company did not submit a comparison with best supportive care. It considered that best supportive a care would not be appropriate for people well enough to be offered treatment with atezolizumab, and that there were not enough data for comparison with best supportive care. The committee heard that in clinical practice, carboplatin plus gemcitabine may not be suitable for a significant proportion of people for whom cisplatin is unsuitable and this group of people therefore have best supportive care. The committee understood that because atezolizumab is an immunotherapy with a different side effect profile to carboplatin plus gemcitabine, there may be some people for whom atezolizumab is suitable who would otherwise have best supportive care. The committee concluded that best supportive care was an appropriate comparator for the population with untreated disease for whom cisplatin is unsuitable, but acknowledged the lack of data would make a comparison difficult.

Paclitaxel, docetaxel and best supportive care are relevant comparators in treated disease

3.4 For the population who have had previous chemotherapy, the company submitted analyses comparing atezolizumab with paclitaxel, docetaxel and best supportive care, although the NICE scope also included re-

treatment with first-line platinum-based therapy. The committee considered this approach to be sufficient for decision-making.

Stopping treatment

Most people will stop treatment with atezolizumab when their disease progresses, but some people may benefit from continuing treatment

3.5 The committee noted that in the IMvigor 210 trial, patients continued to take atezolizumab until unmanageable toxicity or lack of clinical efficacy. This means that some people continued to take atezolizumab after disease progression. The committee understood that for other immunotherapies in the same class, consideration has been given to stopping treatment after a defined period of time, assuming that benefits of treatment would continue. The committee was concerned that there was no standard definition of loss of clinical efficacy. The clinical experts explained that the symptoms associated with locally advanced or metastatic urothelial carcinoma can be very unpleasant, so it is possible to use the severity of a person's symptoms, alongside radiological scans and blood tests, to assess whether the drug is benefitting them despite their disease progression. The clinical experts further explained that in clinical practice treatment with atezolizumab would only continue after disease progression for people who have had previous chemotherapy, and that around 25% of patients in IMvigor 210 continued treatment beyond progression. People with progressive disease having atezolizumab as their first treatment would be moved onto a chemotherapy regimen as soon as possible. The committee concluded that most people would stop treatment with atezolizumab when their disease progresses, but some people who have had previous chemotherapy and for whom the drug remains beneficial would continue treatment.

Clinical trial evidence

Atezolizumab appears to be an effective treatment but there is substantial uncertainty in the clinical effectiveness evidence

3.6 The clinical effectiveness evidence for atezolizumab came from a phase II, single-arm trial, IMvigor 210. The trial included:

- 119 patients who had not had chemotherapy and for whom cisplatin was considered unsuitable and
- 310 patients with disease progression after treatment with at least 1 platinum-containing chemotherapy regimen.

For patients who had not had chemotherapy and for whom cisplatin was unsuitable, the objective response rate was 22.7% at 15 months (95% confidence interval [CI] 15.52 to 31.27). For patients who had previous chemotherapy, the objective response rate was 15.8% at 20 months (95% CI 11.9 to 20.4). The committee heard from the clinical experts that historically, overall response rates have been around 25% and 10% for untreated and previously treated disease respectively. Median overall survival was 15.9 months (95% CI 10.4 to not estimable) for patients who had not had chemotherapy and for whom cisplatin is unsuitable, and 7.9 months (95% CI 6.7 to 9.3) for patients who had previous chemotherapy. The committee was concerned that without a trial directly comparing atezolizumab with other treatments, it was difficult to assess the relative treatment benefit of atezolizumab. In addition, the committee noted that the trial data were immature and based on a small number of patients, especially for patients with untreated disease for whom cisplatin is considered unsuitable, and so there is considerable uncertainty about the results. The clinical experts further explained that the response rates and overall survival data from IMvigor 210 match their clinical experience with atezolizumab; some people whose disease initially responds well to treatment sustain a lasting response. Moreover, people whose disease responds to treatment can have a good quality of life and some patients

survive for a significant period of time. They noted that this was something they had not seen before with chemotherapies and as such atezolizumab represents a major change in clinical practice. The committee concluded that atezolizumab appeared to be an effective treatment option for both populations, but there was considerable uncertainty in the clinical data.

