NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable [ID939]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Roche**
   - **Action Bladder Cancer UK**

   Please note notification of no comments was received from the Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - **Clinical Expert,** nominated by Roche and NCRI-ACP-RCP-

4. **ERG critique** prepared by SHTAC

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

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Roche	**All comments refer only to the appraisal of atezolizumab in untreated locally advanced or metastatic urothelial carcinoma in adults for whom cisplatin-based chemotherapy is unsuitable (1st Line).** **Comments in response to the appraisal of atezolizumab in locally advanced or metastatic urothelial carcinoma in adults after prior platinum-containing chemotherapy (2nd Line) will be provided in a separate response** Roche are disappointed the committee is minded not to recommend atezolizumab as an option for untreated locally advanced or metastatic urothelial carcinoma (mUC) in adults for whom cisplatin-based chemotherapy is unsuitable (1st Line). However, we are pleased the committee have recommended a proposal for including atezolizumab in the Cancer Drugs Fund (CDF) for this population. Roche intends to submit a proposal to the CDF for this population, and have begun engagement with NHS England on this proposal. However, we are not in a position to finalise a commercial agreement with the CDF as we have concerns regarding the committee's decision that the ERG assumptions are appropriate for decision making, and a reasonable interpretation of the evidence. Use of the ERG approach to overall survival (OS) extrapolation results in clinically implausible survival curves. This is further discussed in comments 2, 2a and 2b below. Our full response is provided in the comments below. We are pleased the committee recognised the unmet need of patients with mUC, the clinical benefit and tolerability of atezolizumab in mUC, and the fulfilment of the end-of-life criteria. Our response relates to the main points of disparity between our manufacturer base case, and the NICE preferred	Comments noted. Please see detailed responses for the individual issues below.

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			assumptions. We have provided additional analyses to support a reversal of this preliminary negative recommendation. As can be seen in comment 6, in all scenarios, atezolizumab is a cost-effective use of NHS resource as per the generally accepted threshold for end-of-life medicines. This is true when accounting for the proposed simple PAS for atezolizumab. Comment summary: 1) Summary 2) Assumptions regarding overall survival extrapolation a) Alternative OS extrapolation scenarios b) Interpretation of objective response rate 3) Committee concerns regarding certainty of the indirect treatment comparison 4) Assumptions regarding time to treatment discontinuation extrapolation 5) Utility values for patients off treatment 6) Alternative scenario analyses to support company base case 7) Uncertainty to be resolved through CDF entry and data collection Comments addressing other factual inaccuracies 8) Interpretation of missing phase III data 9) Comparison with best supportive care 10) Evidence of prolonged response to atezolizumab 11) Atezolizumab is well tolerated in clinical practice 12) References	
2	Company	Roche	**Assumptions regarding overall survival extrapolation** The ACD states: *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:	Comment noted. The committee discussed the overall survival extrapolations in detail, and considered that they were highly uncertain. On balance, the committee considered that the ERG's overall survival extrapolation predicted 5-year survival rates which were more plausible and consistent with the observed data than the company's extrapolation. The committee accepted that the ERG's approach of fitting a different distribution to the progression-free survival data to avoid the progression-free and overall survival curves crossing was reasonable. The committee concluded that based on the evidence it had available, the ERG's approach was more appropriate for decision-making. Please see section 3.9 of the FAD.

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			1. The ERG choice of distribution results in a crossing of the OS and PFS curves for chemotherapy, and a meeting of the curves for atezolizumab. 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 for 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. 2. As shown in figure 1 below, the resulting OS, PFS and time on treatment curves for the comparator (gemcitabine + carboplatin) are clinically implausible, as they cross from 2.7 years when around 10% of patients are still alive in the model. As shown in figure 2 below, the resulting OS and PFS curves for atezolizumab are also clinically implausible, as they meet after 6 years. **Figure 1: OS, PFS and Time on Treatment Curves for comparator: ERG assumptions** *[Figure provided but not reproduced here]* **Figure 2: OS, PFS and Time on Treatment Curves for atezolizumab: ERG assumptions** *[Figure provided but not reproduced here]* *1.* 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 cytotoxic chemotherapy. This is at odds with the clinical advice received by Roche, and provided by the clinical experts within the 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 cytotoxic chemotherapy. This difference in treatment response is supported by the expert personal perspectives submitted from clinical experts as part of this submission; which state the following:	

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			a. *'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.'* b. *'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 key 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 cytotoxic chemotherapy data. Rather the fit should be assessed relative to atezolizumab data.	
2a	Company	Roche	**Alternative OS extrapolation scenarios** We recognise there is uncertainty in the most appropriate choice of OS extrapolation, as atezolizumab survival data are relatively immature. We provide some alternative extrapolation scenarios to aid committee decision making. (Figures 3-9 below). This includes full parameterisation, and Kaplan Meier (KM) plus extrapolated tail. The resulting ICERs for these extrapolations are provided in comment 6. For these scenarios, extrapolation choice is based on statistical fit to observed atezolizumab data. The standard parametric functions with the three lowest AIC/BIC values are provided (table 1). Please note, these AIC/BIC values differ to those on page 159, table 53 of the company submission, as the fits within the company submission were based on the mix-cure rate model. As can be seen in comment 6, whilst use of alternative extrapolations does impact the resulting ICER, in all scenarios atezolizumab remains under the generally accepted threshold for end-of-life medicines. **Table 1: Summary of parametric function goodness of fit for OS (1L)** *[Table provided but not reproduced here]*	Comment noted. The committee discussed the overall survival extrapolations in detail, and considered that they were highly uncertain. On balance, the committee considered that the ERG's overall survival extrapolation predicted 5-year survival rates which were more plausible and consistent with the observed data than the company's extrapolation. The committee concluded that based on the evidence it had available, the ERG's approach was more appropriate for decision-making. Please see section 3.9 of the FAD.

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			Figures 3-9 *[Figures provided but not reproduced here]*	
2b	Company	Roche	**Interpretation of objective response rate** The ACD states: '*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%)'* We are concerned this interpretation of objective response rate is not a reasonable interpretation of the evidence. It is plausible that more patients benefit from atezolizumab than achieve objective anti-tumour responses. The inadequacies of judging the long-term benefits of immunotherapy on short-term measures of radiographic response or progression-free survival have been much discussed (Hodi et al; 2016) and can be readily demonstrated with reference to both atezolizumab and other immunotherapies across a range of tumours. For example, and as shown in Table 2, Phase III trials of atezolizumab in relapsed non-small-cell lung cancer (NSCLC) and mUC both show that atezolizumab improves OS compared with cytotoxic chemotherapy in unselected patients whilst in neither case is response rate or risk of progression noticeably increased; with median PFS actually numerically worse, using conventional measures. **Table 2. Mismatch between end-points based on radiographic progression and OS in phase III studies of atezolizumab** *[Table provided but not reproduced here]* Similarly, the anti-PD-1 antibody, pembrolizumab, improves OS in mUC relative to cytotoxic chemotherapy without improving the risk of disease progression, and results in median PFS which is numerically inferior to that seen with cytotoxic chemotherapy (Bellmunt et al, 2017) Current evidence suggests there is no clear correlation between radiographic response and its derivative progression-free and overall survival benefit to cancer immunotherapies and, as such, it is a misinterpretation to conclude that it is implausible to have a 5-year OS that	Comment noted. The committee recognised this view; however, it noted that the company's extrapolation also predicted 12% survival at 5 years for gemcitabine plus carboplatin, which was substantially higher than the observed 5-year survival in the De Santis trial (1%). The committee concluded that the ERG's approach was more appropriate, as it predicted 5-year survival rates which were more plausible and consistent with the available data. Please see section 3.9 of the FAD.

