NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using atezolizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using atezolizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 23 August 2017

Second appraisal committee meeting: 30 August 2017

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

1 Recommendations

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

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

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

1.3 This recommendation is not intended to affect treatment with atezolizumab that was started in the NHS before this guidance was

published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

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

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

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

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

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

2 The technology

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

3 Committee discussion

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

The condition

Metastatic urothelial carcinoma substantially decreases quality of life

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

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

Current treatments

There is unmet need for effective treatment options

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

Comparators

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

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

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

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

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

Stopping treatment

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

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

Clinical trial evidence

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

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

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

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

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

Indirect comparison

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

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

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

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

Adverse events

Atezolizumab is well tolerated in clinical practice

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

Assumptions used in the economic model

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

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

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

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

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

The atezolizumab treatment effect is very uncertain

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

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

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

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

Cost-effectiveness estimates

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

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

The uncertainty around the treatment effect will further increase the ICERs

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

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

3.16 The ERG's analysis included:

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

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

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

PD-L1 subgroups

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

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

End of life

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

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

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

Atezolizumab is likely to extend life by at least 3 months

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

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

Atezolizumab meets the criteria for end-of-life treatments

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

Routine commissioning

Atezolizumab is not recommended for routine use in the NHS

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

Cancer Drugs Fund

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

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

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

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

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

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

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

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

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

3.27 Additional uncertainties include:

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

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

Other factors

3.28 No equality issues were identified.

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

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

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
July 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ross Dent
Technical Lead

Ian Watson
Technical Adviser

Jenna Dilkes
Project Manager

ISBN: [to be added at publication]

Helen Knight

Associate Director – Appraisals,

Centre for Health Technology Evaluation

National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

8th September 2017

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

Dear Helen,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of atezolizumab for treating urothelial carcinoma after platinum-based chemotherapy. Roche Products Ltd are disappointed the NICE Appraisal Committee has issued a negative preliminary recommendation for atezolizumab for treating patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy (2nd line).

We would like to highlight that we are concerned with some of the Appraisal Committee's preferred assumptions in the ACD, namely those relating to the overall survival extrapolation, the utility value for progressed disease and the time to treatment discontinuation. These concerns are discussed in more detail in the current document.

In addition, it is stated in the ACD that *"The committee was not presented with evidence from the* [phase III] *IMvigor 211 trial in people with previously treated locally advanced or metastatic*

urothelial carcinoma, which reported results in May 2017". We would like advise that results from IMvigor 211 (NCT02302807) were not available at the time of the initial company submission from Roche or at the time of the Appraisal Committee meeting. However, in our response to the ACD we are hereby submitting additional evidence from the IMvigor 211phase III study, for patients who have received prior platinum therapy.

The additional evidence include both an overview of the clinical results from the study as well as revised economic analyses based on IMvigor 211 for patients who have received prior platinum therapy (2nd line). As data are now available from a phase III controlled study, including the most relevant comparators for this appraisal, we believe this is the most appropriate basis for evidence-based decision making; as such, the economic results hereby provided form our new company base case.

The following sections of this document provide further discussion on our concerns regarding the ACD, a presentation of the key clinical evidence and outcomes from the IMvigor 211 study (study design, patient characteristics, efficacy results, and safety profile) as well as updated economic analyses for patients who have received prior platinum therapy, based on an economic model informed by IMvigor 211. These will allow the Committee to make a more considered recommendation for atezolizumab for treating metastatic urothelial carcinoma in adults after prior platinum-containing chemotherapy, based on the latest available clinical evidence.

Yours sincerely,

Eleftherios Sideris, Health Economist

Roche Products Limited

Concerns regarding ACD

Assumptions regarding overall survival extrapolation

The ACD states that *"The committee recognised that the extrapolation of overall survival was highly uncertain, and had a significant effect on the cost effectiveness. It considered that it was possible that the overall survival extrapolation could fall between the company and ERG's approaches. However, based on the evidence it had available it concluded that the ERG's approach was more appropriate for decision-making, as it used more data and produced more clinically plausible results."*

We are concerned that the ERG approach is not appropriate for decision-making for the following two reasons:

1. The ERG choice of distribution results in the OS and PFS curves meeting for atezolizumab and chemotherapy comparators within the time horizon of the model. This is clinically implausible. The approach taken in the company submission for selection of the most appropriate parametric function was based on statistical best fit to the atezolizumab observed data and assessment of the resulting curves in terms of internal and external validity, including discussion with expert clinical advisors. The ERG approach selected the best statistical fit to the comparator observed data, but did not assess clinical plausibility of the resulting curves.

   Figure 1 - Figure 3 show the resulting OS and PFS curves for atezolizumab and the comparators in the model, based on the ERG assumptions. These are clinically implausible, as OS and PFS meet at approximately 3 years for paclitaxel and docetaxel (when around 5% of patients are still alive in the model) and at approximately 6 years for atezolizumab (when 2% of patients are still alive in the model).

Figure 1: OS and PFS curves for atezolizumab: ERG assumptions

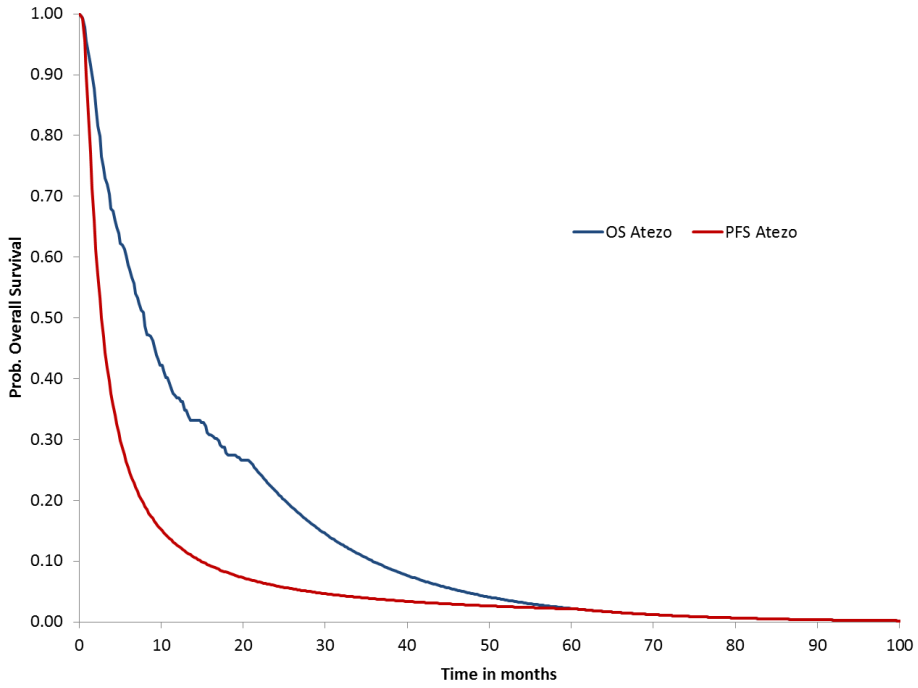


Figure 2: OS and PFS curves for paclitaxel: ERG assumptions

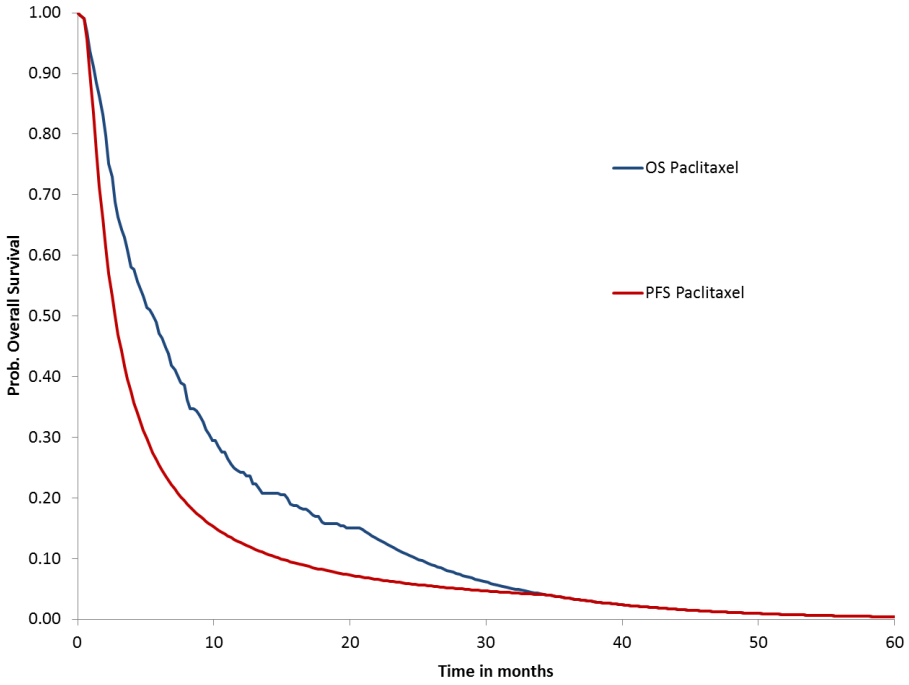
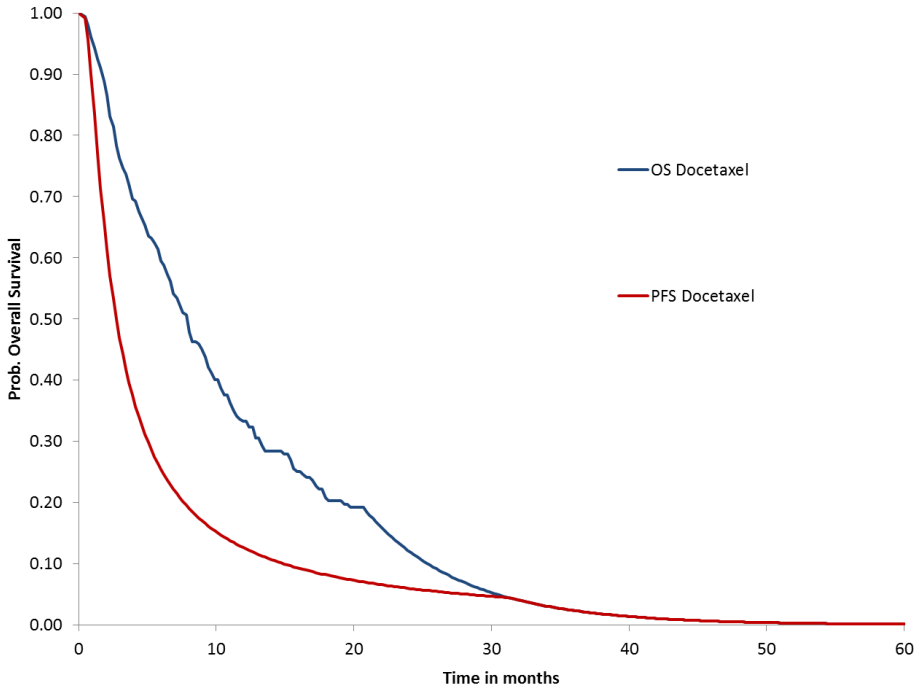


Figure 3: OS and PFS curves for docetaxel: ERG assumptions



2. The ERG choice of distribution was based on best fit to comparator trial data, rather than to atezolizumab observed data. This is inappropriate as it assumes no difference in mode of action, or treatment effect for immunotherapy as compared to chemotherapy. This is at odds with the clinical advice received by Roche, and provided by the clinical experts within the Appraisal Committee Meeting. As seen in previous immunotherapy NICE appraisals in other tumour types, treatment with cancer immunotherapy results in different long term survival curves to those observed with chemotherapy. This difference in treatment response is supported by the personal views submitted from clinical experts as part of this submission, which state the following:

    - *"Atezolizumab is associated with long term durable remissions in both the PD-L1 positive and negative populations. There is enrichment in the PD-L1 positive subgroup. These durable responses do not occur with*

chemotherapy, especially in refractory bladder cancer. This is attractive to patients."

- *"Atezolizumab is innovative and its potential impact on health related benefits with improved efficacy in terms of response rate and durability of response while maintaining an excellent quality of life is important to highlight. This technology is likely to provide a step change in the management of urothelial cancer."*

As such, we do not believe it is appropriate, or a reasonable interpretation of the evidence, to determine the choice of parametric extrapolation based on the chemotherapy data. Rather, the fit should be assessed relative to atezolizumab data.

Utility of progressed disease

The ACD states that *"The committee was concerned that the utility value of 0.71 used for the progressed disease health state was too high"* and that *"The committee noted a company sensitivity analysis in which the post-progression utility value was 0.5 rather than 0.71. Although this value was arbitrarily chosen, it had a large impact on the cost-effectiveness results, increasing the list-price incremental cost-effectiveness ratio (ICER) by £22,000 to £28,000 per quality-adjusted life year (QALY) gained depending on the comparator. The committee concluded that the post-progression utility value is an important driver of the model"*

Within the company submission, it is recognised that due to the lack of HRQoL and utility research in metastatic urothelial carcinoma (mUC), there is uncertainty regarding the utility values used (page 177, section 5.4.6).

We would like to advise that subsequent to our initial submission and the first Appraisal Committee Meeting, health related quality-of-life data for atezolizumab and chemotherapy comparators have become available from study IMvigor 211 (1), a phase III study in patients who have received prior-platinum therapy (2nd line). These data are available from EQ-5D,

collected directly from patients within the study. The resulting utility value for progressed disease (i.e. for patients off treatment) is 0.547. We consider the health related quality-of-life data from IMvigor 211 are a more appropriate basis for decision making. These utility results are fully presented in following sections of this document and are used in the revised economic analyses which are provided.

Time to treatment discontinuation

The ACD states that *"The Company extrapolated the observed duration of atezolizumab treatment from IMvigor 210 because the trial was ongoing. The company chose a generalised gamma distribution for both populations. However, the ERG noted that the Weibull and log-logistic distributions provided better fits for the untreated and previously treated populations respectively. The committee agreed that it was more appropriate to use the distributions which best fitted the data".*

We do not consider that this assumption is necessarily the most appropriate in the context of this appraisal. Section 5.5.5 of the company submission justifies the choice of parametric extrapolation for time to treatment discontinuation, which accounts for both the statistical best fit, and visual examination of the extrapolation. As the AIC statistics only reflect the parametric distribution fit to observed data, they do not allow conclusions to be drawn regarding the appropriateness of the tail of the distributions. This is a key consideration given that much of the perceived clinical value of immunotherapies derives from their ability to produce much more long-lasting remissions than chemotherapy in a small proportion of patients. Considering the AIC combined with visual examination of the extrapolation, a generalised gamma is deemed the most appropriate option for 2L patients.

Provision of evidence from the IMvigor 211

The ACD states that *"The committee was not presented with evidence from the IMvigor 211 trial in people with previously treated locally advanced or metastatic urothelial carcinoma, which reported results in May 2017".*

We would like to advise that results from IMvigor 211 (NCT02302807) (1) were not available at the time of the initial submission from Roche or at the time of the first Appraisal Committee Meeting and could therefore not be presented sooner. However, in the following sections of this document we provide additional evidence from IMvigor 211 for patients who have received prior platinum therapy. The additional evidence include both an overview of the clinical results from IMvigor 211 as well as revised economic analyses informed by IMvigor 211, for patients who have received prior platinum therapy (2nd line).

This statement in the ACD could also be interpreted as meaning the Roche withheld this evidence. This is not the case and as such, re-wording would be appreciated to prevent misinterpretation.

Evidence of prolonged response to atezolizumab

The ACD states that "*The clinical experts further explained that the response rates and overall survival data from IMvigor 210 match their clinical experience with atezolizumab; some people whose disease initially responds well to treatment sustain a lasting response. Moreover, people whose disease responds to treatment can have a good quality of life and some patients survive for a significant period of time. They noted that this was something they had not seen before with chemotherapies and as such atezolizumab represents a major change in clinical practice. The committee concluded that atezolizumab appeared to be an effective treatment option for both populations, but there was considerable uncertainty in the clinical data"*

This statement could suggest the only evidence of prolonged responses to atezolizumab comes from clinician experience. In fact evidence was submitted by Roche of prolonged

response duration from Phase 1 study PCD4989g (median duration of response 22.1 months; 95% CI 12.12, NE) as well as the fact that in Cohort 1 of IMvigor210 over 70% of responses were ongoing after a median follow-up of 17.2 months. Durability of response is an important characteristic of immunotherapy, and advice received by Roche suggests it is one of the key reasons clinicians are keen to have access to it. The remarkable durability of atezolizumab responses relative to those induced by chemotherapy is clearly demonstrated in data recently available from the IMvigor211 study (1) (discussed in this document) as well as in the OAK study in NSCLC where median duration of response is almost tripled from 6.2 months with docetaxel chemotherapy to 16.3 months (2)

Atezolizumab is well tolerated in clinical practice

The ACD states that *"The clinical experts explained that in their experience of using atezolizumab, it is well tolerated and associated with fewer severe adverse events than chemotherapy. However, the committee was concerned that because there are no comparative clinical trial data it is difficult to draw conclusions about the relative safety profile of the drug."*

In the absence of randomised data, recognition of the relative tolerability of atezolizumab and cytotoxic chemotherapy was restrained. However the subsequent availability of results from the IMvigor211 study (1) clearly demonstrates that despite an incidence of immune related adverse events, atezolizumab is better tolerated than cytotoxic chemotherapy in patients with mUC. This is discussed in more detail in the clinical results section of the current document. In addition, this finding is entirely consistent with the observation that atezolizumab is better tolerated than docetaxel in a large randomised trial in NSCLC (2) as presented in the original Roche's submission. This is important since the tolerability of immunotherapy is prized by clinicians and their patients with mUC, especially as many such patients are already frail and suffering from disease symptoms and various co-morbidities.

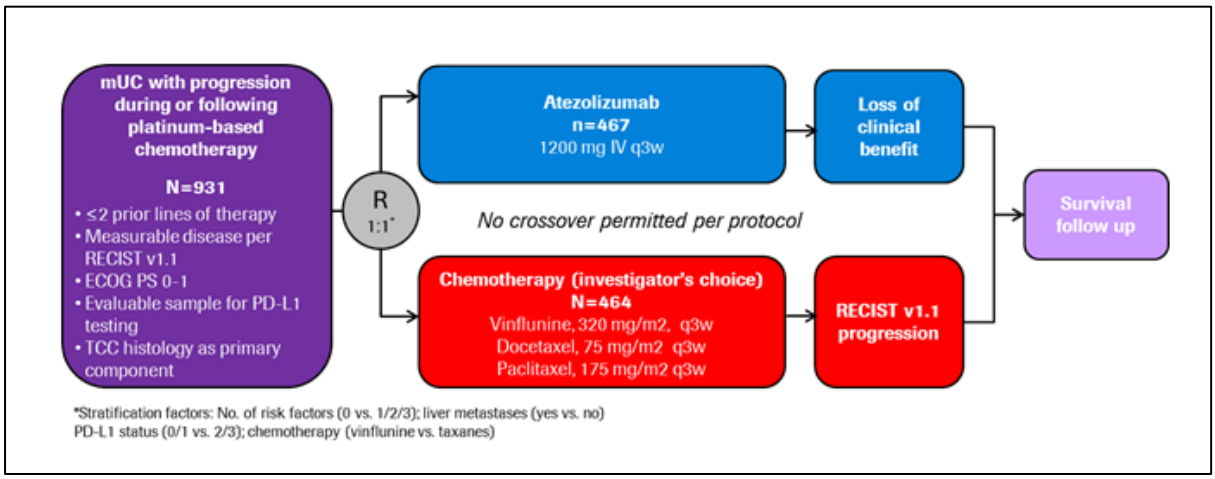
IMvigor 211 clinical results

Study design

IMvigor 211 was a Phase III, global, multicentre, open-label, two-arm, randomised, controlled study to evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial carcinoma (mUC) who have progressed during or following a platinum-containing regimen (NCT02302807) (1).

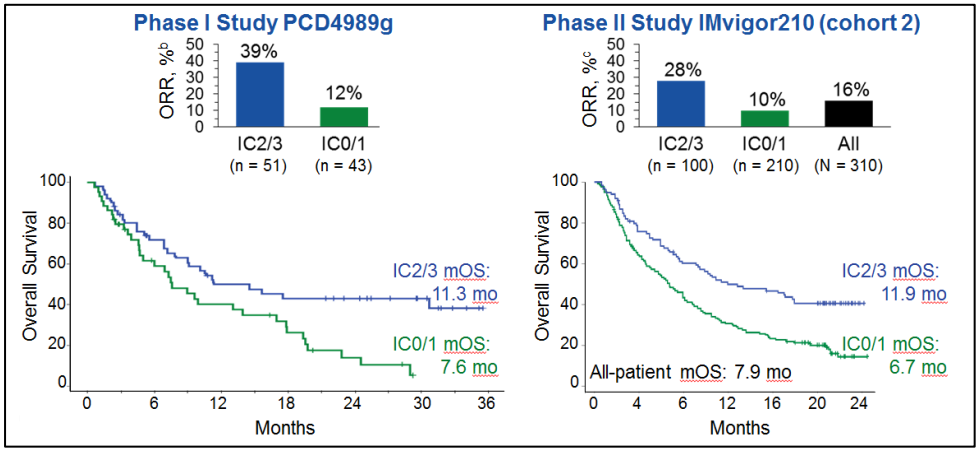
Patients were randomised in a 1:1 ratio to receive either atezolizumab or an investigator's choice of chemotherapy (vinflunine, paclitaxel, or docetaxel). Investigator chemotherapy choice was made prior to randomisation.

Figure 4: Study design



The primary endpoint of IMvigor 211 was overall survival (OS), tested hierarchically in selected populations with the Immune cell (IC) 2/3 patient group (Programmed death-ligand 1(PD-L1) ≥5%) used for the primary endpoint analysis, followed by IC1/2/3 (PD-L1 ≥1%) and the intent-to-treat (ITT) population. This was based on the observation made in uncontrolled early-phase studies that patients with higher levels of immune-cell PD-L1 staining experienced longer survival when treated with atezolizumab as shown in Figure 5 (3, 4).

Figure 5: Overall survival in Phase I and II studies of atezolizumab in advanced urothelial carcinoma according to immune cell PD-L1 expression



Secondary efficacy endpoints included objective response rate (ORR) per investigator with use of RECIST v1.1; progression-free survival (PFS) per investigator with use of RECIST v1.1 and duration of objective response (DOR) per investigator with use of RECIST v1.1.

The safety and tolerability of atezolizumab compared with chemotherapy was also assessed, along with patient-reported outcomes of health-related quality of life, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and the EuroQoL 5 dimension (EQ-5D) [3L] questionnaire .

Patient characteristics

A total of 931 patients were enrolled (ITT population). The treated population included 902 patients; 459 in the atezolizumab arm and 443 in the chemotherapy arm (vinflunine, n=242 [55%]; paclitaxel, n=148 [33%]; docetaxel, n=53 [12%]). Baseline characteristics in the ITT population were generally balanced between treatment arms.

Table 1: Baseline characteristics

Characteristic	ITT Population	
	Atezolizumab n=467	Chemotherapy n=464
Median age, years (range)	67 (33–88)	67 (31–84)
Male, %	76	78

ECOG PS, %		
0	47	45
1	53	55
Tobacco use, %		
Current	13	13
Former	57	61
Never	30	26
Haemoglobin < 10 g/dL, %	14	16
No. of risk factors, %		
0	31	30
1	46	45
2	18	21
3	5	4
Primary tumour site, %		
Lower tract (bladder / urethra)	69 / 2	73 / 2
Upper tract (renal pelvis / ureter / other)	14 / 13 / 2	11 / 13 / 2
Metastatic disease, %	91	93
Sites of metastases, %		
Lymph node only	12	14
Visceral*	77	77
Liver	30	28
Prior cystectomy, %	43	43
Previous chemotherapy < 3 months, %	34	35
Prior regimens (metastatic setting), %		
0	28	26
1	53	56
2	17	16
≥3[†]	2	2
PD-L1 status, %		
IC2/3	25	25
IC1	43	41
IC0	32	33

*Visceral metastasis defined as liver, lung, bone, any non–lymph node or soft tissue metastasis
[†]1 patient in the chemotherapy arm received 4 prior systemic regimens for mUC

Efficacy findings in IMvigor 211

The primary endpoint of OS was not met in the IC2/3 population (Table 2; Figure 6); however, numerical improvements in OS were observed for the primary end-point population (IC2/3), for the IC1/2/3 and the unselected ITT population. The latter reached statistical significance in an exploratory test (Table 2). For patients responding to treatment the durability of atezolizumab responses far exceeded that of those achieved with chemotherapy (see Figure 7). At the time of analysis, the median duration of follow-up in the ITT population was 17.3 months (range 0–

24.5 months) at this point; 63% of patients in the atezolizumab arm compared with only 21% in the chemotherapy arm had ongoing responses.

Table 2: Efficacy endpoints in IMvigor211

	IC2/3		IC1/2/3		ITT	
	Atezo n=116	Chemo n=118	Atezo n=316	Chemo n=309	Atezo n=467	Chemo n=464
Median OS, mo (95% CI)	11.1 (8.6–15.5)	10.6 (8.4–12.2)	8.9 (8.2–10.9)	8.2 (7.4–9.5)	8.6 (7.8–9.6)	8.0 (7.2–8.6)
HR (95% CI) p value	0.87 (0.63–1.21) p=0.41		0.87 (0.71–1.05) p=0.14*		0.85 (0.73–0.99) p=0.038*	
12 month OS, % (95% CI)	46.4 (37.3–55.6)	41.2 (32.2–50.3)	40.0 (34.6–45.5)	33.2 (27.7–38.6)	39.2 (34.8–43.7)	32.4 (28.0–36.8)
Median PFS, mo (95% CI)	2.4 (2.1–4.2)	4.2 (3.7–5.0)	2.1 (2.1–2.2)	4.1 (3.6–4.2)	2.1 (2.1–2.2)	4.0 (3.4–4.2)
ORR, %	23.0	21.6	14.1	14.7	13.4	13.4
CR rate, %	7.1	6.9	3.5	4.2	3.5	3.5
Median DOR, mo (95% CI)	15.9 (10.4–NE)	8.3 (5.6–13.2)	15.9 (9.9–NE)	8.3 (6.3–13.2)	21.7 (13.0–21.7)	7.4 (6.1–10.3)

*p values for the IC1/2/3 and ITT populations are provided for descriptive purposes only

Figure 6: Overall survival in the IC2/3 population

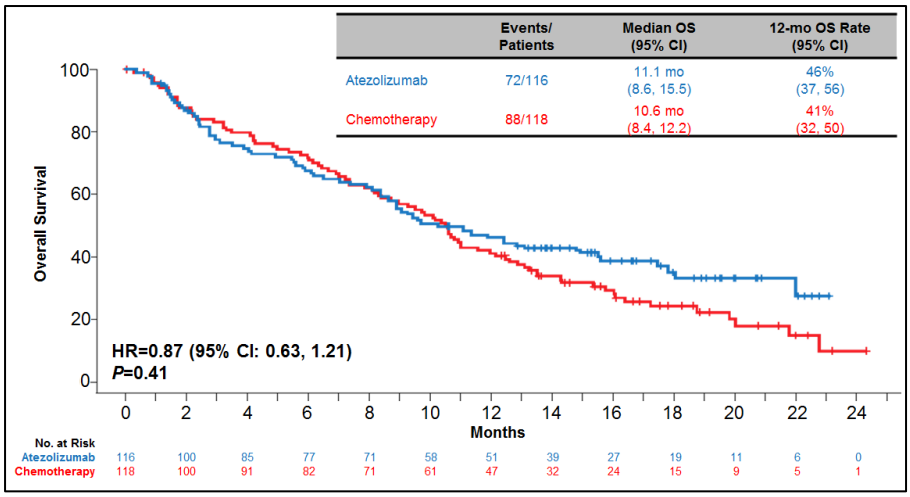
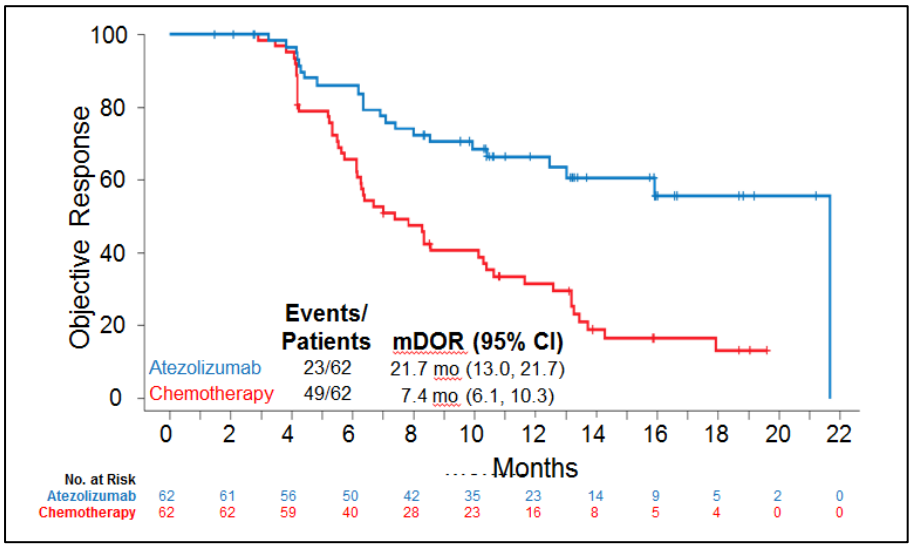


Figure 7: Duration of response in the ITT population



Exploratory outcomes

In exploratory analyses, OS and PFS were examined in subgroups based on chemotherapy type at randomisation. Atezolizumab demonstrated improved OS over chemotherapy in the ITT population with taxanes (HR, 0.73; 95% CI, 0.58–0.92), but not in the vinflunine subgroup (HR, 0.97; 95% CI, 0.78–1.19). Vinflunine is not recommended in the UK; as such the results compared to taxane therapies only are most relevant for the UK. PFS analysis in chemotherapy subgroups was consistent with the ITT analysis.