Indirect comparison

The simulated treatment comparison is uncertain because it did not account for all of the important prognostic factors

3.7 Atezolizumab has only been studied in a single-arm trial, so to compare atezolizumab with the comparators, the company did a simulated treatment comparison and network meta-analysis. The committee was aware that the simulated treatment comparison relies on assuming that all of the important prognostic factors are accounted for, but heard from the ERG that the company had used a relatively limited number of prognostic factors. The clinical experts explained that, of the prognostic factors identified by the company, performance status and the presence of liver metastases on study entry are the most important. The committee also heard from the clinical experts that haemoglobin levels and primary tumour site may also have an important effect on prognosis, so considered that it would have been appropriate for these to be included. The committee was concerned that some of the studies providing evidence for the comparators did not report data for liver metastases, potentially limiting the results of the simulated treatment comparison. The committee considered that it was unlikely that all of the important prognostic factors had been accounted for in the simulated treatment comparison and that the results of the simulated treatment comparison were very uncertain.

The network meta-analysis is uncertain as it is based on the simulated treatment comparison and the evidence networks are sparse

3.8 The company linked the results of the individual simulated treatment comparisons together through a network meta-analysis. This was done for several outcomes, but only overall survival was used in the economic model. The committee was also concerned that, for the network meta-analysis, the evidence networks were sparse (including only 1 or 2 trials for each comparator), that most of these trials had been done more than 5 years ago and that the trials included only a small number of patients. In addition, it was difficult to assess how similar the patients in each of these trials were, because the number of previous therapies and other baseline characteristics were not consistently reported. The committee concluded that, because of the limitations in accounting for prognostic factors and in the evidence networks, the results of the indirect comparison were highly uncertain. The committee heard from the company that they had subsequently explored a matching-adjusted indirect comparison. The committee did not see this analysis but noted that it could potentially reduce the uncertainty about the relative effectiveness of atezolizumab.

Adverse events

Atezolizumab is well tolerated in clinical practice

3.9 The clinical experts explained that in their experience of using atezolizumab, it is well tolerated and associated with fewer severe adverse events than chemotherapy. However, the committee was concerned that because there are no comparative clinical trial data it is difficult to draw conclusions about the relative safety profile of the drug. The committee understood that atezolizumab is still associated with some unpleasant and potentially serious adverse events but heard from the clinical experts that they are actively working on ways to identify and manage the adverse events of immunotherapies.

Assumptions used in the economic model

There are several plausible overall survival extrapolations but the ERG's approach is acceptable for decision-making

3.10 The company used a generalised gamma distribution to model atezolizumab overall survival, because this distribution fitted the observed data well. The committee noted that the ERG proposed an approach in which it used the Kaplan–Meier overall survival curves from the atezolizumab trial and extrapolated the tail using an exponential or Weibull distribution for the populations with untreated disease and previously treated disease respectively. The choice of distribution was based on the best fit to the comparator trial with the longest follow-up and the largest number of patients for each of the populations (the De Santis and Bellmunt trials). The committee was concerned that for the population with untreated disease for whom cisplatin is unsuitable, the company's approach led to a 5-year survival estimate of around 28% which was higher than the proportion of patients whose disease had responded to treatment at 15 months (23%). The committee considered that this was implausible and noted that the ERG's approach produced a more plausible estimate of 10% survival at 5 years. The committee recognised that the extrapolation of overall survival was highly uncertain, and had a significant effect on the cost effectiveness. It considered that it was possible that the overall survival extrapolation could fall between the company and ERG's approaches. However, based on the evidence it had available it concluded that the ERG's approach was more appropriate for decision-making, as it used more data and produced more clinically plausible results.

