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

Technology appraisal guidance
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nice.org.uk/guidance/ta525
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 are 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.

 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.
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1 Recommendations

1.1 Atezolizumab is recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and
- the company provides atezolizumab with the discount agreed in the patient access scheme.

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

These recommendations only cover people with locally advanced or metastatic urothelial carcinoma who have had platinum-containing 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-containing 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.

Atezolizumab meets NICE’s criteria to be considered a life-extending treatment at the end of life.

Although there are uncertainties in the economic model, the most plausible cost-effectiveness estimates for atezolizumab compared with taxanes are within the range NICE considers an acceptable use of NHS resources. Therefore, atezolizumab can be recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy.
## Information about atezolizumab

<table>
<thead>
<tr>
<th>Marketing authorisation indication</th>
<th>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'.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage in the marketing authorisation</td>
<td>1,200 mg by intravenous infusion every 3 weeks.</td>
</tr>
<tr>
<td>Price</td>
<td>A 1,200 mg vial costs £3,807.69 excluding VAT (company submission). 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.</td>
</tr>
</tbody>
</table>
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. 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 effect 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 substantial effect 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 effect 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 (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 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.

Clinical evidence

Atezolizumab is an effective treatment option

3.4 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 (cohort 2).

- 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 clinical experts noted that this was something they had not seen with chemotherapy 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 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

3.5 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 stated 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 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 3.4). The committee concluded that the comparison with taxanes was relevant to decision-making.
Adverse events

Atezolizumab is well tolerated in clinical practice

3.6 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

3.7 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 patients had disease that 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

3.8 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 to 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. The log-logistic distribution had a similar statistical fit to the taxane data as the generalised gamma distribution, but 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 effect 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

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 did not meet or cross when the log-logistic distribution was used.
for both (the committee's preferred approach to extrapolating overall survival used the log-logistic distribution, see section 3.8). The committee noted that the choice of extrapolation for atezolizumab time to treatment discontinuation had a large effect 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.

**Duration of treatment**

**Some people will continue to take atezolizumab when their disease progresses**

3.10 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 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 committee concluded that some people who have had previous chemotherapy and for whom atezolizumab remains beneficial would continue treatment after their disease progresses.

**Stopping rule**

**The committee prefers a 2-year stopping rule in the model**

3.11 The committee understood that for other immunotherapies in the same class as atezolizumab, consideration has been given to stopping treatment after a defined period of time (a 'stopping rule'). In its additional evidence, the company included a 2-year treatment stopping rule in its revised economic analysis. The committee noted that the evidence for atezolizumab and its summary of
product characteristics did not include a stopping rule. The company considered that there is a lack of clinical evidence to show that imposing a stopping rule is of benefit to patients in the long term. However, the committee recognised that in previous NICE technology appraisals clinicians have highlighted growing concern about using immunotherapies beyond 2 years. The Cancer Drugs Fund clinical lead clarified that a 2-year stopping rule is acceptable to both patients and clinicians, and would be implementable. The committee also recognised that NICE guidance for other immunotherapies for metastatic urothelial carcinoma and other cancers include 2-year stopping rules. The committee concluded that it is appropriate to include a 2-year stopping rule in the economic model.

A lifetime treatment effect for atezolizumab after stopping is implausible

3.12 The committee noted that, in previous technology appraisals, it has been highlighted that atezolizumab's mechanism of action suggests its effects would continue after treatment stopped. However, there was limited evidence to support this. It understood that the duration of any continued treatment effect was uncertain and is an area of ongoing research. Alongside the analyses including a stopping rule, the company provided scenario analyses in which the treatment effect for atezolizumab was capped at 3 or 5 years after stopping atezolizumab. It highlighted that this was consistent with committees' considerations in other technology appraisals of immunotherapies which have included a stopping rule. The committee agreed that it was implausible that the treatment effect for atezolizumab would continue life long after stopping treatment. It acknowledged that previous guidance took into account analyses using a 3-year treatment effect cap after stopping treatment, but noted that there was not enough evidence to support a specific duration of benefit. It concluded that, although the duration of continued treatment effect after stopping atezolizumab remains uncertain, a lifetime treatment effect is implausible. The committee agreed that it should take into account in its decision-making the analysis including a treatment effect cap at 3 years after stopping.

Cost-effectiveness estimates

The company's updated analyses include the committee's preferred assumptions

3.13 The company's base-case ICER using the list price for atezolizumab (excluding the 2-year stopping rule and capped duration of treatment effect) was £100,844
per quality-adjusted life year (QALY) gained compared with the taxanes, but 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 Social Care 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 its preferred assumptions were:

- taxane progression-free survival based on the Kaplan–Meier curve alone (see section 3.7)
- overall survival based on the Kaplan–Meier curves with the tails extrapolated from the point when 20% of patients are still alive, using the log-logistic distribution (see section 3.8)
- duration of atezolizumab treatment based on the Kaplan–Meier curve with the tail extrapolated using the log-logistic distribution (see section 3.9)
- applying a 2-year stopping rule (see section 3.11).

The committee also took into account the analyses assuming that the effects of atezolizumab last for up to 3 or 5 years after stopping treatment (see section 3.12). In response to consultation, the company did not challenge the committee's preferred assumptions about extrapolating progression-free survival and time to treatment discontinuation. However, it argued that the committee's preferred approach to extrapolating overall survival disregards the IMvigor 211 data and relies only on expert validation of predicted survival at 5 years; the generalised gamma distribution used in the company's base case is more appropriate. The committee reiterated that the company's approach underestimates 5-year survival for people taking taxanes but the ERG's approach produces plausible estimates for both the taxanes and atezolizumab (see section 3.8). It also noted that the company had highlighted that if overall survival and time to treatment discontinuation are extrapolated with a generalised gamma and log-logistic distribution respectively (the approach implied in the company's consultation response), the atezolizumab curves meet, which is implausible (see section 3.9). The committee considered that the company's updated analyses including a 2-year stopping rule reflected its preferred assumptions, and noted the effect on the ICER of the 3-year cap on the duration of treatment effect after stopping. The most plausible ICER, including the patient access scheme discount and the committee's preferred assumptions, was confidential so cannot be reported here.
**PD-L1 subgroups**

The committee cannot make recommendations for subgroups based on PD-L1 expression because no substantial differences in survival were identified and cost-effectiveness analyses were not provided.

3.14 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 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. It 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

3.15 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 models 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 models 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.
Conclusion

Atezolizumab is cost effective for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy

3.16 The committee concluded that the most plausible ICER with the patient access scheme was within the range considered cost effective for end-of-life treatments. It recommended atezolizumab for routine use in the NHS for people with previously treated locally advanced or metastatic urothelial carcinoma who have had platinum-containing chemotherapy, only if atezolizumab is stopped at 2 years (or earlier if the disease progresses).

Other factors

3.17 No equality issues were identified.

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

4.3 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 locally advanced or metastatic urothelial carcinoma and has had platinum-containing chemotherapy and the doctor responsible for their care thinks that atezolizumab 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 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.

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