Table 3: Overall survival in chemotherapy subgroups

	Atezo n=215	**Taxane n=214**
Median OS, mo (95% CI)	8.3 (6.6–9.8)	7.5 (6.7–8.6)
HR (95% CI)	0.73 (0.58–0.92)	
	Atezo n=252	**Vinflunine n=250**
Median OS, mo (95% CI)	9.2 (7.9–10.4)	8.3 (6.9–9.6)
HR (95% CI)	0.97 (0.78–1.19)	

Table 4: Progression-free survival in chemotherapy subgroups

	Atezo n=215	Taxane n=214
Median PFS, mo (95% CI)	2.1 (2.1–2.3)	3.7 (2.2–4.1)
HR (95% CI)	1.00 (0.81–1.23)	
	Atezo n=252	**Vinflunine n=250**
Median PFS, mo (95% CI)	2.1 (2.1–2.2)	4.1 (3.7–4.3)
HR (95% CI)	1.19 (0.98–1.44)	

Safety

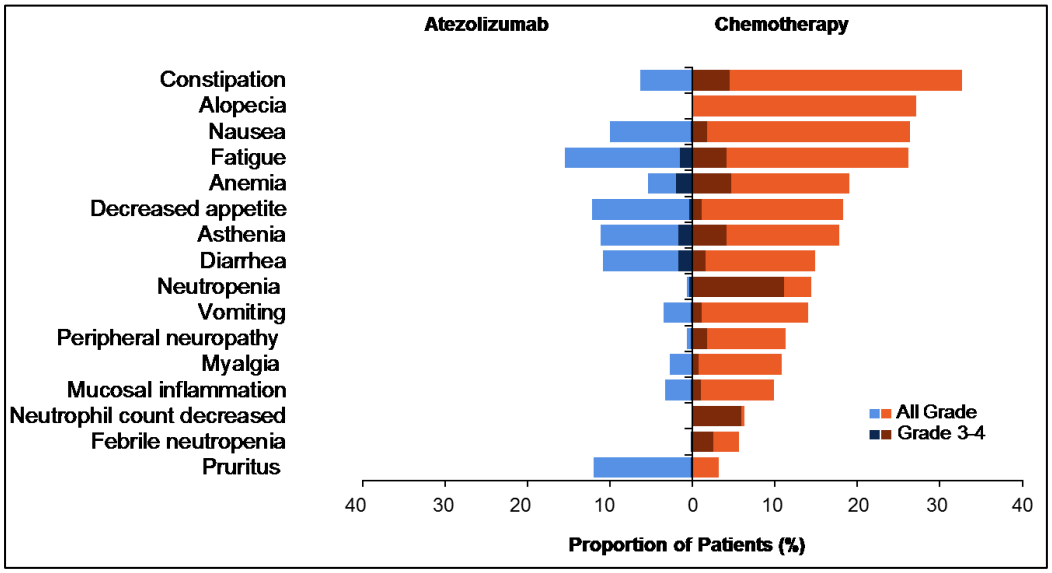
No new safety signals were identified in IMvigor211 and atezolizumab had a favourable safety profile when compared to chemotherapy. Fewer patients in the atezolizumab arm had Grade 3 or 4 treatment-related adverse events (19.8% vs 42.7%), dose modification, delay or interruption (29% vs 47%), or discontinued due to AEs (7.4% vs 17.6%). The incidence of treatment-related adverse events in each arm is summarised in Figure 8.

Table 5: IMvigor211 safety summary

AE, n (%)	All cause		Treatment related	
	Atezo n=459	Chemo n=443	Atezo n=459	Chemo n=443
All Grade AEs	438 (95)	435 (98)	319 (70)	395 (89)
Grade 3 or 4 AEs	233 (51)	249 (56)	91 (20)	189 (43)
Grade 5 AEs	17 (4)	18 (4)	3 (1)	8 (2)
Any grade AESIs	139 (30)	98 (22)	–	–
Grade 3 or 4 AESIs	37 (8)	13 (3)	–	–
Grade 5 AESIs	0	1 (< 1)	–	–
SAE	188 (41)	191 (43)	72 (16)	110 (25)
AEs leading to treatment discontinuation	34 (7)	78 (18)	16 (3)	63 (14)
AEs leading to dose modification, delay or interruption	134 (29)	210 (47)	–	–

AE, adverse event; AESI, AE of special interest; SAE; serious adverse event

Figure 8: Treatment-related adverse events in ≥10% (all Grades) or ≥4% (Grades 3–4) for either arm



Patient reported outcomes

The IMvigor211 trial measured health related quality of life via the EORTC QLQ-C30 and EuroQoL 5 dimension (EQ-5D) [3L] questionnaires.

EORTC QLQ-C30 assessments were completed prior to any healthcare interaction on day 1 of each cycle and at the treatment discontinuation visit after the last treatment dose. In patient reported outcome evaluable patients, median time-to-deterioration of global health status was similar in both arms, while those of physical function and fatigue were prolonged with atezolizumab. Mean changes in the global health, physical functioning, and fatigue scores deteriorated initially but returned to baseline values more quickly with atezolizumab than with chemotherapy.

The EQ-5D questionnaire was included to generate utility values to be used in cost-effectiveness analyses. Details are provided in the economic analyses section.

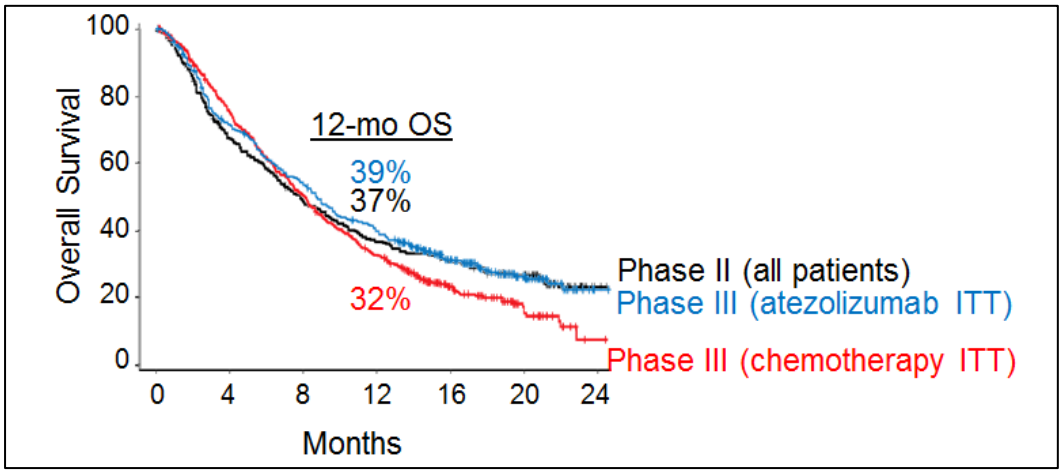
Discussion on clinical effectiveness of atezolizumab in IMvigor211

In IMvigor211, the primary endpoint of OS in the IC2/3 population (N=234) was not met. In designing the study, it was assumed, based on uncontrolled, early-phase studies, (see Figure

5) that IC PD-L1 expression is a predictor of benefit to atezolizumab treatment in urothelial carcinoma. However, the results of IMvigor211 show that high IC PD-L1 expression is prognostic of good outcome regardless of treatment type. This had the effect of transforming the planned primary analysis of OS in the sub-group of patients with the highest PD-L1 expression levels from a test of the benefit of atezolizumab in the most sensitive patients, into an underpowered comparison of OS between two groups of good prognosis patients. In retrospect, the more meaningful test of atezolizumab efficacy is that in the ITT population, where the impact on OS (defined by the HR) is similar to that measured in the higher expressing sub-groups but the larger population gives greater statistical power. Had the statistical design of the study put this end-point at the start of the testing hierarchy rather than the bottom the study would have been likely to meet its primary end-point.

Although the anticipated predictive value of IC PD-L1 status was not seen in IMvigor 211, in other respects atezolizumab behaved exactly as expected from early Phase trials – Figure 9 shows the similarity between the IMvigor211 OS curve and that from the precursor IMvigor210 study, which itself produced similar outcomes to the Phase I study , PCD4989g (see Figure 5). In addition, as previously reported, and as shown in Figure 7, patients responding to atezolizumab generally have very long-lasting responses in contrast to the rather transient ones generally obtained with chemotherapy.

Figure 9: Consistency of OS outcomes with atezolizumab in Phase II and III studies



Although atezolizumab produced outcomes in line with earlier studies, the efficacy of vinflunine (received by 55% of patients in the chemotherapy arm) outperformed original study assumptions and randomised historical data (median OS of 6.9 months in the pivotal vinflunine phase III study (5), where it failed to produce a statistically significant improvement in OS versus Best Supportive Care in the trial ITT population). The reasons for this are unclear, though they may be related to the fact that 77% of patients in the study were treated in other European countries where vinflunine has been freely accessible for many years and clinicians are now better able to manage its toxicities.

The unexpected efficacy of vinflunine in IMvigor211 reduced the size of OS benefit achieved with atezolizumab compared to chemotherapy and produces a distorted impression of the potential benefits of atezolizumab to UK patients who have no routine access to vinflunine and for whom the appropriate reference treatment is taxane therapy. As already stated, in the ITT population the OS benefit of atezolizumab over taxanes (HR, 0.73; 95% CI, 0.58–0.92) was substantially greater than that over vinflunine (HR, 0.97; 95% CI, 0.78–1.19).

Clinical effectiveness conclusion

Although the statistical analysis plan for IMvigor211 meant that the primary end-point of the study was not met, the study confirmed the value atezolizumab in pre-treated, advanced urothelial carcinoma. In unselected patients, it produces short-term survival outcomes very similar to those already reported and better than those with chemotherapy, particularly the taxanes that are the standard of care in the UK. In addition, patients achieving disease remission with atezolizumab have much longer lasting periods free of disease than those treated with chemotherapy. The shape of both OS and PFS Kaplan-Meyer curves suggest that there is a proportion of patients treated with atezolizumab who survive and remain without disease-progression far in excess of what is considered possible with cytotoxic chemotherapy. These atezolizumab benefits are associated with toxicities substantially less than those that attend current second-line chemotherapy and superior patient-reported outcomes, indicating the value of these objective anti-tumour measures to patients.

Overall, the IMvigor211 results support the significant advance that atezolizumab represents for patients relapsing after cisplatin-based chemotherapy.

Revised economic analyses

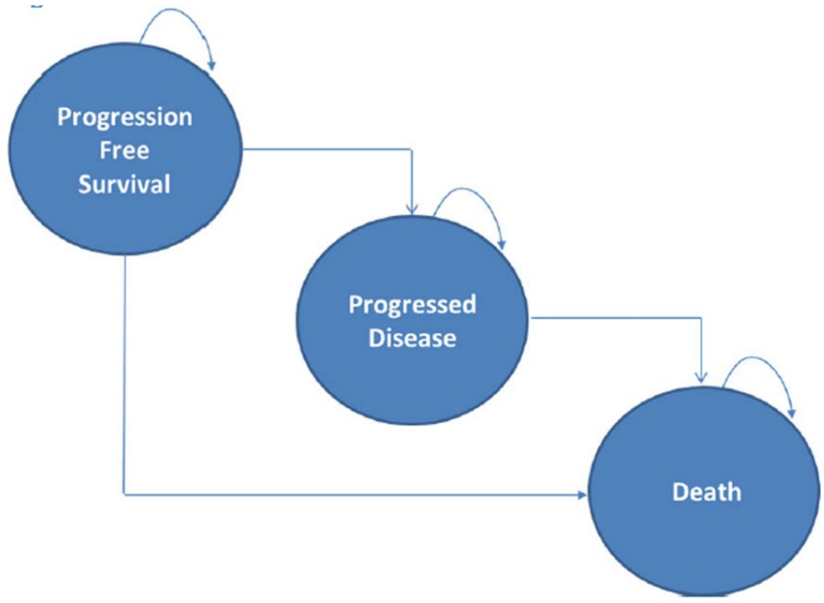
Based on the clinical results from IMvigor 211 that are now available and are discussed in the previous section, analyses and results from an updated economic model informed by IMvigor 211 are presented for the Committee's consideration.

The IMvigor 211 study is the only data source for clinical outcomes, adverse events, and duration of treatment for atezolizumab and comparator in the updated economic model. Given that the comparator of interest was included in IMvigor 211 no indirect treatment comparison was necessary to inform the economic model.

Economic model

A de novo three-state partitioned survival analysis model was developed in Microsoft Excel and its structure is presented in Figure 10. The structure of this model is consistent with our original company submission and has been previously described there (Section 5.2). As such, it is not discussed in more detail in this document. The time horizon of the model is 20 years and takes the perspective of NHS and Personal Social Services in England.

Figure 10: Cost-effectiveness model schematic



Population

The patient population in the revised economic analyses is based on IMvigor 211, i.e. adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum containing chemotherapy (2nd line). This is consisted with the anticipated Marketing Authorisation for 2nd line mUC patients.

Comparators

The comparators included in the model are atezolizumab and taxanes (paclitaxel or docetaxel). The rationale for the choice of comparators is as follows:

- Expert clinical advisors have confirmed that paclitaxel is the most relevant comparator for second-line (or more) treatment of mUC in England and Wales. This is consistent with London Cancer Alliance guidelines (6), and is also reflected in the recruitment of patients into the IMvigor 211 study, where taxane choice for patients is heavily weighted towards paclitaxel (n=148) vs. docetaxel (n=53)
- A comparison to paclitaxel only, however, cannot be performed based on evidence from the IMvigor 211 study. In the chemotherapy arm of IMvigor 211, patients received a pre-specified investigator choice of chemotherapy (vinflunine, docetaxel or paclitaxel). Whilst the choice between vinflunine and taxanes (paclitaxel or docetaxel) was included as a stratification factor in the study design, the choice between taxanes was not. Additionally, the small patient numbers for those receiving docetaxel would be unlikely to support such an analysis. Therefore, in IMvigor 211 taxanes can be disaggregated from vinflunine and used as a comparator in the economic model, while a comparison of atezolizumab vs. paclitaxel only (the most relevant comparator in England and Wales) cannot be performed and would result in breaking study randomisation. A comparison to paclitaxel is only presented as an exploratory scenario.
- As such, the base case of the economic analyses uses pooled taxanes (paclitaxel and docetaxel) as a comparator. The pooled taxanes comparator uses the efficacy results

of atezolizumab vs. taxanes, presented in the clinical section. In terms of costs, the proportion of paclitaxel vs docetaxel is assumed to be 75% / 25%, reflecting the proportion of taxanes administered in the study. The comparison to pooled taxanes (paclitaxel and docetaxel) is also consistent with the appraisal of pembrolizumab in previously treated mUC. (7)

- Although included in the final scope from NICE for this appraisal, BSC is not a key comparator for previously treated mUC patients, as alternative active treatments (e.g. docetaxel and paclitaxel) are available. During the first Appraisal Committee meeting for this appraisal, discussion was almost entirely focused on the comparisons of atezolizumab with taxanes, and the importance of this comparison was supported by the expert clinical advisors. As such, a comparison to BSC is not included in this updated economic model.
- Re-treatment with first-line chemotherapy was not included as a comparator, consistent with the opinion of the Appraisal Committee during the first Appraisal Committee meeting and with the pembrolizumab appraisal and ACD in previously treated mUC (7).

Extrapolation of clinical data in the model

PFS and OS results from IMvigor 211 are extrapolated to the 20 year time-horizon of the model, as life-time results are not available for all patients in the IMvigor 211 study.

Guidance from the NICE DSU was followed to identify parametric survival models for OS and PFS (8) in the base-case of the model. In summary, the steps that were followed include:

1. Testing the proportional hazard (PH) assumption, to assess whether joint or separate statistical models were more appropriate for the atezolizumab and taxanes treatment arms. Visual inspection of the OS and PFS KM curves and the log-cumulative hazard plots for atezolizumab vs. taxanes confirmed that the PH assumption does not hold, as

both the KM and the log-cumulative hazard plots for atezolizumab and taxanes cross (see Figure 11 - Figure 14).

2. Separate survival models were then explored. Models were separately fitted to each arm using data from the relevant treatment arm. Following the recommendation from the NICE DSU (8), the same functional form was selected for the parametric models according to that fitting the overall data most closely.
3. Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to assess statistical fit.
4. Lastly, the choice of base case parametric models was validated in terms of clinical plausibility of both short-term and long-term extrapolations.

Figure 11: OS KM curves (atezolizumab vs taxanes)

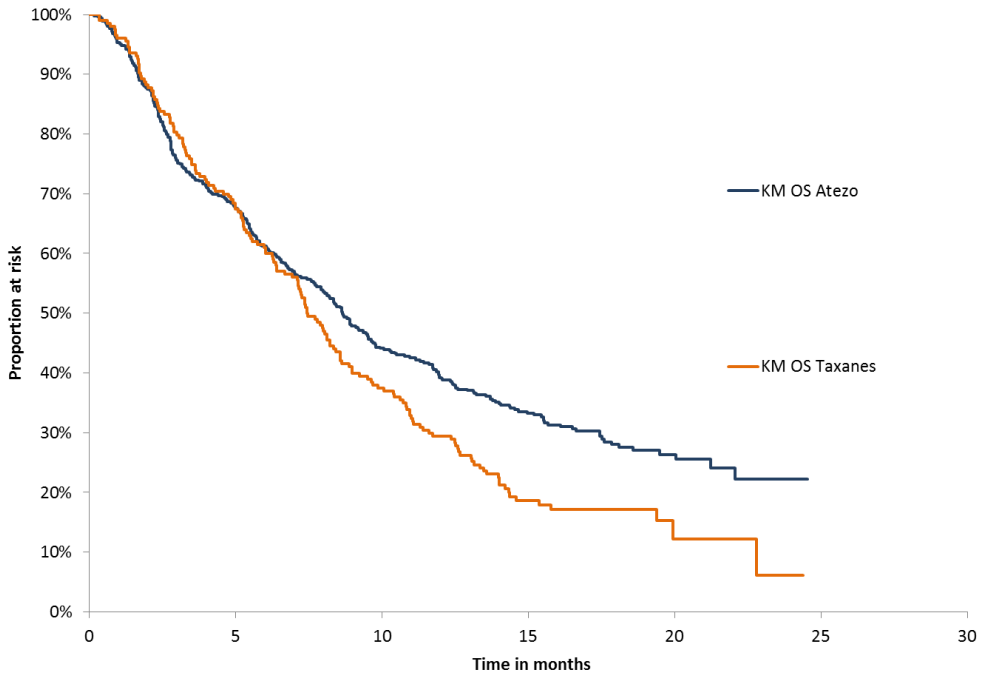


Figure 12: PFS KM curves (atezolizumab vs taxanes)

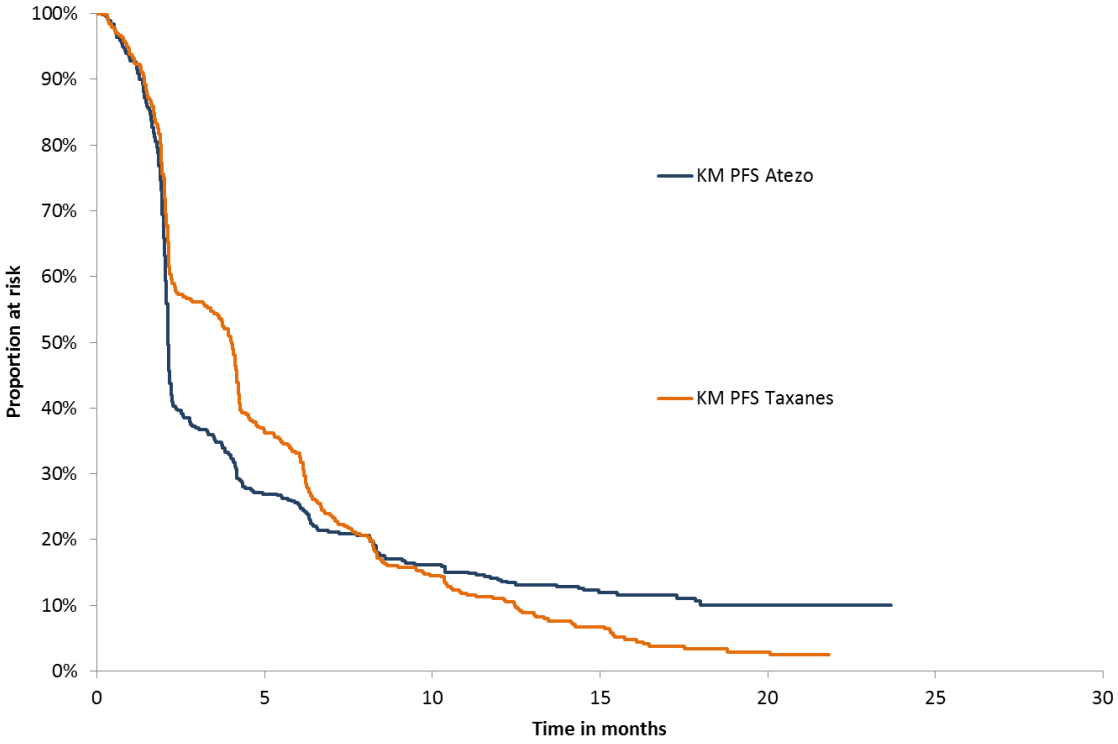


Figure 13: Log-cumulative hazard plot for OS in IMvigor 211

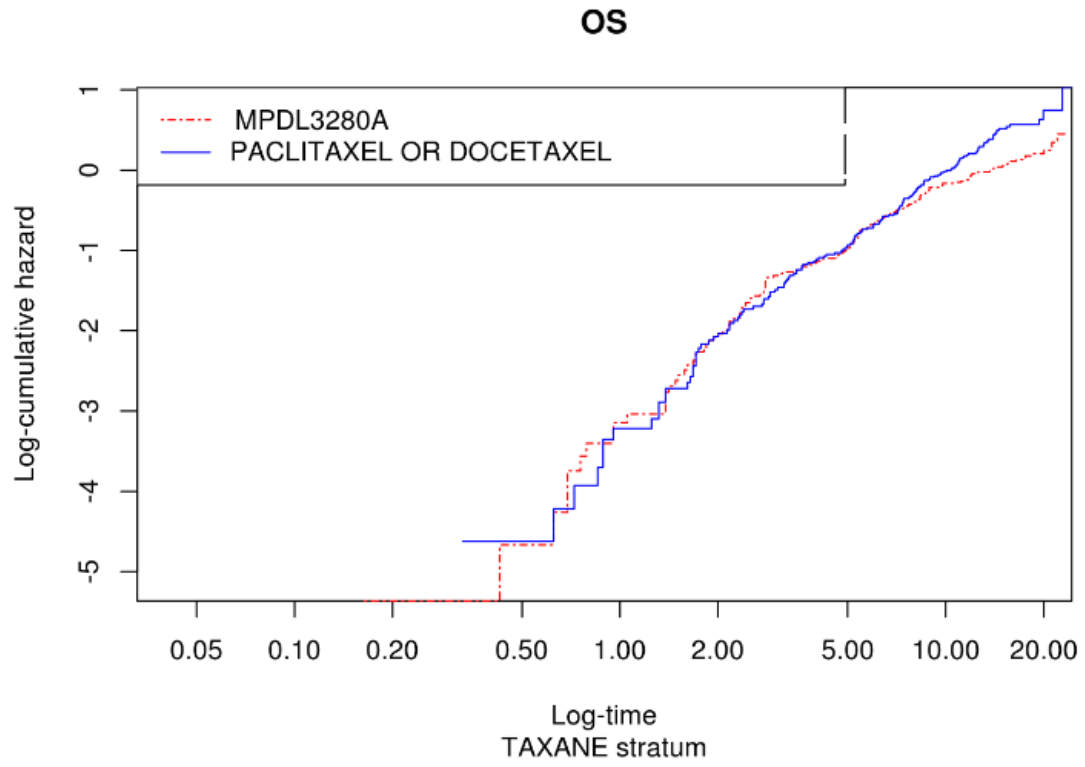
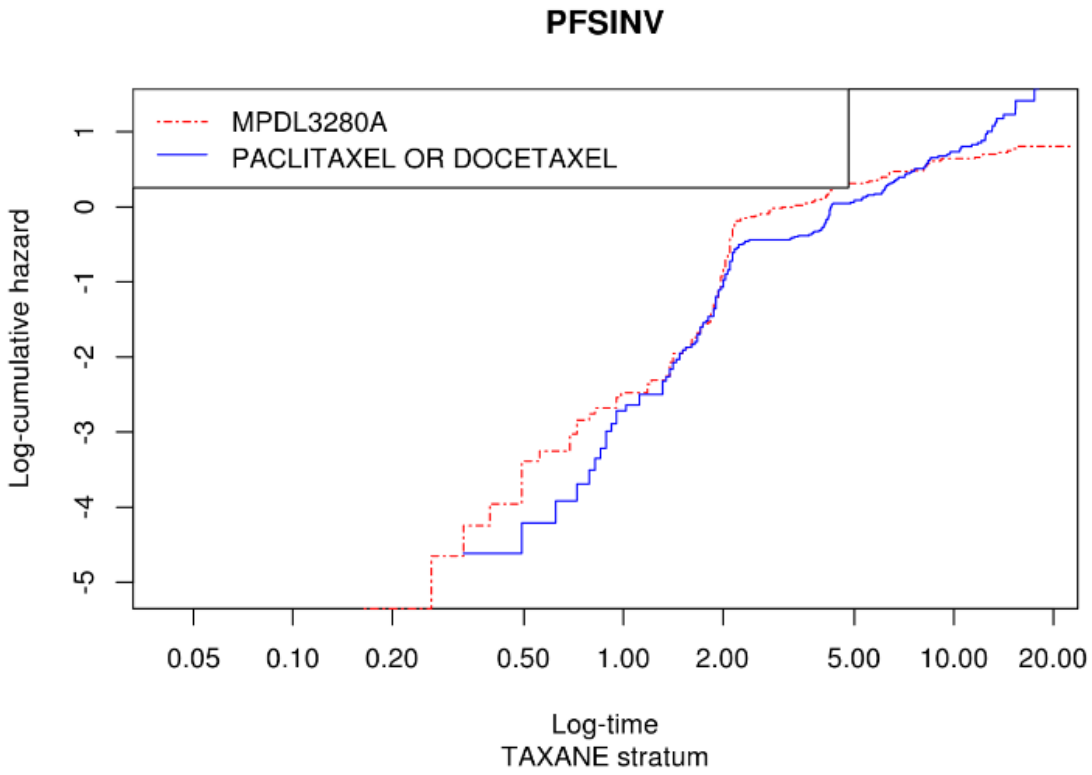


Figure 14: Log-cumulative hazard plot for PFS in IMvigor 211



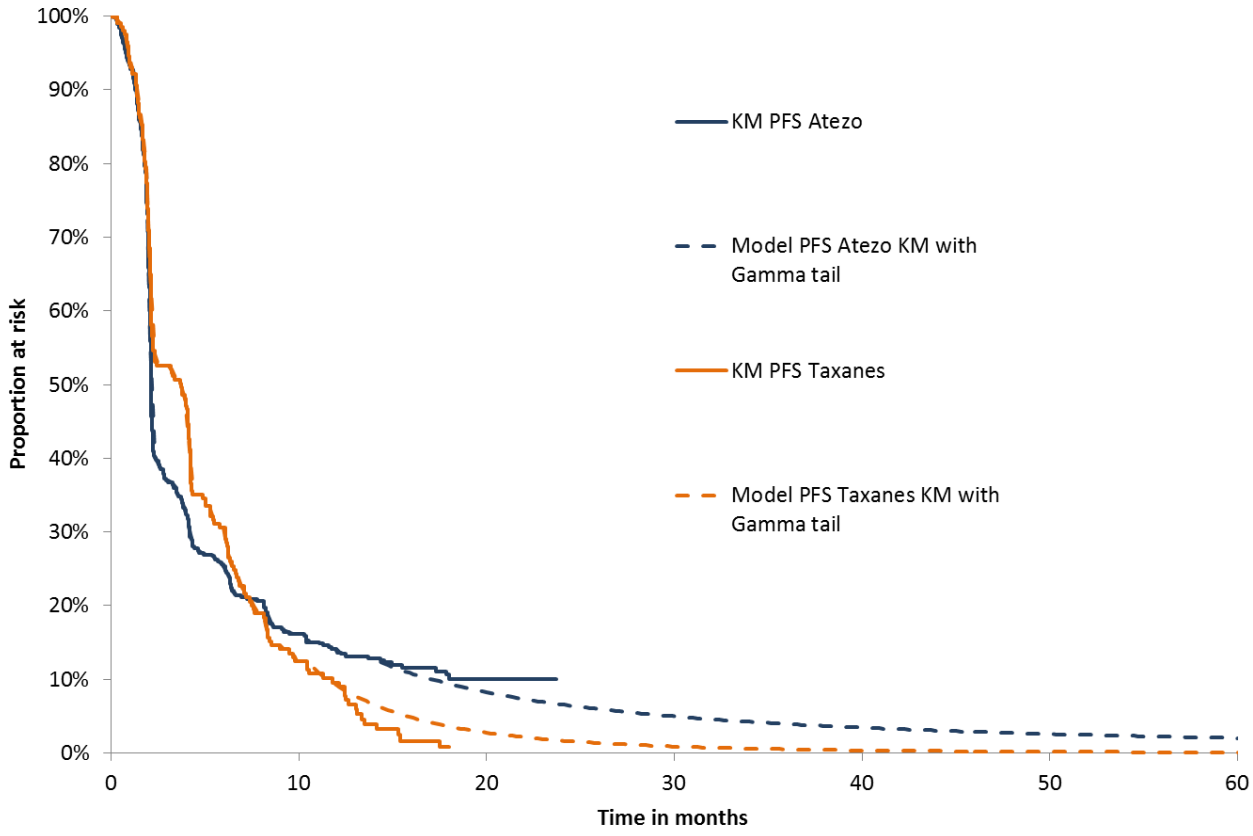
PFS Extrapolation

The following candidate distributions were fitted to the observed PFS data for atezolizumab from the IMvigor 211 study: Exponential, Weibull, Log-logistic, Log-normal, Generalised gamma and Gompertz. Based on the AIC and BIC statistics (Table 6), visual inspection and clinical plausibility, the GenGamma distribution was considered to be the most appropriate functional form. Since PFS data for atezolizumab in the study are rather mature a KM with GenGamma tail was applied. The extrapolation is illustrated in Figure 15. Alternative extrapolations are explored in scenario analyses.

