

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Atezolizumab for treating locally advanced or
metastatic urothelial carcinoma after platinum-
containing chemotherapy**

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: 17 January 2018

Second appraisal committee meeting: TBC

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

This guidance only includes recommendations for treating urothelial carcinoma after platinum-based chemotherapy.

The scope for this technology appraisal also includes untreated urothelial carcinoma when cisplatin-based chemotherapy is unsuitable. There is separate guidance on [atezolizumab](#) for this indication.

1 Recommendations

- 1.1 Atezolizumab is not recommended for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy.
- 1.2 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

The recommendations only cover people with locally advanced or metastatic urothelial carcinoma who have had platinum-based chemotherapy. There is separate guidance on [atezolizumab](#) for untreated disease for people who cannot have cisplatin.

Treatment options for people whose disease has progressed after platinum-based chemotherapy include docetaxel, paclitaxel or best supportive care.

Evidence from 2 clinical trials, one of which compares atezolizumab directly with chemotherapy, suggests that atezolizumab is an effective

treatment. According to clinical experts, the trial results compare favourably with their experience of current treatments for the disease.

However the cost of atezolizumab is very high relative to the benefits it provides, and there are uncertainties in the economic model, including how long people take atezolizumab for and its long-term benefits.

Atezolizumab meets NICE’s criteria to be considered a life-extending treatment at the end of life. But the most plausible cost-effectiveness estimate is much higher than what NICE normally considers acceptable for end-of-life treatments and so it is not recommended for routine use in the NHS.

Ongoing data collection might answer some of the clinical uncertainties, but because of its high cost-effectiveness estimate atezolizumab does not have the potential to be cost effective. Atezolizumab is not recommended for use within the Cancer Drugs Fund.

2 Information about atezolizumab

Marketing authorisation indication	Atezolizumab (Tecentriq, Roche) has a marketing authorisation for ‘the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible’.
Dosage in the marketing authorisation	1,200 mg by intravenous infusion every 3 weeks.
Price	A 1,200 mg vial costs £3,807.69 excluding VAT. 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](#)

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[papers](#) for full details of the evidence. This guidance only includes recommendations on atezolizumab for urothelial carcinoma after platinum-containing chemotherapy; there is separate guidance on [atezolizumab](#) for untreated disease when cisplatin-containing chemotherapy is unsuitable.

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 Treatment options for people whose disease has progressed after platinum-containing chemotherapy include docetaxel, paclitaxel or best supportive care. The clinical experts explained that none of the current treatments offer lasting benefit and the prognosis is poor. The patient experts explained that the side effects of chemotherapy can have a major negative impact on quality of life and 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 after platinum-containing chemotherapy. The

committee concluded that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial carcinoma.

Comparators

The comparison with taxanes is sufficient for decision-making, but the committee would have liked to see a comparison with best supportive care

3.3 The company submitted analyses comparing atezolizumab with taxanes (pooled results for docetaxel and paclitaxel). The committee understood that docetaxel and paclitaxel are considered to be similarly effective and represent the standard of care in the NHS. It concluded that the comparison with pooled taxanes was adequate for decision-making in this appraisal. The committee recalled that best supportive care is included as a comparator in the NICE scope. It would have preferred to also see a comparison with best supportive care, but acknowledged that a lack of data would have made this difficult.

Duration of treatment

Some people will continue to take atezolizumab when their disease progresses

3.4 In the IMvigor 210 and IMvigor 211 trials, patients continued to take atezolizumab until unmanageable toxicity or lack of clinical efficacy. This means that some people continued to take atezolizumab after their disease progressed. The committee understood that for other immunotherapies in the same class, consideration has been given to stopping treatment after a defined period of time (that is, a 'stopping rule'), consistent with the evidence for those technologies. It noted that the evidence for atezolizumab did not include a stopping rule, and none had been proposed by the company. It concluded that it was not able to consider any such rule in decision-making. The committee was also 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 committee concluded that some people who have had previous chemotherapy and for whom the drug remains beneficial would continue treatment after their disease progresses.

Clinical trial evidence

Atezolizumab is an effective treatment option

3.5 The company's clinical effectiveness evidence for atezolizumab came from 2 sources:

- IMvigor 210, a phase 2, single-arm trial that included 310 patients whose disease progressed after at least 1 platinum-containing chemotherapy regimen.
- IMvigor 211, a phase 3, open-label trial that included 931 patients randomised to atezolizumab or chemotherapy (docetaxel, paclitaxel or vinflunine).

