NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]

The following documents are made available to the consultees and commentators:

1. **Appraisal Consultation Document (ACD) as issued to consultees and commentators**

2. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Roche**

   No comment' response received from the Department of Health

4. **Additional analysis prepared by Roche**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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

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

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

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

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

ISBN: [to be added at publication]

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1327]
Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Roche	**Treatment stopping rule** The ACD states in Section 3.4 *"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."* We would like to highlight that the implementation of such a treatment stopping rule would be arbitrary, since a stopping rule was neither included in the clinical trial design for atezolizumab, nor is there any clinical evidence to suggest that implementing a treatment stopping rule is of benefit to patient outcomes. On the contrary, results from CheckMate 153, a randomised trial exploring the impact of continuous versus 1-year fixed duration of an immunotherapy in patients with advanced NSCLC, were presented at the ESMO congress in September 2017 and demonstrated that patients who stopped treatment had a statistically significant higher risk of progressing (HR: 0.42 [95% CI: 0.25, 0.71]), and a numerically higher risk of dying (HR: 0.63 [95% CI: 0.33, 1.20]) (1). Since this data were published, there has been growing concerns among the clinical community regarding a stopping rule that has shown a detrimental effect on patients. In light of the above evidence, we wanted to point out that a treatment stopping rule is not in the best interest of patients or the NHS.	Comment noted. We note that this comment has been superseded by an additional submission from the company, which presented analyses including a 2-year treatment stopping rule. Section 3.11 of the FAD had been amended.
2	Company	Roche	**Definition of loss of clinical efficacy** The ACD states in Section 3.4 *"The committee was also concerned that there was no standard definition of loss of clinical efficacy".* Loss of clinical efficacy is clearly defined in the clinical trial program of atezolizumab. The protocol of study IMvigor 211 clearly states that patients will be permitted to continue atezolizumab, after RECIST v1.1 criteria for progressive disease are met, if they meet all of the following criteria: - Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator - Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease - No decline in ECOG performance status that can be attributed to disease progression - Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing	Comment noted. No action required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Patients who demonstrate confirmed radiographic disease progression may be considered for continued study treatment at the discretion of the investigator, provided they continue to meet all the criteria above.	
3	Company	Roche	The ACD states in Section 3.4 "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." We would like to request to please replace *"for whom the drug remains beneficial"* to *"for whom atezolizumab remains beneficial"*	Comment noted. The text in section 3.10 of the FAD has been amended.
4	Company	Roche	**Proportional hazards assumption** The ACD states in Section 3.5 *"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."* Whilst we agree that this statement from the ACD is factually accurate for the hazard ratios reported in the clinical section of our submission and in the clinical study report, we want to point out that the presentation of hazard ratios is standard practice in terms of reporting efficacy results from clinical studies. However, this is not the approach that was used in the economic analyses that we provided. Our economic model does not rely on the proportional hazards assumption for any of the outcomes of interest (overall survival (OS), progression-free survival (PFS), time to treatment discontinuation (TTD)). Within the economic model, after testing the proportional hazards assumption, we fitted separate parametric models for the extrapolation OS, PFS and TTD to the atezolizumab and chemotherapy arms, to account for the fact that the hazards for atezolizumab and taxanes are not likely to be proportional.	Comment noted. No action required.
5	Company	Roche	The ACD refers to study IMvigor 210 at several Sections. For clarity, could this please be replaced to *"study IMvigor 210 (Cohort 2)"* since only this cohort of patients in study IMvigor210 included patients whose disease has progressed during or following a prior platinum-based chemotherapy regimen.	Comment noted. Section 3.4 of the FAD has been amended.
6	Company	Roche	**Overall survival extrapolation** The ACD states in Section 3.9: "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*	Comment noted. The committee considered that using the generalised gamma distribution underestimates 5-year survival for people taking taxanes whereas the ERG's approach produces plausible estimates for both the taxanes and atezolizumab. It also noted that if overall survival and time to treatment discontinuation are extrapolated with a generalised gamma and log-logistic distribution respectively (the committee's preferred approach to extrapolating time to treatment discontinuation), the atezolizumab curves meet, which is implausible. The committee concluded that the log-logistic distribution should be used to extrapolate overall survival. See section 3.13 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			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." We acknowledge that the uncertainty around the extrapolation of overall survival (OS) is an ongoing challenge in the evaluation of immunotherapies. We are however concerned that the ERG and committee-preferred approach for OS extrapolation in this appraisal (Kaplan–Meier curve plus log-logistic distribution for both atezolizumab and taxanes) is based only on validation against clinical expert opinion, for the proportion of patients expected to be alive at 5 years on treatment with taxanes. This approach, completely disregards the IMvigor 211 trial data, ignores any assessment of statistical or visual fit of the resulting OS extrapolation compared to IMvigor 211 data, and selects the most optimistic parametric distribution for the OS extrapolation of taxanes, on the basis of clinical expert opinion alone. We consider that our approach for OS extrapolation makes the best use of the available clinical trial data for atezolizumab and taxane therapies from study IMvigor 211 and, as such, should be used as an appropriate basis for decision-making. Our base case OS extrapolation followed existing recommendation from the NICE DSU (2) to fit separate survival models to each treatment arm and selected the same functional form for the parametric models according to that fitting the overall data most closely. When using all other committee-preferred assumptions and using our initial base-case OS extrapolation, the ICER for atezolizumab vs. taxane therapies is £131,427 at list price and [redacted] at PAS price for atezolizumab.	

Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5:00pm, Wednesday 17 January 2018 email: TACommE@nice.org.uk /NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	**Eleftherios Sideris**

Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Roche are disappointed with the second negative preliminary recommendation for appraisal [ID1327]. Our response to this recommendation is provided below and addresses some factual inaccuracies, as well as a key concern regarding the extrapolation of overall survival.
1	**Treatment stopping rule** The ACD states in Section 3.4 *"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."* We would like to highlight that the implementation of such a treatment stopping rule would be arbitrary, since a stopping rule was neither included in the clinical trial design for atezolizumab, nor is there any clinical evidence to suggest that implementing a treatment stopping rule is of benefit to patient outcomes. On the contrary, results from CheckMate 153, a randomised trial exploring the impact of continuous versus 1-year fixed duration of an immunotherapy in patients with advanced NSCLC, were presented at the ESMO congress in September 2017 and demonstrated that patients who stopped treatment had a statistically significant higher risk of progressing (HR: 0.42 [95% CI: 0.25, 0.71]), and a numerically higher risk of dying (HR: 0.63 [95% CI: 0.33, 1.20]) (1). Since this data were published, there has been growing concerns among the clinical community regarding a stopping rule that has shown a detrimental effect on patients. In light of the above evidence, we wanted to point out that a treatment stopping rule is not in the best interest of patients or the NHS.
2	**Definition of loss of clinical efficacy** The ACD states in Section 3.4 *"The committee was also concerned that there was no standard definition of loss of clinical efficacy".* Loss of clinical efficacy is clearly defined in the clinical trial program of atezolizumab. The protocol of study IMvigor 211 clearly states that patients will be permitted to continue atezolizumab, after RECIST v1.1 criteria for progressive disease are met, if they meet all of the following criteria: – Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator – Absence of symptoms and signs (including worsening of laboratory values [e.g., new or

	worsening hypercalcemia]) indicating unequivocal progression of disease – No decline in ECOG performance status that can be attributed to disease progression – Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing – Patients who demonstrate confirmed radiographic disease progression may be considered for continued study treatment at the discretion of the investigator, provided they continue to meet all the criteria above.
3	The ACD states in Section 3.4 "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." We would like to request to please replace *"for whom the drug remains beneficial"* to *"for whom atezolizumab remains beneficial"*
4	**Proportional hazards assumption** The ACD states in Section 3.5 *"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."* Whilst we agree that this statement from the ACD is factually accurate for the hazard ratios reported in the clinical section of our submission and in the clinical study report, we want to point out that the presentation of hazard ratios is standard practice in terms of reporting efficacy results from clinical studies. However, this is not the approach that was used in the economic analyses that we provided. Our economic model does not rely on the proportional hazards assumption for any of the outcomes of interest (overall survival (OS), progression-free survival (PFS), time to treatment discontinuation (TTD)). Within the economic model, after testing the proportional hazards assumption, we fitted separate parametric models for the extrapolation OS, PFS and TTD to the atezolizumab and chemotherapy arms, to account for the fact that the hazards for atezolizumab and taxanes are not likely to be proportional.
5	The ACD refers to study IMvigor 210 at several Sections. For clarity, could this please be replaced to *"study IMvigor 210 (Cohort 2)"* since only this cohort of patients in study IMvigor210 included patients whose disease has progressed during or following a prior platinum-based chemotherapy regimen.

Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]

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6	**Overall survival extrapolation** The ACD states in Section 3.9: "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."* We acknowledge that the uncertainty around the extrapolation of overall survival (OS) is an ongoing challenge in the evaluation of immunotherapies. We are however concerned that the ERG and committee-preferred approach for OS extrapolation in this appraisal (Kaplan–Meier curve plus log-logistic distribution for both atezolizumab and taxanes) is based only on validation against clinical expert opinion, for the proportion of patients expected to be alive at 5 years on treatment with taxanes. This approach, completely disregards the IMvigor 211 trial data, ignores any assessment of statistical or visual fit of the resulting OS extrapolation compared to IMvigor 211 data, and selects the most optimistic parametric distribution for the OS extrapolation of taxanes, on the basis of clinical expert opinion alone. We consider that our approach for OS extrapolation makes the best use of the available clinical trial data for atezolizumab and taxane therapies from study IMvigor 211 and, as such, should be used as an appropriate basis for decision-making. Our base case OS extrapolation followed existing recommendation from the NICE DSU (2) to fit separate survival models to each treatment arm and selected the same functional form for the parametric models according to that fitting the overall data most closely. When using all other committee-preferred assumptions and using our initial base-case OS extrapolation, the ICER for atezolizumab vs. taxane therapies is £131,427 at list price and [redacted] at PAS price for atezolizumab.

Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]

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Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. Spigel D, editor CheckMate 153: Randomized Results of Continuous vs 1-Year Fixed-Duration Nivolumab in Patients With Advanced Non -Small Cell Lung Cancer. ESMO; 2017; Madrid.
2. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making. 2013;33(6):743-54.

Single Technology Appraisal (STA)

Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]

Dear Jo,

Following the update to the atezolizumab PAS that has recently been sent to the Department of Health, we wanted to update the cost-effectiveness results for the committee-preferred base case for appraisal [ID1327]. The updated discount for atezolizumab is [redacted] resulting in a net pack price of [redacted].

In this document, in addition to the results for the committee-preferred base-case with the updated PAS, we also provide additional analyses incorporating a 2-year treatment stopping rule for atezolizumab and a treatment effect duration cap following treatment discontinuation, to reflect the committee preferred assumptions for atezolizumab in second-line NSCLC in [ID970].

Please let me know in case of any questions.

Best Regards,

[redacted] [redacted]
[redacted]

Health Economist
Roche Products Ltd

Confidential Appendix to [ID1327] with updated PAS and additional analyses

Committee-preferred base-case – updated results

Cost-effectiveness results for the committee-preferred base-case for atezolizumab in metastatic urothelial cancer after platinum-based chemotherapy [ID1327], as per the ACD released in December 2017, incorporating the updated PAS, are presented in Table 1.

Table 1: Committee-preferred base-case – updated PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.56	0.97	[redacted]	0.57	0.40	[redacted]
Taxanes	[redacted]	1.00	0.57				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Additional analyses

Consistent with the appraisal atezolizumab in second-line NSCLC in [ID970], we provide additional analyses incorporating a 2-year treatment stopping rule and a range of treatment benefit duration scenarios; either with a lifetime treatment effect (Table 2) or a treatment effect duration cap (at 3 or 5 years following treatment discontinuation; Table 3 - Table 4) for atezolizumab, to reflect the committee-preferred assumptions in [ID970]. In all scenarios presented, atezolizumab is cost-effective compared to taxane therapies. Table 3 reflects the set of committee-preferred assumptions for atezolizumab in second-line NSCLC in [ID970], i.e. 2-year treatment stopping rule and 3-year treatment effect duration cap.

Table 2: Committee-preferred base-case – updated PAS, including 2-year treatment stopping rule (and lifetime treatment effect)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.56	0.97	[redacted]	0.57	0.40	[redacted]
Taxanes	[redacted]	1.00	0.57				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 3: Committee-preferred base-case – updated PAS, including 2-year treatment stopping rule and no treatment effect after 3 years following treatment discontinuation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.50	0.94	[redacted]	0.50	0.36	[redacted]
Taxanes	[redacted]	1.00	0.57				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 4: Committee-preferred base-case – updated PAS, including 2-year treatment stopping rule and no treatment effect after 5 years following treatment discontinuation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.53	0.95	[redacted]	0.53	0.38	[redacted]
Taxanes	[redacted]	1.00	0.57				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

New company base case

Whilst we consider that there is a lack of clinical evidence to demonstrate that imposing a treatment stopping rule is of benefit to patients in the long-term, we acknowledge that existing recommendations from NICE for other immunotherapies have incorporated a treatment stopping rule, and so has the committee-preferred analysis for atezolizumab in second-line NSCLC in [ID970]. The inclusion of such a stopping rule in this appraisal, together with the new PAS, would enable patients with metastatic urothelial cancer after platinum-based chemotherapy [ID1327] with access to atezolizumab. Given the inadequacy of current treatment options in this indication, access to atezolizumab, even with the implementation of a 2-year stopping rule, would represent a valuable and radically different treatment option compared to taxane chemotherapy.

Therefore, the analysis in Table 3 represents our new company base case. We consider that the new base case is appropriate for decision making, as the inclusion of such a stopping rule is consistent with the committee-preferred assumptions for atezolizumab in second-line NSCLC in [ID970] and existing NICE recommendations for other immunotherapies. Committee D has already considered a treatment stopping rule for another immunotherapy in this indication (nivolumab in [ID995]) and has stated that it is inappropriate to implement a stopping rule while assuming lifetime treatment benefit. For this reason, we here addressed the uncertainty relating to the duration of treatment benefit, by applying a cap on treatment effect duration, in line with NICE's preferences in other immunotherapy appraisals and atezolizumab in second-line NSCLC.

The results of our new base case demonstrate that at the updated PAS price and considering the criteria for end of life therapies, atezolizumab is a cost-effective use of NHS resources compared to taxane therapies.