Table 6: Summary of parametric function goodness of fit for PFS – atezolizumab

Parametric distribution	AIC	BIC
Exponential	1,457.66 (5)	1,461.81 (4)
Weibull	1,456.90 (4)	1,465.19 (5)
Log-logistic	1,296.75 (2)	1,305.04 (2)
Log- normal	1,313.02 (3)	1,321.31 (3)
GenGamma	1,264.86 (1)	1,277.30 (1)
Gompertz	1,459.66 (6)	1,467.95 (6)

Figure 15: Parametric (Gamma) and KM estimates for PFS



The extrapolated PFS results for atezolizumab as compared to clinical trial results from studies IMvigor 211 and IMvigor 210 (Cohort 2) are shown in Table 7 below.

Table 7: Comparison of modelled and trial results for PFS – atezolizumab

	Median (model)	Median (trial)	12 month (model)	12 month (trial)
IMvigor 211	2.06 months	2.1 months	12.0%	NR
IMvigor 210 (2L)		2.1 months		NR

A similar approach was taken for taxanes. The goodness of fit criteria for the alternative parametric distributions are shown in Table 8. Based on the AIC and BIC statistics (Table 8) the curves presenting the closest statistical fit to the data are log- normal and GenGamma. However, the observed PFS data for taxanes in IMvigor 211 are almost complete and

therefore the choice of a parametric distribution for the period beyond the trial horizon does not have a big impact. As such, the PFS KM curve was used for taxanes followed by a GenGamma distribution. GenGamma is the second best-fitting distribution for taxanes and consistent with the NICE DSU recommendation, for the use of the same functional form for parametric extrapolation across the separate arms of the trial. The resulting PFS extrapolation for taxanes is illustrated in Figure 15. Alternative extrapolations are explored in scenario analyses.

Table 8: Summary of parametric function goodness of fit for PFS – taxanes

Parametric distribution	AIC	BIC
Exponential	547.26 (6)	550.63 (5)
Weibull	532.67 (4)	539.41 (4)
Log-logistic	516.01 (3)	522.74 (3)
Log- normal	507.96 (1)	514.70 (1)
GenGamma	509.67 (2)	519.77 (2)
Gompertz	545.33 (5)	552.06 (6)

OS extrapolation

Experience with immunotherapy agents has increased over the last few years. Data available for immunotherapy agents suggest there is plausibility that a proportion of patients experience sustained response and survival over time. The belief that long term survival will be possible for some mUC patients, given the mechanism of action of atezolizumab, has been validated by clinical experts.

At this time, long term evidence is not available from clinical trials. Furthermore, with relatively immature OS data from the IMvigor 211 study, use of traditional parametric survival analysis – which relies on the observed data for atezolizumab – will fail to account for this change in mortality rate and lead to an inappropriate 'flattening' of the survival curve tail.

Various methods have been utilised in previous immunotherapy appraisals, with NICE assessments highlighting both strengths and weaknesses of the approaches. An important consideration is the clinical plausibility of the resulting extrapolated survival curve.

Mix-cure rate model

The OS estimates for this analysis were modelled using the mixture cure-rate methodology, as previously described in appraisal TA414 (9) and in our original company submission for the current appraisal (Section 5.3.5).

The mix-cure rate model accounts for the decrease in cancer-related mortality-risk over time. Statistically, this decrease in the cancer-related mortality-risk is accounted for by an estimation of the overall mortality risk at a given point in time, as a mixture between the cancer-related and background mortality risk. The estimation uses a dataset including the observed survival times in the IMvigor 211 trial and the background mortality risks from life-tables. The weight assigned to the background mortality is referred to as the "cured fraction". However this 'cure rate fraction', should not be interpreted as a clinical 'cure' from cancer. Rather, the proportion of patients for whom their disease is stable, and the risk of death attributable to cancer, is equivalent to the risk of death from other causes. This can be interpreted as a proportion of patients whom are as likely to die of non-cancer causes as from cancer. These two populations (those with low risk of cancer related death, and those with high risk of cancer related death) are combined to produce an average survival for the whole population.

In order to ascertain the 'cure fraction', long term survival data for mUC patients are required. Registry data are the most useful source for such data, however, exploration of available registries did not highlight suitable and robust data to validate an assumed 'cure fraction' in mUC.

Given the lack of robust, long term data in mUC, a strong assumption would be required to estimate a 'cure fraction' for implementation into the OS extrapolation. Over time, it is

anticipated clinical data for immunotherapies will support such a cure fraction. For the OS extrapolation of atezolizumab in the model, it was assumed 0% of patients will be at a lower risk of death due to their disease (i.e. a 0% cure fraction). This is a conservative assumption, and when long-term data are available, this will be further explored.

The mix-cure method is still appropriate to use, even when assuming a 0% cure fraction. Incorporation of background mortality in the extrapolation of the observed survival data mean the tail of the survival curve will never be above that of background mortality. This prevents an implausible scenario whereby long-term atezolizumab treated mUC survivors have a reduced risk of death vs. that of the age matched general population. Use of the method within this submission also allow for examination in results of scenario analyses which assume a positive cure fraction.

Generating parametric models for OS from IMvigor211

Atezolizumab

The Exponential, Weibull, Log-logistic, Log-normal, Gompertz, Gamma and Generalized Gamma parametric mix-cure rate models were fit to the IMvigor 211 results. The 'cure fraction' was set to 0%, as described above. The resulting AIC and BIC values for the 0% cure fraction models are displayed in Table 9 below.

Table 9: Summary of parametric function goodness of fit for OS - atezolizumab

Parametric distribution	AIC	BIC
Exponential	715.13 (7)	719.28 (7)
Weibull	715.10 (6)	719.25 (6)
Log-logistic	696.08 (3)	700.23 (3)
Log-normal	687.67 (2)	691.82 (2)
Gompertz	710.58 (4)	714.73 (4)
Gamma	714.36 (5)	718.50 (5)
GenGamma	686.89 (1)	691.04 (1)

According to visual fit and the AIC and BIC criteria (Table 9), the generalised gamma model was the most appropriate fit. The resulting curves were assessed as compared to available trial data. Table 10 demonstrates the model results correlate highly with trial data, thus validating the chosen parametric function.

Table 10: Comparison of modelled and trial results for OS

	Median (model)	Median (trial)	12 month (model)	12 month (trial)
IMvigor 211	8.5 months	8.6 months	39.9%	39.2%
IMvigor 210 (2L)		7.9 months		36.9%

Expert clinical advice received during the original CS, and also during the first Appraisal Committee meeting, suggested the proportion of 2L treated atezolizumab patients anticipated to be alive at 5, 10, and 20 years. Although robust evidence is not available to support this, these views are based on experience with immunotherapies to date and their expertise in clinical research. As seen in Table 11, the estimated results from the model are conservative versus the estimates from expert opinion.

In addition, the mean OS estimated in the model for patients treated with atezolizumab (1.55 years) is conservative compared to the mean OS estimated in our original submission, based on the IMvigor 210 study (1.89 years).

Table 11: Comparison of modelled and expert opinion results for OS

	5 year OS	10 year OS	20 year OS
Expert clinical advice	10-20%	5-10%	0-5%
Atezolizumab IMvigor 211 model	7.7%	2.7%	0.7%

OS extrapolations with alternative cure rates for atezolizumab are explored in scenario analyses.

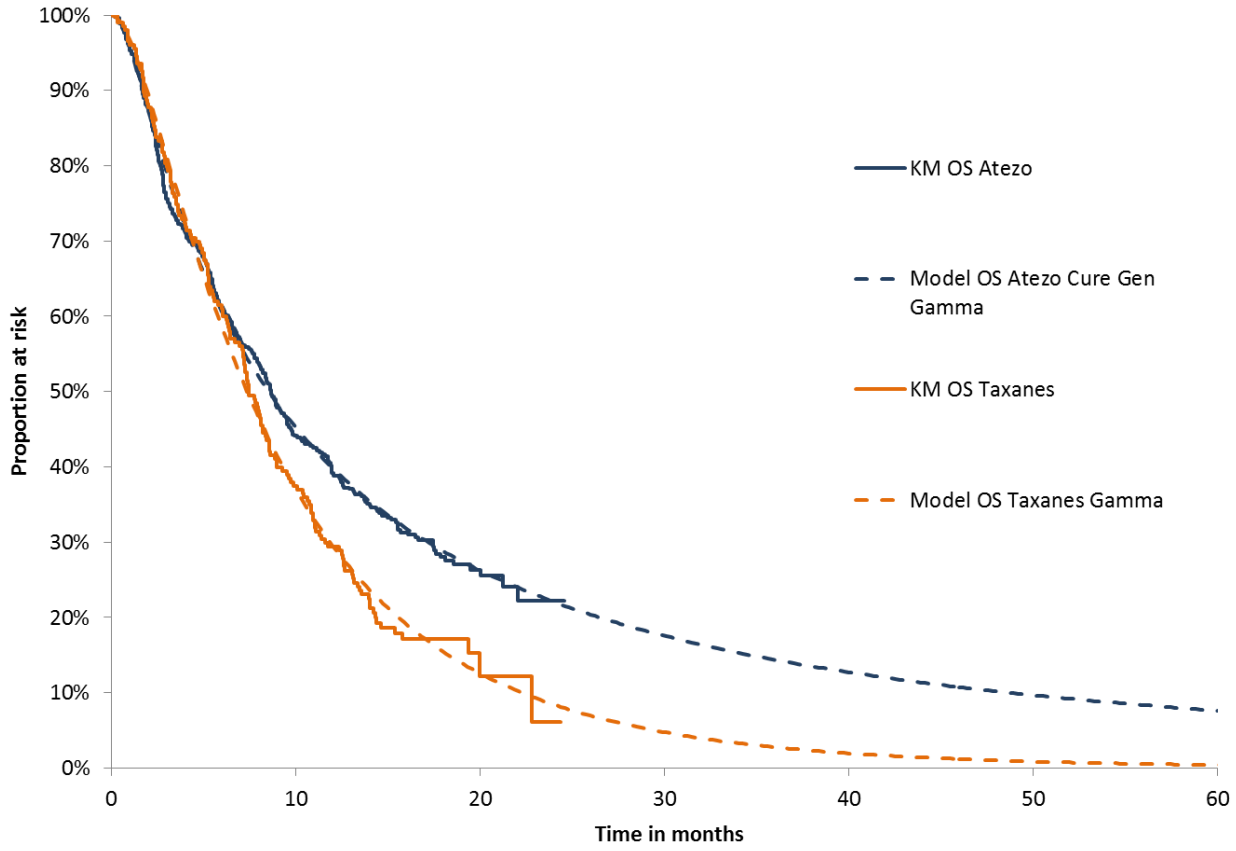
Taxanes

For taxanes, the following candidate parametric distributions were fitted to the observed OS data from the IMvigor 211 study: Exponential, Weibull, Log-logistic, Log-normal, Generalised gamma and Gompertz. The goodness of fit for these functions was assessed using AIC, BIC and visual assessment of each fitted curve against the observed data. Based on these, the log-logistic and GenGamma distributions were considered to be the two most appropriate functional forms. GenGamma was chosen, in order to be compliant with the NICE DSU recommendation to use the same functional form across the separate trial arms. The OS extrapolation applied to trial data for both atezolizumab and taxanes is illustrated in Figure 16.

Table 12: Summary of parametric function goodness of fit for OS – taxanes

Parametric distribution	AIC	BIC
Exponential	563.20 (6)	566.57 (5)
Weibull	553.41 (4)	560.14 (3)
Log-logistic	550.81 (2)	557.54 (1)
Log- normal	552.01 (3)	558.74 (2)
GenGamma	550.75 (1)	560.85 (4)
Gompertz	561.07 (5)	567.81 (6)

Figure 16: Parametric and KM estimates for OS



Health-related quality-of-life

The economic model includes the health states PFS, PD and death. However, it is recognised that progression, as measured via the RECIST criteria, does not always signify loss of clinical benefit for patients being treated with atezolizumab. This is in line with the anticipated marketing authorisation for atezolizumab, where it is recommended that patients remain on treatment until loss of clinical benefit or unmanageable toxicity.

As such, it is appropriate to assume that patients on treatment are receiving clinical benefit, including HRQoL benefit. Utilities are therefore implemented in the economic model via 'on treatment' or 'off treatment' states. Should this approach not be taken, the model contains an inconsistency in which cost is being generated for atezolizumab patients beyond progression, without any resulting HRQoL benefit being accounted for.

HRQoL data were collected in the IMvigor 211 study via the EQ-5D-3L questionnaire directly from 2L mUC patients treated with atezolizumab and taxanes. EQ-5D-3L data were collected prior to any administration of study treatment and/or prior to any other study assessment(s) and at 6, 12, and 24 weeks after disease progression.

The number of patients and observations included in the utility analyses are reported in Table 13.

Table 13: Number of patients and observations for utility analyses from IMvigor 211

State	Number of patients	Number of observations	Source
Atezolizumab	395	3494	IMvigor 211 study
Taxanes	167	783	IMvigor 211 study
Off treatment	695	3474	IMvigor 211 study

EQ-5D-3L data from IMvigor 211 were transformed into utility values using UK specific weights (10). Utility results were derived based on linear mixed effects models with a random

intercept term. These models account for the longitudinal structure of the data via subject specific random effects i.e. inducing correlation between observations from the same patient. The models were adjusted for the following baseline characteristics: sex, age, ECOG (0 or >0), liver metastasis, and haemoglobin level below 10 g/dl.

The resulting utility values that were used in the model are presented in Table 14. No difference is assumed for off treatment utilities between treatments.

Table 14: Summary of utility values from IMvigor 211

State	Atezolizumab (SE)	Taxanes (SE)	Source
On treatment	0.684 (0.011)	0.660 (0.012)	IMvigor 211 study
Off treatment	0.547 (0.010)	0.547 (0.010)	IMvigor 211 study

Alternative utility values from the NICE appraisal of pembrolizumab in previously treated advanced or metastatic urothelial carcinoma [ID1019] (7) are used in a scenario analysis. These are presented in Table 15.

Table 15: Utility values from pembrolizumab in previously treated mUC

State	Pooled utilities (SE)	Source
Progression-Free	0.731 (0.007)	Pembrolizumab appraisal [ID1019] (7)
Progressed	0.641 (0.013)	Pembrolizumab appraisal [ID1019] (7)

The utilities used in our initial company submission (Section 5.4.6) from a vinflunine assessment in PBAC (11), are also explored in a scenario analysis.

Cost and Resource use

The categories of cost and resource use included in the model are: drug acquisition costs, treatment duration, drug administration costs, health state-related resource use for pre-progression and post-progression states, costs to manage AEs. These have been presented in more detail in Section 5.5 of the initial Roche submission and have been updated if appropriate. Costs used to inform the current model are presented in tabular form (Table 16 - Table 19).

Prices for taxanes were taken from latest update of the drugs and pharmaceutical electronic market information tool (eMIT) (12) as these are more representative of the price paid within the NHS. List prices for taxanes are considered in a scenario analysis.

All grade ⩾3 treatment related AEs with an incidence of ⩾2% in the atezolizumab or the taxanes arm are included in the base case analysis.

Treatment duration is derived from IMvigor 211 and is discussed in the following section.

Table 16: Dose and drug costs for intervention and comparators

	Dose	Source	List price (BNF) (13)	eMIT price
Atezolizumab	1200mg IV over 60 mins for first infusion, thereafter 30 mins Day 1 of each 21 day cycle	Draft SmPC	1200mg vial £3807.69	n/a
Paclitaxel	80 mg/m^2 IV over 60 mins Weekly	Guideline, expert clinical advice	30mg vial £100.26 150mg vial £455.47 (average price in BNF)	30mg vial £3.70 150mg vial £12.55
Docetaxel	75 mg/m^2 IV over 60 mins Day 1 of each 21-day cycle	SmPC, pIII trial	20mg vial £155.38 140mg vial £810.05 (average price in BNF)	20mg vial £3.85 140mg vial £20.62

Table 17: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient Setting	SB12Z	£236.19	NHS reference costs 2015-16
Docetaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z	£236.19	NHS reference costs 2015-16
Paclitaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB14Z	£383.13	NHS reference costs 2015-16

Table 18: Adverse event costs

Adverse event	Cost	Reference
Anemia	£329.92	HRG 2015/16 (Day case SA04G,H,J,K,L (Iron Deficiency Anaemia, average of CC scores)
Asthenia	£3082.59	Nivolumab NSCLC appraisals ID811 and ID900 (14, 15)
Diarrhoea	£114.00	Non-consultant led first visit - gastroenterology - service code 301
Fatigue	£3082.59	Nivolumab NSCLC appraisals ID811 and ID900 (14, 15)
Neuropathy peripheral (sensory or motor)	£139.12	HRG service code 191, pain management
Neutropenia	£354.72	Nivolumab NSCLC appraisals ID811 and ID900 (14, 15)
Neutrophil count decreased	£0	Nivolumab NSCLC appraisals ID811 and ID900 (14, 15)
White blood cell count decreased	£423.00	Nivolumab NSCLC appraisals ID811 and ID900 (14, 15)

Table 19: Resource utilisation and cost by health-state

	Frequency per month	Unit cost	Per cycle cost	Source for cost
Pre-progression				
GP consultation	1	£36	£8.31	Curtis 2016
Community nurse visit	4	£38	£28	Community health services – district nurse Service code NO2AF 2015-16 costs
Health home visit	1	£40	£9.23	Curtis 2016
Dietician	1	£81	£18.69	Community health services - dietitian Service code A03 2015-16 costs
Oncologist consultation (consultant)	1	£163	£37.62	Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs
Total			**£111.85**	

Post-progression				
GP consultation	1	£36	£8.31	Curtis 2016
Community nurse visit	4	£38	£38	Community health services – district nurse Service code NO2AF 2015-16 costs
Health home visit	1	£40	£9.23	Curtis 2016
Dietician	1	£81	£18.69	Community health services - dietitian Service code A03 2015-16 costs
Hospice care	70% of patients	£1119	£30.13	Curtis 2016 (Assumed proportion from vinflunine appraisal TA272, assumed 6 months survival)
Oncologist consultation (non-consultant)	1	£100	£23.08	Non-consultant led - Medical oncology. Service code 370 2015-16 costs
Pain medication	30 (Daily)	£3.69	£0.85	eMIT £1.23 per 10mg/1ml morphine sulphate solution for infection – 10 pack
Palliative radiation therapy		£283		SC47Z: Preparation for simple radiotherapy with imaging and simple calculation (outpatient)
		£105		SC22Z: Deliver a fraction of treatment on a megavoltage machine (outpatient)
Proportion of patients	42.70%			Vinflunine appraisal TA272
Number of courses	1.9			Vinflunine appraisal TA272
Total dose		£314.78	£12.11	Over assumed 6 month survival
Palliative chemotherapy		£277		Outpatient – Procure chemotherapy drugs for regimens in Band 2 – SB02Z
Proportion of patients	30%			Vinflunine appraisal TA272
Number of cycles (of 21 days)	2			Vinflunine appraisal TA272
Total dose		£27.70	£6.39	Over assumed 6 month survival
Total cost			**£146.79**	

Treatment duration

Atezolizumab will be licensed for use until loss of clinical benefit or unmanageable toxicity. Results from the IMvigor 211 study, and clinical trial evidence from other indications for atezolizumab, suggests that patients continue to receive treatment with atezolizumab beyond disease progression. As such, PFS is not a good surrogate for treatment duration as it is likely to underestimate the true treatment duration expected in clinical practice, and subsequently, treatment cost.

Data on time to treatment discontinuation (TTD) are available for both atezolizumab and taxane therapies in IMvigor 211. As such, TTD directly from the IMvigor 211 study was used to inform treatment duration in the economic model.

As not all patients had discontinued treatment in IMvigor 211, it was necessary to extrapolate the study results such that treatment duration could be estimated beyond the trial period. Parametric distributions were fitted to the TTD Kaplan–Meier curves and assessed for their goodness of fit to the data using the AIC / BIC statistics, visual assessment and clinical plausibility of each of the extrapolations.

Table 20 and Table 21 provide the AIC and BIC goodness of fit results for the functions used to model TTD for atezolizumab and taxanes respectively. Based on the AIC and BIC statistics, the best-fitting distribution for atezolizumab is Log-logistic, followed by GenGamma. For taxane therapies, the best fit according to AIC/BIC is demonstrated with GenGamma and Exponential distribution. Therefore, the parametric distribution providing the best fit to the overall TTD data (i.e. across both the atezolizumab and the taxanes arms) is GenGamma. Use of the same parametric functional form (GenGamma) for both arms of the study, according to best fit to the overall data, is also compliant with the recommendation from NICE DSU.

In addition, if a Log-logistic extrapolation is selected for atezolizumab, the extrapolated TTD curve crosses the OS curve at 13 years and is below the OS curve for the remaining of the time horizon of the model. Although only a small proportion of patients are still alive in the model at this point, this cannot be considered clinically plausible. When using GenGamma for atezolizumab, the TTD curve remains below the OS curve for the duration of the model's time horizon. As such, the GenGamma distribution is deemed to be the most appropriate choice of parametric distribution.

Given that the observed TTD data for taxanes in IMvigor 211 are almost complete, it was deemed appropriate to use the TTD KM curve for taxanes followed by the GenGamma distribution. For consistency, the same approach was used for atezolizumab (KM curve with GenGamma tail) but with a different cut-off point for switching from KM to parametric extrapolation (at 20% of patients at risk), due to the TTD data for atezolizumab being less complete.

The resulting extrapolations are displayed in Figure 17 below.

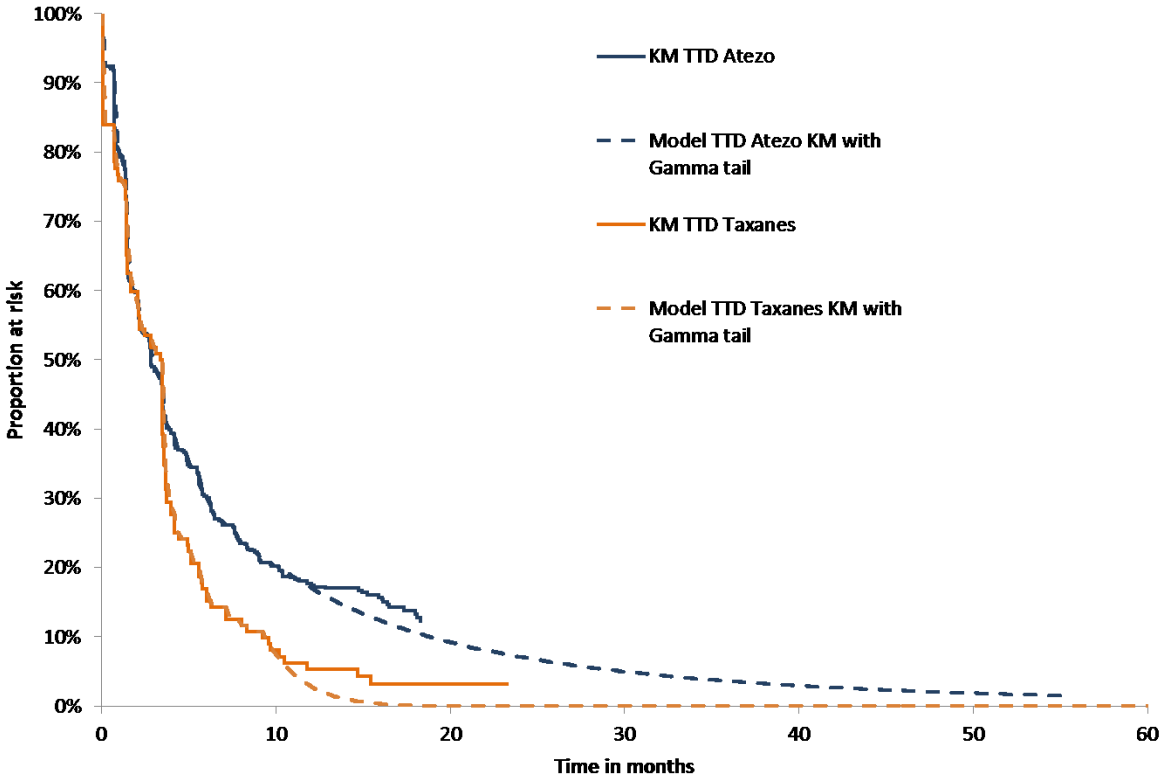
Table 20: AIC and BIC for TTD - atezolizumab

Parametric distribution	AIC	BIC
Exponential	1,795.69 (5)	1,799.82 (5)
Weibull	1,716.02 (3)	1,724.28 (3)
Log-logistic	1,696.22 (1)	1,704.48 (1)
Log-normal	1,730.44 (4)	1,738.70 (4)
GenGamma	1,709.18 (2)	1,721.57 (2)
Gompertz	1,797.69 (6)	1,805.95 (6)

Table 21: AIC and BIC for TTD - taxanes

Parametric distribution	AIC	BIC
Exponential	664.70 (2)	668.01 (1)
Weibull	666.55 (4)	673.16 (4)
Log-logistic	714.07 (5)	720.68 (5)
Log-normal	741.58 (6)	748.18 (6)
GenGamma	660.57 (1)	670.48 (2)
Gompertz	665.58 (3)	672.19 (3)

Figure 17: KM and extrapolated time to treatment discontinuation (TTD)



Summary of inputs in the economic analysis

The parameter inputs used in the economic model can be found in Table 22.

Table 22: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty (CI) and distribution:
General parameters		
Patient age	67	Fixed
Discount rate (costs)	3.5%	Fixed
Discount rate (efficacy)	3.5%	Fixed
Time horizon	20 years	Fixed
Utility values		
On treatment atezolizumab	0.684	Beta distribution (0.011 standard error)
On treatment taxanes	0.660	Beta distribution (0.012 standard error)
Off treatment	0.547	Beta distribution (0.010 standard error)
Parametric survival curves		
PFS atezolizumab	KM+Generalised gamma	Multivariate normal distribution
PFS taxanes	KM+Generalised gamma	Multivariate normal distribution
OS atezolizumab	Cure generalised gamma (0% cure fraction)	Multivariate normal distribution
OS taxanes	Generalised gamma	Multivariate normal distribution
Parametric survival tail for treatment duration		
TTD atezolizumab	KM+Generalised gamma	Multivariate normal distribution
TTD taxanes	KM+Generalised gamma	Multivariate normal distribution
Treatment costs		
Atezolizumab 1200mg	£3807.69	Fixed
Taxanes	Table 16	Fixed
Administration atezolizumab	£199	Log-normal distribution
Administration docetaxel	£199	Log-normal distribution
Administration paclitaxel	£304	Log-normal distribution
Health state costs		
Pre-progression cost	£111.85	Log-normal distribution
Post-progression cost	£146.79	Log-normal distribution
Adverse event		
Individual AE costs	Table 18	Log-normal distribution

Assumptions in the economic analysis

Key assumptions used in the economic analysis are listed in Table 23 below

Table 23: Key assumptions within economic model

Area	Assumption	Justification
Perspective	NHS and Personal Social Services	As per NICE reference case
Time horizon	20 years	Appropriate to capture all associated costs and benefits
Clinical efficacy and safety	Efficacy and safety results for atezolizumab seen in the IMvigor 211 study are transferable to UK population	The IMvigor 211 study included UK patients (84 patients out of the treated population (n=902) were recruited in the UK)
Treatment duration	Treatment duration for atezolizumab and taxanes is based on time on treatment results of the IMvigor 211 study	IMvigor 210 and IMvigor 211 results suggest patients in 2nd line continue to receive treatment with atezolizumab beyond progression Time to treatment discontinuation data for taxanes in IMvigor 211 are almost complete and as such appropriate to use for taxanes treatment duration
Resource use	As per initial company submission	Assumptions based on prior appraisals, and feedback received from ERG appraisal reviews.