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			exceeds the 15 month response rate.	
3	Company	Roche	**Committee concerns regarding certainty of the indirect treatment comparison** The ACD states: *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.* Subsequent to submission of the dossier, a matching adjusted indirect comparison (MAIC) was carried out to validate results of the prediction model. These were not available at the submission date for inclusion within the company submission. To support the results of the indirect treatment comparison (ITC) included in the base case, and to aid committee decision making, we provide the MAIC results here. These results have not been incorporated into the economic model. The systematic literature review (SLR) identified 2 studies for inclusion in the ITC for atezolizumab vs. gemcitabine + carboplatin. These studies were Bamias et al. 2007 and DeSantis et al. 2012. Within the company submission, and as referenced in the ACD, results of the simulated treatment comparison (STC) were utilised in the base case to provide comparative efficacy. Using the Bamias and DeSantis studies, the predicted atezolizumab curves were derived using propensity weighting, as per the NICE DSU worked example (Phillippo, D.M et al. 2016) The predicted atezolizumab curves are presented below in figure 10 for Bamias, and in figure 11 for DeSantis. The figures compare the MAIC atezolizumab KM curve using all available covariates (red) against the STC atezolizumab KM curve (blue). For Bamias, the MAIC led to slightly lower predictions early on, and slightly more uncertainty compared to the simulated treatment comparison. For DeSantis, the STC was more conservative compared to MAIC.	Comment noted. The committee found the matching-adjusted indirect comparison useful, but continued to be concerned that it was unlikely that all effect modifiers and prognostic factors were accounted for, because some prognostic factors were not reported in the published studies. The committee concluded that the indirect comparison remained very uncertain. Please see section 3.6 of the FAD.

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			In summary, the predictions obtained with the more sophisticated MAIC approach were consistent with the simulated treatment comparison results presented in the company submission. It is appropriate to conclude results would have been similar if the MAIC had been used in the analysis. **Figures 10-11** *[Figures provided but not reproduced here]*	
5	Company	Roche	**Utility values for patients off treatment** The ACD states: '*The committee was concerned that the utility value of 0.71 used for the progressed disease health state was too high…….'* *'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 mUC, there is uncertainty regarding the utility values used (page 177, section 5.4.6). Indeed, collection of utility data for 1st Line cis-ineligible populations are expected to form part of the data collection agreement with the CDF. Subsequent to the appraisal submission, and first appraisal committee meeting; phase III data have become available for the 2nd Line population (clinical study - IMvigor211). These data will provide updated utility values for atezolizumab and comparators in patients having received prior-platinum therapy; and will be provided in response to the ACD for the 2nd Line population. As discussed with the NICE appraisal team these are not provided within this 1st Line response, as: • The data are from a new evidence source, not yet critiqued by the ERG • The data are from a 2nd Line, rather than 1st Line population • The available comparators in the phase III study are not the relevant comparators for the 1st Line populations. As such,	Comment noted. The committee concluded that a utility value of 0.5 may be too low and that the ICER that results from it too high. Please see section 3.12 of the FAD.

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			comparator utility data are not available from the correct population However, to address the committee's concern regarding off treatment utility values, scenarios analyses are provided in comment 6. These scenarios include the company base case, the ERG base case, and the NICE base case for utilities. Alternative OS scenarios are also provided relative to the NICE base case for utilities. The NICE base case is a conservative approach, as the arbitrarily chosen 'off treatment' utility value of 0.5 is lower than the off treatment values available from the 2L phase III study. Whilst use of this utility value impacts the resulting ICER, even with this conservative approach all scenarios in comment 6 are below the acceptable threshold for end-of-life treatments. This supports inclusion of atezolizumab in the CDF, as the therapy is plausibly cost-effective. Utility value uncertainty will be resolved through availability of EQ5D data from the phase III, 1st Line study (IMvigor130); the proposed key data collection source for the CDF managed access agreement.	
6	Company	Roche	**Alternative scenario analyses** As described in comments 2, 2a, 4 and 5 above, alternative scenario analyses are provided to support the company base case. As per comment 2, the ERG preferred survival extrapolation results in clinically implausible curves. Recognising uncertainty regarding extrapolated OS, alternative extrapolations are provided below. The 3 parametric distributions with the best statistical fit are applied, with full parameterisation and KM + tail provided. Alternative utility scenarios are also provided, taking into account the committee's concerns regarding off treatment utility. In all scenarios (with the simple PAS applied), the resulting ICER is below the acceptable threshold for end of life treatments. **Tables 3-4** *[Tables provided but not reproduced here]*	Comment noted. The committee considered the alternative scenarios, but these did not include the committee's preferred assumptions. Please see sections 3.13 and 3.15 of the FAD.
7	Company	Roche	**Uncertainty to be resolved through CDF entry and data collection** The ACD states:	Comment noted. The committee concluded that the IMvigor 130 trial supplemented by data from the Systemic Anti-Cancer Therapy dataset would provide

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			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. *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.* As demonstrated in comment 6, in all plausible scenarios, atezolizumab in 1L mUC is a cost-effective use of NHS resources. However, the uncertainty of phase II single arm data are recognised. As such, Roche plan to submit to the CDF for inclusion of atezolizumab for 1L mUC patients. Discussions with NHS England are under way. As per the draft 'Cancer Drugs Find - Data Collection Arrangement', relative efficacy, treatment duration and health related quality of life data will be available from the proposed data collection source – the phase III study, IMvigor130 (clinicaltrials.gov; 2017). Patients in the study will be stratified by PDL1 expression, although based on existing evidence for atezolizumab in mUC this is not anticipated to predict enhanced response.	evidence to address most the uncertainties in the clinical evidence. Please see section 3.25 of the FAD.
8	Company	Roche	**Interpretation of missing phase III data** The ACD states: *The committee was not presented with evidence from the IMvigor 211 trial in people with previously treated locally advanced or*	Comment noted. This statement refers to the evidence for treating urothelial carcinoma that has progressed after prior platinum-containing chemotherapy, which will be covered in a separate document. It has therefore been removed from the FAD.

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			metastatic urothelial carcinoma, which reported results in May 2017. This statement could be interpreted as meaning the Roche withheld this evidence. This is not the case – this evidence was not available either at the time of Roche's submission or the Appraisal Committee meeting. As such, re-wording would be appreciated to prevent misinterpretation.	
9	Company	Roche	**Comparison with best supportive care** The ACD states: *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.* It may be worth noting that this may be true, but if it is true and if such less fit patients were included in the IMvigor210 study it would result in a negative bias in outcomes in IMvigor 210 compared with those achieved in comparator studies with gemcitabine and carboplatin where, by definition, entry required patients to be fit enough for cytotoxic chemotherapy.	Comment noted. The committee considered all comparators identified in the final NICE scope and made judgements on their appropriateness (in line with NICE Methods Guide Section 6.2). It concluded that best supportive care was an appropriate comparator, but acknowledged the lack of data would make a comparison difficult.
10	Company	Roche	**Evidence of prolonged response to atezolizumab** The ACD states: *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*	Comment noted. The committee considered all the evidence in the company submission. No changes to the FAD are needed.