The objective response rate in IMvigor 210 was 15.8% at 20 months (95% confidence interval [CI] 11.9 to 20.4) and median overall survival was 7.9 months (95% CI 6.7 to 9.3) for atezolizumab. The clinical experts 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. The experts noted that this was something they had not seen before with chemotherapies and as such atezolizumab represents a major change in clinical practice. The primary outcome of IMvigor 211 was overall survival in the group with the highest level of PD-L1 expression (5% or more, n=234). In this group, median overall survival was not

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statistically significantly higher with atezolizumab (11.1 months) than with chemotherapy (10.6 months, hazard ratio 0.87; 95% CI 0.63 to 1.21). The company argued that because overall survival was longer than expected in the comparator arm, not enough patients were included in the analysis to be able to detect whether the difference was statistically significant. Median overall survival for the overall population was 8.6 months with atezolizumab and 8.0 months with chemotherapy, resulting in a similar hazard ratio, 0.85 (95% CI 0.73 to 0.99). The company argued that because the overall population is larger (n=931) this analysis has more power to detect whether the difference is statistically significant, and so these results are more meaningful. However, the committee was concerned that because the overall survival Kaplan–Meier curves cross, the hazards are unlikely to be proportional and so the hazard ratios may not adequately represent the effectiveness of atezolizumab. Median progression-free survival for the overall population was shorter with atezolizumab than with chemotherapy (2.1 months compared with 4.0 months), but the duration of response was longer. The committee accepted that the evidence from the overall population was relevant for decision-making, and concluded that atezolizumab is an effective treatment option compared with chemotherapy.

The comparison with taxanes in IMvigor 211 is relevant for decision-making

- 3.6 The company also presented evidence from IMvigor 211 according to whether the patients in the comparator arm had vinflunine (n=242) or taxanes (docetaxel or paclitaxel, n=214). The company argued that because vinflunine is not used in the NHS and is not a comparator in the scope for this appraisal, exploratory analyses comparing atezolizumab with taxanes are more relevant than analyses including vinflunine. In this comparison, median overall survival was 8.3 months with atezolizumab and 7.5 months with taxanes, resulting in a hazard ratio of 0.73 (95% CI 0.58 to 0.92). Progression-free survival was shorter with atezolizumab (2.1 months) than with taxanes (3.7 months). The committee noted that the overall survival hazard ratio is lower when the comparison does not

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include patients taking vinflunine. The committee was again concerned that the hazard ratios may not adequately represent the effectiveness of atezolizumab, because the overall survival Kaplan–Meier curves cross (see section 3.5). The committee concluded that the comparison with taxanes was relevant to decision-making.

Adverse events

Atezolizumab is well tolerated in clinical practice

3.7 Fewer patients in the atezolizumab arm of IMvigor 211 had grade 3 or 4 treatment-related adverse events than in the comparator arm (20% compared with 43%) or stopped treatment because of adverse events (7% compared with 18%). The clinical experts explained that in their experience of using atezolizumab, it is well tolerated and associated with fewer severe adverse events than chemotherapy. The committee understood that atezolizumab is still associated with some unpleasant and potentially serious adverse events, but it heard from the clinical experts that they are actively working on ways to identify and manage the adverse events of immunotherapies. The committee concluded that atezolizumab is a well-tolerated treatment option.

Assumptions used in the economic model

The taxane progression-free survival data are mature and do not need to be extrapolated

3.8 The company used the Kaplan–Meier curves for progression-free survival and extrapolated the tails using a generalised gamma distribution from the point when 10% of patient's had disease which had not progressed. The ERG explained that the company's choice of distribution was appropriate, but because almost all patients in the taxane arm (99.5%) had progressed disease by the end of the trial, the Kaplan–Meier curve alone could be used, effectively without extrapolation. The committee agreed that because the taxane progression-free survival data are mature, there was

no need to extrapolate the tail of the Kaplan–Meier curve. The committee noted that this has a marginal effect on the cost-effectiveness results.

Kaplan–Meier curves for overall survival extrapolated with a log-logistic distribution produce more plausible estimates for taxanes

3.9 The company used a generalised gamma distribution to model overall survival for atezolizumab and the taxanes in its base case, because it had the best statistical fit to the observed data. It also presented scenario analyses using alternative parametric distributions. The ERG noted that the company's base-case approach predicted that at 5 years, 0.4% of patients in the taxane arm would be alive. However, the committee recalled that it had heard from clinical experts that about 2–3% of people taking taxanes would be alive at 5 years. The ERG suggested an alternative approach, using the Kaplan–Meier curves with the tails extrapolated from the point when 20% of patients are still alive, using a log-logistic distribution for both atezolizumab and the taxanes. This approach predicted that 2.4% of people in the taxane arm would be alive at 5 years; the committee considered that this was more in line with what clinicians would expect. For atezolizumab, the ERG's curve had a similar visual fit to the company's base-case choice of generalised gamma distribution and predicted a similar proportion of people alive at 5 years (7.3% compared with 7.6% in the company's base case). The committee noted that the choice of distribution had a large impact on the cost-effectiveness results, and each of the company's scenario analyses increased the incremental cost-effectiveness ratio (ICER). It concluded that modelling overall survival using Kaplan–Meier curves with the tails extrapolated with a log-logistic distribution (the ERG's approach) was more appropriate than the company's approach, because it produced more plausible estimates for the taxanes.