End of life criteria

Metastatic UC is recognized as having short survival duration. It was stated in the ACD for ID939, that the Appraisal Committee concluded it was most likely that the end-of-life criteria would be met for both populations. Atezolizumab is also believed to meet end of life criteria in previously treated mUC based on evidence from IMvigor 211, taking into account the extrapolated mean OS for atezolizumab and comparators (Table 24).

Table 24: End of life criteria

<table>
<tr><th>Criterion</th><th>Data available</th><th>Reference</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>The average life expectancy for mUC is 14 -15 months in the fittest patients who receive systemic cisplatin-based treatment and 8 months without treatment</td><td>(16, 17)</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>Due to the shape of treatment response, and long survival tail, median OS results do not accurately capture the survival gains for atezolizumab treated patients.
Significant long-term gains can be made, thus the mean OS results better reflect the clinical outcomes of patients.
Incremental mean OS is >3 months for atezolizumab compared to taxanes, when taking results from the economic analysis, as shown below.
<table>
<tr><td></td><td>Mean</td><td>Median</td></tr>
<tr><td>Atezolizumab</td><td>18.6 months</td><td>8.5 months</td></tr>
<tr><td>Taxanes</td><td>10.2 months</td><td>7.4 months</td></tr>
</table></td><td>Economic model</td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>Locally advanced or metastatic urothelial bladder cancer population (at diagnosis): 4-10% of 10,000 annual incidence (CRUK) – 400-1000 patients per year</td><td>(18, 19)</td></tr>
</table>

Base-case incremental cost effectiveness analysis results

Base-case results of the economic model based on the list price for atezolizumab are presented in Table 25.

At list price, atezolizumab 2L provided a QALY gain of 0.93, and life-year gain of 1.55, at a total drug cost of £41, 174, and total overall cost of £54,573. The taxanes comparator provided a gain of 0.49 QALYs and 0.96 life years, at drug costs of £429 and total costs of £10.253. The resulting ICER for atezolizumab compared to taxanes is £100,844 per QALY.

The equivalent ICER incorporating the updated PAS recently submitted for atezolizumab is [redacted] vs. taxanes (Table 26). As such, at PAS price and considering end of life criteria, these results show atezolizumab to be a cost-effective use of NHS resources compared to taxanes.

Table 25: Base-case results (2L) – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£54,573	1.55	0.93	£44,321	0.71	0.44	£100,844
Taxanes	£10,253	0.85	0.49				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 26: Base-case results (2L) – PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.55	0.93	[redacted]	0.71	0.44	[redacted]
Taxanes	[redacted]	0.85	0.49				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Clinical outcomes from the model

Comparison of results from the model to existing observed data from studies IMvigor 211 IMvigor 210 allows an assessment of the accuracy of the modelled survival. Results for PFS and OS from the model are compared to trial data in Table 27 and Table 28-Table 29 respectively.

The model is accurate in terms of median PFS and OS results as compared to the IMvigor 211 study, thus supporting the approach taken for PFS and OS extrapolation. In addition, as seen in Table 29, the estimated results from the model at 5, 10 or 20 years are conservative versus estimates from clinical expert opinion, received during the initial company submission and also during the first Appraisal Committee meeting.

Table 27: Summary of PFS model results compared with observed clinical data

	Median (model)	Median (trial)	12 month (model)	12 month (trial)
IMvigor 211	2.06 months	2.1 months	12.0%	NR
IMvigor 210 (2L)		2.1 months		NR

Table 28: Summary of OS model results compared with observed clinical data

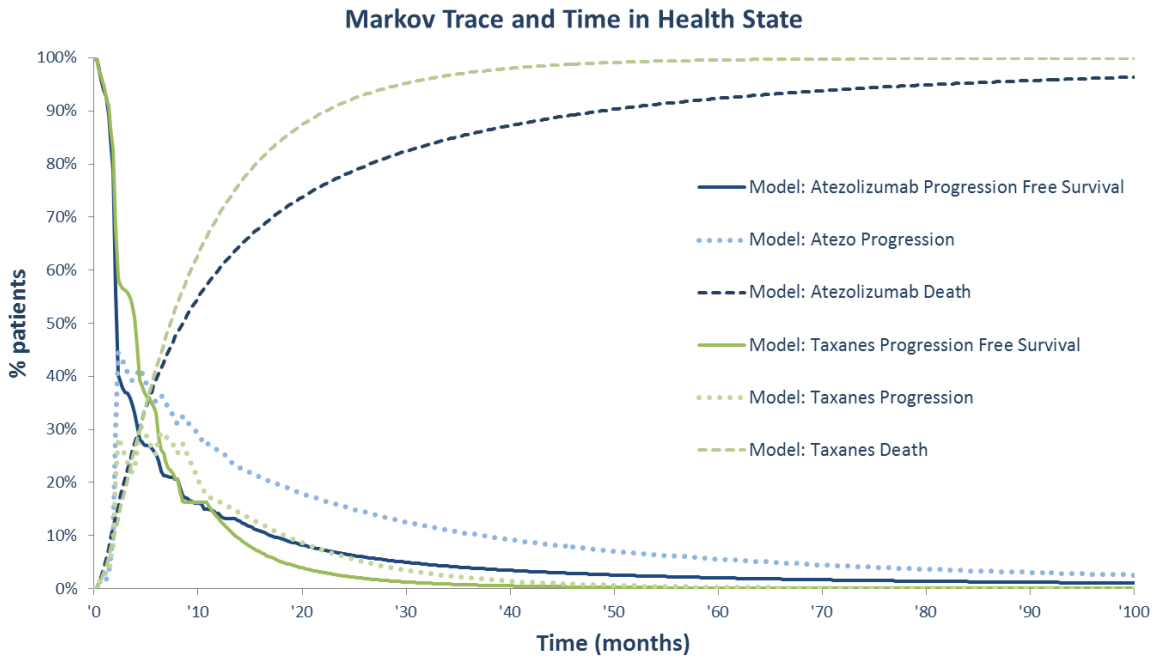
	Median (model)	Median (trial)	12 month (model)	12 month (trial)
IMvigor 211	8.5 months	8.6 months	39.9%	39.2%
IMvigor 210 (2L)		7.9 months		36.9%

Table 29: Comparison of modelled and expert opinion results for OS

	5 year OS	10 year OS	20 year OS
Expert clinical advice	10-20%	5-10%	0-5%
Atezolizumab IMvigor 211 model	7.7%	2.7%	0.7%

Figure 18 shows aggregated results from the model for all health states for the comparison of atezolizumab and taxanes. It can be seen that over the time horizon of the model, a greater proportion of patients spend more time in the PFS state and experience longer OS when receiving atezolizumab as compared to taxanes.

Figure 18: Markov trace: combined for results for atezolizumab and taxanes



Disaggregated results of the base case incremental cost effectiveness analysis

The QALY gain disaggregated by health states allows exploration of which health state is driving QALY gain (Table 30). Since health state occupancy in the model is driven by time to treatment discontinuation, PFS and PD states effectively mirror patients being on and off treatment. The incremental QALY gain for atezolizumab is achieved both when patients are on the PFS and PD heath states (i.e. on and off treatment).

Table 30: Summary of QALY gain by health state – comparison to taxanes

Health state	QALYs atezolizumab	QALYs taxanes	Incremental QALYs	% absolute increment QALYs
PFS	0.412	0.168	0.245	56%
PD	0.520	0.325	0.195	44%
Total	0.932	0.493	0.440	100%

A breakdown of the difference in costs by health state can be found in Table 31-Table 32 and a by resource use is found in Table 33-Table 34.

Table 31: Summary of costs by health state – list price

Health state	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
PFS	£47,473	£7,089	£40.384	91%
PD	£7,101	£3,164	£3,937	9%
Total	£54,573	£10,253	£44,321	100%

Table 32: Summary of costs by health state –PAS

Health state	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 33: Summary of predicted resource use by category of cost – list price

Cost Item	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
Treatment	£41,174	£429	£40,745	92%
Administration	£2,554	£4,090	£-1,536	-3%
Adverse events	£90	£31	£58	0%
Supportive care (PFS)	£3,656	£2,538	£1,117	3%
Supportive care (PD)	£7,101	£3,164	£3,937	9%
Total	£54,573	£10,253	£44,321	100%

Table 34: Summary of predicted resource use by category of cost – PAS

Cost Item	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Supportive care (PFS)	[redacted]	[redacted]	[redacted]	[redacted]
Supportive care (PD)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted using 1000 simulations, to assess uncertainty surrounding model inputs. The distributions to estimate parameters can be found in Table 22 summarising the model inputs.

PSA results of the compared to deterministic results for atezolizumab at list price are presented in Table 35 below. Deterministic and probabilistic results are very similar, not indicating signs of non-linearity in the model. A scatterplot of PSA results at list price is shown in Figure 19. Cost effectiveness acceptability curves at list price are shown in Figure 20.

The respective analyses at the PAS price are presented below (Table 36 and Figure 21-Figure 22)

Table 35: PSA results compared to base-case – list price

	Costs		QALYs		ICER	
	Deterministic	**PSA**	**Deterministic**	**PSA**	**Deterministic**	**PSA**
Atezolizumab	£54,573	£55,894	0.93	0.95		
Taxanes	£10,253	£10,850	0.49	0.50	£100,844	£101,319

Figure 19: Scatterplot of PSA results for cost effectiveness plane – list price

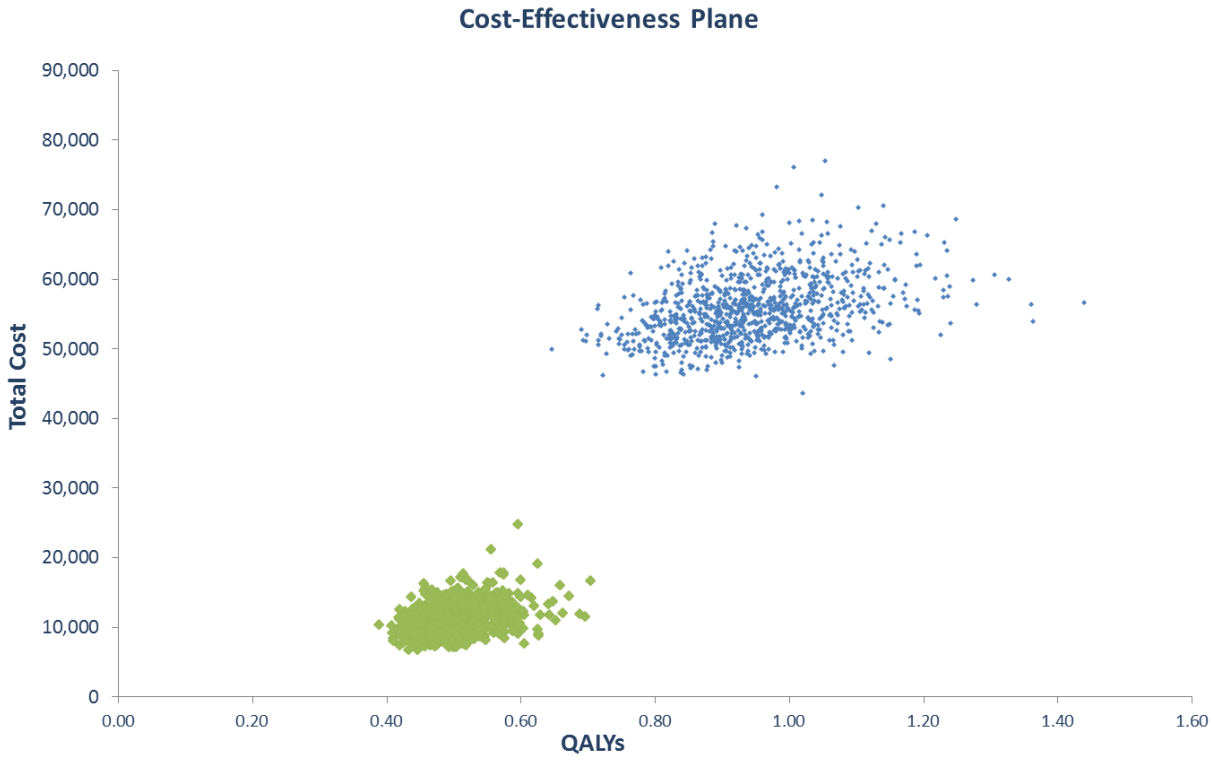


Figure 20: Cost-effectiveness acceptability curve – list price

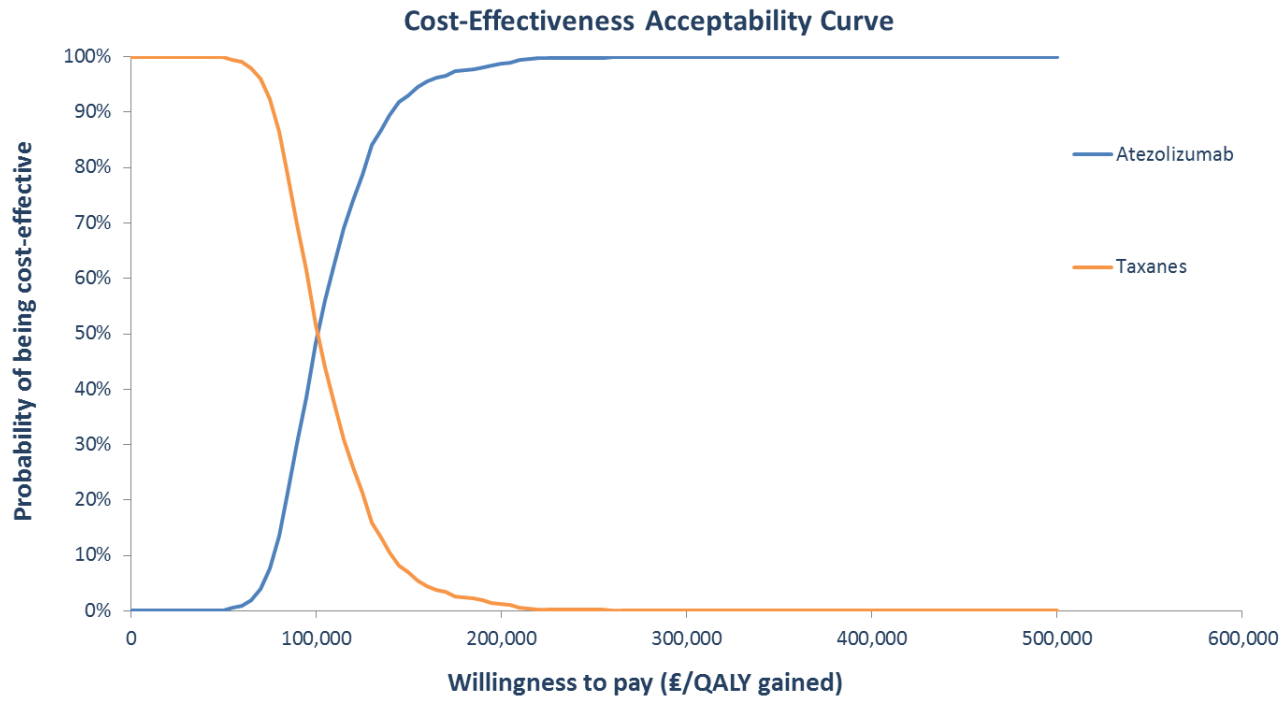


Table 36: PSA results compared to base-case – PAS

	Costs		QALYs		ICER	
	Deterministic	**PSA**	**Deterministic**	**PSA**	**Deterministic**	**PSA**
Atezolizumab	[redacted]	[redacted]	0.93	0.95		
Taxanes	[redacted]	[redacted]	0.49	0.50	[redacted]	[redacted]

Figure 21: Scatterplot of PSA results for cost effectiveness plane – PAS

Figure 22: Cost-effectiveness acceptability curve – PAS

Deterministic sensitivity analyses

The choice of parameters to vary in the deterministic sensitivity analyses was made on the basis of impact on the resulting ICER. The list of parameters included can be found in Table 37 below. Results of the analyses are displayed in Figure 23, and Figure 24. Key remaining model parameters were tested in scenario analyses in the following section.

Table 37: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value	Rationale for value range
Cost of atezolizumab	£3,807.69	+ 50%	- 50%	
Atezolizumab on treatment utility	0.684	0.662	0.705	95% confidence interval
Taxanes on treatment utility	0.660	0.637	0.684	95% confidence interval
Off treatment utility	0.547	0.527	0.567	95% confidence interval
Atezo off treatment supportive care costs	£146.79	+50%	-50%	
Comparator off treatment supportive care costs	£146.79	+50%	-50%	

Figure 23: Comparison to taxanes univariate sensitivity analysis (dark blue = lower value; light blue = higher value) – list price

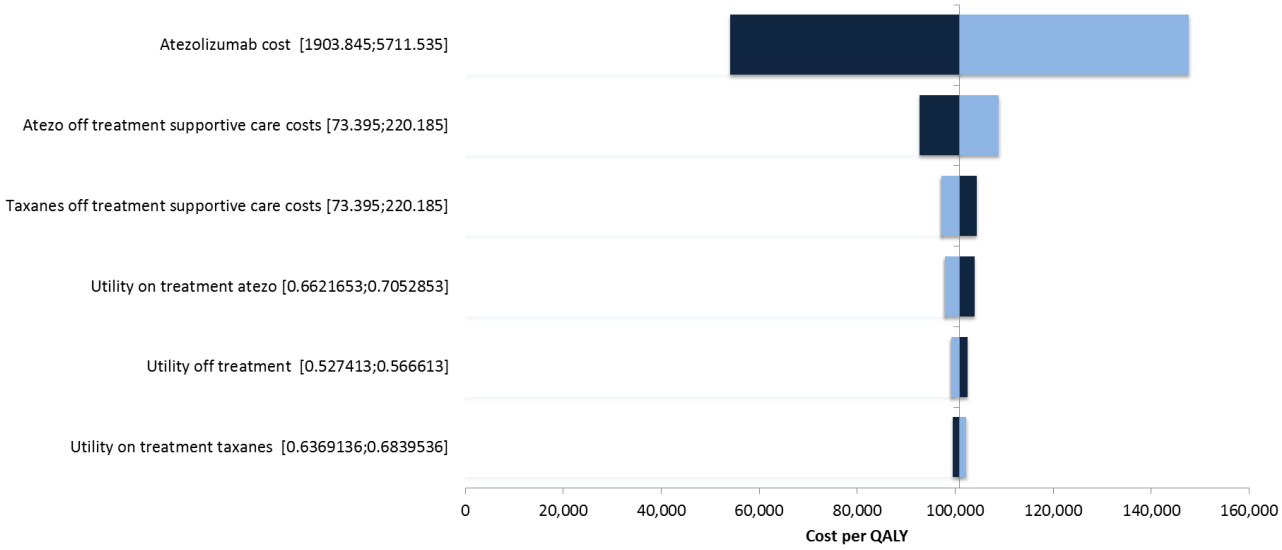


Figure 24: Comparison to BSC univariate sensitivity analysis (dark blue = lower value; light blue = higher value) – PAS

[redacted]

Scenario analyses

Scenario analyses were conducted to assess uncertainty around key model parameters and structural assumptions of the model. Results are shown in Table 38-Table 39 for the following scenarios exploring parameter changes:

- Comparators at list prices
- Alternative OS cure-rates for atezolizumab
- Alternative OS for atezolizumab and taxanes (best fitting alternative distributions with full parameterisation and KM + tail)
- Alternative PFS for atezolizumab and taxanes (best fitting alternative distributions with full parameterisation and KM + tail)
- Alternative TTD for atezolizumab and taxanes (best fitting alternative distributions with full parameterisation and KM + tail)
- Comparison to paclitaxel-only
- Alternative utility values from
    - Vinflunine PBAC assessment (11)
    - pembrolizumab 2nd line mUC NICE appraisal (7)
- Time horizon of 10 / 15 years
- Cost discount rate (1.5% rather than 3.5%)
- Effects discount rate (1.5% rather than 3.5%)

The scenarios indicate that at PAS price, there are many conditions at which the ICER remains below the acceptable threshold for end of life treatments.

Table 38: Resulting ICERs vs. taxanes from scenario analyses – list price

Scenario	Parameter	Value	ICER vs. taxanes
Base case	Comparator price	eMIT drug prices	£100,844
		List prices (BNF)	£69,196
Base case	OS Cure rate	0%	£100,844
		1%	£94,678
		2%	£89,184
		3%	£84,258
Base case	OS Atezolizumab + taxanes	Cure GenGamma 0% + GenGamma	£100,844
		GenGamma	£101,156
		Log-logistic	£126,552
		Log-normal	£129,338
Base case	PFS Atezolizumab + taxanes	KM+GenGamma	£100,844
		GenGamma	£100,946
		KM+Log-logistic	£101,336
		Log-logistic	£101,669
Base case	TTD Atezolizumab + taxanes	KM+GenGamma	£100,844
		GenGamma	£106,133
		KM+Log-logistic	£130,981

		Log-logistic	£136,334
Base case	Comparator	Pooled taxanes	£100,844
		Paclitaxel	£110,403
Base case	Utilities	IMvigor 211	£100,844
		Pembrolizumab 2L mUC NICE appraisal	£91,653
		Vinflunine PBAC assessment	£86,095
Base case	Time horizon	20	£100,844
		15	£103,870
		10	£111,441
Base case	Discount rate – effects and costs	3.5% for both	£100,844
	Discount rate - costs	1.5% (3.5% for effects)	£103,601
	Discount rate – effects	1.5% (3.5% for costs)	£92,562
	Discount rate – effects and costs	1.5% for both	£95,093

Table 39: Resulting ICERs vs. taxanes from scenario analyses – PAS

Scenario	Parameter	Value	ICER vs. taxanes
Base case	Comparator price	eMIT drug prices	[redacted]
		List prices	[redacted]
Base case	OS Cure rate	0%	[redacted]
		1%	[redacted]
		2%	[redacted]
		3%	[redacted]
Base case	OS Atezolizumab + taxanes	Cure GenGamma 0%	[redacted]
		GenGamma	[redacted]
		Log-logistic	[redacted]
		Log-normal	[redacted]
Base case	PFS Atezolizumab + taxanes	KM+GenGamma	[redacted]
		GenGamma	[redacted]
		KM+Log-logistic	[redacted]
		Log-logistic	[redacted]
Base case	TTD Atezolizumab + taxanes	KM+GenGamma	[redacted]
		GenGamma	[redacted]
		KM+Log-logistic	[redacted]
		Log-logistic	[redacted]
Base case	Comparator	Pooled taxanes	[redacted]

		Paclitaxel	[redacted]
Base case	Utilities	IMvigor 211	[redacted]
		Pembrolizumab 2L mUC NICE appraisal	[redacted]
		Vinflunine PBSC assessment	[redacted]
Base case	Time horizon	20	[redacted]
		15	[redacted]
		10	[redacted]
Base case	Discount rate – effects and costs	3.5% for both	[redacted]
	Discount rate - costs	1.5% (3.5% for effects)	[redacted]
	Discount rate – effects	1.5% (3.5% for costs)	[redacted]
	Discount rate – effects and costs	1.5% for both	[redacted]

Summary of sensitivity analyses results

Sensitivity analyses allow determination of the main drivers of the economic analysis, and exploration of alternative parameter inputs.

As it can be seen in the deterministic analyses and scenario analyses, the ICER is most sensitive to the price of atezolizumab, the price of comparators (eMIT vs. list price), the OS extrapolation, the time to treatment discontinuation, the utility values used and the discount rates considered.

Interpretation and conclusions of IMvigor211 economic evidence

The cost-effectiveness analysis presented makes use of the best and latest available evidence to inform the economic model:

- Results from IMvigor 211 provide head to head, comparative evidence for atezolizumab versus taxanes in previously treated mUC patients (2nd line); these are used to inform OS, PFS and TTD in the economic model
- EQ5D utility values are obtained from IMvigor 211 for both atezolizumab and taxanes, providing greater certainty around the economic results.
- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice.
- IMvigor 211 recruited patients from the UK and as such, the results of the economic analyses presented are generalizable to patients with previously treated mUC in England and Wales.

The model structure used captures clinically relevant health states and outcomes for mUC patients. The model predictions accurately matched available observed OS and PFS data for atezolizumab from existing studies (IMvigor210 and IMvigor 211). In addition, the long-term survival outcomes predicted in the model for atezolizumab are in line with what clinical experts anticipate in clinical practice.

Sensitivity and scenario analyses were conducted to inform the uncertainty around model inputs. The results presented, both in the base-case as well as in many of the scenarios, support the conclusion that, when considering the PAS price and within the context end-of-life therapies, atezolizumab is a cost-effective therapeutic option for the treatment of patients with previously treated advanced or metastatic urothelial carcinoma.

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Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments, 5pm on 23/08/17 email: jenna.dilkes@nice.org.uk or via 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):	Action Bladder Cancer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	Allen Knight, Chair ABC UK

Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments, 5pm on 23/08/17 email: jenna.dilkes@nice.org.uk or via NICE DOCS

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.
Example 1	We are concerned that this recommendation may imply that ……..
1	ABC UK is disappointed with the draft recommendations. We feel this disadvantages, even prejudices against, bladder cancer patients. According to CRUK the 5 year survival since 1980 of the most prevalent cancers has increased dramatically: Lung from 5% to 10%, Bowel from 33% to 59%, Prostate from 38% to 85% and Breast from 61% to 88%, yet for Bladder Cancer 5 year survival has actually DECREASED from 56% to 53%. This treatment has the potential to provide long term remission for c20% of BC patients, or increasing overall survival to about 63%.
2	We understand the arguments for cost effectiveness and QALYs, but given the lack of hope for these patients and lack of investment in research in BC (only 0.6% of the cancer research spend), we feel that the treatment deserves to be made available.
3	We dispute that this is an end of life treatment and that the '3 months' life extension is grossly misleading. The company has said that the drug is ineffective for c80% of patients and currently has no way of understanding which c20% would respond best. However those who do respond can enter very long term remission and have a very high QoL.
4	The Committee cites 'uncertainty' as a major reason for making their recommendations. This includes uncertainty around the effectiveness and action of the new treatment and equally about uncertainty around the efficacy and standards associated with current treatments. We feel that the best way of increasing certainty is to recommend the new treatment for routine commissioning and then reviewing once greater data has been obtained.
5	We understand that trials data is being generated all the time and that the most recent data, which was not available at the time of the committee consultation meeting, shows greater efficacy. We trust that this has been taken into account but this is not apparent.
6	We believe that some of the Committee's modelling is unduly pessimistic leading to an adverse opinion of cost effectiveness based on mathematical modelling alone. Had an appreciation of the mechanism of action of the treatment been fully taken into account we believe its cost effectiveness would have been more accurately and positively expressed..

Insert extra rows as needed

Checklist for submitting comments

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- 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.

Single Technology Appraisal (STA)

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

1. Please provide the clinical study report for the IMvigor 211 trial, including the protocol and analysis plan.

2. Please provide the following reference: “Powles T, Loriot Y, Durán I, Ravaud A, Retz M, Vogelzang NJ, et al., editors. IMvigor211: A Phase III Randomized Study Examining Atezolizumab vs. Chemotherapy for Platinum-Treated Advanced Urothelial Carcinoma. European Association for Cancer Research; 2017.”

3. Please provide an explanation of why the sample sizes for the atezolizumab subgroups in Tables 3 and 4 of the submission are different for the comparisons against taxanes and the comparisons against vinflunine, including any calculations and assumptions that were used in determining these subgroups.

4. Please provide full baseline characteristics of subjects for the following subgroups:

    i) the subgroup of chemotherapy patients who received taxanes

    ii) the subgroup of chemotherapy patients who received vinflunine

    iii) the 2 subgroups of patients in the atezolizumab arm that were used for comparisons against taxanes (Tables 3 and 4, n=215) and against vinflunine (Tables 3 and 4, n=252)

    iv) the 6 subgroups in Table 2 of the submission (i.e. according to treatment arm and PD-L1 expression).

Single Technology Appraisal (STA)

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

1. Please provide the clinical study report for the IMvigor 211 trial, including the protocol and analysis plan.

The clinical study report for study IMvigor 211 has been uploaded as a separate file (file name: Clinical Study Report_IMvigor211_ core report). Please treat this document as Commercial in Confidence.