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			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 (see separate submission) 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 (Rittmeyer et al, 2016)	
11	Company	Roche	**Atezolizumab is well tolerated in clinical practice** The ACD states: *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 is restrained. However the subsequent availability of results from the IMvigor211 study (Powles et al. 2017) clearly demonstrates that despite an incidence of immune-related adverse events, atezolizumab is better tolerated than cytotoxic chemotherapy in patients with mUC, a finding which is entirely consistent with the observation that atezolizumab is better tolerated than docetaxel in a large randomised trial in NSCLC (Rittmeyer et al, 2016) as presented in the original Roche's submission. Again 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.	Comment noted. The FAD has been updated to reflect the evidence on adverse events from IMvigor 211. See section 3.8.
12	Company	Roche	**References**	

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			[References provided but not reproduced here]	
13	Patient organisation	Action Bladder Cancer UK	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%.	Comment noted. The committee understood that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial carcinoma. Please see section 3.2 of the FAD.
14	Patient organisation	Action Bladder Cancer UK	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.	Comment noted. The committee has recommended atezolizumab for use within the Cancer Drugs Fund for people with untreated locally advanced or metastatic urothelial carcinoma when cisplatin is unsuitable. Please see section 1.1 of the FAD.
15	Patient organisation	Action Bladder Cancer UK	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.	Comment noted. The committee concluded that average life expectancy is less than 24 months and that atezolizumab is likely to extend life by more than 3 months on average. This meant that the end of life criteria were met and that the committee could consider higher cost effectiveness estimates, in line with NICE's final Cancer Drugs Fund technology appraisal process and methods
16	Patient organisation	Action Bladder Cancer UK	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.	Comment noted. The committee feels that most of the clinical uncertainty will be addressed by the ongoing IMvigor 130 trial and data collected by the Systemic Anti-Cancer Therapy dataset. For this reason, the committee recommended atezolizumab for use within the Cancer Drugs Fund. Please see sections 3.24 and 3.25 of the FAD.
17	Patient organisation	Action Bladder Cancer UK	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.	Comment noted. The committee will consider the data from the IMvigor211 trial for people who have had previous platinum-containing chemotherapy at a later meeting. Please see the box on page 1 of the FAD.
18	Patient organisation	Action Bladder Cancer UK	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.	Comment noted. The committee acknowledged that the main driver of cost effectiveness was overall survival, and although the committee thought the ERG's approach was appropriate for decision-making, it might later prove conservative as more evidence becomes available. The committee was aware that under other assumptions, atezolizumab has the plausible potential to be cost-effective. For this reason, the committee

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				recommended atezolizumab for use within the Cancer Drugs Fund for people with untreated disease for whom cisplatin is unsuitable. Please see sections 3.23, 3.24 and 3.25 of the FAD.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

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

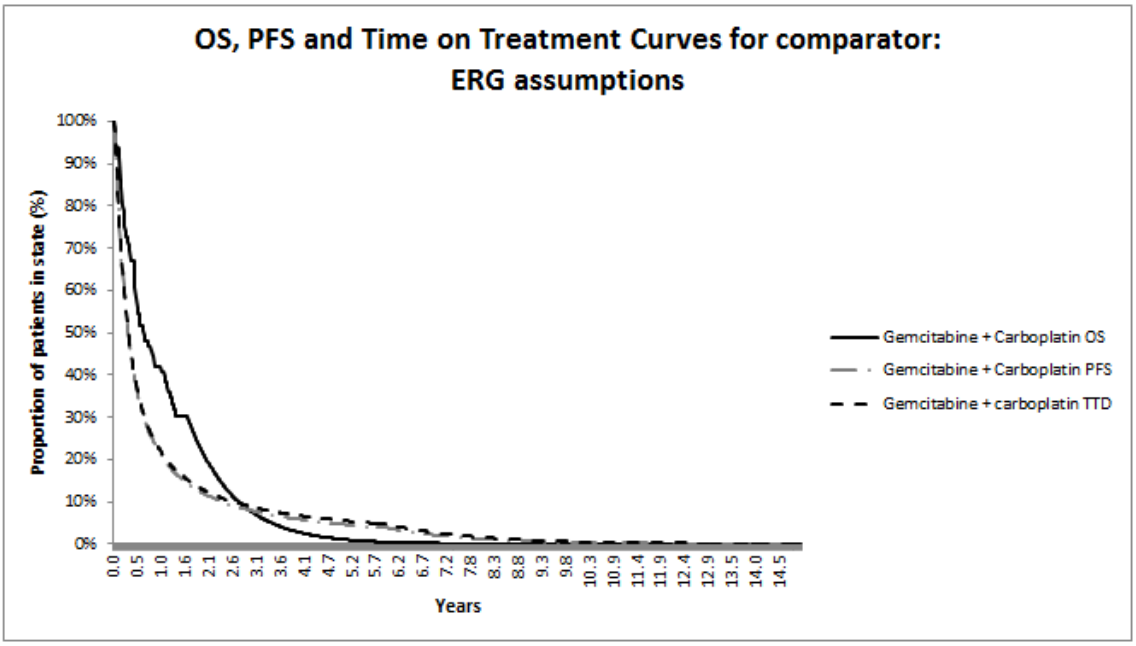
	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical 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):	**Roche Products Ltd.**; hereinafter "Roche"
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**n/a**]
Name of commentator person completing form:	**Catherine Huertas**
Commen	**Comments**

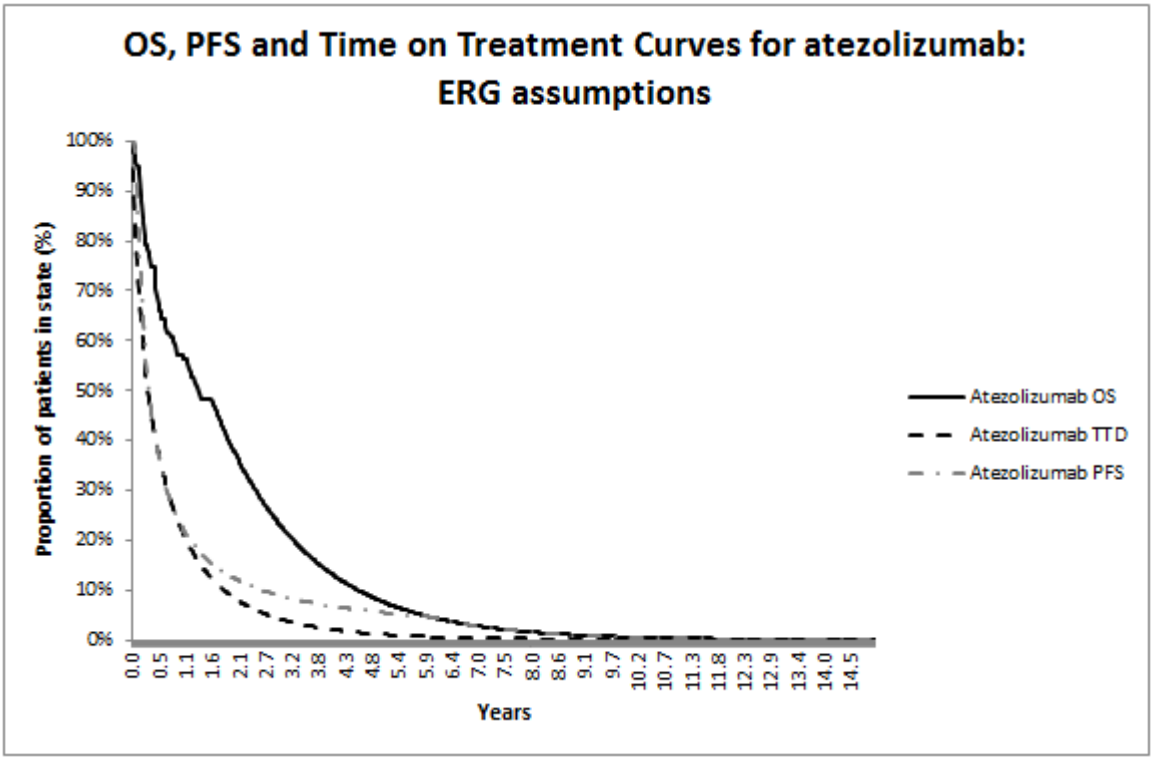
Atezolizumab for treating metastatic urothelial bladder cancer after platinum-based chemotherapy [ID939]