The extrapolation of treatment duration should use the distribution that best fits the data for each population

3.11 The company extrapolated the observed duration of atezolizumab treatment from IMvigor 210 because the trial was ongoing. The company

chose a generalised gamma distribution for both populations. However, the ERG noted that the Weibull and log-logistic distributions provided better fits for the untreated and previously treated populations respectively. The committee agreed that it was more appropriate to use the distributions which best fitted the data.

The atezolizumab treatment effect is very uncertain

3.12 The relative treatment effect for overall survival was based on the results of the indirect comparison (see section 3.7). The committee considered these results to be very uncertain, because they are based on limited data. It also noted that because some of the results were considered by the company to be implausible, the company had chosen to cap the hazard ratios. The committee noted ERG exploratory analyses which varied the initial hazard ratio using the confidence intervals from the network meta-analysis. The cost-effectiveness results were very sensitive to whether the upper or lower bound was used, because the confidence intervals are very wide, reflecting the uncertainty of the comparisons. The committee was also concerned that the company assumed in their model that the treatment effect did not diminish for people continuing treatment after disease progression; they would have the same treatment benefit from atezolizumab as people whose disease has not progressed. The committee thought that this was implausible and would have preferred to see a scenario modelling a declining treatment benefit for people taking atezolizumab after disease progression.

The utility value for the progressed disease health state is implausibly high

3.13 No health-related quality-of-life data were collected in IMvigor 210. Instead, the company used utility values from an Australian health technology assessment of vinflunine for metastatic urothelial bladder cancer. The committee was concerned that the utility value of 0.71 used for the progressed disease health state was too high. This is because the average age of people in IMvigor 210 was around 70, and the utility value

for the age-matched general population was likely to also be around 0.71. The committee also heard from the clinical experts that they would expect health-related quality of life to decline as people's disease progressed. The ERG did a scenario analysis which reduced the on-treatment utility for the comparators reflecting the greater number of adverse events associated with chemotherapy, but this did not address the committee's concerns about the utility value for the progressed disease health state. The committee noted a company sensitivity analysis in which the post-progression utility value was 0.5 rather than 0.71. Although this value was arbitrarily chosen, it had a large impact on the cost-effectiveness results, increasing the list-price incremental cost-effectiveness ratio (ICER) by £22,000 to £28,000 per quality-adjusted life year (QALY) gained depending on the comparator. The committee concluded that the post-progression utility value is an important driver of the model.

Cost-effectiveness estimates

The ERG's ICERs are higher than the company's ICERs

3.14 The company's base-case ICER using the list-price for the population with untreated disease for whom cisplatin is unsuitable was £44,158 per QALY gained compared with carboplatin plus gemcitabine, whereas the ERG's preferred ICER was £93,948 per QALY gained. For the population with previously treated disease, all of the company's list-price pairwise ICERs comparing atezolizumab with best supportive care, docetaxel and paclitaxel were above £98,000 per QALY gained, whereas the ERG's were all above £166,000 per QALY gained. The company agreed a confidential discount with the Department of Health and the committee considered analyses incorporating the discount. However, the results of these analyses cannot be reported here as they are considered confidential by the company.

The uncertainty around the treatment effect will further increase the ICERs

3.15 The probabilistic sensitivity analyses submitted by the company increased the ICERs by up to 20%. The company explained that the probabilistic results were unlikely to be reliable, because the uncertainty in the network meta-analysis meant that at extreme draws in the probabilistic analysis, an implausible proportion of patients in the comparator arms were alive at 20 years. The committee concluded that because of this problem, the company's probabilistic analysis may not necessarily be suitable for decision-making, but given that the probabilistic ICERs were so much higher, it was likely that accounting for the significant uncertainty around the treatment effect would increase the ICERs. The committee highlighted that robust probabilistic sensitivity analysis is an essential requirement of company submissions.

The most plausible ICERs are higher than the ERG's preferred ICERs

3.16 The ERG's analysis included:

- the atezolizumab overall survival based on the Kaplan–Meier curves with the tails extrapolated using the distributions best fitting the comparator trials with the most data (see section 3.10)
- the duration of atezolizumab treatment extrapolated using distributions that best fit the data for each separate population (see section 3.11) and
- a lower on-treatment utility value for the comparators (see section 3.13).