2. Please provide the following reference: "Powles T, Loriot Y, Durán I, Ravaud A, Retz M, Vogelzang NJ, et al., editors. IMvigor211: A Phase III Randomized Study Examining Atezolizumab vs. Chemotherapy for Platinum-Treated Advanced Urothelial Carcinoma. European Association for Cancer Research; 2017."

This reference has been uploaded as a separate file (file name: Powles et al_IMvigor211).

3. Please provide an explanation of why the sample sizes for the atezolizumab subgroups in Tables 3 and 4 of the submission are different for the comparisons against taxanes and the comparisons against vinflunine, including any calculations and assumptions that were used in determining these subgroups.

The type of chemotherapy (taxane or vinflunine) was a stratification factor in the IMvigor211 study. The subgroup comparisons in Tables 3 and 4 are performed within these strata. The demographic and baseline characteristics table shows that within the atezolizumab arm, 252 patients belonged to the vinflunine stratum, and 215 to the taxane stratum.

Chemotherapy stratification, n (%)	Chemotherapy n=464	Atezolizumab n=467	All patients N=931
Vinflunine	250 (53.9)	252 (54.0)	502 (53.9)
Taxane	214 (46.1)	215 (46.0)	429 (46.1)

A 40% cap on randomisation to the taxanes within the chemotherapy arm was implemented as a protocol amendment after enrolment had begun. Due to the rapid accrual rate and late implementation of this cap, the final proportion of patients receiving a taxane was 46.1%. Overall, 29 patients (3.1%) did not receive any study treatment (21 patients [4.5%] in the chemotherapy arm vs. 8 patients [1.7%] in the atezolizumab arm).

4. Please provide full baseline characteristics of subjects for the following subgroups:

i) the subgroup of chemotherapy patients who received taxanes

	Taxane chemotherapy n=214	Atezolizumab n=215	All patients N=429
Median age, years (range)	67.0 (31–84)	68.0 (33–83)	67.0 (31–84)
Male, n (%)	165 (77.1)	167 (77.7)	332 (77.4)
Race			
Asian	33 (15.4)	44 (20.5)	77 (17.9)
Black or African American	1 (0.5)	1 (0.5)	2 (0.5)
White	154 (72.0)	139 (64.7)	293 (68.3)
Multiple	1 (0.5)	0	1 (0.2)
Unknown	25 (11.7)	31 (14.4)	56 (13.1)
Mean weight, kg (SD)	76.49 (16.8)	75.76 (16.86)	76.11 (16.81)
Smoking history			
Current	24 (11.2)	31 (14.5)	55 (12.9)
Previous	138 (64.5)	123 (57.5)	261 (61.0)
Never	52 (24.3)	60 (28.0)	112 (26.2)
Mean creatinine clearance, mL/min (SD)	66.89 (23.05)	67.06 (22.64)	66.98 (22.81)
Creatinine clearance category, n (%)			
<60 mL/min	80 (37.4)	86 (40.0)	166 (38.7)
≥60 mL/min	108 (50.5)	107 (49.8)	215 (50.1)
Unknown	26 (12.1)	22 (10.2)	48 (11.2)
Alkaline phosphatase category, n (%)			
<ULN	139 (69.8)	156 (73.6)	295 (71.8)
≥ULN	60 (30.2)	56 (26.4)	116 (28.2)
GFR category, n (%)			
<60 mL/min	85 (43.4)	81 (38.6)	166 (40.9)
≥60 mL/min	111 (56.6)	129 (61.4)	240 (59.1)
Albumin category, n (%)			
<LLN	60 (30.0)	66 (31.1)	126 (30.6)
≥LLN	140 (70.0)	146 (68.9)	286 (69.4)
Haemoglobin, <10 g/dL, n (%)			
Yes	35 (16.4)	26 (12.1)	61 (14.2)
No	179 (83.6)	189 (87.9)	368 (85.8)
ECOG score, n (%)			
0	99 (46.3)	106 (49.3)	205 (47.8)
1	115 (53.7)	109 (50.7)	224 (52.2)
Time from prior chemotherapy (<3 mo), n (%)			
Yes	80 (37.4)	80 (37.2)	160 (37.3)
No	134 (62.6)	135 (62.8)	269 (62.7)
Liver metastases, n (%)			
Yes	57 (26.6)	62 (28.8)	119 (27.7)
No	157 (73.4)	153 (71.2)	310 (72.3)
Number of prognostic risk factors, n (%)			
0	63 (29.4)	59 (27.4)	122 (28.4)
1/2/3	151 (70.6)	156 (72.6)	307 (71.6)
Number of Bellmunt risk factors, n (%)			
0	70 (32.7)	70 (32.6)	140 (32.6)
1	88 (41.1)	97 (45.1)	185 (43.1)
2	49 (22.9)	44 (20.5)	93 (21.7)
3	7 (3.3)	4 (1.9)	11 (2.6)

PD-L1 IC score, n (%)			
IC2/3	53 (24.8)	53 (24.7)	106 (24.7)
IC1	94 (43.9)	90 (41.9)	184 (42.9)
IC0	67 (31.3)	72 (33.5)	139 (32.4)

Number of Prognostic Risk Factors was based on baseline ECOG score ≥1, prior chemo <3 month, haemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score ≥1, liver metastases, hemoglobin <10 g/dL.
ULN, Upper Limit of Normal; LLN, Lower Limit of Normal

ii) the subgroup of chemotherapy patients who received vinflunine

	Vinflunine chemotherapy n=250	**Atezolizumab n=252**	**All patients N=502**
Median age, years (range)	67.0 (32–84)	66.0 (39–89)	67.0 (32–88)
Male, n (%)	196 (78.4)	190 (75.4)	386 (76.9)
Race			
Asian	22 (8.8)	19 (7.5)	41 (8.2)
Black or African American	1 (0.4)	0	1 (0.2)
White	182 (72.8)	196 (77.8)	378 (75.3)
Unknown	45 (18.0)	37 (14.7)	82 (16.3)
Mean weight, kg (SD)	75.65 (14.45)	75.67 (15.35)	75.66 (14.89)
Smoking history			
Current	36 (14.5)	29 (11.5)	65 (13.0)
Previous	142 (57.3)	143 (56.7)	285 (57.0)
Never	70 (28.2)	80 (31.7)	150 (30.0)
Mean creatinine clearance, mL/min (SD)	65.09 (24.06)	67.51 (22.60)	66.29 (23.36)
Creatinine clearance category, n (%)			
<60 mL/min	100 (40.0) 118	93 (36.9)	193 (38.4)
≥60 mL/min	(47.2)	120 (47.6)	238 (47.4)
Unknown	32 (12.8)	39 (15.5)	71 (14.1)
Alkaline phosphatase category, n (%)			
<ULN	178 (74.5)	174 (72.2)	352 (73.3)
≥ULN	61 (25.5)	67 (27.8)	128 (26.7)
GFR category, n (%)			
<60 mL/min	107 (45.1)	95 (40.1)	202 (42.6)
≥60 mL/min	130 (54.9)	142 (59.9)	272 (57.4)
Albumin category, n (%)			
<LLN	49 (20.2)	55 (22.4)	104 (21.4)
≥LLN	193 (79.8)	190 (77.6)	383 (78.6)
Haemoglobin, <10 g/dL, n (%)			
Yes	38 (15.2)	39 (15.5)	77 (15.3)
No	212 (84.8)	213 (84.5)	425 (84.7)
ECOG score, n (%)			
0	108 (43.2)	112 (44.4)	220 (43.8)
1	142 (56.8)	140 (55.6)	282 (56.2)
Time from prior chemotherapy (<3 mo), n (%)			
Yes	80 (32.0)	80 (31.7)	160 (31.9)
No	170 (68.0)	172 (68.3)	342 (68.1)
Liver metastases, n (%)			
Yes	73 (29.2)	76 (30.2)	149 (29.7)
No	177 (70.8)	176 (69.8)	353 (70.3)

Number of prognostic risk factors, n (%)			
0	67 (26.8)	77 (30.6)	144 (28.7)
1/2/3	183 (73.2)	175 (69.4)	358 (71.3)
Number of Bellmunt risk factors, n (%)			
0	70 (28.0)	75 (29.8)	145 (28.9)
1	120 (48.0)	117 (46.4)	237 (47.2)
2	47 (18.8)	42 (16.7)	89 (17.7)
3	13 (5.2)	18 (7.1)	31 (6.2)
PD-L1 IC score, n (%)			
IC2/3	65 (26.0)	63 (25.0)	128 (25.5)
IC1	97 (38.8)	110 (43.7)	207 (41.2)
IC0	88 (35.2)	79 (31.3)	167 (33.3)

Number of Prognostic Risk Factors was based on baseline ECOG score ≥1, prior chemo <3 month, haemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score ≥1, liver metastases, hemoglobin <10 g/dL.
ULN, Upper Limit of Normal; LLN, Lower Limit of Normal

iii) the 2 subgroups of patients in the atezolizumab arm that were used for comparisons against taxanes (Tables 3 and 4, n=215) and against vinflunine (Tables 3 and 4, n=252)

Please see tables above.

iv) the 6 subgroups in Table 2 of the submission (i.e. according to treatment arm and PD-L1 expression).

	IC1/2/3		IC2/3		ITT	
	Chemotherapy n=309	**Atezolizumab n=316**	**Chemotherapy n=118**	**Atezolizumab n=116**	**Chemotherapy n=464**	**Atezolizumab n=467**
Median age, years (range)	67.0 (31–84)	67.0 (41–88)	66.5 (36–84)	67.0 (43–88)	67 (31–84)	67 (33–88)
Male, n (%)	238 (77.0)	242 (76.6)	95 (80.5)	81 (69.8)	361 (77.8)	357 (76.4)
Race						
Asian	35 (11.3)	39 (12.3)	12 (10.2)	16 (13.8)	55 (11.9)	63 (13.5)
Black or African American	1 (0.3)	1 (0.3)	1 (0.8)	0	2 (0.4)	1 (0.2)
White	227 (73.5)	234 (74.1)	88 (74.6)	86 (74.1)	336 (72.4)	335 (71.7)
Multiple	1 (0.3)	0	1 (0.8)	0	1 (0.2)	0
Unknown	45 (14.6)	42 (13.3)	16 (13.6)	14 (12.1)	70 (15.1)	68 (14.6)
Mean weight, kg (SD)	75.90 (15.42)	75.78 (16.12)	76.69 (14.17)	76.05 (15.73)	76.03 (15.54)	75.71 (16.06)
Smoking history						
Current	39 (12.7)	43 (13.7)	18 (15.3)	12 (10.4)	60 (13.0)	60 (12.9)
Previous	179 (58.3)	179 (56.8)	68 (57.6)	68 (59.1)	280 (60.6)	266 (57.1)
Never	89 (29.0)	93 (29.5)	32 (27.1)	35 (30.4)	122 (26.4)	140 (30.0)
Mean creatinine clearance, mL/min (SD)	66.59 (23.95)	69.35 (23.70)	66.44 (21.30)	68.65 (22.63)	65.93 (23.59)	67.30 (22.59)
Creatinine clearance category, n (%)						
<60 mL/min	118 (38.2)	112 (35.4)	41 (34.7)	38 (32.8)	180 (38.8)	179 (38.3)
≥60 mL/min	151 (48.9)	163 (51.6)	63 (53.4)	64 (55.2)	226 (48.7)	227 (48.6)
Unknown	40 (12.9)	41 (13.0)	14 (11.9)	14 (12.1)	58 (12.5)	61 (13.1)
Alkaline phosphatase category, n (%)						
<ULN	215 (73.1)	225 (73.3)	84 (77.1)	84 (76.4)	317 (72.4)	330 (72.8)
≥ULN	79 (26.9)	82 (26.7)	25 (22.9)	26 (23.6)	121 (27.6)	123 (27.2)
GFR category, n (%)						
<60 mL/min	125 (43.4)	112 (36.7)	44 (40.7)	39 (35.5)	192 (44.3)	176 (39.4)
≥60 mL/min	163 (56.6)	193 (63.3)	64 (59.3)	71 (64.5)	241 (55.7)	271 (60.6)
Albumin category, n (%)						
<LLN	71 (24.0)	84 (27.0)	22 (19.8)	32 (28.1)	109 (24.7)	121 (26.5)
≥LLN	225 (76.0)	227 (73.0)	89 (80.2)	82 (71.9)	333 (75.3)	336 (73.5)

Haemoglobin, <10 g/dL, n (%)						
Yes	45 (14.6)	39 (12.3)	19 (16.1)	17 (14.7)	73 (15.7)	65 (13.9)
No	264 (85.4)	277 (87.7)	99 (83.9)	99 (85.3)	391 (84.3)	402 (86.1)
ECOG score, n (%)						
0	140 (45.3)	155 (49.1)	57 (48.3)	61 (52.6)	207 (44.6)	218 (46.7)
1	169 (54.7)	161 (50.9)	61 (51.7)	55 (47.4)	257 (55.4)	249 (53.3)
Time from prior chemotherapy (<3 mo), n (%)						
Yes	112 (36.2)	105 (33.2)	43 (36.4)	35 (30.2)	160 (34.5)	160 (34.3)
No	197 (63.8)	211 (66.8)	75 (63.6)	81 (69.8)	304 (65.5)	307 (65.7)
Liver metastases, n (%)						
Yes	84 (27.2)	94 (29.7)	30 (25.4)	28 (24.1)	130 (28.0)	138 (29.6)
No	225 (72.8)	222 (70.3)	88 (74.6)	88 (75.9)	334 (72.0)	329 (70.4)
Number of prognostic risk factors, n (%)						
0	84 (27.2)	101 (32.0)	34 (28.8)	44 (37.9)	130 (28.0)	136 (29.1)
1/2/3	225 (72.8)	215 (68.0)	84 (71.2)	72 (62.1)	334 (72.0)	331 (70.9)
Number of Bellmunt risk factors, n (%)						
0	97 (31.4)	105 (33.2)	41 (34.7)	44 (37.9)	140 (30.2)	145 (31.0)
1	139 (45.0)	144 (45.6)	48 (40.7)	50 (43.1)	208 (44.8)	214 (45.8)
2	60 (19.4)	51 (16.1)	25 (21.2)	16 (13.8)	96 (20.7)	86 (18.4)
3	13 (4.2)	16 (5.1)	4 (3.4)	6 (5.2)	20 (4.3)	22 (4.7)
PD-L1 IC score, n (%)						
IC2/3	118 (38.2)	116 (36.7)	118 (100)	116 (100)	118 (25.4)	116 (24.8)
IC1	191 (61.8)	200 (63.3)	-	-	191 (41.2)	200 (42.8)
IC0	-	-	-	-	155 (33.4)	151 (32.3)

Number of Prognostic Risk Factors was based on baseline ECOG score ≥1, prior chemo <3 month, haemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score ≥1, liver metastases, hemoglobin <10 g/dL.
ULN, Upper Limit of Normal; LLN, Lower Limit of Normal

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Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]: ERG critique of the company's updated analyses for second-line therapy

Confidential appendix to the Evidence Review Group report

Produced by Southampton Health Technology Assessments Centre

Authors Keith Cooper, Senior Research Fellow, SHTAC
Neelam Kalita, Research Fellow, SHTAC
Geoff Frampton, Senior Research Fellow, SHTAC

Correspondence to Dr Geoff Frampton
Southampton Health Technology Assessments Centre
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

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This appendix contains commercial in confidence information which is highlighted in blue and underlined

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1 Introduction

Following the second NICE Appraisal Committee Meeting (ACM) for the Single Technology Appraisal (STA) of atezolizumab for treating locally advanced or metastatic urothelial carcinoma, NICE produced an Appraisal Consultation Document (ACD). The ACD does not recommend atezolizumab for treating locally advanced or metastatic urothelial carcinoma in adults after prior platinum-containing chemotherapy. Reasons for the Committee's recommendation are provided in full within the ACD. In summary, the main areas of concern were:

- Clinical effectiveness outcomes were based on a phase II single-arm clinical study, IMvigor210. A simulated treatment comparison (STC) was necessary to support a network meta-analysis (NMA) to enable the clinical effectiveness of atezolizumab to be compared against that of chemotherapy. Due to the sparse network of studies available and other limitations in the STC and NMA methodology, overall survival (OS) results of the NMA, used for the company's economic analysis, were highly uncertain.
- Health-related quality of life (HRQoL) outcomes were not measured in IMvigor210 and were instead estimated by the company. The Committee was concerned that the utility estimates provided by the company were not appropriate and the Committee noted that no existing HRQoL datasets provided plausible utility values.
- The Committee had concerns about the company's approach for the extrapolation of overall survival and other time-to-event outcomes, noting that the OS data from IMvigor210 were relatively immature. The Committee recognised that the extrapolation of overall survival was highly uncertain and had a large effect on the cost-effectiveness of atezolizumab.
- The Committee noted that the uncertainties in clinical effectiveness and utility estimates might be reduced by outcomes from the phase III IMvigor211 randomised controlled trial (RCT), which directly compared atezolizumab against chemotherapy. However, the company was unable to provide results of IMvigor211 at the time of the second ACM. The Committee concluded that, for previously-treated disease, atezolizumab was not plausibly cost-effective and was not suitable to be recommended for use in the Cancer Drugs Fund.

2 Company's additional evidence submission

In response to the ACD the company has submitted new clinical effectiveness evidence to NICE and updated their cost-effectiveness analysis. The company's updated analyses are based on the IMvigor211 RCT, which compared atezolizumab against investigators' choice

of chemotherapy in patients who had advanced or metastatic urothelial bladder carcinoma that had progressed after prior platinum-based chemotherapy. IMvigor211 addresses some of the concerns raised by the Committee in the ACD by providing:

- a direct head-to-head comparison of atezolizumab against chemotherapy;
- HRQoL data (EQ-5D) upon which to base utility estimates;
- more mature data for OS.

The current document provides the Evidence Review Group (ERG)'s critique of the company's new clinical effectiveness evidence (section 3 below) and our critique of their updated cost-effectiveness analyses (section 4 below).

The company's updated submission was received by the ERG on 11th September 2017 and details of the company's Patient Access Scheme (PAS) price were received on 15th September 2017. Unless otherwise stated, analyses presented in this appendix use the company's confidential PAS price for atezolizumab.

Following receipt of the company's updated analyses the ERG requested clarification from the company via NICE on some aspects of the company's analyses. The company's clarification responses were received by the ERG on 3rd October 2017.

In addition to the information provided by the company, we note that 'topline' results from the ongoing IMvigor211 RCT had been discussed by the European Medicines Agency (EMA) in support of the atezolizumab marketing authorisation and these are referred to in the European Public Assessment Report (EPAR) for atezolizumab[1] (although 'topline' is not defined in the EPAR in relation to a specific data analysis cut-off date).

In summary, the current ERG critique is based on the following sources of information:

- the company's updated submission (comprising a report and economic analysis model);
- the company's clarification response, which includes the IMvigor211 clinical study report (CSR)[2] and a conference presentation on IMvigor211 by Powles et al. 2017;[3]
- reference to the atezolizumab EPAR.[1]

The company's updated submission provides relatively limited information on IMvigor211 and we have therefore provided additional information from the CSR[2] below.

3 ERG's critique of the company's clinical effectiveness evidence

3.1 Summary of trial methods in IMvigor211

IMvigor211 is an open-label trial that compared atezolizumab against chemotherapy for advanced or metatstatic urothelial bladder cancer in patients who had progressed following platinum-based chemotherapy. The trial randomised 931 patients: 467 to atezolizumab and 464 to chemotherapy. The trial was conducted at [redacted], and included [redacted] (CSR section 4.1).[2] The majority of the patients (77%) were in Europe.[3] Patients in the chemotherapy arm received investigator's choice' of one of three chemotherapies: vinflunine, docetaxel or paclitaxel. The CSR (section 3.2)[2] states these were chosen to reflect the most commonly-used therapies worldwide in this indication, given that a standard of care was not available.

3.1.1 Patient allocation

The randomisation of patients (1:1 ratio atezolizumab to chemotherapy) was stratified on 4 factors (Figure 4 in the company's updated submission): the number of risk factors (0 or 1/2/3), presence of liver metastases (yes or no), PD-L1 status (0/1 or 2/3); and the chemotherapy type (vinflunine or taxane). Investigator's choice of chemotherapy was made prior to randomisation (company's updated submission, page 10). However, according to the company's clarification response, a protocol amendment was made after enrolment had begun, in which a 40% cap on randomisation to the taxanes within the chemotherapy arm was implemented. Neither the company's submission nor the CSR[2] explain the reason for this. The CSR states that until that cap was reached, the selection of the specific chemotherapy (vinflunine or taxane) was per investigator's choice (CSR section 3.1).[2] According to the company's clarification response, a high accrual rate and late implementation of the cap meant that the final proportion of patients receiving a taxane was 46.1%.

3.1.2 Intervention and comparator regimens

The company's updated submission does not provide information on the therapy regimens in IMvigor211. According to the CSR,[2] patients randomised to atezolizumab received a fixed dose of 1200mg on day 1 of each 21-day cycle, for as long as they continued to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity or symptomatic deterioration attributed to progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients

were permitted to continue to receive atezolizumab after RECIST v1.1 criteria for progressive disease were met, if they: showed evidence of clinical benefit; had absence of symptoms and signs indicating unequivocal progression; had no decline in ECOG performance status that could be attributed to progression; and absence of tumour progression at critical anatomical sites that could not be managed and stabilised by protocol-allowed medical interventions (CSR[2] section 3.1). Dosages of chemotherapy were vinflunine 320 mg/m^2, paclitaxel 155 mg/m^2 or docetaxel 75 mg/m^2 on day 1 of each 21-day cycle (CSR section 3.1),[2] administered until disease progression or unacceptable toxicity.

3.1.3 Eligibility criteria

The company's updated submission does not specify the eligibility criteria for IMvigor211. According to the CSR (section 3.6),[2] the key inclusion criteria were: age ≥18 years; documented locally advanced or metastatic urothelial carcinoma; disease progression on or following previous platinum-based chemotherapy; ECOG performance status <2; life expectancy ≥12 weeks; measurable disease; adequate haematological and end-organ function; and any level of PD-L1 expression.

3.1.4 Outcomes

The primary outcome was OS. Secondary outcomes were progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR) as assessed using standard RECIST v1 criteria. According to the company's updated submission, OS and PFS examined in subgroups based on chemotherapy type at randomisation were regarded as exploratory outcomes. The company state that the safety and tolerability of atezolizumab compared with chemotherapy was also assessed, along with patient-reported outcomes of health-related quality of life (HRQoL), as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and the EuroQoL 5 dimension (EQ-5D) [3L] questionnaire. According to the CSR,[2] the [redacted]

The EQ-5D data were collected prior to any administration of study treatment and/or prior to any other study assessment(s) and at 6, 12, and 24 weeks after disease progression (company's submission, page 34).

Table 13 in the company's updated submission shows the numbers of patients and observations that were included in utility analyses: 395 of the patients on atezolizumab (i.e.

85% of the 467 who were randomised to atezolizumab) and 167 of the patients on taxanes (i.e. 78% of the 214 who were allocated to taxanes). The reasons for, and timing of, the missing utility data are not explained. It appears from the data given in Table 13 of the company's updated submission that the mean number of utility observations per patient was higher for patients on atezolizumab (3494/395=8.8) than for those on taxanes (783/167=4.7) or those who were off treatment (3474/695=5.0%). The company does not explain these imbalances. Bias could be introduced if the times for which utility data were available or unavailable differed systematically between the study groups (e.g. if missing data occurred earlier in one group than the other).

The company transformed EQ-5D data from IMvigor211 into utility values using UK specific weights (company's updated submission, page 34). Utility results for the economic analysis were derived based on linear mixed effects models with a random intercept term to account for the longitudinal structure of the data via subject-specific random effects (i.e. inducing correlation between observations from the same patient). The models were adjusted for the following baseline characteristics: sex, age, ECOG (0 or >0), liver metastasis, and haemoglobin level below 10 g/dl. The resulting utility values that were used in the company's economic model are presented in Table 10 below where we critique the company's economic analysis (see section 4). The company assumes there would be no difference in patients' off-treatment utilities between treatments. The ERG agrees that the company's approach for calculating the utility values is appropriate.

3.1.5 Analysis approach

The company's updated submission provides limited information about clinical effectiveness analyses. According to the CSR,[2] [redacted] The primary analysis was planned for when [redacted] (CSR[2] section 3.10.1.2). The company's updated submission does not formally define the analysis populations. According to the CSR,[2] the ITT population was defined as all randomised patients, irrespective of whether the assigned treatment was actually received

The clinical data cut-off for analyses was 13th March 2017 (CSR; [2] Powles et al.[3]), when 160, 452 and 674 deaths had occurred in the IC2/3, IC1/2/3 and ITT subgroups respectively. The median follow up duration in the ITT population was 17.3 months (rage 0 to 24.5 months)

(Powles et al.[3]). According to the analysis plan, OS differences between atezolizumab and chemotherapy arms would be tested hierarchically, first in the IC2/3 subgroup (Figure 1).

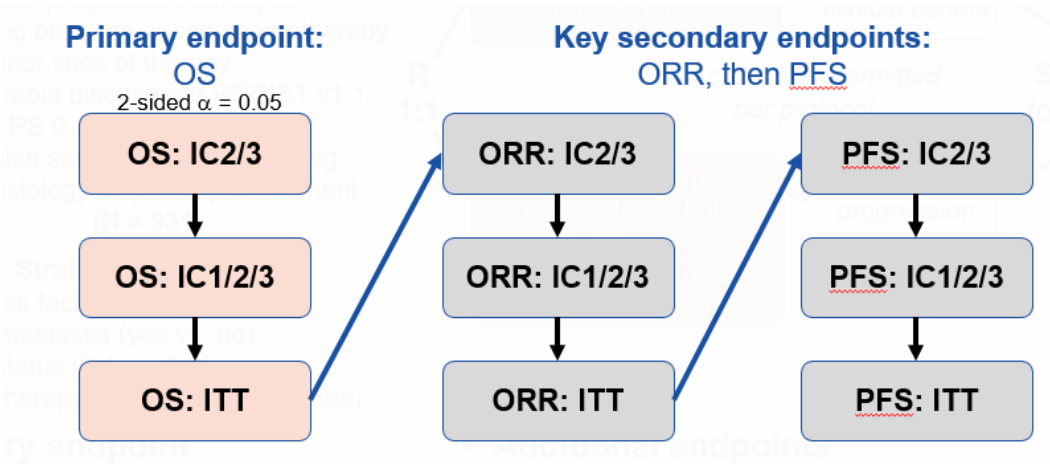


Figure 1 Hierarchical statistical testing of outcomes in IMvigor211 (Powles et al. 2017[3])

According to the hierarchical statistical testing strategy, the secondary outcomes were to be tested statistically only if the primary (OS) outcome was found to be statistically significant in the ITT population analysis (Powles et al.[3]).

Although not reported in the company's submission, the CSR[2] states that IMvigor211 was [redacted] (CSR section 3.10.3.1).[2] The CSR[2] states that results from an [redacted] analysis are also presented, although this is not provided or discussed by the company. Statistical power is stated (CSR section 3.10.1.2)[2] as follows:

- IC2/3 subgroup: [redacted]
- IC1/2/3 subgroup: [redacted]
- ITT population: [redacted]

A rationale is not given for the selection of these specific differences in OS per subgroup and the variance estimates used in the sample size calculation are not reported.

The company's updated analysis does not specify patient censoring. According to the CSR,[2] for OS, [redacted]

3.1.6 Baseline characteristics of patients

Patients' baseline characteristics in IMvigor211 are given in the company's updated submission for the overall atezolizumab and chemotherapy arms. The company provided further baseline characteristics for chemotherapy and PD-L1 expression subgroups in their clarification response (reproduced in Table 1 to Table 3 below). The sample sizes in the subgroups of patients in the atezolizumab-versus-chemotherapy comparisons (252 atezolizumab patients compared against 250 vinflunine patients, and 215 atezolizumab patients compared against 214 taxane patients) were determined by the stratification of randomisation by chemotherapy type.