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

t number	
1	**All comments refer only to the appraisal of atezolizumab in untreated locally advanced or metastatic urothelial carcinoma in adults for whom cisplatin-based chemotherapy is unsuitable (1st Line).** **Comments in response to the appraisal of atezolizumab in locally advanced or metastatic urothelial carcinoma in adults after prior platinum-containing chemotherapy (2nd Line) will be provided in a separate response** Roche are disappointed the committee is minded not to recommend atezolizumab as an option for untreated locally advanced or metastatic urothelial carcinoma (mUC) in adults for whom cisplatin-based chemotherapy is unsuitable (1st Line). However, we are pleased the committee have recommended a proposal for including atezolizumab in the Cancer Drugs Fund (CDF) for this population. Roche intends to submit a proposal to the CDF for this population, and have begun engagement with NHS England on this proposal. However, we are not in a position to finalise a commercial agreement with the CDF as we have concerns regarding the committee's decision that the ERG assumptions are appropriate for decision making, and a reasonable interpretation of the evidence. Use of the ERG approach to overall survival (OS) extrapolation results in clinically implausible survival curves. This is further discussed in comments 2, 2a and 2b below. Our full response is provided in the comments below. We are pleased the committee recognised the unmet need of patients with mUC, the clinical benefit and tolerability of atezolizumab in mUC, and the fulfilment of the end-of-life criteria. Our response relates to the main points of disparity between our manufacturer base case, and the NICE preferred assumptions. We have provided additional analyses to support a reversal of this preliminary negative recommendation. As can be seen in comment 6, in all scenarios, atezolizumab is a cost-effective use of NHS resource as per the generally accepted threshold for end-of-life medicines. This is true when accounting for the proposed simple PAS for atezolizumab. Comment summary: 1) Summary 2) Assumptions regarding overall survival extrapolation a) Alternative OS extrapolation scenarios b) Interpretation of objective response rate 3) Committee concerns regarding certainty of the indirect treatment comparison 4) Assumptions regarding time to treatment discontinuation extrapolation 5) Utility values for patients off treatment 6) Alternative scenario analyses to support company base case 7) Uncertainty to be resolved through CDF entry and data collection Comments addressing other factual inaccuracies 8) Interpretation of missing phase III data 9) Comparison with best supportive care 10) Evidence of prolonged response to atezolizumab 11) Atezolizumab is well tolerated in clinical practice 12) References

2	**Assumptions regarding overall survival extrapolation** The ACD states: *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 a crossing of the OS and PFS curves for chemotherapy, and a meeting of the curves for atezolizumab. 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 for 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. As shown in figure 1 below, the resulting OS, PFS and time on treatment curves for the comparator (gemcitabine + carboplatin) are clinically implausible, as they cross from 2.7 years when around 10% of patients are still alive in the model. As shown in figure 2 below, the resulting OS and PFS curves for atezolizumab are also clinically implausible, as they meet after 6 years. **Figure 1: OS, PFS and Time on Treatment Curves for comparator: ERG assumptions**  **Figure 2: OS, PFS and Time on Treatment Curves for atezolizumab: 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 cytotoxic chemotherapy. This is at odds with the clinical advice received by Roche, and provided by the clinical experts within the 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 cytotoxic chemotherapy. This difference in treatment response is supported by the expert personal perspectives submitted from clinical experts as part of this submission; which state the following:

    a. *'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.'*
    b. *'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 key 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 cytotoxic chemotherapy data. Rather the fit should be assessed relative to atezolizumab data.

2a	**Alternative OS extrapolation scenarios** We recognise there is uncertainty in the most appropriate choice of OS extrapolation, as atezolizumab survival data are relatively immature. We provide some alternative extrapolation scenarios to aid committee decision making. (Figures 3-9 below). This includes full

parameterisation, and Kaplan Meier (KM) plus extrapolated tail. The resulting ICERs for these extrapolations are provided in comment 6.

For these scenarios, extrapolation choice is based on statistical fit to observed atezolizumab data. The standard parametric functions with the three lowest AIC/BIC values are provided (table 1). Please note, these AIC/BIC values differ to those on page 159, table 53 of the company submission, as the fits within the company submission were based on the mix-cure rate model.

As can be seen in comment 6, whilst use of alternative extrapolations does impact the resulting ICER, in all scenarios atezolizumab remains under the generally accepted threshold for end-of-life medicines.

Table 1: Summary of parametric function goodness of fit for OS (1L)

Parametric distribution	AIC	BIC
Exponential	322.03 (5)	324.81 (4)
Weibull	321.29 (4)	326.84 (6)
Log-normal	**314.69 (1)**	**320.25 (1)**
Gamma	**314.86 (2)**	**323.20 (2)**
Log-logistic	**317.81 (3)**	**323.37 (3)**
Gompertz	324.03 (6)	329.59 (5)

Figure 3: OS Parametric extrapolation: cure generalised gamma (base case)

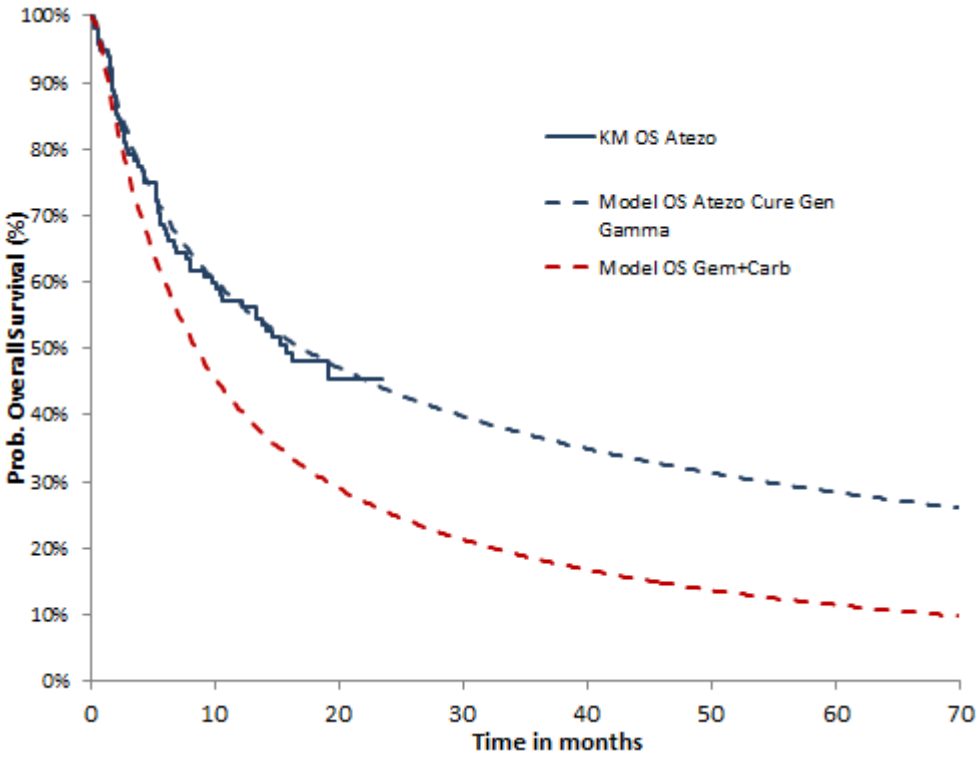


Figure 4: OS Parametric extrapolation: gamma (alternative scenario)

