NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable

1 Recommendations

1.1 Atezolizumab is recommended, within its marketing authorisation, as an option for untreated locally advanced or metastatic urothelial cancer in adults whose tumours express PD-L1 at a level of 5% or more and when cisplatin-containing chemotherapy is unsuitable. This is only if the company provides atezolizumab according to the commercial arrangement (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (NICE technology appraisal guidance 492).

The new evidence includes data from a clinical trial and from people having treatment in the NHS, while this treatment was available in the Cancer Drugs Fund in England. The clinical trial shows that people who have atezolizumab are likely to live longer than those who have platinum-based chemotherapy.

Atezolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. The cost-effectiveness estimates are likely to be within what NICE considers an acceptable use of NHS resources. So atezolizumab is recommended.

Issue date: September 2021

2 Information about atezolizumab

Marketing authorisation indication

2.1 Atezolizumab (Tecentriq, Roche) as a monotherapy is indicated for 'the treatment of adult patients with locally advanced or metastatic urothelial cancer who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression of 5% or more'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £3,807.69 per 1200-mg vial (excluding VAT; BNF online, accessed August 2021), which is an annual cost of around £66,000. The company has a commercial arrangement (simple discount patient access scheme). This makes atezolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect efficacy data from the IMvigor 130 study. Data was also collected using the Systemic Anti-Cancer Therapy (SACT) dataset. After entry to the Cancer Drugs Fund the EMA restricted the marketing authorisation for atezolizumab to people with

high levels of PD-L1. This guidance includes recommendations only for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable.

The committee was aware that there were remaining areas of uncertainty associated with the analyses presented (see technical report pages 8 to 10) and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- the IMvigor 130 trial treatment estimates were based on a small subgroup of the trial's total population
- there were baseline differences between trial arms in IMvigor 130
- the overall survival estimates from the SACT dataset and the IMvigor 130 trial differed
- no comparison was made between atezolizumab and best supportive care in the company's base case
- the approach to modelling the long-term outcomes of overall survival and time to treatment discontinuation.

The condition and clinical management

Locally advanced or metastatic urothelial cancer substantially decreases quality of life

3.1 Urothelial cancer 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 nausea and has limited effectiveness. In the original appraisal the committee recognised that many people with locally advanced or metastatic urothelial cancer are older and may have comorbidities, which can affect treatment decisions. The committee

concluded that locally advanced or metastatic urothelial cancer has a significant impact on quality of life.

There is an 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 for whom cisplatin is unsuitable will usually be offered carboplatin plus gemcitabine. If they are not well enough to tolerate this or they choose not to have it, they will be offered best supportive care. Patient and clinical experts explained that none of the current treatments offer lasting benefit and the prognosis is poor. The patient experts explained that the disease has a substantial impact on the ability to work and travel, and that the side effects of chemotherapy can have a major negative impact on quality of life. In the committee meeting, the patient experts noted that there have been no new treatments recommended for locally advanced or metastatic urothelial cancer for a number of years. The patient experts also noted that pembrolizumab is no longer recommended for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable, and so there are limited treatment options for this disease. The committee concluded that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial cancer.

Platinum-based chemotherapy and best supportive care are relevant comparators in untreated disease when cisplatin is unsuitable

3.3 The company submitted clinical- and cost-effectiveness analyses comparing atezolizumab with carboplatin plus gemcitabine. Although it was included in the NICE scope, the company did not submit a comparison with best supportive care. It considered that there was not enough data for comparison with best supportive care. In the original appraisal, 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. It 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. For this review, the committee noted that collecting best supportive care data was not part of the managed access agreement. It also acknowledged that there was a lack of evidence in the literature for people who may have best supportive care in the population for whom cisplatin is unsuitable and who have high levels of PD-L1. The committee concluded that best supportive care was an appropriate comparator for the population with untreated disease for whom cisplatin is unsuitable, but as in the original appraisal, acknowledged the lack of data would make a comparison difficult.