Table 1 Baseline characteristics for stratified taxane and atezolizumab subgroups in IMvigor211 (from the company's clarification response)

	Taxane chemotherapy n=214	Atezolizumab n=215	All patients N=429
Median age, years (range)	67.0 (31–84)	68.0 (33–83)	67.0 (31–84)
Male, n (%)	165 (77.1)	167 (77.7)	332 (77.4)
Race			
Asian	33 (15.4)	44 (20.5)	77 (17.9)
Black or African American	1 (0.5)	1 (0.5)	2 (0.5)
White	154 (72.0)	139 (64.7)	293 (68.3)
Multiple	1 (0.5)	0	1 (0.2)
Unknown	25 (11.7)	31 (14.4)	56 (13.1)
Mean weight, kg (SD)	76.49 (16.8)	75.76 (16.86)	76.11 (16.81)
Smoking history			
Current	24 (11.2)	31 (14.5)	55 (12.9)
Previous	138 (64.5)	123 (57.5)	261 (61.0)
Never	52 (24.3)	60 (28.0)	112 (26.2)
Mean creatinine clearance, mL/min (SD)	66.89 (23.05)	67.06 (22.64)	66.98 (22.81)
Creatinine clearance category, n (%)			
<60 mL/min	80 (37.4)	86 (40.0)	166 (38.7)
≥60 mL/min	108 (50.5)	107 (49.8)	215 (50.1)
Unknown	26 (12.1)	22 (10.2)	48 (11.2)
Alkaline phosphatase category, n (%)			
<ULN	139 (69.8)	156 (73.6)	295 (71.8)
≥ULN	60 (30.2)	56 (26.4)	116 (28.2)
GFR category, n (%)			
<60 mL/min	85 (43.4)	81 (38.6)	166 (40.9)
≥60 mL/min	111 (56.6)	129 (61.4)	240 (59.1)
Albumin category, n (%)			
<LLN	60 (30.0)	66 (31.1)	126 (30.6)
≥LLN	140 (70.0)	146 (68.9)	286 (69.4)
Haemoglobin, <10 g/dL, n (%)			
Yes	35 (16.4)	26 (12.1)	61 (14.2)
No	179 (83.6)	189 (87.9)	368 (85.8)
ECOG score, n (%)			
0	99 (46.3)	106 (49.3)	205 (47.8)
1	115 (53.7)	109 (50.7)	224 (52.2)
Time from prior chemotherapy (<3 mo), n (%)			
Yes	80 (37.4)	80 (37.2)	160 (37.3)
No	134 (62.6)	135 (62.8)	269 (62.7)
Liver metastases, n (%)			
Yes	57 (26.6)	62 (28.8)	119 (27.7)
No	157 (73.4)	153 (71.2)	310 (72.3)
Number of prognostic risk factors, n (%)			
0	63 (29.4)	59 (27.4)	122 (28.4)
1/2/3	151 (70.6)	156 (72.6)	307 (71.6)

Number of Bellmunt risk factors, n (%)			
0	70 (32.7)	70 (32.6)	140 (32.6)
1	88 (41.1)	97 (45.1)	185 (43.1)
2	49 (22.9)	44 (20.5)	93 (21.7)
3	7 (3.3)	4 (1.9)	11 (2.6)
PD-L1 IC score, n (%)			
IC2/3	53 (24.8)	53 (24.7)	106 (24.7)
IC1	94 (43.9)	90 (41.9)	184 (42.9)
IC0	67 (31.3)	72 (33.5)	139 (32.4)

Number of Prognostic Risk Factors was based on baseline ECOG score ≥1, prior chemo <3 month, haemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score ≥1, liver metastases, hemoglobin <10 g/dL.
ULN, Upper Limit of Normal; LLN, Lower Limit of Normal

Table 2 Baseline characteristics for stratified vinflunine and atezolizumab subgroups in IMvigor211 (from the company's clarification response)

	Vinflunine chemotherapy n=250	Atezolizumab n=252	All patients N=502
Median age, years (range)	67.0 (32–84)	66.0 (39–89)	67.0 (32–88)
Male, n (%)	196 (78.4)	190 (75.4)	386 (76.9)
Race			
Asian	22 (8.8)	19 (7.5)	41 (8.2)
Black or African American	1 (0.4)	0	1 (0.2)
White	182 (72.8)	196 (77.8)	378 (75.3)
Unknown	45 (18.0)	37 (14.7)	82 (16.3)
Mean weight, kg (SD)	75.65 (14.45)	75.67 (15.35)	75.66 (14.89)
Smoking history			
Current	36 (14.5)	29 (11.5)	65 (13.0)
Previous	142 (57.3)	143 (56.7)	285 (57.0)
Never	70 (28.2)	80 (31.7)	150 (30.0)
Mean creatinine clearance, mL/min (SD)	65.09 (24.06)	67.51 (22.60)	66.29 (23.36)
Creatinine clearance category, n (%)			
<60 mL/min	100 (40.0) 118	93 (36.9)	193 (38.4)
≥60 mL/min	(47.2)	120 (47.6)	238 (47.4)
Unknown	32 (12.8)	39 (15.5)	71 (14.1)
Alkaline phosphatase category, n (%)			
<ULN	178 (74.5)	174 (72.2)	352 (73.3)
≥ULN	61 (25.5)	67 (27.8)	128 (26.7)
GFR category, n (%)			
<60 mL/min	107 (45.1)	95 (40.1)	202 (42.6)
≥60 mL/min	130 (54.9)	142 (59.9)	272 (57.4)
Albumin category, n (%)			
<LLN	49 (20.2)	55 (22.4)	104 (21.4)
≥LLN	193 (79.8)	190 (77.6)	383 (78.6)
Haemoglobin, <10 g/dL, n (%)			
Yes	38 (15.2)	39 (15.5)	77 (15.3)
No	212 (84.8)	213 (84.5)	425 (84.7)
ECOG score, n (%)			
0	108 (43.2)	112 (44.4)	220 (43.8)
1	142 (56.8)	140 (55.6)	282 (56.2)

Time from prior chemotherapy (<3 mo), n (%)			
Yes	80 (32.0)	80 (31.7)	160 (31.9)
No	170 (68.0)	172 (68.3)	342 (68.1)
Liver metastases, n (%)			
Yes	73 (29.2)	76 (30.2)	149 (29.7)
No	177 (70.8)	176 (69.8)	353 (70.3)
Number of prognostic risk factors, n (%)			
0	67 (26.8)	77 (30.6)	144 (28.7)
1/2/3	183 (73.2)	175 (69.4)	358 (71.3)
Number of Bellmunt risk factors, n (%)			
0	70 (28.0)	75 (29.8)	145 (28.9)
1	120 (48.0)	117 (46.4)	237 (47.2)
2	47 (18.8)	42 (16.7)	89 (17.7)
3	13 (5.2)	18 (7.1)	31 (6.2)
PD-L1 IC score, n (%)			
IC2/3	65 (26.0)	63 (25.0)	128 (25.5)
IC1	97 (38.8)	110 (43.7)	207 (41.2)
IC0	88 (35.2)	79 (31.3)	167 (33.3)

Number of Prognostic Risk Factors was based on baseline ECOG score ≥1, prior chemo <3 month, haemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score ≥1, liver metastases, hemoglobin <10 g/dL.
ULN, Upper Limit of Normal; LLN, Lower Limit of Normal

The ERG considers patients' baseline characteristics to be generally well-balanced across the stratified subgroups for atezolizumab and taxanes (Table 1) and atezolizumab and vinflunine (Table 2), and no obvious imbalances that are likely to be of prognostic importance are evident when all four of these subgroups are compared. Overall, patients had a median age of 67 years, were around 77% male, had a mean weight of 76kg, and the majority were of white ethnicity. Just over 90% of patients had metastatic disease, approximately 30% had liver metastases, approximately 15% had baseline haemoglobin <10g/dL, around 70% had alkaline phosphatase levels below the lower limit of normal, and around 40% had a glomerular filtration rate (GFR) <60 mL/minute. The company's updated submission reports that 69% of patients on atezolizumab and 73% of those on chemotherapy had urothelial carcinoma in the bladder, with the renal pelvis or ureter being the second most common sites (both approximately 13%).

Table 3 Baseline characteristics for PD-L1 expression subgroups in IMvigor211 (from the company's clarification response)

Differences between chemotherapy and atezolizumab which exceeded 5% are shown in bold	IC1/2/3		IC2/3		ITT	
	Chemotherapy n=309	**Atezolizumab n=316**	**Chemotherapy n=118**	**Atezolizumab n=116**	**Chemotherapy n=464**	**Atezolizumab n=467**
Median age, years (range)	67.0 (31–84)	67.0 (41–88)	66.5 (36–84)	67.0 (43–88)	67 (31–84)	67 (33–88)
Male, n (%)	238 (77.0)	242 (76.6)	**95 (80.5)**	**81 (69.8)**	361 (77.8)	357 (76.4)
Race						
Asian	35 (11.3)	39 (12.3)	12 (10.2)	16 (13.8)	55 (11.9)	63 (13.5)
Black or African American	1 (0.3)	1 (0.3)	1 (0.8)	0	2 (0.4)	1 (0.2)
White	227 (73.5)	234 (74.1)	88 (74.6)	86 (74.1)	336 (72.4)	335 (71.7)
Multiple	1 (0.3)	0	1 (0.8)	0	1 (0.2)	0
Unknown	45 (14.6)	42 (13.3)	16 (13.6)	14 (12.1)	70 (15.1)	68 (14.6)
Mean weight, kg (SD)	75.90 (15.42)	75.78 (16.12)	76.69 (14.17)	76.05 (15.73)	76.03 (15.54)	75.71 (16.06)
Smoking history						
Current	39 (12.7)	43 (13.7)	18 (15.3)	12 (10.4)	60 (13.0)	60 (12.9)
Previous	179 (58.3)	179 (56.8)	68 (57.6)	68 (59.1)	280 (60.6)	266 (57.1)
Never	89 (29.0)	93 (29.5)	32 (27.1)	35 (30.4)	122 (26.4)	140 (30.0)
Mean creatinine clearance, mL/min (SD)	66.59 (23.95)	69.35 (23.70)	66.44 (21.30)	68.65 (22.63)	65.93 (23.59)	67.30 (22.59)
Creatinine clearance category, n (%)						
<60 mL/min	118 (38.2)	112 (35.4)	41 (34.7)	38 (32.8)	180 (38.8)	179 (38.3)
≥60 mL/min	151 (48.9)	163 (51.6)	63 (53.4)	64 (55.2)	226 (48.7)	227 (48.6)
Unknown	40 (12.9)	41 (13.0)	14 (11.9)	14 (12.1)	58 (12.5)	61 (13.1)
Alkaline phosphatase category, n (%)						
<ULN	215 (73.1)	225 (73.3)	84 (77.1)	84 (76.4)	317 (72.4)	330 (72.8)
≥ULN	79 (26.9)	82 (26.7)	25 (22.9)	26 (23.6)	121 (27.6)	123 (27.2)
GFR category, n (%)						
<60 mL/min	**125 (43.4)**	**112 (36.7)**	**44 (40.7)**	**39 (35.5)**	192 (44.3)	176 (39.4)
≥60 mL/min	**163 (56.6)**	**193 (63.3)**	**64 (59.3)**	**71 (64.5)**	241 (55.7)	271 (60.6)
Albumin category, n (%)						
<LLN	71 (24.0)	84 (27.0)	22 (19.8)	32 (28.1)	109 (24.7)	121 (26.5)
≥LLN	225 (76.0)	227 (73.0)	89 (80.2)	82 (71.9)	333 (75.3)	336 (73.5)
Haemoglobin, <10 g/dL, n (%)						
Yes	45 (14.6)	39 (12.3)	19 (16.1)	17 (14.7)	73 (15.7)	65 (13.9)

No	264 (85.4)	277 (87.7)	99 (83.9)	99 (85.3)	391 (84.3)	402 (86.1)
ECOG score, n (%)						
0	140 (45.3)	155 (49.1)	57 (48.3)	61 (52.6)	207 (44.6)	218 (46.7)
1	169 (54.7)	161 (50.9)	61 (51.7)	55 (47.4)	257 (55.4)	249 (53.3)
Time from prior chemotherapy (<3 mo), n (%)						
Yes	112 (36.2)	105 (33.2)	**43 (36.4)**	**35 (30.2)**	160 (34.5)	160 (34.3)
No	197 (63.8)	211 (66.8)	**75 (63.6)**	**81 (69.8)**	304 (65.5)	307 (65.7)
Liver metastases, n (%)						
Yes	84 (27.2)	94 (29.7)	30 (25.4)	28 (24.1)	130 (28.0)	138 (29.6)
No	225 (72.8)	222 (70.3)	88 (74.6)	88 (75.9)	334 (72.0)	329 (70.4)
Number of prognostic risk factors, n (%)						
0	84 (27.2)	101 (32.0)	**34 (28.8)**	**44 (37.9)**	130 (28.0)	136 (29.1)
1/2/3	225 (72.8)	215 (68.0)	**84 (71.2)**	**72 (62.1)**	334 (72.0)	331 (70.9)
Number of Bellmunt risk factors, n (%)						
0	97 (31.4)	105 (33.2)	41 (34.7)	44 (37.9)	140 (30.2)	145 (31.0)
1	139 (45.0)	144 (45.6)	48 (40.7)	50 (43.1)	208 (44.8)	214 (45.8)
2	60 (19.4)	51 (16.1)	**25 (21.2)**	**16 (13.8)**	96 (20.7)	86 (18.4)
3	13 (4.2)	16 (5.1)	4 (3.4)	6 (5.2)	20 (4.3)	22 (4.7)
PD-L1 IC score, n (%)						
IC2/3	118 (38.2)	116 (36.7)	118 (100)	116 (100)	118 (25.4)	116 (24.8)
IC1	191 (61.8)	200 (63.3)	-	-	191 (41.2)	200 (42.8)
IC0	-	-	-	-	155 (33.4)	151 (32.3)

Number of Prognostic Risk Factors was based on baseline ECOG score ≥1, prior chemo <3 month, haemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score ≥1, liver metastases, hemoglobin <10 g/dL.
ULN, Upper Limit of Normal; LLN, Lower Limit of Normal

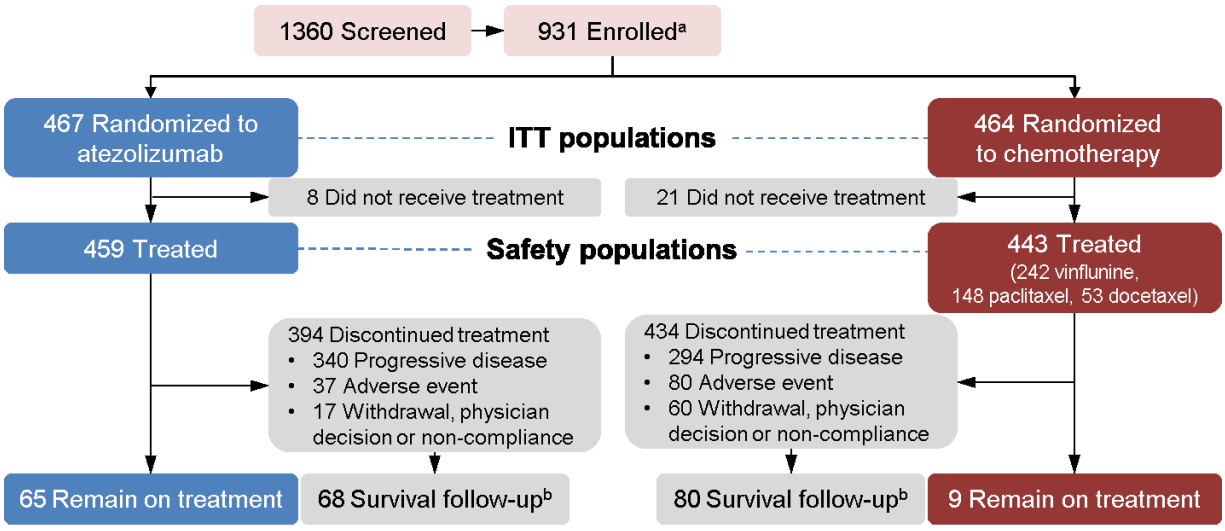
Overall, the baseline characteristics of patients appear to be generally well-balanced between the atezolizumab and chemotherapy arms within each immunohistochemistry PD-L1 expression subgroup (Table 3), with the exception of some differences between the atezolizumab and chemotherapy arms within each subgroup which exceeded 5% (highlighted in bold in Table 3):

- **IC2/3 subgroup:** the chemotherapy arm had 9.1% more patients who had at least one prognostic risk factor (71.2% versus 62.1%), 7.4% more patients who had 2 Bellmunt risk factors (21.2% versus13.8%), 6.2% more patients whose time from prior chemotherapy was <3 months (36.4% versus 30.2%), and 5.2% more patients whose GFR was <60 mL/minute (40.7% versus 35.5%).
- **IC1/2/3 subgroup:** the chemotherapy arm had 6.7% more patients whose GFR was <60 mL/minute (43.4% versus 36.7%).

These differences suggest that after splitting into PD-L1 expression subgroups the atezolizumab patients, particularly in the IC2/3 subgroup, had some slightly more favourable prognostic characteristics than the chemotherapy patients, but overall the differences are relatively small and unlikely to indicate a clinically important prognostic imbalance. No other differences between the intervention and comparator arms within subgroups reached 5%.

3.2 Clinical effectiveness results from IMvigor211

The patient flow chart for IMvigor211, reproduced from Powles et al.,[3] is shown in Figure 2.



[a] 1 patient was randomized to chemotherapy twice due to a randomization error but counted only once in this analysis.
[b] An additional 5 deaths (4 in the chemotherapy arm; 1 in the atezolizumab arm) were collected from public records and included as uncensored deaths in the efficacy analyses.

Figure 2 Patient flow chart for IMvigor211

Overall, 8 patients in the atezolizumab arm (1.7%) and 21 in the chemotherapy arm (4.5%) did not receive any study treatment. At the clinical data cut-off of 13 March 2017, 28.5% of patients in the atezolizumab arm were still on study compared with 19.2% in the chemotherapy arm (Figure 2).

3.2.1 Time-to-event outcomes

The company's updated submission and the presentation by Powles et al.[3] together provide several Kaplan-Meier OS curves which we have reproduced below. According to the a priori analysis plan the PD-L1 subgroup analyses were of primary interest and were powered statistically whilst the chemotherapy subgroup analyses comparing atezolizumab against taxanes or vinflunine were "exploratory".

PD-L1 expression subgroups and ITT population

OS curves comparing atezolizumab against chemotherapy are presented below for the PD-L1 expression IC2/3 subgroup (Figure 3), the IC1/2/3 subgroup (Figure 4) and the ITT population (Figure 5). The company has not reported PFS curves for these subgroup comparisons.

The OS, PFS, ORR and DOR outcomes from IMvigor211 are summarised for the PD-L1 expression subgroups and for the overall ITT population in Table 4. The company state in their updated submission that in IMvigor211 the primary endpoint of OS in the IC2/3 population (N=234) was not met. Therefore, according to the hierarchical statistical analysis testing plan (Figure 1), no further statistical testing of the primary or secondary outcomes was conducted.

As stated in the company's updated submission (page 22), visual inspection of the Kaplan-Meier OS curves confirms that the proportional hazards assumption does not hold, since the atezolizumab and chemotherapy curves cross. The hazard ratios presented by the company and reproduced here in the Figures and Tables are therefore unlikely to accurately represent the underlying hazard functions, and should not be relied upon for drawing statistical inferences regarding differences between the atezolizumab and chemotherapy groups.

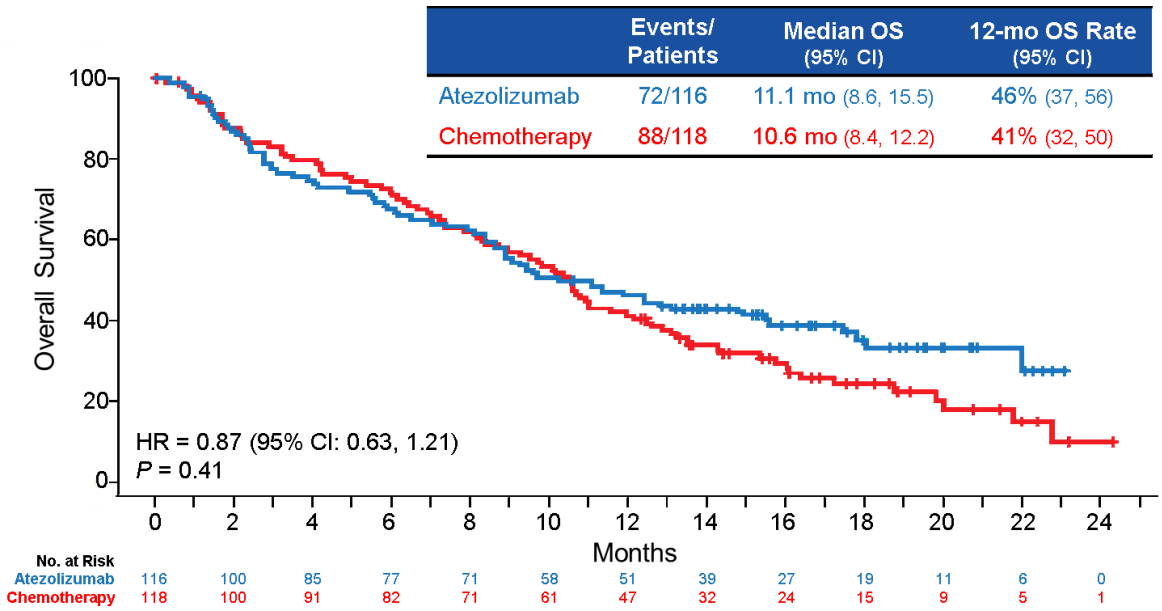


Figure 3 Overall survival in the IC2/3 subgroup

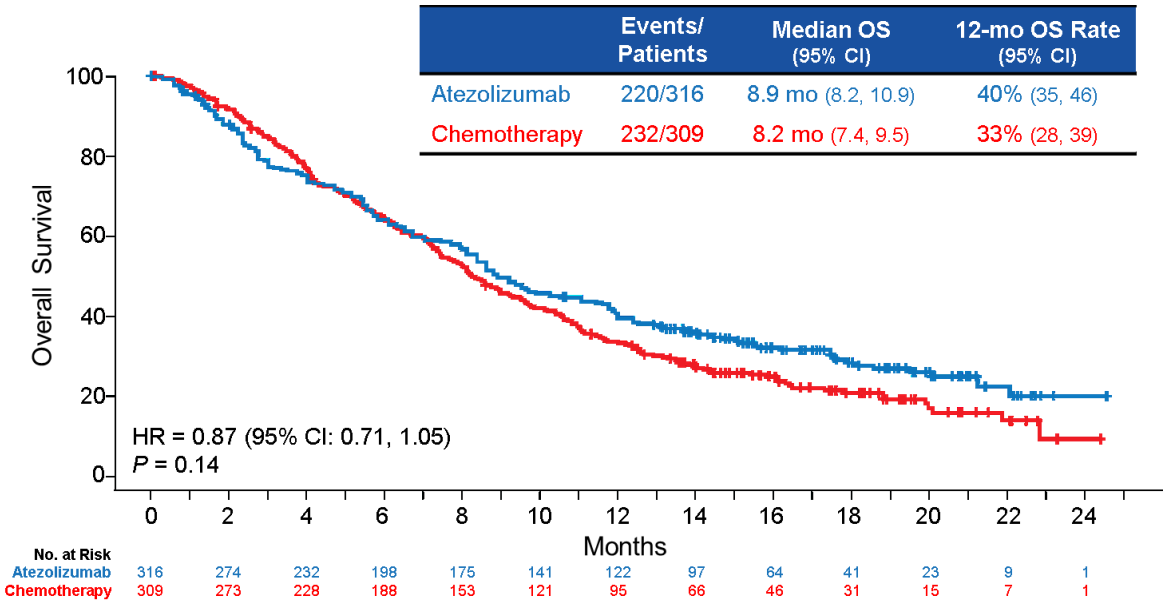


Figure 4 Overall survival in the IC1/2/3 subgroup

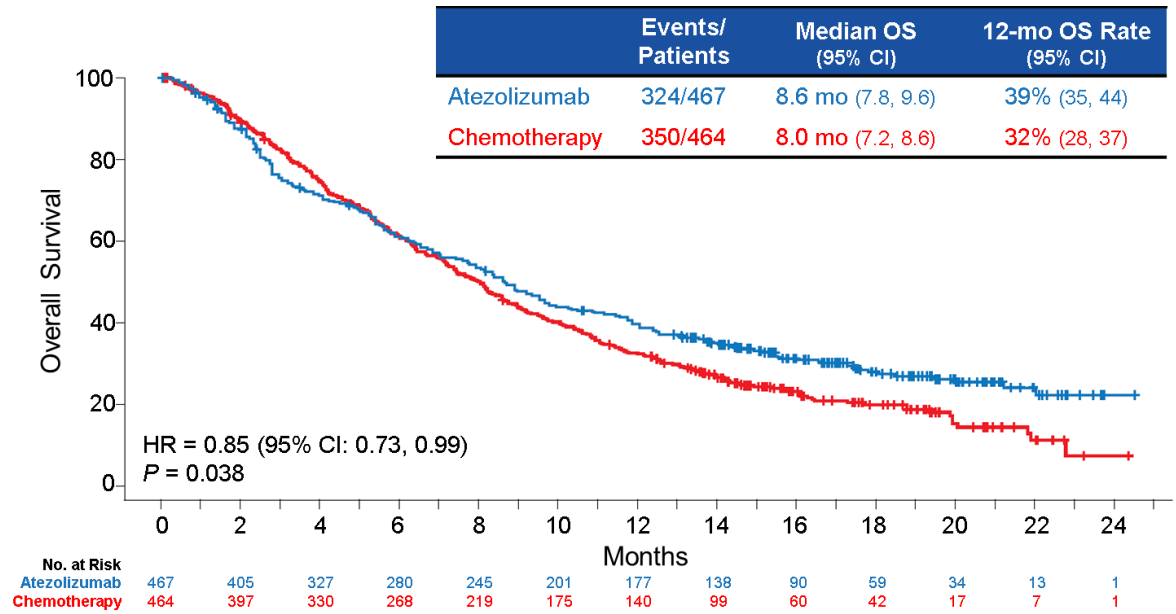


Figure 5 Overall survival in the ITT population

Table 4 Effectiveness outcomes (Table 2 in the company's updated submission)

	IC2/3		IC1/2/3		ITT	
	Atezo n=116	**Chemo n=118**	**Atezo n=316**	**Chemo n=309**	**Atezo n=467**	**Chemo n=464**
Median OS, months (95% CI)	11.1 (8.6–15.5)	10.6 (8.4–12.2)	8.9 (8.2–10.9)	8.2 (7.4–9.5)	8.6 (7.8–9.6)	8.0 (7.2–8.6)
HR (95% CI) p value	0.87 (0.63–1.21) p=0.41		0.87 (0.71–1.05) p=0.14[a]		0.85 (0.73–0.99) p=0.038 [a]	
12 month OS, % (95% CI)	46.4 (37.3–55.6)	41.2 (32.2–50.3)	40.0 (34.6–45.5)	33.2 (27.7–38.6)	39.2 (34.8–43.7)	32.4 (28.0–36.8)
Median PFS, months (95% CI)	2.4 (2.1–4.2)	4.2 (3.7–5.0)	2.1 (2.1–2.2)	4.1 (3.6–4.2)	2.1 (2.1–2.2)	4.0 (3.4–4.2)
ORR, %	23.0	21.6	14.1	14.7	13.4	13.4
CR rate, %	7.1	6.9	3.5	4.2	3.5	3.5
Median DOR, months (95% CI)	15.9 (10.4–NE)	8.3 (5.6–13.2)	15.9 (9.9–NE)	8.3 (6.3–13.2)	21.7 (13.0–21.7)	7.4 (6.1–10.3)

CR: complete response; HR: hazard ratio; ORR: objective response rate
[a] stated that p-values for the IC1/2/3 and ITT populations are provided for descriptive purposes only

Although the differences were not statistically significant according to the IMvigor211 a priori analysis plan, the median OS and 12-month OS were longer for the atezolizumab-treated patients than for the chemotherapy-treated patients in both the PD-L1 expression subgroups and the ITT population, and the EPAR[1] refers to these as "numerically favourable" results. Median PFS, in contrast, was shorter in atezolizumab-treated patients in both the subgroups and the ITT population, without overlap of the confidence intervals between the

atezolizumab and chemotherapy arms (Table 4). The company does not comment on this difference between the OS and PFS outcomes, for example whether it could reflect 'pseudoprogression' in atezolizumab-treated patients (increases in tumour volume related to the immunomodulatory activity of atezolizumab). The ERG and our clinical expert advisor agree that OS is the more objective outcome and it is reasonable for the company to focus on OS rather than PFS.

The ERG concurs with the following conclusions reported by the company and Powles et al.[3] concerning the treatment response outcomes:

- ORR were similar between atezolizumab and chemotherapy arms;
- Responses to atezolizumab were durable regardless of PD-L1 status;
- 63% of patients in the atezolizumab arm and 21% in the chemotherapy arm had ongoing responses at data cut-off;
- The median duration of response in the ITT population was 21.7 months for atezolizumab-treated patients and 7.4 months for chemotherapy-treated patients.

Chemotherapy subgroups

Comparisons between OS curves for atezolizumab and chemotherapy are provided by the company and Powles et al.[3] for the "exploratory analyses" in the chemotherapy subgroups, for taxanes (reproduced in Figure 6) and vinflunine (reproduced in Figure 7).