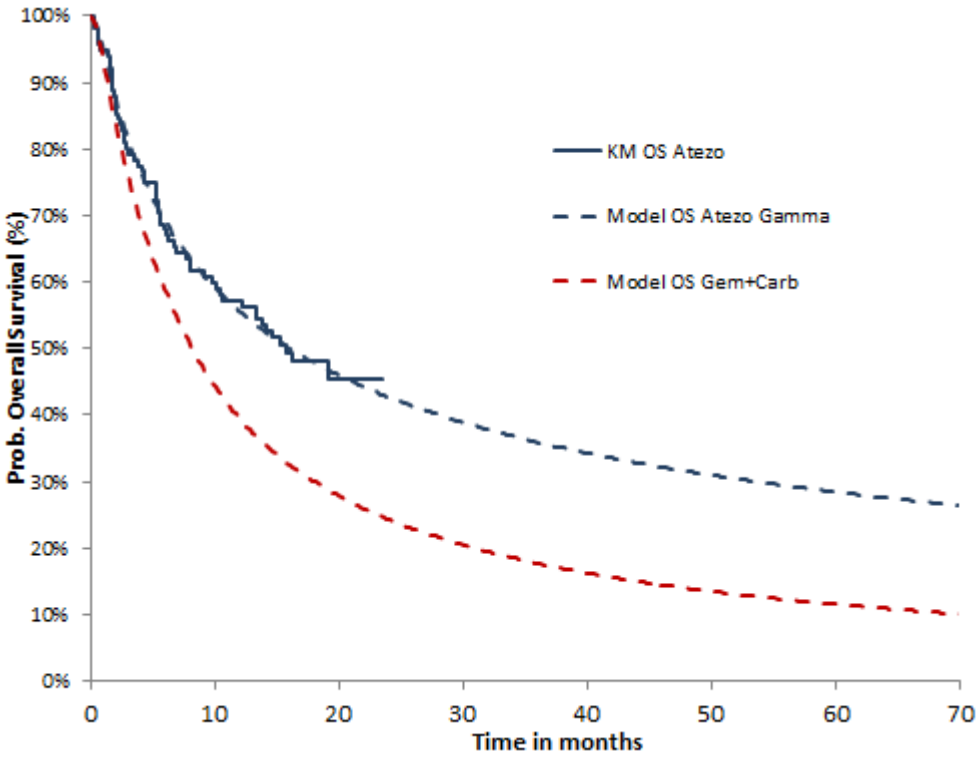


Figure 5: OS Parametric extrapolation: log-normal (alternative scenario)

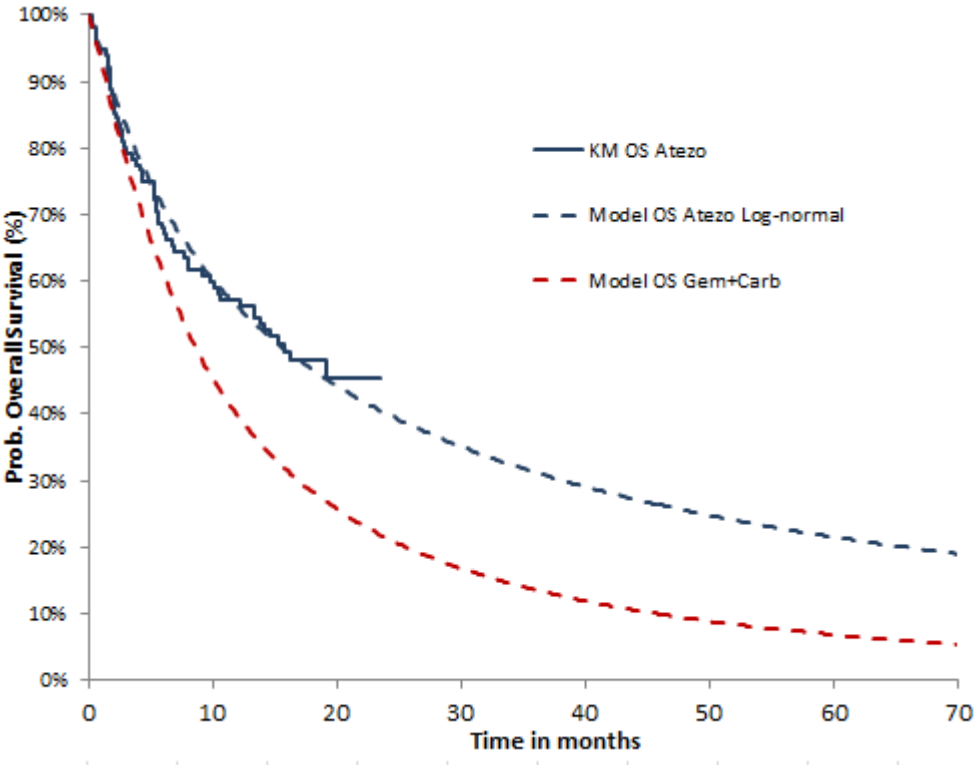


Figure 6: OS Parametric extrapolation: log-logistic (alternative scenario)

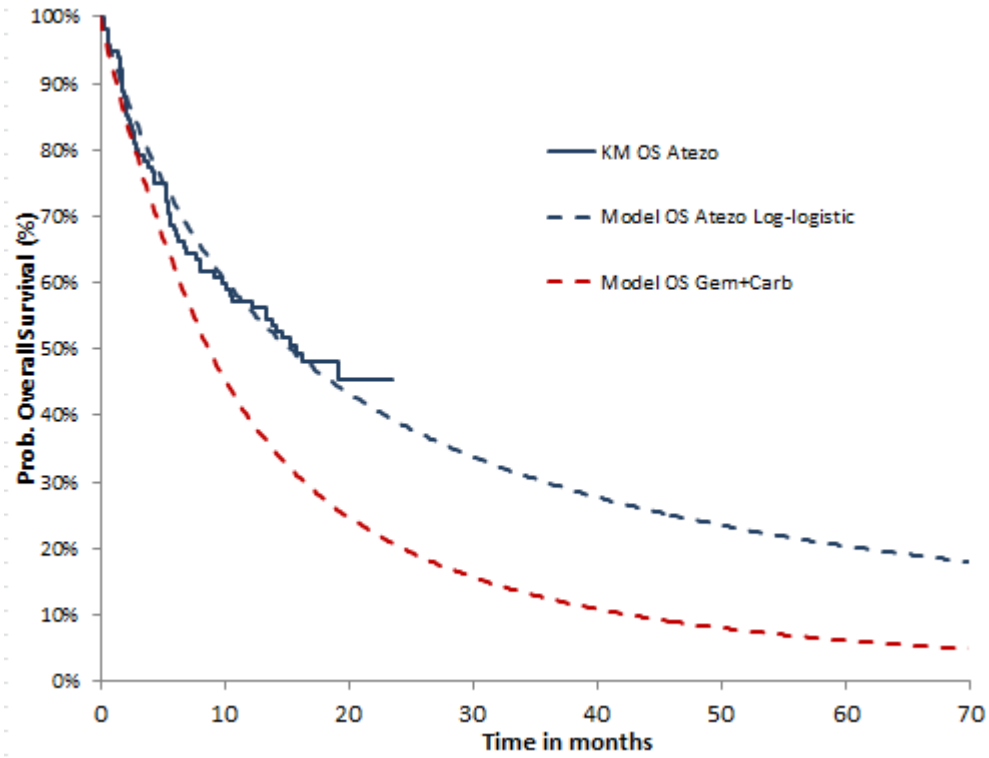


Figure 7: OS Parametric extrapolation: KM + gamma (alternative scenario)