The committee agreed with the ERG's choice of atezolizumab overall survival and treatment duration extrapolation, but noted that the ERG's analysis did not reflect all of its preferred assumptions. Firstly, the ERG continued to use a utility value of 0.71 for the progressed disease health state, which the committee believed was implausibly high. A lower utility value, such as that used in the company sensitivity analysis, would have increased the ICERs (see section 3.13). Secondly, if the treatment benefit

decreases for people taking atezolizumab after disease progression then the ICERs would increase further. Finally, if the uncertainty had been appropriately reflected in probabilistic results, then the ICERs are likely to have increased further still (see sections 3.15). Therefore the committee concluded that the most plausible ICERs were highly uncertain and would be higher than the ERG's preferred ICERs.

PD-L1 subgroups

There were no cost-effectiveness analyses based on PD-L1 expression

3.17 The committee considered whether there were any subgroups for whom atezolizumab may be more cost effective. The committee was aware that atezolizumab works by inhibiting the PD-L1 protein and that other immunotherapies with similar mechanisms of action had reported greater effectiveness in patients with higher levels of PD-L1 expression. The committee considered that it was therefore possible that atezolizumab might be more cost effective in some groups. The committee was aware that the company presented clinical results from IMvigor 210 based on PD-L1 expression greater than 1% and greater than 5%. These showed a higher objective response rate associated with a higher expression of PD-L1 in the population who had previously had chemotherapy. This did not appear to be the case for the population with untreated disease for whom cisplatin is unsuitable, and the clinical experts explained that the PD-L1 biomarker appears to be a less good predictor of outcomes in this population. However, the committee noted that the company had not provided cost-effectiveness analyses based on PD-L1 subgroup data. The committee would have liked to have seen these analyses. It was unable to make recommendations for any subgroups based on PD-L1 expression.

End of life

3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods.

Life expectancy for people with urothelial carcinoma is less than 24 months

3.19 For people with untreated disease for whom cisplatin is unsuitable and for people who have had previous chemotherapy, data from the company's model and from the literature showed that median overall survival was substantially less than 24 months for people having treatment with any standard care. The clinical experts also agreed that they would expect people with locally advanced or metastatic urothelial carcinoma to live for less than 24 months. The committee concluded that both populations met the short life expectancy criterion.

Atezolizumab is likely to extend life by at least 3 months

3.20 The committee noted that because of the lack of phase III data directly comparing atezolizumab with other treatments it was difficult to draw conclusions about overall survival gain. However, the evidence that was available and the views of the clinical experts indicated that the overall survival gain with atezolizumab would likely be more than 3 months. For the population with untreated disease for whom cisplatin is unsuitable, the data from the company's model and from the literature suggested a difference in median survival of at least 7 months. For people who have had previous chemotherapy, the difference in median overall survival based on data from the company's model and the literature was between 0 and 4 months. The company suggested that the long survival tail associated with atezolizumab means that the median overall survival results do not accurately capture the survival gains for people who have atezolizumab and that the difference in mean survival is a better measure. The estimates from the company's model showed a difference in mean

overall survival of 30 months for the population with untreated disease and between 10 and 13 months for the population with previously treated disease. The committee emphasised the limitations in the evidence available, but concluded that it was most likely that atezolizumab would extend life by more than 3 months.

Atezolizumab meets the criteria for end-of-life treatments

3.21 The committee recognised that there were important limitations in the evidence available. It concluded that, on balance, it was most likely that the end-of-life criteria would be met for both populations, although it had not been presented with robust evidence for the extension-to-life criterion.