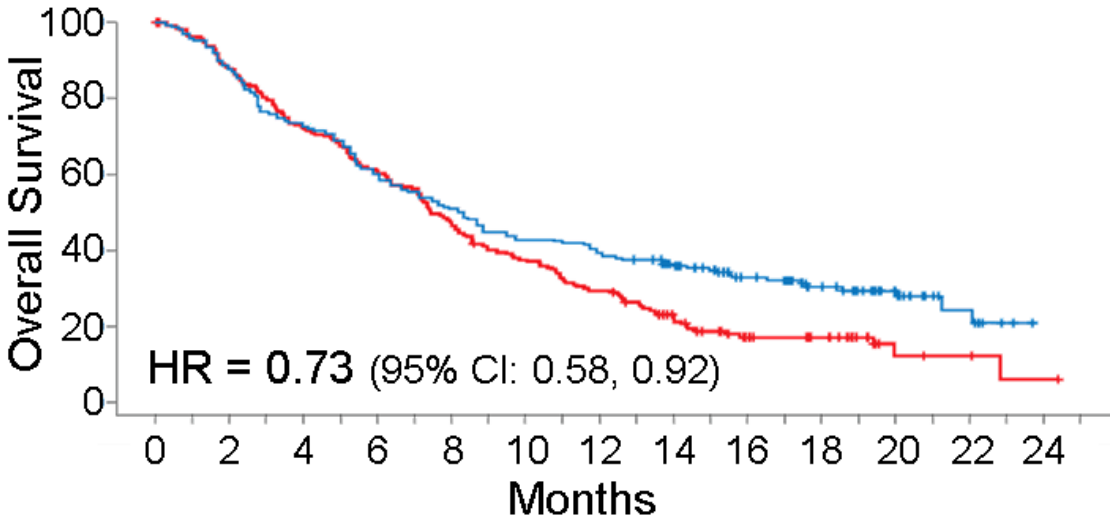


Figure 6 Overall survival comparing atezolizumab and taxane subgroups

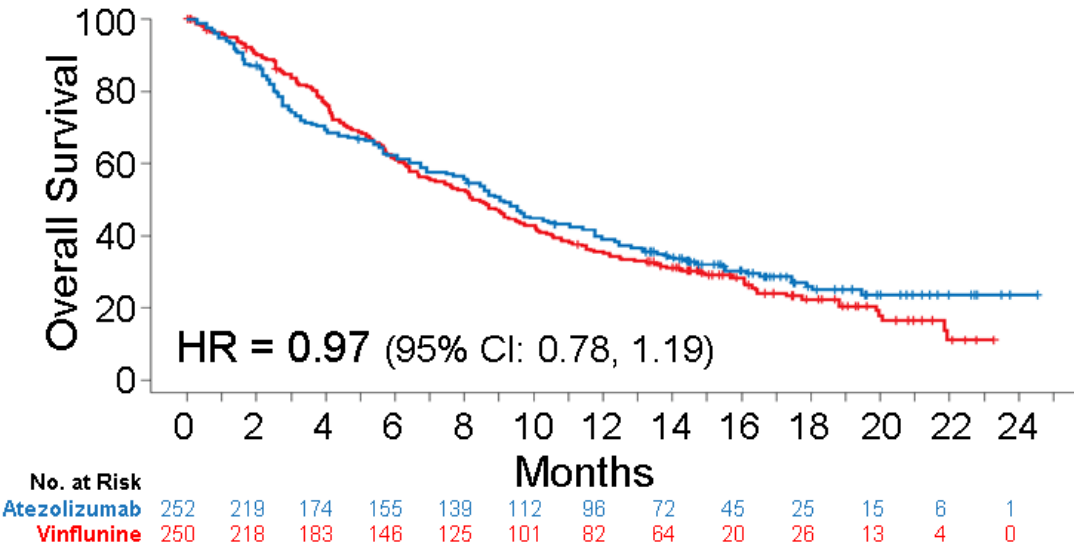


Figure 7 Overall survival comparing atezolizumab and vinflunine subgroups

The company's updated submission focuses on OS. Kaplan-Meier PFS curves are presented only for the chemotherapy subgroup comparison of atezolizumab against taxanes (reproduced in Figure 8). As with the OS outcome, the PFS curves for atezolizumab and taxanes cross, indicating that the proportional hazards assumption does not hold.

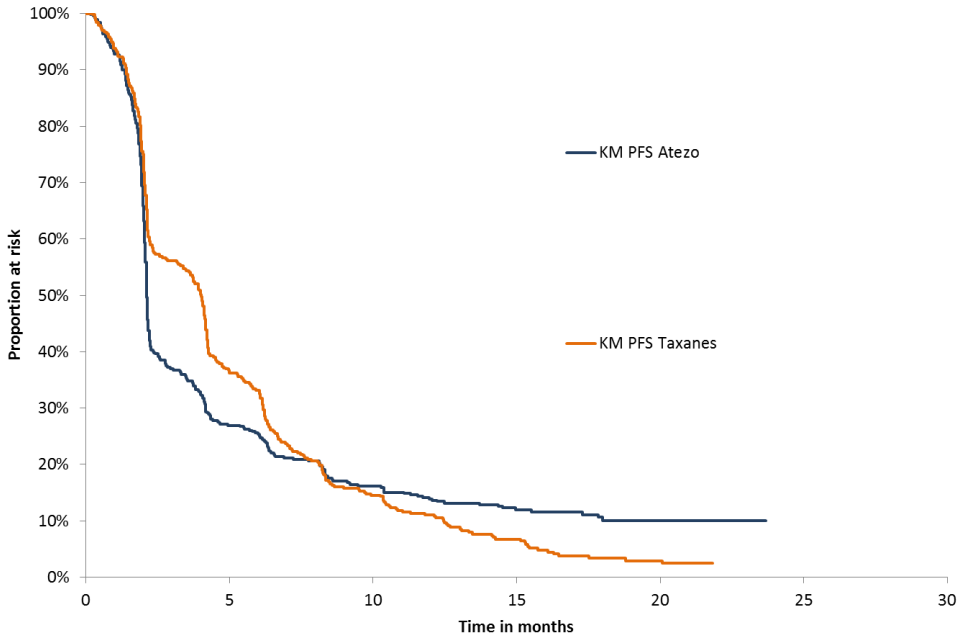


Figure 8 PFS comparing atezolizumab and taxane subgroups

Summary results of the subgroup analyses by chemotherapy type are shown for OS in Table 5 and for PFS in Table 6, reproduced from the company's updated submission. The company concludes that atezolizumab demonstrated improved OS over chemotherapy in the taxane subgroup but not the vinflunine subgroup. They point out that the taxane subgroup is most relevant for the UK, since vinflunine is not recommended in this patient population. The lack of effectiveness of atezolizumab compared to vinflunine reflects longer OS in the vinflunine-treated group than had been expected based on historical data. As acknowledged by the company, it is unclear why patients who received vinflunine performed better than had been expected. The baseline characteristics of the vinflunine subgroup do not suggest that patients receiving vinflunine had better or worse prognostic characteristics than those receiving atezolizumab.

Table 5 OS in chemotherapy subgroups (Table 3 in the company's updated submission)

	Atezo n=215	**Taxane n=214**
Median OS, months (95% CI)	8.3 (6.6–9.8)	7.5 (6.7–8.6)
Hazard ratio (95% CI)	0.73 (0.58–0.92)	
	Atezo n=252	**Vinflunine n=250**
Median OS, months (95% CI)	9.2 (7.9–10.4)	8.3 (6.9–9.6)
Hazard ratio (95% CI)	0.97 (0.78–1.19)	

Table 6 PFS in chemotherapy subgroups (Table 4 in the company's updated submission)

	Atezo n=215	**Taxane n=214**
Median PFS, months (95% CI)	2.1 (2.1–2.3)	3.7 (2.2–4.1)
Hazard ratio (95% CI)	1.00 (0.81–1.23)	
	Atezo n=252	**Vinflunine n=250**
Median PFS, months (95% CI)	2.1 (2.1–2.2)	4.1 (3.7–4.3)
Hazard ratio (95% CI)	1.19 (0.98–1.44)	

The company does not comment on the subgroup results for PFS (Table 6) other than to say that the analysis in subgroups was consistent with the ITT analysis. We note that PFS was shorter in the atezolizumab subgroup than the chemotherapy subgroup both for the comparison with taxanes and the comparison with vinflunine.

3.2.2 HRQoL results

The company has provided very limited information on HRQoL. No HRQoL outcome scores are included in their updated submission (the presentation by Powles et al.[3] provides a graph showing the time-course of changes in EORTC-QLQ-C30 scores but does not give absolute scores; this is not reproduced here since only the EQ-5D informs the company's health utility calculation for the economic analysis).

Although point estimates for utility values are reported based on the transformed EQ-5D scores (Table 10 below), no actual EQ-5D scores are provided, either in the company's updated submission, the CSR,[2] EPAR,[1] or study presentation.[3] As such, it is unclear how well the single point estimate of utility for each study group captures patients' EQ-5D scores. Rather than being fixed, patients' EQ-5D scores would likely vary in relation to their time on treatment (and possibly other factors), but temporal variability of scores, and whether this differed systematically between study groups, is not discussed by the company.

3.2.3 Safety results

The company's updated submission, CSR,[2] trial publication (Powles et al.[3]) and EPAR[1] concluded that the data from IMvigor211 demonstrate atezolizumab to have a favourable safety profile when compared to chemotherapy, with no new safety signals being identified compared to the previous studies PCD4989g and IMvigor210. The ERG notes that immune-related adverse events (classed as adverse events of special interest [AESI] in IMvigor211), which are a particular risk with immune checkpoint inhibitors such as atezolizumab, were more frequent in the atezolizumab arm than the chemotherapy arm (Table 7) although the company's updated submission does not specifically discuss AESI. The CSR[2] reports that AESI were observed at a [redacted] (CSR[2] section 8.9). Overall, the majority of patients with AESIs experienced events of [redacted] (CSR section 8.9).[2] In contrast

to the CSR,[2] the company's updated submission states there were no grade 5 AESI in the atezolizumab arm.

Table 7 IMvigor211 safety summary (Table 5 in the company's updated submission)

Adverse event (AE), n (%)	All cause		Treatment related	
	Atezo n=459	Chemo n=443	Atezo n=459	Chemo n=443
All Grade AE	438 (95)	435 (98)	319 (70)	395 (89)
Grade 3 or 4 AE	233 (51)	249 (56)	91 (20)	189 (43)
Grade 5 AE	17 (4)	18 (4)	3 (1)	8 (2)
Any grade AESI	139 (30)	98 (22)	–	–
Grade 3 or 4 AESI	37 (8)	13 (3)	–	–
Grade 5 AESI	0	1 (< 1)	–	–
Serious AE	188 (41)	191 (43)	72 (16)	110 (25)
AE leading to treatment discontinuation	34 (7)	78 (18)	16 (3)	63 (14)
AE leading to dose modification, delay or interruption	134 (29)	210 (47)	–	–

The company's updated submission does not discuss whether any adverse events differed in frequency between the PD-L1 expression subgroups. The CSR[2] states that the adverse event profile of atezolizumab was [redacted]. Data provided in the CSR[2] [redacted], although there were some [redacted] (Table 8).

Table 8 Adverse events in PD-L1 expression subgroups (from Table 60 in the CSR[2])

Adverse event (AE) %	IC2/3 subgroup		IC1/2/3 subgroup	
	Atezolizumab N=114	Chemotherapy N=112	Atezolizumab N=312	Chemotherapy N=297
AE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AE	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related serious AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4 AE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related Grade 3-4 AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 AE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related Grade 5 AE	[redacted]	[redacted]	[redacted]	[redacted]
AESI	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AESI	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to dose modification or interruption	[redacted]	[redacted]	[redacted]	[redacted]

Bold highlight indicates >5% difference between PD-L1 expression subgroups

The atezolizumab EPAR[1] considers that the development of anti-therapeutic antibodies (ATA) is potentially important in the risk management plan for atezolizumab and notes that this is being investigated in IMvigor211. The company does not comment on this in their updated submission. The CSR provides data showing that the treatment-emergent ATA rate was [redacted] atezolizumab-treated patients but the development of ATAs [redacted] (CSR section 10.4; data not reproduced here).[2] The EPAR[1] reports that frequencies of Grade 3-4 adverse events, serious adverse events, and adverse events leading to dose discontinuation were slightly (approximately 8%) higher in ATA-positive patients than those who were ATA-negative (EPAR[1] Table 93). The ERG's clinical advisor commented that whilst it is important to note the presence and potential effects of ATA, clinical experience with how to manage patients with ATA is currently limited and these findings concerning ATA in IMvigor211 would be unlikely to influence the current clinical management of patients receiving atezolizumab.

In conclusion, the ERG agrees that results from IMvigor211 do not identify any new safety concerns that would be unexpected for an immune checkpoint inhibitor and overall the safety profile of atezolizumab is more favourable than that of both taxanes and vinflunine.

3.3 ERG's critical appraisal of the IMvigor211 trial

The ERG has critiqued the methods of the IMvigor211 trial using standard critical appraisal criteria, as shown in Table 9. Overall, IMvigor211 was a well-conducted RCT but has the primary limitation of being open-label, meaning that several types of bias risk (e.g. risk of performance bias or detection bias) cannot be ruled out. The study population is representative for patients with advanced or metastatic urothelial carcinoma who have progressed on a prior platinum-containing therapy, and the population characteristics are generally well-balanced across the study arms and across the stratified subgroups. There is some uncertainty around precisely how randomisation was conducted. There is also uncertainty about why some data for EQ-5D outcomes are missing and whether the missing data were balanced across the study arms.

Table 9 ERG assessment of trial quality for IMvigor211

Quality assessment question	ERG judgement	Comments
1. Was randomisation carried out appropriately?	Unclear	Investigators could choose chemotherapy assignment before randomisation and a cap was set on taxane assignment but it is not explained how these were incorporated in the treatment assignment strategy without breaking randomisation
2. Was concealment of treatment allocation adequate?	No	Open-label study
3. Were groups similar at outset in terms of prognostic factors?	Yes	Baseline characteristics are balanced across arms in the total population and also within PD-L1 expression and chemotherapy subgroups
4. Were care providers, participants and outcome assessors blind to treatment allocation?	No	Open-label study

5. Were there any unexpected imbalances in drop-outs between groups?	Time-to-event outcomes: No HRQoL: Unclear	Limited attrition data are reported for the EORTC QLQ-C30 and none are reported for the EQ-5D
6. Is there any evidence that authors measured more outcomes than they reported?	Yes	EQ-5D was assessed but no EQ-5D data are reported in any of the documents provided by the company
7. Did the trial include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Effectiveness outcomes: Yes HRQoL outcomes: No	The ITT definition is appropriate. Missing data were censored for primary time-to-event outcomes, but missing HRQoL data were excluded, with the reasons and timing not reported.

3.4 Summary of clinical effectiveness and safety

The ERG agrees broadly with the company's interpretation of the evidence but we caution that the calculation of the utility value is not transparent, since none of the EQ-5D scores that it is based on are reported; and hazard ratios for OS and PFS are unlikely to accurately reflect the underlying hazard functions since the assumption of proportional hazards was not met.

Overall, the ERG agrees with the EMA's risk-benefit assessment based on the results of IMvigor211 which concluded that: atezolizumab does not appear to be inferior to chemotherapy in terms of overall survival; atezolizumab has a more favourable safety profile compared to chemotherapy; and patients who responded to atezoliumab therapy exhibited durable responses (EPAR section 4.7.2). Note that the EMA's conclusion of 'non-inferiority' of OS is qualitative rather than statistically-based since the IMvigor211 trial tested a superiority hypothesis and did not specify a non-inferiority margin.

4 ERG's critique of the company's economic analysis

4.1 Overview of the company's revised analysis

The company provided a revised economic analysis with the following changes to the original submission:

i) New clinical effectiveness evidence

Time-to-event outcomes and utility data are provided from the IMvigor211 RCT, as discussed above in section 3.

ii) Updated health state costs, drug administration costs, and adverse event costs

These are shown in Tables 16-19 of the company's updated submission. The drug costs for docetaxel and paclitaxel have been updated with the latest prices on the UK Drugs and Pharmaceuticals Electronic Market Information Database (eMIT). It is unclear why the administration costs have been updated as they appear to be derived from the same year's reference costs as used in the original company submission. They appear to have been taken from the total Healthcare Resource Groups (HRG) costs, rather than the costs specific to the outpatient setting which was used in the original company submission. The company's updated submission includes adverse event costs for asthenia, neutropenia and white blood cell count decrease which were not included in the original submission. However, the ERG concludes that the changes to the costs in the company's updated submission have a minimal effect on cost-effectiveness results.

iii) Changes in the comparators used

In their original submission the company had three comparators: docetaxel, paclitaxel and best supportive care. The company's updated analysis differs in two respects:

- A single chemotherapy comparator of taxanes is used (i.e. docetaxel and paclitaxel combined). The company state that comparing atezolizumab to docetaxel and paclitaxel separately would be inappropriate because study randomisation would be broken and there were small numbers of patients receiving each of the treatments (paclitaxel n=148; docetaxel n=53). The ERG consider that it is appropriate to combine paclitaxel and docetaxel as a single comparator for the economic analysis as this is consistent with the chemotherapy arm for IMvigor211 and represents current standard of care for patients in the UK. The company have provided an exploratory analysis for atezolizumab compared to paclitaxel in their updated submission and the ERG agrees that this approach is appropriate.
- The company have not included best supportive care as a comparator. The ERG notes that although the IMvigor211 trial did not provide new information on BSC, this is not a reason to remove the BSC comparator that was included in the company's original submission. We suggest that the company should have presented their updated results compared to BSC, to be consistent with the NICE scope.

iv) Provision of a new PAS price

The atezolizumab PAS discount of [redacted] reduces the cost of atezolizumab from a list price of £3807.69 to a net price of [redacted] per vial (1,200mg).

v) Changes to the modelling approach, which is no longer based on fractional polynomials

In the company's original submission, the company fitted parametric survival curves to the atezolizumab and comparator individual study arms and then used the results of a fractional polynomial NMA applied to the comparator arms. The company used this approach as the proportional hazards assumption did not hold. In the company's updated submission, the company has fitted separate survival models to the atezolizumab and chemotherapy arms of the IMvigor211 trial. The company does not discuss the differences in the modelling approach between this submission and the previous version of the model and whether this approach assumes proportional hazards or varying hazards. However, the ERG notes that the data provided are fairly mature and so this issue may not have a large impact on model results. The extrapolation of the clinical data is described in more detail below (section 4.2).

vi) Updated utility values

The economic model includes new utility values collected from the IMvigor211 trial via the EQ-5D 3L questionnaire with UK-specific weights from patients treated with atezolizumab and taxanes. These are shown in Table 10. The company also ran a sensitivity analysis using utility values from the NICE appraisal of pembrolizumab in previously-treated advanced or metastatic urothelial carcinoma (utility values for PFS 0.731, progressed disease 0.641).[4] In this sensitivity analysis the ICER reduces by about £9,000 to £91,653 per QALY. While we have some concerns with the reporting of these data (as noted above in section 3.2.2), we consider these data to be an improvement on the data used in the company's original submission (which were mapped from EORTC QLQ-C30 to EQ-5D).

Table 10 Mean (SE) utility values from IMvigor211

State	Atezolizumab	Taxanes

On treatment	0.684 (0.011)	0.660 (0.012)
Off treatment	0.547 (0.010)	0.547 (0.010)

4.2 Extrapolation of clinical data

The company considered parametric distributions fitted to the observed PFS, time to treatment discontinuation (TTD) and OS data for atezolizumab and taxanes from the IMvigor211 trial. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated to assess the statistical fit of the curves to the observed data. The choice of base-case parametric model was based upon the best statistical fit and the clinical plausibility of the short-term and long-term extrapolations.

4.2.1 PFS extrapolation

Based on the AIC and BIC statistics, visual inspection and clinical plausibility, the company considered the generalised gamma distribution to be the most appropriate distribution for the atezolizumab and taxanes treatment arms. The generalised gamma was the best fit based on AIC and BIC for atezolizumab and the second-best fit for taxanes. The company therefore used the Kaplan-Meier data with a generalised gamma tail extrapolation.

The ERG notes that the Kaplan-Meier data for the taxanes study arm were mature and therefore we suggest it would be more appropriate to use the Kaplan-Meier data alone for the taxanes arm without the need for extrapolation of the tail. We agree that the Kaplan-Meier data with a generalised gamma tail is an appropriate distribution to use for PFS based on the observed study data for the atezolizumab arm. Changes to the distribution used for PFS have a minimal effect on the cost effectiveness results (Table 14). Figure 9 shows the parametric curves for PFS compared to the trial Kaplan-Meier data with the ERG's preferred assumptions.

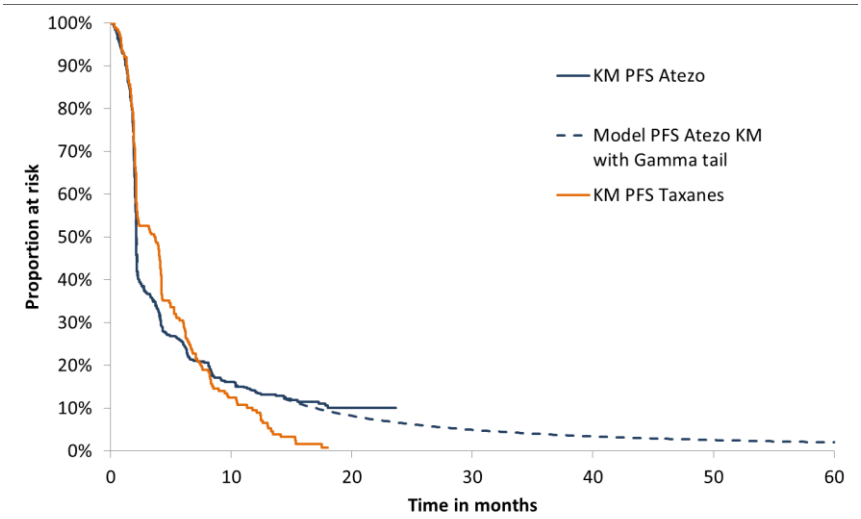


Figure 9 Parametric distributions used for PFS and KM data from IMVigor211 (ERG base case)

4.2.2 TTD extrapolation

The company states that atezolizumab is licensed for use until loss of clinical benefit or unmanageable toxicity and that, in the IMvigor211 trial, some patients continued to receive treatment beyond disease progression. TTD parametric curves were fitted to the observed TTD data in the IMvigor211 trial. The best fit to the atezolizumab arm based on the AIC and BIC statistics was the log-logistic distribution. However, the company state that if this distribution is chosen the extrapolated TTD curve would cross the OS curve at 13 years and then lie below the OS curve for the remainder of the time horizon of the model. They therefore consider that the generalised gamma is more appropriate, as this gave the second best fit, based on AIC and BIC data, to the observed data and they used the Kaplan-Meier data with a generalised gamma tail. The company provides sensitivity analyses using alternative distributions for TTD, reproduced here in Table 14 (see 4.4 Company's sensitivity analyses below). We note that the cost-effectiveness of atezolizumab is very sensitive to the extrapolation of TTD.

We suggest that the company is mistaken with their assertion that the TTD and OS curves cross, as we can see no evidence of this. As with PFS, we observe that the Kaplan-Meier data are mature for the taxanes arm and we suggest that the TTD Kaplan-Meier data can be used with no extrapolation of the tail needed. As the log-logistic distribution is the best fit to the atezolizumab TTD data, we suggest this would be the most appropriate distribution to be used (i.e. a Kaplan-Meier curve with a log-logistic tail). Figure 10 shows the parametric distributions used for TTD compared to the trial Kaplan-Meier data with the ERG's preferred assumptions.

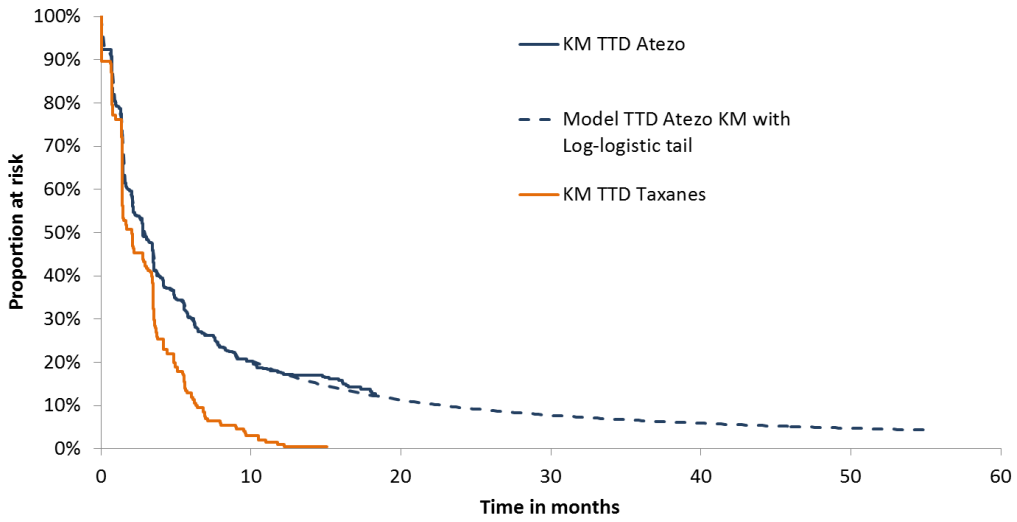


Figure 10 Parametric distributions used for TTD and KM data from IMVigor211 (ERG base case)

4.2.3 OS extrapolation

The company suggest it is plausible that a proportion of patients experience a sustained response and survive over a longer time; but they acknowledge that the OS data from the IMvigor211 trial are not sufficiently mature to show a sustained response for OS in this patient group. However, the company argue that the mix-cure rate model is appropriate for OS as it allows a mixture of cancer-related mortality risk and background mortality. The company has used a mixed cure rate of 0%, meaning that no patients are assumed to have the same mortality rate as that of the general population. Furthermore, the company state that using the mix-cure rate methodology means that the tail of the survival curve will never be above that of the background (general population) mortality.

The company's analysis of distribution fit using AIC and BIC statistics showed that the generalised gamma distribution was the best fit to the atezolizumab and taxane arms. The company therefore used a mix-cure rate model with the generalised gamma distribution for the atezolizumab arm and Kaplan-Meier data with a generalised gamma tail for the taxanes arm. The company extrapolated the tail from the point when 30% of patients were at risk. The company ran sensitivity analyses using alternative distributions for OS, as shown in Table 14 (see 4.4 Company's sensitivity analysis section below). We note that the cost-effectiveness of atezolizumab is very sensitive to changes to the extrapolation of OS.

The ERG observes that the visual fit using the mix-cure rate model with the generalised gamma for atezolizumab is similar to that for Kaplan-Meier data with a lognormal tail, the

Kaplan-Meier data with log-logistic tail, or the Kaplan-Meier data with a gamma tail. The company does not provide a rationale for extrapolating the tail from the point where 30% of patients are still at risk and the ERG suggests that a better approach would be to extrapolate the tail where 20% of patients were at risk as this proportion is sufficient. The ERG notes that in the pembrolizumab technology appraisal for advanced / metastatic urothelial bladder cancer[4] clinical experts estimated the 5-year survival of patients treated with docetaxel / paclitaxel to be 2-3%. Therefore, we consider that using Kaplan-Meier data with a gamma distribution for taxanes would underestimate the survival of patients receiving docetaxel and paclitaxel and that the more appropriate distribution to use would be a Kaplan-Meier curve with a log-logistic tail (Table 11). Figure 11 shows the parametric distributions used for OS compared to the trial Kaplan-Meier data with the ERG's preferred assumptions.

Table 11 Patient survival at 5 years estimated using alternative extrapolation distributions

Distribution for atezolizumab and taxanes	Proportion alive at 5 years	
	Atezolizumab arm	Taxanes arm
Company base case	7.6%	0.4%
Kaplan-Meier curve with a log-logistic tail	7.3%	2.4%
Kaplan-Meier curve with a generalised gamma tail	7.5%	0.4%
Kaplan-Meier curve with a lognormal tail	6.5%	1.5%

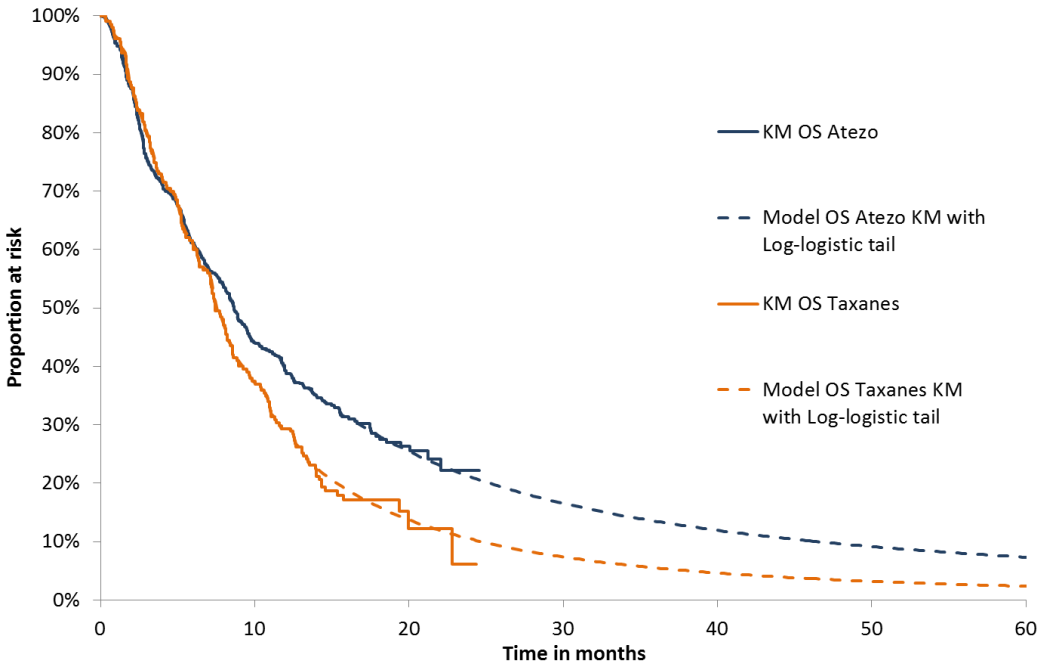


Figure 11 Parametric distributions used for OS and KM data from IMVigor211 (ERG base case)

4.3 Company's base case results

The company's base case results are shown for the list price for atezolizumab in Table 12 and with the confidential PAS price for atezolizumab in Table 13. The ICERs presented in the original company submission were £131,579 per QALY for atezolizumab compared to docetaxel and £104,850 per QALY for atezolizumab compared to paclitaxel.