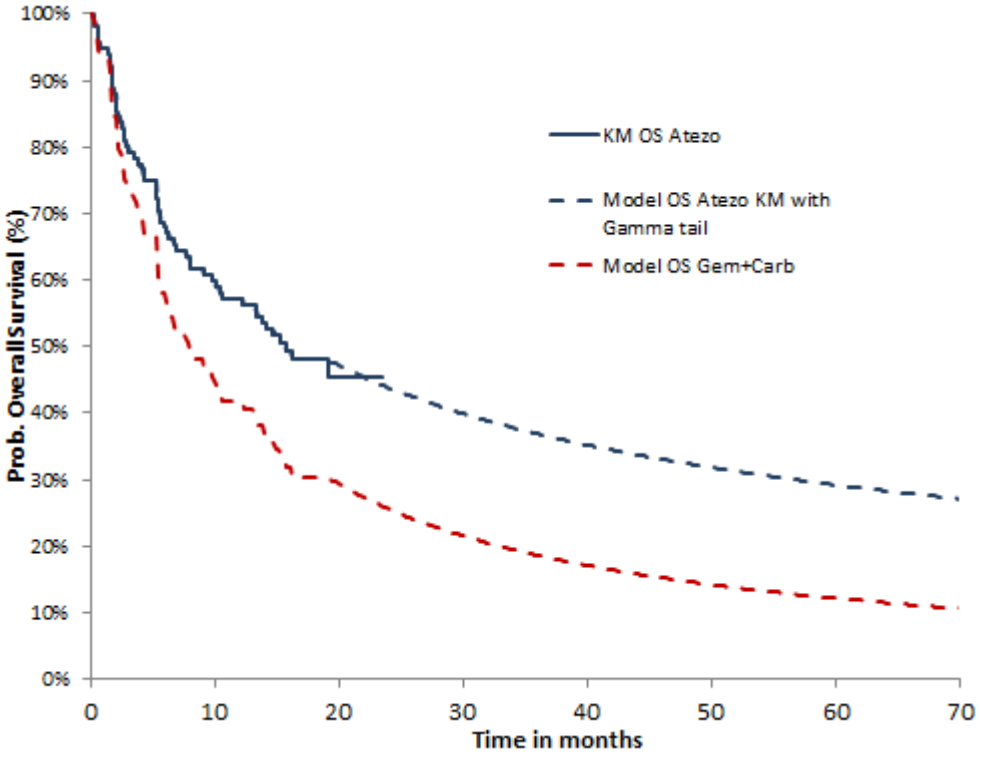


Figure 8: OS Parametric extrapolation: KM + log-normal (alternative scenario)

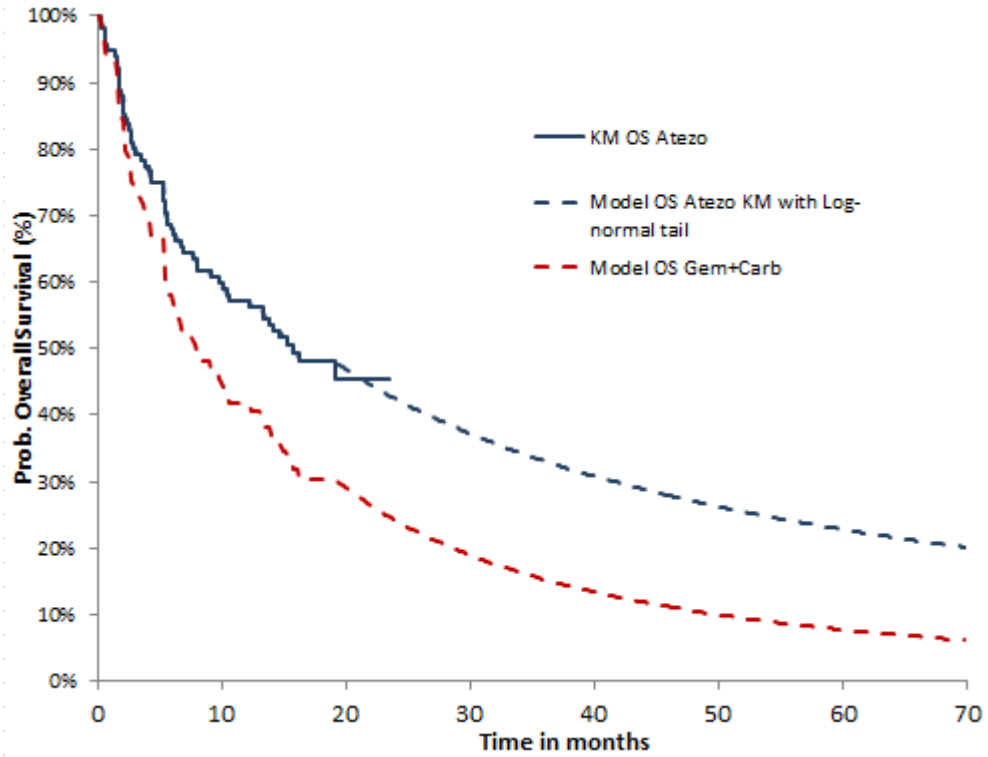
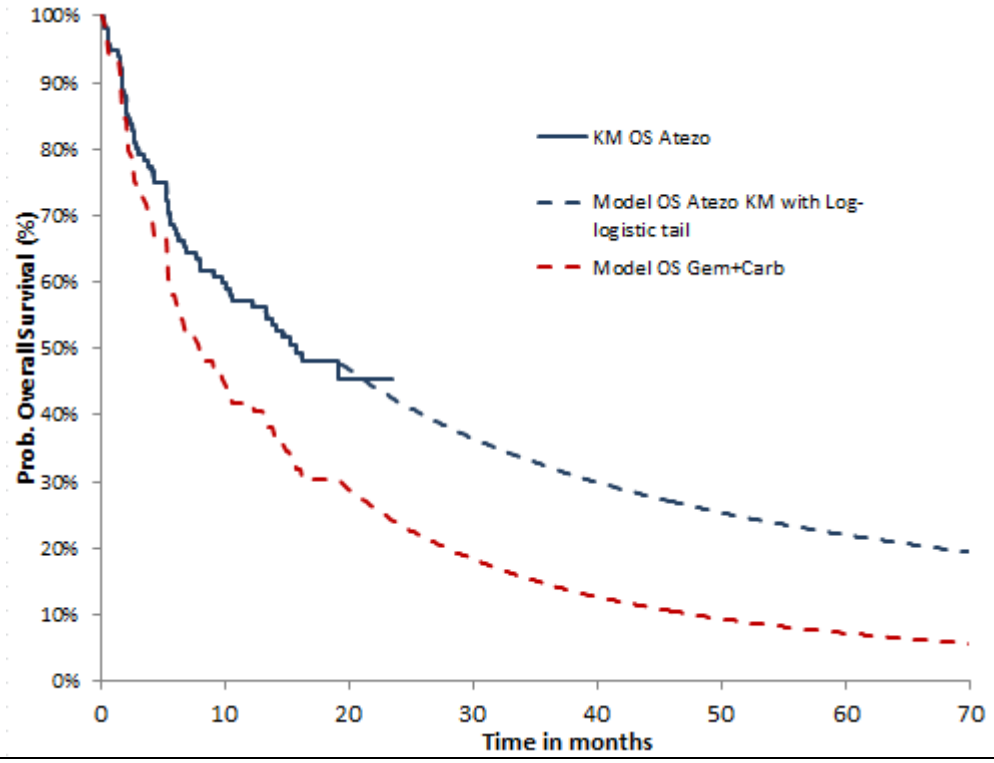


Figure 9: OS Parametric extrapolation: KM + log-logistic (alternative scenario)



2b	**Interpretation of objective response rate** The ACD states: '*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%)'

We are concerned this interpretation of objective response rate is not a reasonable interpretation of the evidence. It is plausible that more patients benefit from atezolizumab than achieve objective anti-tumour responses. The inadequacies of judging the long-term benefits of immunotherapy on short-term measures of radiographic response or progression-free survival have been much discussed (Hodi et al; 2016) and can be readily demonstrated with reference to both atezolizumab and other immunotherapies across a range of tumours.

For example, and as shown in Table 2, Phase III trials of atezolizumab in relapsed non-small-cell lung cancer (NSCLC) and mUC both show that atezolizumab improves OS compared with cytotoxic chemotherapy in unselected patients whilst in neither case is response rate or risk of progression noticeably increased; with median PFS actually numerically worse, using conventional measures.

Table 2. Mismatch between end-points based on radiographic progression and OS in phase III studies of atezolizumab

Trial	Setting	N	versus cytotoxic chemotherapy				
			Response rate%	PFS Hazard ratio (95% CI)	Median PFS (months)	OS Hazard ratio (95% CI)	Median OS (months)
IMvigor211 (Powles et al. 2017)	Urothelial cancer relapsing after prior platinum therapy	931	13.4% vs. 13.4%	1.10 (0.95, 1.26)	2.1 vs 4.0	0.85 (0.73, 0.99)	8.6 vs. 8.0
OAK (Rittmeyer et al. 2016)	Non-small – cell lung cancer 2nd/3rd line	850	14% vs. 13%	0.95 (0.82,1.10)	2.1 vs 3.3	0.73 (0.62,0.87)	13.8 vs. 9.6

Similarly, the anti-PD-1 antibody, pembrolizumab, improves OS in mUC relative to cytotoxic chemotherapy without improving the risk of disease progression, and results in median PFS which is numerically inferior to that seen with cytotoxic chemotherapy (Bellmunt et al, 2017)

Current evidence suggests there is no clear correlation between radiographic response and its derivative progression-free and overall survival benefit to cancer immunotherapies and, as such, it is a misinterpretation to conclude that it is implausible to have a 5-year OS that exceeds the 15 month response rate.