Stopping treatment

Most people will stop treatment with atezolizumab when their disease progresses

3.4 In the original appraisal the committee concluded that most people with untreated locally advanced or metastatic urothelial cancer would stop treatment with atezolizumab when their disease progresses and a 2-year stopping rule was not appropriate. The committee did not hear any relevant new evidence and so concluded that its view from the original appraisal had not changed.

Clinical-effectiveness evidence

Atezolizumab is more effective than the comparators

3.5 In the original appraisal the clinical-effectiveness evidence for atezolizumab came from IMvigor 210, a phase II single-arm study. The company did a simulated treatment comparison and network meta-analysis to compare atezolizumab with gemcitabine plus carboplatin. The committee in the original appraisal was concerned that the simulated

treatment comparison was not robust and had concerns about the reliability and robustness of the network meta-analysis. To address the committee's concerns from the original appraisal, the company provided the clinical-effectiveness evidence for atezolizumab from IMvigor 130, a phase III randomised controlled trial. The trial included 1,213 adults with previously untreated locally advanced or metastatic urothelial cancer, who were in the investigators' judgement eligible to receive platinum-based therapy. Only a subgroup of 93 people, which included people with untreated PD-L1-positive (tumour expression of 5% or more) locally advanced or metastatic urothelial cancer and who were ineligible to be treated with cisplatin, was relevant to this appraisal. This was the result of the restricted EMA marketing authorisation, which stated atezolizumab should only be used in adults with high levels of PD-L1. The median overall survival was 18.6 months for atezolizumab and 10.0 months for platinum-based chemotherapy. The stratified hazard ratio was 0.50 (95% confidence interval [CI] 0.29 to 0.87, p=0.0125), showing atezolizumab was associated with a statistically significant improvement in overall survival compared with platinum-based chemotherapy. The median progression-free survival for atezolizumab was 6.4 months compared with 6.0 months for platinum-based chemotherapy. The stratified hazard ratio was 0.56 (95% CI 0.34 to 0.93, p=0.0235), showing atezolizumab was associated with a statistically significant improvement in progression-free survival compared with platinum-based chemotherapy. The ERG noted that there was uncertainty in the treatment effects as they were based on an interim data analysis of a small subgroup of the trial's total population. Also, the hazard ratio CIs were wide (but did not cross 1). The committee recalled that the small sample size was a result of the restricted marketing authorisation for atezolizumab for people with high levels of PD-L1. The committee also noted that the survival data was 87% mature. The committee concluded that the data from IMvigor 130 was the most appropriate evidence for decision making.

The difference in baseline characteristics between trial arms are acceptable

3.6 Within the IMvigor 130 subgroup there were baseline differences between trial arms in terms of gender and racial characteristics. The ERG explained that some of the imbalances were likely to bias treatment effects but that the direction and magnitude of the bias were unclear. The committee noted that the gender and racial characteristics may bias in favour of atezolizumab but the Bajorin risk factor and Eastern Cooperative Oncology Group Performance Scores may bias in favour of platinum-based chemotherapy. The committee concluded that the small sample size and opposing influences meant it was not possible to determine the magnitude of direction of any potential bias and the differences in baseline characteristics were acceptable.

There are differences between the population in the IMvigor 130 trial and the people eligible to have atezolizumab in the NHS

3.7 NHS England also provided data from the SACT dataset. It was collected from 64 people who had atezolizumab through the Cancer Drugs Fund between July 2018 and August 2020. The clinical expert explained that the clinical experience with atezolizumab is positive. The committee noted that the median overall survival in the trial was longer (18.6 months, 95% CI 14.0 to not evaluable) than in the SACT dataset (12.4 months, 95% CI 8.3 to 20.1). However, the 95% CIs overlapped. Both the clinical expert and the lead for the Cancer Drugs Fund explained that people included in the SACT dataset were older and had a poorer performance status, which may have contributed to the differences in the median survival estimates. The clinical expert also noted that there may have been selection bias of good prognostic features for people enrolled in IMvigor 130, who were eligible to have chemotherapy, compared with the SACT dataset in which people were not necessarily able to have chemotherapy. The lead for the Cancer Drugs Fund explained that the COVID-19 pandemic may have affected people's choice to continue treatment, even if they were

responding, which would have impacted the SACT dataset. But the IMvigor 130 trial would likely not have been impacted by the COVID-19 pandemic. The committee concluded that these population differences and impact of the COVID-19 pandemic likely contributed to the differences in treatment effects between the IMvigor 130 trial and SACT dataset.