The log-logistic distribution should be used to extrapolate atezolizumab time to treatment discontinuation, because it fits the data best

3.10 The company extrapolated time to treatment discontinuation because some people were still taking atezolizumab at the end of the trial. It used the Kaplan–Meier curves with the tails extrapolated using a generalised gamma distribution. This distribution fitted the taxane data best, but was the second-best fit to the atezolizumab data, for which the log-logistic distribution was the best fit. The company argued that it was inappropriate to use the log-logistic distribution, because for the atezolizumab arm, the resulting extrapolation curve meets the extrapolated overall survival curve at 13 years, which is not plausible. The ERG presented an alternative approach. It noted that nearly all of the patients in the taxane arm had stopped treatment by the end of the trial, so it used the taxane Kaplan–Meier data alone, effectively without extrapolating the tail. For atezolizumab, it extrapolated the tail of the Kaplan–Meier curve using the log-logistic distribution, because it fitted the data best. The extrapolated atezolizumab time to treatment discontinuation curve and overall survival curve do not meet or cross when the log-logistic distribution is used for both (the committee’s preferred approach to extrapolating overall survival uses the log-logistic distribution, see section 3.9). The committee noted that the choice of extrapolation for atezolizumab time to treatment discontinuation had a large impact on the cost-effectiveness results. This is because more people remain on treatment in later years when the log-logistic distribution is used than when the generalised gamma is used (4% at year 5 compared with 1.2%) and this increases costs. The committee considered that 4% of patients could plausibly still be having atezolizumab at year 5. This is because some tumours have a very long response to atezolizumab and people can remain on treatment as long as there is clinical benefit. The committee concluded that the ERG’s approach to extrapolating time to treatment discontinuation was more appropriate.

Cost-effectiveness estimates

The ERG's analysis reflects the committee's preferred assumptions

3.11 The company's base-case ICER using the list price for atezolizumab was £100,844 per quality-adjusted life year (QALY) gained compared with the taxanes, whereas the ERG's ICER was £154,282 per QALY gained. The company agreed a confidential patient access scheme discount with the Department of Health and the committee considered analyses incorporating the discount. However, the results of these analyses cannot be reported here because they are considered confidential by the company. The committee considered that the ERG's analysis reflected its preferred assumptions:

- taxane progression-free survival based on the Kaplan–Meier curve alone (see section 3.8)
- overall survival based on the Kaplan–Meier curves with the tails extrapolated from the point when 20% of patients still alive, using the log-logistic distribution (see section 3.9)
- duration of atezolizumab treatment based on the Kaplan–Meier curve with the tail extrapolated using the log-logistic distribution (see section 3.10).

Therefore the committee concluded that the most plausible ICER using the company's list price was £154,282 per QALY gained. The most plausible ICER with the patient access scheme discount was confidential so cannot be reported here.

PD-L1 subgroups

The committee could not make recommendations for subgroups based on PD-L1 expression because cost-effectiveness analyses were not provided

3.12 The committee was aware that atezolizumab works by inhibiting the PD-L1 protein and that for other immunotherapies with similar mechanisms of action greater effectiveness was reported in patients with higher levels of

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PD-L1 expression. The committee considered that it was therefore possible that atezolizumab might be more cost effective for some groups. The company presented clinical results from IMvigor 210 and 211 based on different PD-L1 expression levels. These showed that the objective response rate was higher for patients with higher levels of PD-L1 expression. However, the committee could not identify substantial differences in progression-free or overall survival based on PD-L1 expression. The committee noted that the company had not provided cost-effectiveness analyses based on PD-L1 subgroup data. The committee was unable to make recommendations for any subgroups based on PD-L1 expression.

End of life

Atezolizumab meets the end-of-life criteria

3.13 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](#). Data from the company's and the ERG's model showed that mean overall survival is much less than 24 months (around 12 months) for people having treatment with taxanes. The clinical experts also agreed that they would expect people with locally advanced or metastatic urothelial carcinoma to live for less than 24 months. Both the company's and the ERG's model predict that atezolizumab extends life by a mean of around 8 months compared with taxanes. The committee concluded that atezolizumab meets the end-of-life criteria.

Routine commissioning

Atezolizumab is not recommended for routine use in the NHS

3.14 The committee concluded that the most plausible ICER with the patient access scheme was higher than that usually considered a cost-effective use of NHS resources, even for end-of-life treatments. The committee did

not recommend atezolizumab for routine use in the NHS for people with previously treated locally advanced or metastatic urothelial carcinoma.

Cancer Drugs Fund

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

3.15 Having concluded that atezolizumab could not be recommended for routine use, the committee then considered if it could be recommended for previously treated 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 noted that the company had not submitted a proposal for atezolizumab to be considered for use in the Cancer Drugs Fund for people with previously treated locally advanced or metastatic urothelial carcinoma. The committee's preferred ICER was substantially higher than the range usually considered a cost-effective use of NHS resources for end-of-life treatments. The main uncertainties relate to the extrapolation of overall survival and time to treatment discontinuation, and each of the company's scenario analyses using alternative distributions increased the ICER. Therefore, the committee concluded that there was no plausible potential for atezolizumab to satisfy the criteria for routine use. It acknowledged that data collection was ongoing in IMvigor 211, which could help to address some of the uncertainties. 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.

Other factors

3.16 No equality issues were identified.

- 3.17 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

December 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 and Joanne Ekeledo

Project Manager

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