3 **Committee concerns regarding certainty of the indirect treatment comparison**

The ACD states: *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.*

Subsequent to submission of the dossier, a matching adjusted indirect comparison (MAIC) was carried out to validate results of the prediction model. These were not available at the submission date for inclusion within the company submission. To support the results of the indirect treatment comparison (ITC) included in the base case, and to aid committee decision making, we provide the MAIC results here. These results have not been incorporated into the economic model.

The systematic literature review (SLR) identified 2 studies for inclusion in the ITC for atezolizumab vs. gemcitabine + carboplatin. These studies were Bamias et al. 2007 and DeSantis et al. 2012. Within the company submission, and as referenced in the ACD, results of the simulated treatment

comparison (STC) were utilised in the base case to provide comparative efficacy.

Using the Bamias and DeSantis studies, the predicted atezolizumab curves were derived using propensity weighting, as per the NICE DSU worked example (Phillippo, D.M et al. 2016)

The predicted atezolizumab curves are presented below in figure 10 for Bamias, and in figure 11 for DeSantis. The figures compare the MAIC atezolizumab KM curve using all available covariates (red) against the STC atezolizumab KM curve (blue). For Bamias, the MAIC led to slightly lower predictions early on, and slightly more uncertainty compared to the simulated treatment comparison. For DeSantis, the STC was more conservative compared to MAIC.

In summary, the predictions obtained with the more sophisticated MAIC approach were consistent with the simulated treatment comparison results presented in the company submission. It is appropriate to conclude results would have been similar if the MAIC had been used in the analysis.

Figure 10: Matching adjusted KM curve (red) using all available covariates against KM curve from prediction model used in dossier (blue)

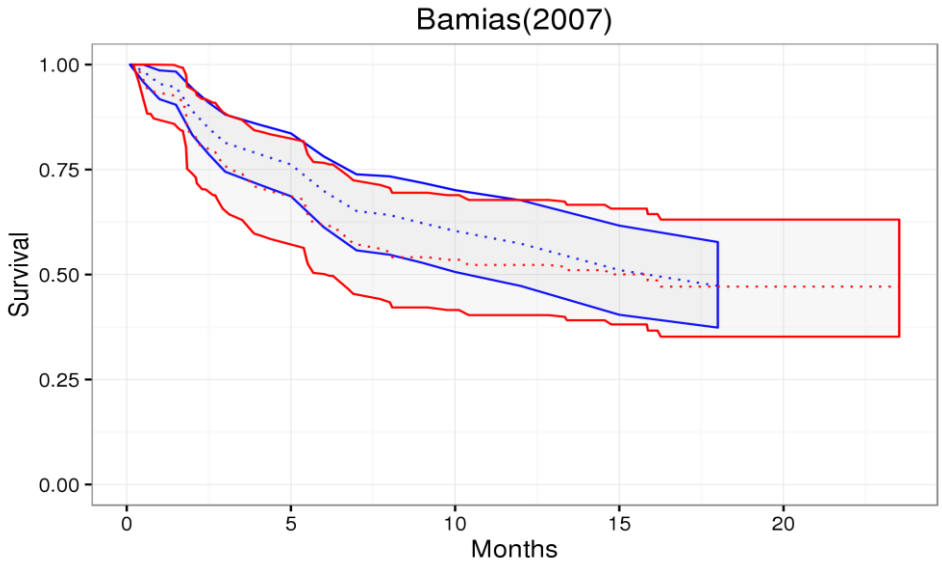
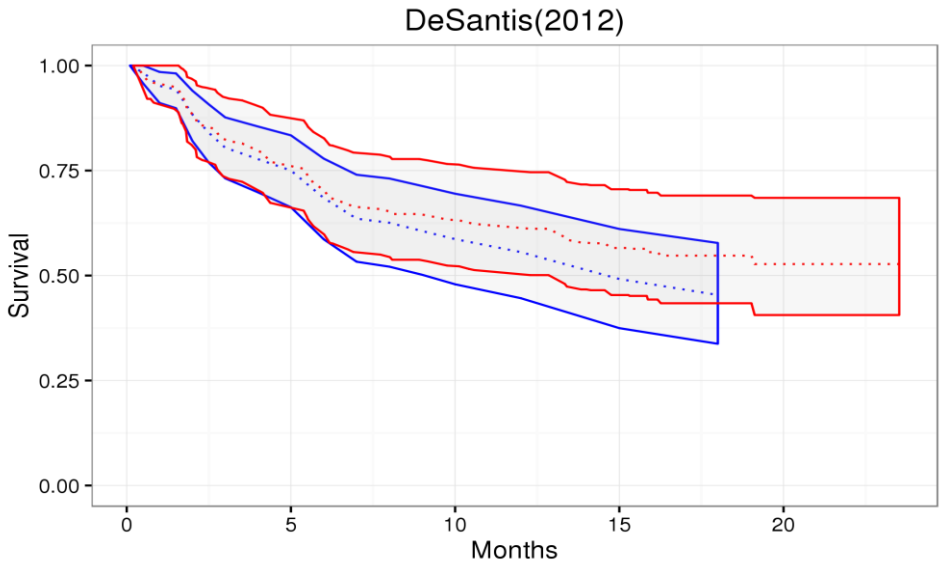


Figure 11. Matching adjusted KM curve (red) using all available covariates against KM curve from prediction model used in dossier (blue)

	
4	**Assumptions regarding time to treatment discontinuation extrapolation** The ACD states: *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.* 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. Considering the AIC combined with visual examination of the extrapolation, a generalised gamma is deemed the most appropriate option for 1L. Comment 6 below provides scenario analyses with both the generalised gamma and Weibull distributions for time to treatment discontinuation. Whilst we do not agree the Weibull distribution is the most appropriate, the resulting impact of the ICER is minimal.
5	**Utility values for patients off treatment** The ACD states: '*The committee was concerned that the utility value of 0.71 used for the progressed disease health state was too high…….'* *'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 mUC, there is uncertainty regarding the utility values used (page 177, section 5.4.6). Indeed, collection of utility data for 1st Line cis-ineligible populations are expected to form part of the data

collection agreement with the CDF.

Subsequent to the appraisal submission, and first appraisal committee meeting; phase III data have become available for the 2nd Line population (clinical study - IMvigor211). These data will provide updated utility values for atezolizumab and comparators in patients having received prior-platinum therapy; and will be provided in response to the ACD for the 2nd Line population.

As discussed with the NICE appraisal team these are not provided within this 1st Line response, as:

- The data are from a new evidence source, not yet critiqued by the ERG
- The data are from a 2nd Line, rather than 1st Line population
- The available comparators in the phase III study are not the relevant comparators for the 1st Line populations. As such, comparator utility data are not available from the correct population

However, to address the committee's concern regarding off treatment utility values, scenarios analyses are provided in comment 6. These scenarios include the company base case, the ERG base case, and the NICE base case for utilities. Alternative OS scenarios are also provided relative to the NICE base case for utilities.

The NICE base case is a conservative approach, as the arbitrarily chosen 'off treatment' utility value of 0.5 is lower than the off treatment values available from the 2L phase III study. Whilst use of this utility value impacts the resulting ICER, even with this conservative approach all scenarios in comment 6 are below the acceptable threshold for end-of-life treatments. This supports inclusion of atezolizumab in the CDF, as the therapy is plausibly cost-effective. Utility value uncertainty will be resolved through availability of EQ5D data from the phase III, 1st Line study (IMvigor130); the proposed key data collection source for the CDF managed access agreement.