Adverse events

Atezolizumab is reasonably well tolerated in clinical practice

3.8 In the original appraisal the clinical experts explained that in their experience of using atezolizumab, it is well tolerated and associated with fewer adverse events than chemotherapy. However, the committee in the original appraisal also understood that atezolizumab was associated with some unpleasant and potentially serious adverse events. A clinical expert in this review stated that toxicities are well managed by specialist hospitals in collaboration with other specialities. The committee concluded that atezolizumab is reasonably well tolerated in clinical practice.

Modelling overall survival and time to treatment discontinuation

The estimates of overall survival for atezolizumab and platinum-based chemotherapy from each approach to modelling are similar

3.9 The company used data from the subgroup of people with untreated PD-L1-positive locally advanced or metastatic urothelial cancer, who were ineligible to be treated with cisplatin. It used the Kaplan–Meier overall survival curve from the clinical trial until 20% of people were at risk and extrapolated the tail using the exponential distribution. The ERG proposed an approach in which it used an exponential parametric function over the whole time period. The ERG explained that it proposed this approach as there was considerable uncertainty with the small sample size in the cisplatin-ineligible, PD-L1-positive subgroup from IMvigor 130. This approach resulted in a 5-year survival of 16%. The clinical expert estimated that it was plausible that between 5% and 30% of people

having atezolizumab would be alive at 5 years. In its response to technical engagement, the company updated its approach to use the Kaplan–Meier curve to model the early part of the overall survival curve until 24 (48%) people were at risk, to maintain consistency with the original appraisal. This resulted in a 5-year survival estimate of 15%. The committee concluded that the company and ERG's approaches were both clinically plausible and estimated similar 5-year survival estimates and cost-effectiveness results.

The most plausible estimate for time to treatment discontinuation is less than 5% of people still having treatment at 5-years

3.10 Treatment in the platinum-based chemotherapy arm was restricted to 6 cycles, so curve selection had a negligible impact on costs and the discussion around time to treatment discontinuation curve selection focused on the atezolizumab arm. The company used the Kaplan–Meier time to treatment discontinuation curve for atezolizumab from the clinical trial, until 48% of people were at risk, and extrapolated the tail using the exponential distribution. This resulted in a 5-year time to treatment discontinuation estimate of 1% for atezolizumab. The clinical experts estimated 5-year time to treatment discontinuation for atezolizumab would be between 0% and 2%. The committee heard that this approach was clinically plausible, provided a good statistical fit to the data, and was a conservative extrapolation that aligned with the SACT data. The ERG noted that this approach assumed a constant probability of treatment discontinuation over time, whereas this probability decreased in the trial. The ERG explained that using this approach overestimated the probability of treatment discontinuation and underestimated the costs. The ERG preferred to use the Weibull parametric function over the whole time period, resulting in a 5-year time to treatment discontinuation estimate of 7%. The committee noted that using the Weibull parametric function to extrapolate progression-free survival, the approach proposed by the ERG and accepted by the company in its response to technical engagement, resulted in 5-year progression-free survival estimates of 5%. Using the

ERG's approach to extrapolate time to treatment discontinuation would result in more people having treatment than were progression free, which the committee considered to be implausible. The committee heard that the SACT dataset showed that no one was on treatment after 2 years, but the lead for the Cancer Drugs Fund cautioned that the maximum follow up for the SACT dataset was 25 months. The committee recalled that there is no stopping rule for atezolizumab (see section 3.4). The committee concluded that the most plausible estimate of time to treatment discontinuation would be less than 5% of people having treatment at 5 years to align with the 5-year progression-free survival estimate and clinical expectations.