Table 12: Base-case results (2L) – list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£54,573	0.93	£44,321	0.44	£100,844
Taxanes	£10,253	0.49			

Table 13: Base-case results (2L) – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	0.93	[redacted]	0.44	[redacted]
Taxanes	[redacted]	0.49			

4.4 Company's sensitivity analyses

The company's sensitivity analyses for selected analyses are shown in Table 14 for the list price of atezolizumab and Table 15 for the PAS price.

Table 14: Resulting ICERs vs. taxanes from scenario analyses – list price

Scenario	Parameter	Value	ICER vs. taxanes
Base case	OS Atezolizumab + taxanes	Cure GenGamma 0% + GenGamma	£100,844
		GenGamma	£101,156
		Log-logistic	£126,552

		Log-normal	£129,338
Base case	PFS Atezolizumab + taxanes	KM+GenGamma	£100,844
		GenGamma	£100,946
		KM+Log-logistic	£101,336
		Log-logistic	£101,669
Base case	TTD Atezolizumab + taxanes	KM+GenGamma	£100,844
		GenGamma	£106,133
		KM+Log-logistic	£130,981
		Log-logistic	£136,334
Base case	Comparator	Pooled taxanes	£100,844
		Paclitaxel	£110,403
Base case	Utilities	IMvigor211	£100,844
		Pembrolizumab 2L mUC NICE appraisal	£91,653
		Vinflunine PBAC assessment	£86,095

GenGamma: generalised gamma; KM: Kaplan-Meier; mUC: metastatic urothelial cancer; 2L: second-line

Table 15: Resulting ICERs vs. taxanes from scenario analyses – PAS price

Scenario	Parameter	Value	ICER vs. taxanes
Base case	OS Atezolizumab + taxanes	Cure GenGamma 0%	[redacted]
		GenGamma	[redacted]
		Log-logistic	[redacted]
		Log-normal	[redacted]
Base case	PFS Atezolizumab + taxanes	KM+GenGamma	[redacted]
		GenGamma	[redacted]

		KM+Log-logistic	[redacted]
		Log-logistic	[redacted]
Base case	TTD Atezolizumab + taxanes	KM+GenGamma	[redacted]
		GenGamma	[redacted]
		KM+Log-logistic	[redacted]
		Log-logistic	[redacted]
Base case	Comparator	Pooled taxanes	[redacted]
		Paclitaxel	[redacted]
Base case	Utilities	IMvigor211	[redacted]
		Pembrolizumab 2L mUC NICE appraisal	[redacted]
		Vinflunine PBSC assessment	[redacted]

GenGamma: generalised gamma; KM: Kaplan-Meier; mUC: metastatic urothelial cancer; 2L: second-line

4.5 ERG's base case

The ERG base case results using the distributions for PFS, OS and TTD as specified in Table 16 are shown in Table 17 for the list price of atezolizumab and Table 18 for the PAS price.

Table 16 Assumptions for the ERG base case analysis

Parameter	Value	Notes
PFS	KM + generalised gamma tail	KM data only used for taxanes arm.
TTD	KM + log-logistic tail	KM data only used for taxanes arm.
OS	KM + log-logistic tail	Extrapolating the tail from the point where 20% of patients are still at risk

KM: Kaplan-Meier; OS: overall survival; TTD: time to treatment discontinuation;

Table 17: ERG base-case results (2L) – list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£73,070	0.97	£61,492	0.40	£154,282
Taxanes	£11,578	0.57			

Table 18: ERG base-case results (2L) – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	0.97	[redacted]	0.40	[redacted]
Taxanes	[redacted]	0.57			

4.6 End of life criteria

The company state that atezolizumab is believed to meet end of life criteria in previously treated metastatic urothelial cancer based on evidence from IMvigor211, taking into account the extrapolated mean OS for atezolizumab and comparators.

The ERG note that the mean OS for the taxane arm in the ERG base case is less than 24 months (12.5 months) and the extension in survival for the atezolizumab arm over the taxane arm is 8.2 months. The ERG therefore agrees that atezolizumab meets the end of life criteria in this population.

4.7 Summary of the company's economic analysis results

In summary, the cost effectiveness results are very sensitive to changes in the assumptions for the extrapolation for OS and TTD. The cost effectiveness results for atezolizumab compared to taxanes vary between £100,844 and £154,282 per QALY using the company's and the ERG's preferred assumptions.

5 References

1. European Medicines Agency. Tecentriq. International proprietary name: atezolizumab. Assessment report. July 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004143/WC500235780.pdf

2. A study of atezolizumab compared with chemotherapy in participants with locally advanced or metastatic urothelial bladder cancer (IMvigor211). Unpublished confidential clinical study report.

3. Powles T, Loriot Y, Durán I, Ravaud A, Retz MM, Vogelzang NJ, et al. IMvigor211: A phase III randomized study examining atezolizumab vs. chemotherapy for platinum-treated advanced urothelial carcinoma. EACR-AACR-SIC Special Conference 2017: The Challenges of Optimizing Immuno- and Targeted Therapies: From Cancer Biology to the Clinic. Florence, Italy, June 2017 (lecture slides).

4. National Institute for Health and Care Excellence. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]. 2017

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

Confidential Appendix to Roche additional evidence submission with updated PAS

This confidential Appendix presents the results of the economic model based on the list price and the updated PAS price for atezolizumab (discount of [redacted]).

Base-case incremental cost effectiveness analysis results

Base-case results of the economic model based at list price for atezolizumab are presented in Table 1.

At list price, atezolizumab 2L provided a QALY gain of 0.93, and life-year gain of 1.55, at a total drug cost of £41, 174, and total overall cost of £54,573. The taxanes comparator provided a gain of 0.49 QALYs and 0.96 life years, at drug costs of £429 and total costs of £10.253. The resulting ICER for atezolizumab compared to taxanes is £100,844 per QALY.

The equivalent ICER incorporating the updated PAS for atezolizumab (discount of [redacted]) is [redacted] vs. taxanes (Table 2). As such, at the updated PAS price and considering end of life criteria, these results show atezolizumab to be a cost-effective use of NHS resources compared to taxanes.

Table 1: Base-case results (2L) – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	£54,573	1.55	0.93	£44,321	0.71	0.44	£100,844
Taxanes	£10,253	0.85	0.49				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 2: Base-case results (2L) – updated PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezolizumab	[redacted]	1.55	0.93	[redacted]	0.71	0.44	[redacted]
Taxanes	[redacted]	0.85	0.49				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Clinical outcomes from the model

Comparison of results from the model to existing observed data from studies IMvigor 211 IMvigor 210 allows an assessment of the accuracy of the modelled survival. Results for PFS and OS from the model are compared to trial data in Table 3 and Table 4-Table 5 respectively.

The model is accurate in terms of median PFS and OS results as compared to the IMvigor 211 study, thus supporting the approach taken for PFS and OS extrapolation. In addition, as seen in Table 5, the estimated results from the model at 5, 10 or 20 years are conservative versus estimates from clinical expert opinion, received during the initial company submission and also during the first Appraisal Committee meeting.

Table 3: Summary of PFS model results compared with observed clinical data

	Median (model)	Median (trial)	12 month (model)	12 month (trial)
IMvigor 211	2.06 months	2.1 months	12.0%	NR
IMvigor 210 (2L)		2.1 months		NR

Table 4: Summary of OS model results compared with observed clinical data

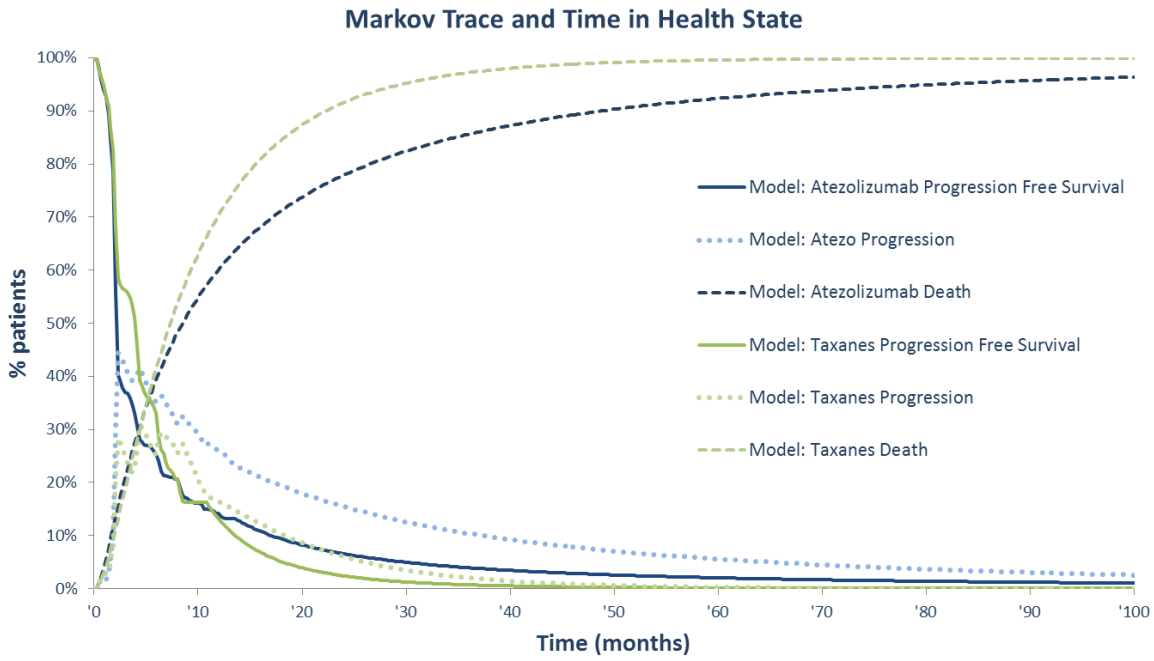
	Median (model)	Median (trial)	12 month (model)	12 month (trial)
IMvigor 211	8.5 months	8.6 months	39.9%	39.2%
IMvigor 210 (2L)		7.9 months		36.9%

Table 5: Comparison of modelled and expert opinion results for OS

	5 year OS	10 year OS	20 year OS
Expert clinical advice	10-20%	5-10%	0-5%
Atezolizumab IMvigor 211 model	7.7%	2.7%	0.7%

Figure 1 shows aggregated results from the model for all health states for the comparison of atezolizumab and taxanes. It can be seen that over the time horizon of the model, a greater proportion of patients spend more time in the PFS state and experience longer OS when receiving atezolizumab as compared to taxanes.

Figure 1: Markov trace: combined for results for atezolizumab and taxanes



Disaggregated results of the base case incremental cost effectiveness analysis

The QALY gain disaggregated by health states allows exploration of which health state is driving QALY gain (Table 6). Since health state occupancy in the model is driven by time to treatment discontinuation, PFS and PD states effectively mirror patients being on and off treatment. The incremental QALY gain for atezolizumab is achieved both when patients are on the PFS and PD heath states (i.e. on and off treatment).

Table 6: Summary of QALY gain by health state – comparison to taxanes

Health state	QALYs atezolizumab	QALYs taxanes	Incremental QALYs	% absolute increment QALYs
PFS	0.412	0.168	0.245	56%
PD	0.520	0.325	0.195	44%
Total	0.932	0.493	0.440	100%

A breakdown of the difference in costs by health state can be found in Table 7-Table 8 and a by resource use is found in Table 9-Table 10.

Table 7: Summary of costs by health state – list price

Health state	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
PFS	£47,473	£7,089	£40.384	91%
PD	£7,101	£3,164	£3,937	9%
Total	£54,573	£10,253	£44,321	100%

Table 8: Summary of costs by health state – updated PAS

Health state	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
PFS	[redacted]	£7,089	[redacted]	[redacted]
PD	[redacted]	£3,164	[redacted]	[redacted]
Total	[redacted]	£10,253	[redacted]	[redacted]

Table 9: Summary of predicted resource use by category of cost – list price

Cost Item	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
Treatment	£41,174	£429	£40,745	92%
Administration	£2,554	£4,090	£-1,536	-3%
Adverse events	£90	£31	£58	0%
Supportive care (PFS)	£3,656	£2,538	£1,117	3%
Supportive care (PD)	£7,101	£3,164	£3,937	9%
Total	£54,573	£10,253	£44,321	100%

Table 10: Summary of predicted resource use by category of cost – updated PAS

Cost Item	Cost atezolizumab	Cost taxanes	Increment	% absolute increment
Treatment	[redacted]	£429	[redacted]	[redacted]
Administration	[redacted]	£4,090	[redacted]	[redacted]
Adverse events	[redacted]	£31	[redacted]	[redacted]
Supportive care (PFS)	[redacted]	£2,538	[redacted]	[redacted]
Supportive care (PD)	[redacted]	£3,164	[redacted]	[redacted]
Total	[redacted]	£10,253	[redacted]	[redacted]

Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted using 1000 simulations, to assess uncertainty surrounding model inputs. The distributions to estimate parameters can be found in **Error! Reference source not found.** summarising the model inputs.

PSA results of the compared to deterministic results for atezolizumab at list price are presented in Table 11 below. Deterministic and probabilistic results are very similar, not indicating signs of non-linearity in the model. A scatterplot of PSA results at list price is shown in Figure **2**. Cost effectiveness acceptability curves at list price are shown in Figure 3.

The respective analyses at the updated PAS price are presented below (Table 12 and Figure 4**Error! Reference source not found.**-

Figure 5)

Table 11: PSA results compared to base-case – list price

	Costs		**QALYs**		**ICER**	
	Deterministic	**PSA**	**Deterministic**	**PSA**	**Deterministic**	**PSA**
Atezolizumab	£54,573	£55,894	0.93	0.95		
Taxanes	£10,253	£10,850	0.49	0.50	£100,844	£101,319

Figure 2: Scatterplot of PSA results for cost effectiveness plane – list price

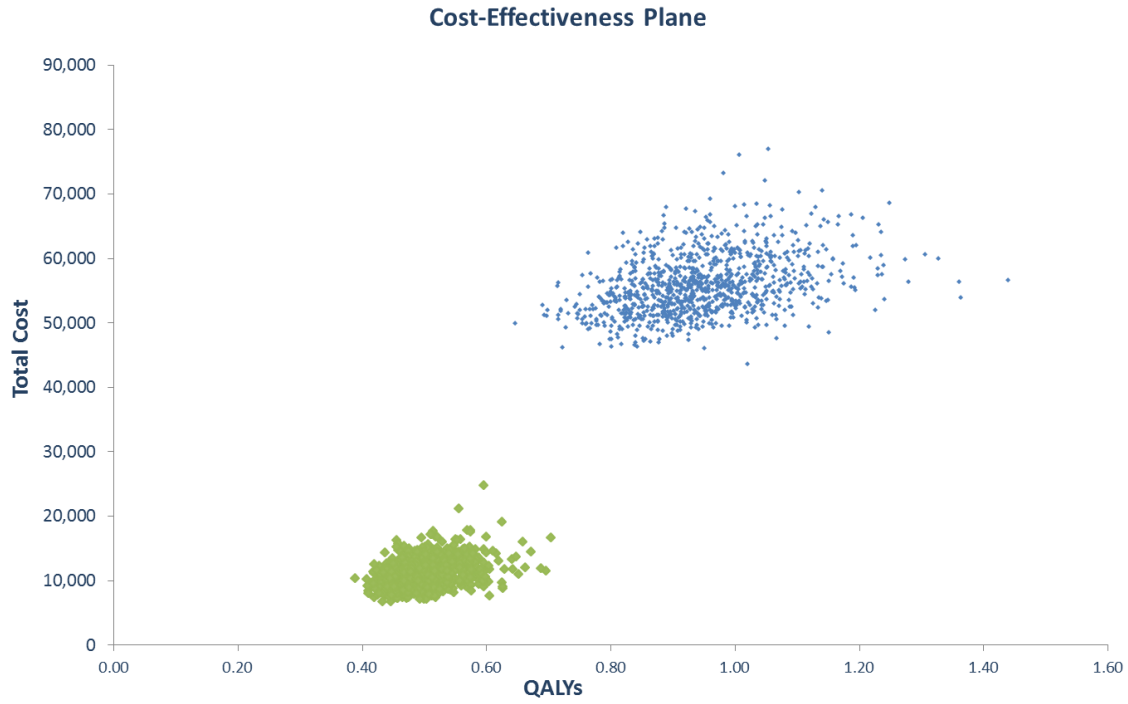


Figure 3: Cost-effectiveness acceptability curve – list price

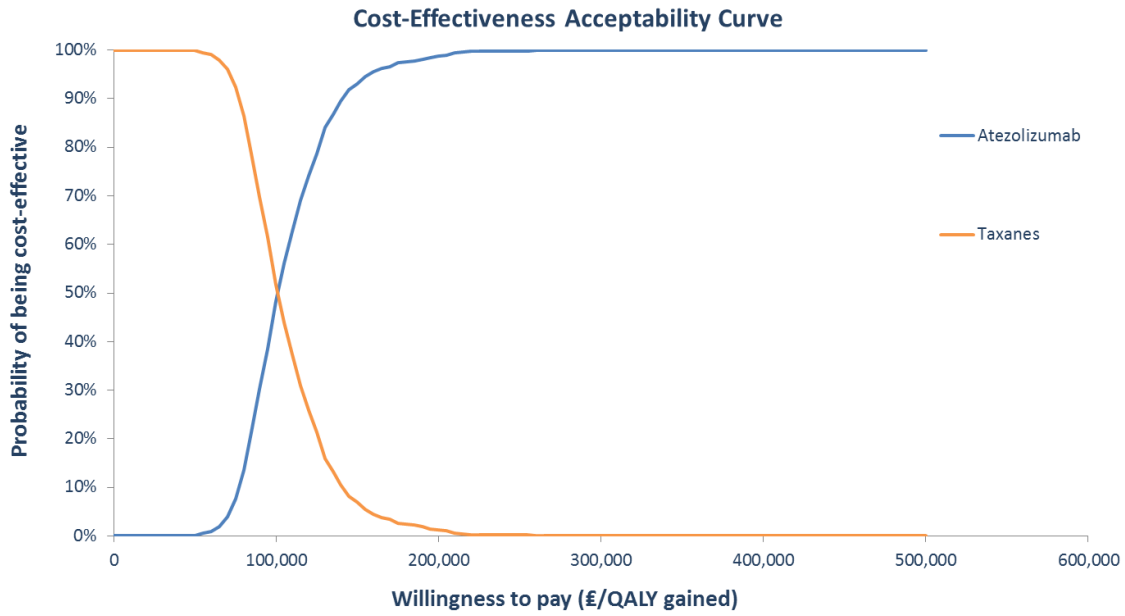


Table 12: PSA results compared to base-case – updated PAS

	Costs		QALYs		ICER	
	Deterministic	**PSA**	**Deterministic**	**PSA**	**Deterministic**	**PSA**
Atezolizumab	[redacted]	[redacted]	0.93	0.95		
Taxanes	[redacted]	[redacted]	0.49	0.50	[redacted]	[redacted]

Figure 4: Scatterplot of PSA results for cost effectiveness plane – updated PAS

Figure 5: Cost-effectiveness acceptability curve – updated PAS

Deterministic sensitivity analyses

The choice of parameters to vary in the deterministic sensitivity analyses was made on the basis of impact on the resulting ICER. The list of parameters included can be found in Table 13 below. Results of the analyses are displayed in Figure 6, and Figure 7. Key remaining model parameters were tested in scenario analyses in the following section.

Table 13: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value	Rationale for value range
Cost of atezolizumab	£3,807.69	+ 50%	- 50%	
Atezolizumab on treatment utility	0.684	0.662	0.705	95% confidence interval
Taxanes on treatment utility	0.660	0.637	0.684	95% confidence interval
Off treatment utility	0.547	0.527	0.567	95% confidence interval
Atezo off treatment supportive care costs	£146.79	+50%	-50%	
Comparator off treatment supportive care costs	£146.79	+50%	-50%	

Figure 6: Comparison to taxanes univariate sensitivity analysis (dark blue = lower value; light blue = higher value) – list price

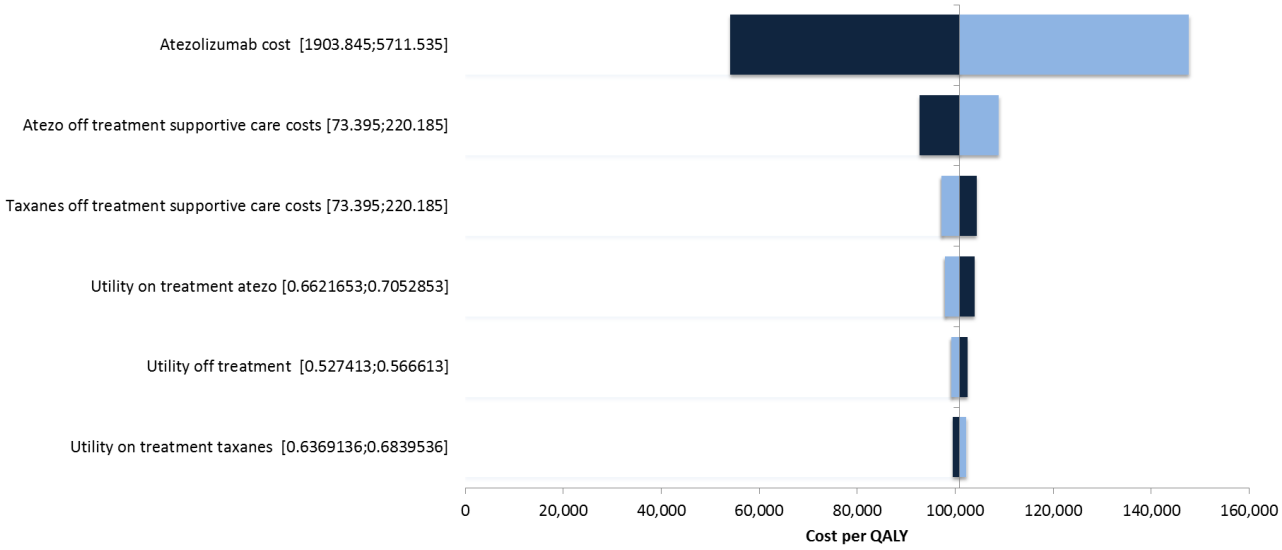


Figure 7: Comparison to BSC univariate sensitivity analysis (dark blue = lower value; light blue = higher value) – updated PAS

[redacted]

Scenario analyses

Scenario analyses were conducted to assess uncertainty around key model parameters and structural assumptions of the model. Results are shown in Table 14-Table 15 for the following scenarios exploring parameter changes:

- Comparators at list prices
- Alternative OS cure-rates for atezolizumab
- Alternative OS for atezolizumab and taxanes (best fitting alternative distributions with full parameterisation and KM + tail)
- Alternative PFS for atezolizumab and taxanes (best fitting alternative distributions with full parameterisation and KM + tail)
- Alternative TTD for atezolizumab and taxanes (best fitting alternative distributions with full parameterisation and KM + tail)
- Comparison to paclitaxel-only
- Alternative utility values from
    - Vinflunine PBAC assessment (1)
    - pembrolizumab 2nd line mUC NICE appraisal (2)
- Time horizon of 10 / 15 years
- Cost discount rate (1.5% rather than 3.5%)
- Effects discount rate (1.5% rather than 3.5%)

The scenarios indicate that at PAS price, there are many conditions at which the ICER remains below the acceptable threshold for end of life treatments.

Table 14: Resulting ICERs vs. taxanes from scenario analyses – list price

Scenario	Parameter	Value	ICER vs. taxanes
Base case	Comparator price	eMIT drug prices	£100,844
		List prices (BNF)	£69,196
Base case	OS Cure rate	0%	£100,844
		1%	£94,678
		2%	£89,184
		3%	£84,258
Base case	OS Atezolizumab + taxanes	Cure GenGamma 0% + GenGamma	£100,844
		GenGamma	£101,156
		Log-logistic	£126,552
		Log-normal	£129,338
Base case	PFS Atezolizumab + taxanes	KM+GenGamma	£100,844
		GenGamma	£100,946
		KM+Log-logistic	£101,336
		Log-logistic	£101,669
Base case	TTD Atezolizumab + taxanes	KM+GenGamma	£100,844
		GenGamma	£106,133
		KM+Log-logistic	£130,981

		Log-logistic	£136,334
Base case	Comparator	Pooled taxanes	£100,844
		Paclitaxel	£110,403
Base case	Utilities	IMvigor 211	£100,844
		Pembrolizumab 2L mUC NICE appraisal	£91,653
		Vinflunine PBAC assessment	£86,095
Base case	Time horizon	20	£100,844
		15	£103,870
		10	£111,441
Base case	Discount rate – effects and costs	3.5% for both	£100,844
	Discount rate - costs	1.5% (3.5% for effects)	£103,601
	Discount rate – effects	1.5% (3.5% for costs)	£92,562
	Discount rate – effects and costs	1.5% for both	£95,093

Table 15: Resulting ICERs vs. taxanes from scenario analyses – updated PAS

Scenario	Parameter	Value	ICER vs. taxanes
Base case	Comparator price	eMIT drug prices	[redacted]
		List prices	[redacted]
Base case	OS Cure rate	0%	[redacted]
		1%	[redacted]
		2%	[redacted]
		3%	[redacted]
Base case	OS Atezolizumab + taxanes	Cure GenGamma 0%	[redacted]
		GenGamma	[redacted]
		Log-logistic	[redacted]
		Log-normal	[redacted]
Base case	PFS Atezolizumab + taxanes	KM+GenGamma	[redacted]
		GenGamma	[redacted]
		KM+Log-logistic	[redacted]
		Log-logistic	[redacted]
Base case	TTD Atezolizumab + taxanes	KM+GenGamma	[redacted]
		GenGamma	[redacted]
		KM+Log-logistic	[redacted]
		Log-logistic	[redacted]
Base case	Comparator	Pooled taxanes	[redacted]

		Paclitaxel	[redacted]
Base case	Utilities	IMvigor 211	[redacted]
		Pembrolizumab 2L mUC NICE appraisal	[redacted]
		Vinflunine PBSC assessment	[redacted]
Base case	Time horizon	20	[redacted]
		15	[redacted]
		10	[redacted]
Base case	Discount rate – effects and costs	3.5% for both	[redacted]
	Discount rate - costs	1.5% (3.5% for effects)	[redacted]
	Discount rate – effects	1.5% (3.5% for costs)	[redacted]
	Discount rate – effects and costs	1.5% for both	[redacted]

Summary of sensitivity analyses results

Sensitivity analyses allow determination of the main drivers of the economic analysis, and exploration of alternative parameter inputs.

As it can be seen in the deterministic analyses and scenario analyses, the ICER is most sensitive to the price of atezolizumab, the price of comparators (eMIT vs. list price), the OS extrapolation, the time to treatment discontinuation, the utility values used and the discount rates considered.

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum therapy: ERG additional scenarios

NICE requested the ERG provide additional scenarios for the separate components of the ERG base case. These analyses are for the updated PAS discount of [redacted]. These are shown in Table 1.

Table 1 ERG scenario analyses and ERG's preferred analysis

	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Company base case (deterministic)	[redacted]	0.44	[redacted]
PFS: K–M data only for taxanes	[redacted]	0.44	[redacted]
TTD: K–M data only for taxanes, K–M + log-logistic for atezolizumab	[redacted]	0.47	[redacted]
OS: K–M + log-logistic tail, starting point of parametric distribution: 20% at risk	[redacted]	0.36	[redacted]
OS: K–M + log-logistic tail, starting point of parametric distribution: 30% at risk	[redacted]	0.33	[redacted]
OS: K-M + log normal tail, starting point of parametric distribution: 20% at risk	[redacted]	0.34	[redacted]
OS: K-M + log normal tail, starting point of parametric distribution: 30% at risk	[redacted]	0.31	[redacted]
OS: K-M + gamma tail, starting point of parametric distribution: 20% at risk	[redacted]	0.44	[redacted]
OS: K-M + gamma tail, starting point of parametric distribution: 30% at risk	[redacted]	0.43	[redacted]
ERG preferred analysis	[redacted]	0.40	[redacted]