Routine commissioning

Atezolizumab is not recommended for routine use in the NHS

3.22 The committee concluded that the most plausible ICERs (see section 3.16) were higher than those usually considered a cost-effective use of NHS resources, even for end-of-life treatments. The clinical and cost-effectiveness evidence were highly uncertain as they were both based on the simulated treatment comparison. The committee did not recommend atezolizumab for routine use in the NHS for people with untreated locally advanced or metastatic urothelial carcinoma for whom cisplatin is unsuitable or for people with previously treated locally advanced or metastatic urothelial carcinoma.

Cancer Drugs Fund

3.23 Having concluded that atezolizumab could not be recommended for routine use in either population, the committee then considered if it could be recommended for treating locally advanced or metastatic urothelial carcinoma within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods

guides. The committee was aware that the company was interested in atezolizumab being considered through the Cancer Drugs Fund.

Atezolizumab does not have the potential to be recommended for routine use for previously treated disease

3.24 The committee's preferred ICERs and both the company's and ERG's base case ICERs for previously treated disease are all substantially higher than the range usually considered a cost-effective use of NHS resources for end-of-life treatments. The committee concluded that there was no plausible potential that atezolizumab would satisfy the criteria for routine use in this population. It acknowledged that there were a number of clinical uncertainties that could be addressed through ongoing data collection (the IMvigor 211 trial). However, because atezolizumab was not plausibly cost effective, the committee concluded that it was not suitable to be recommended for use in the Cancer Drugs Fund for previously treated disease.

Atezolizumab has the potential to be recommended for routine use for untreated disease

3.25 The committee's preferred ICER for the population with untreated disease and for whom cisplatin is unsuitable is greater than the range usually considered a cost-effective use of NHS resources for end-of-life treatments. The committee noted that the ICER was most sensitive to the extrapolation used for the atezolizumab overall survival curve. The committee preferred the ERG's choice of the exponential distribution, because it considered that the number of people estimated to be alive at 5 years in the company's model using the gamma distribution (28%) was implausible. The model using an exponential distribution predicted that around 10% of people would be alive at 5 years. Although the committee agreed that this was more plausible and the most reliable estimate for decision-making at this stage (see section 3.10), it acknowledged that this might later prove to be a conservative estimate. The committee

recognised that as more trial data on clinical effectiveness become available, the true curve may lie somewhere between the company and the ERG's estimates, and that in this situation the ICER would decrease to a level that is considered a cost-effective use of resources and atezolizumab would provide sufficient extension to life to meet the end-of-life criteria. It concluded that atezolizumab has the potential to satisfy the criteria for routine use in the NHS as an end-of-life treatment, but more data are needed.

The company is invited to submit a proposal for the Cancer Drugs Fund

3.26 The committee considered that the main uncertainty is that the relative effectiveness of atezolizumab is difficult to assess, because it has only been studied in a single-arm trial meaning that all comparisons are based on the simulated treatment comparison. This could be addressed by the IMvigor 130 trial, an ongoing randomised controlled trial comparing atezolizumab with carboplatin and gemcitabine in people with previously untreated locally advanced or metastatic urothelial carcinoma. It is likely to finish in July 2020.

3.27 Additional uncertainties include:

- The duration of treatment with atezolizumab, because it is uncertain whether people continue to take it after disease progression, and if they do whether the benefit remains the same as for people taking it whose disease has not progressed. It is also unclear whether there are any other stopping rules that could be applied.
- No health-related quality-of-life data were collected in the trial, and no existing datasets provide plausible utility values.
- The company did not present cost-effectiveness evidence for subgroups based on PD-L1 expression, so the committee could not assess whether atezolizumab is more cost effective for some people with higher PD-L1 expression.

The committee considered that the IMvigor 130 trial could also provide evidence to address the uncertainties listed above and additional evidence collected through the Cancer Drugs Fund could supplement this.

Other factors

3.28 No equality issues were identified.

3.29 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of atezolizumab.

3.30 The company did not highlight any additional benefits that had not been captured in the QALY.

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.

Gary McVeigh
Chair, appraisal committee
July 2017

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 D.

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.

Ross Dent
Technical Lead

Ian Watson
Technical Adviser

Jenna Dilkes
Project Manager

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