Utility values in the economic model

The utility values used in the model are appropriate

3.11 In the original appraisal, no health-related quality-of-life data was collected in IMvigor 210 and the company used alternative utility values. The committee was concerned that the utility value of 0.71 used for the progressed-disease state was too high and concluded that the most plausible value for post-progression utility was likely to be between 0.5 and 0.71. The company submitted new health-state utility values for the atezolizumab and platinum-based chemotherapy arms, based on the IMvigor 130 trial. The company provided naive utility estimates that did not consider the longitudinal nature of the data. To overcome this, the company used a mixed-effects model that accounted for changes in utility over time as well as correlation among observations within people in the trial to estimate the base-case utilities. In its response to technical engagement, the company updated the selection of the mixed-effects model used to estimate the utility values and explained the updated approach was more robust. The ERG agreed that the updated values were more appropriate and clinically plausible. The company's updated base-case utilities were lower than the naive values also presented by the

company and led to higher cost-effectiveness estimates. The committee concluded that the updated base-case utilities were acceptable.

End of life

Atezolizumab meets the short life expectancy criterion

3.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. In the original appraisal, the data showed that life expectancy for people with urothelial cancer was less than 24 months for people having treatment with any standard care. The new evidence from IMvigor 130 also showed that mean overall survival was less than 24 months for people having treatment with UK standard care. The committee concluded that atezolizumab met the short life expectancy criterion.

Atezolizumab extends life by at least 3 months, and meets the criteria for end of life treatments

3.13 The company's economic model also predicted that atezolizumab extended life by at least 3 months, but the exact results are confidential and cannot be reported here. The committee concluded that atezolizumab would extend life by more than 3 months, and therefore met the end of life criteria.

Cost effectiveness

The most plausible incremental cost-effectiveness ratios are below £50,000 per quality-adjusted life year

3.14 NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of uncertainty around the incremental cost-effectiveness ratios (ICERs). It states that the committee will be more cautious about recommending a technology if it is less certain

about the ICERs presented. The committee noted the level of uncertainty, specifically around the size of the relevant population from IMvigor 130 and the time to treatment discontinuation (see sections 3.5 and 3.10). But it acknowledged that the small sample size was a result of the restricted EMA marketing authorisation and concluded that the most plausible estimate of time to treatment discontinuation would be less than the 5-year progression-free survival estimate and clinical expectations. For a life-extending treatment at the end of life, the upper limit of the range usually considered to represent a cost-effective use of NHS resources is £50,000 per quality-adjusted life year (QALY) gained. The committee noted that the company's base-case ICER for atezolizumab, including a patient access scheme and corrected by the ERG who found a minor difference in the results estimated by the company, was £32,235 per QALY gained. The committee's preferred assumptions for decision making at the appraisal committee meeting were to use:

- any of the approaches for extrapolating overall survival for atezolizumab and platinum-based chemotherapy
- less than 5% of people having treatment with atezolizumab at 5-years.

Using these preferred assumptions, the plausible ICER was considerably less than £50,000 per QALY gained. The committee recalled the uncertainty in the clinical evidence but noted the survival estimates were reasonably mature. It concluded the cost-effectiveness estimate for atezolizumab suggest it is an acceptable use of NHS resources for a life-extending treatment at the end of life. So atezolizumab was recommended for routine use in the NHS.

Equality issues

The recommendations apply equally to all people with untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable

3.15 A patient expert questioned whether there is an equality issue regarding gender. The clinical expert confirmed that women tend to present later so are more likely to have advanced disease and worse cancer-specific mortality. The committee heard from the Cancer Drugs Fund clinical lead that data collected by Public Health England from NHS patients in England showed that more men had taken atezolizumab while it was available in the Cancer Drugs Fund. The committee concluded that its recommendation applies equally, regardless of gender, so this difference is not in itself an equality issue.

Other factors

3.16 No additional benefits that had not been captured in the QALY calculations were identified during the course of the appraisal.

4 Implementation

4.1 Section 7 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.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance,

whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

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

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable 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 Proposed date for review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. 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
August 2021

6 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.

Elizabeth Bell
Technical lead

Sally Doss
Technical adviser

Kate Moore
Project manager

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