6

Alternative scenario analyses

As described in comments 2, 2a, 4 and 5 above, alternative scenario analyses are provided to support the company base case. As per comment 2, the ERG preferred survival extrapolation results in clinically implausible curves. Recognising uncertainty regarding extrapolated OS, alternative extrapolations are provided below. The 3 parametric distributions with the best statistical fit are applied, with full parameterisation and KM + tail provided.

Alternative utility scenarios are also provided, taking into account the committee's concerns regarding off treatment utility.

In all scenarios (with the simple PAS applied), the resulting ICER is below the acceptable threshold for end of life treatments.

Table 3: Resulting ICER vs gemcitabine + carboplatin from scenario analyses (1L) with PAS

Scenario	Parameter	Value	ICER vs. gemcitabine + carboplatin
Base case	Distribution OS	Cure Generalised Gamma	[redacted]
		Gamma	[redacted]
		Log-normal	[redacted]
		Log-logistic	[redacted]
		KM + gamma	[redacted]
		KM + log-normal	[redacted]

		KM + log-logistic	[redacted]
Base case	Treatment duration extrapolation	Gamma	[redacted]
		Weibull	[redacted]
Base case (company)	Utility values	0.75 on treatment 0.71 off treatment	[redacted]
ERG scenario		0.75 on treatment atezo 0.71 on treatment chemo 0.71 off treatment all	[redacted]
		0.75 on treatment all 0.50 off treatment all	[redacted]
Committee preferred scenario		0.75 on treatment atezo 0.71 on treatment chemo 0.50 off treatment all	[redacted]
Committee preferred utility scenario	OS extrapolations	Cure generalised gamma	[redacted]
		Gamma	[redacted]
		Log-normal	[redacted]
		Log-logistic	[redacted]
		KM + gamma	[redacted]
		KM + log-normal	[redacted]
		KM + log-logistic	[redacted]

Table 4: Resulting ICER vs gemcitabine + carboplatin from scenario analyses (1L) without PAS

Scenario	Parameter	Value	ICER vs. gemcitabine + carboplatin
Base case	Distribution OS	Cure Generalised Gamma	£44,158
		Gamma	£41,395
		Log-normal	£51,059
		Log-logistic	£51,387
		KM + gamma	£41,100
		KM + log-normal	£50,107
		KM + log-logistic	£50,005
Base case	Treatment duration	Gamma	£44,158

		extrapolation		
			Weibull	£42,683
	Base case (company)	Utility values	0.75 on treatment 0.71 off treatment	£44,158
	ERG scenario		0.75 on treatment atezo 0.71 on treatment chemo 0.71 off treatment all	£42,747
			0.75 on treatment all 0.50 off treatment all	£69,252
	Committee preferred scenario		0.75 on treatment atezo 0.71 on treatment chemo 0.50 off treatment all	£65,842
	Committee preferred utility scenario	OS extrapolations	Cure generalised gamma	£65,842
			Gamma	£61,467
			Log-normal	£76,925
			Log-logistic	£77,452
			KM + gamma	£61,003
			KM + log-normal	£75,386
			KM + log-logistic	£75,220

7

Uncertainty to be resolved through CDF entry and data collection

The ACD states:

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.
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.*

As demonstrated in comment 6, in all plausible scenarios, atezolizumab in 1L mUC is a cost-effective

	use of NHS resources. However, the uncertainty of phase II single arm data are recognised. As such, Roche plan to submit to the CDF for inclusion of atezolizumab for 1L mUC patients. Discussions with NHS England are under way. As per the draft 'Cancer Drugs Find - Data Collection Arrangement', relative efficacy, treatment duration and health related quality of life data will be available from the proposed data collection source – the phase III study, IMvigor130 (clinicaltrials.gov; 2017). Patients in the study will be stratified by PDL1 expression, although based on existing evidence for atezolizumab in mUC this is not anticipated to predict enhanced response.
8	**Interpretation of missing phase III data** The ACD states: *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.* This statement could be interpreted as meaning the Roche withheld this evidence. This is not the case – this evidence was not available either at the time of Roche's submission or the Appraisal Committee meeting. As such, re-wording would be appreciated to prevent misinterpretation.
9	**Comparison with best supportive care** The ACD states: *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.* It may be worth noting that this may be true, but if it is true and if such less fit patients were included in the IMvigor210 study it would result in a negative bias in outcomes in IMvigor 210 compared with those achieved in comparator studies with gemcitabine and carboplatin where, by definition, entry required patients to be fit enough for cytotoxic chemotherapy.
10	**Evidence of prolonged response to atezolizumab** The ACD states: *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 (see separate submission) 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 (Rittmeyer et al, 2016)
11	**Atezolizumab is well tolerated in clinical practice** The ACD states: *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 is restrained. However the subsequent availability of results from the IMvigor211 study (Powles et al. 2017) clearly demonstrates that despite an incidence of immune-related adverse events, atezolizumab is better tolerated than cytotoxic chemotherapy in patients with mUC, a finding which is entirely consistent with the observation that atezolizumab is better tolerated than docetaxel in a large randomised trial in NSCLC (Rittmeyer et al, 2016) as presented in the original Roche's submission. Again 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.
12	**References** Bamias, A et al. 2007. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology, 73, 290-7. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(11):1015-26. https://clinicaltrials.gov/ct2/show/NCT02807636?term=atezolizumab&cond=Urothelial+Carcinoma&draw=1&rank=1 Accessed 17th August 2017 De Santis et al. 2012. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol, 30, 191-9. Hodi S, Hwu W-J, Kefford R, Weber JS, Daud A, Hamid O et al. Evaluation of Immune-Related Response Criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol. 2017; 34: 1510-1517. Phillippo, D.M., Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from. http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/TSD18-Appendix-D-Worked-example-of-MAIC-and-STC.pdf Powles T, Loriot Y, Durán I, Ravaud A, Retz M VN, Mariathasan S, 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. Rittmeyer A, et al.2016. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet.

Insert extra rows as needed

Checklist for submitting comments

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

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

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

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

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

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	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:	[redacted] ABC UK

Please return to: jenna.dilkes@nice.org.uk or via NICE DOCS

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

NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
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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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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the person could be identified.

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Questions from NICE to clinical experts:

In the appraisal consultation document (section 3.10), the committee was concerned that the company's model predicted that for people with untreated disease and for whom cisplatin is unsuitable, the number of people alive at 5 years would be higher than the number who had responded to treatment at 15 months, which did not seem plausible. In their response to the ACD, the company have stated that it is plausible that more patients benefit from atezolizumab than achieve objective tumour responses - citing evidence from other indications that atezolizumab improves survival but doesn't significantly improve objective response rate (e.g. OAK study of atezolizumab vs. chemotherapy for NSCLC: response rates 14% vs.13% but median OS 13.8 vs. 9.6 months)

- Do you consider that the company's rationale is reasonable?
- In your opinion, is it clinically plausible that the proportion of people surviving at 5 years would be higher than the proportion with an objective response?

The committee also needs to understand which predictions for the rates of long-term survival are most likely to be seen in practice. The company and academic group have proposed predictions by extrapolating from the IMvigor 210 study.

- Although we acknowledge there is limited evidence, based on your clinical experience, what do you consider are the most likely rates of survival, at 5 and 10 years, for people with untreated locally advanced or metastatic disease and unsuitable for cisplatin treated with either atezolizumab or gemcitabine + carboplatin?

- Of the predictions in the table below, which would most closely match your expectations?

	Atezolizumab		Gemcitabine + carboplatin	
	5-year survival	**10-year survival**	**5-year survival**	**10-year survival**
Prediction group 1 (base case, gamma)	28–29%	18–21%	12%	5–7%
Prediction group 2 (log-normal, log-logistic)	20–23%	12%	6–8%	2–3%
Prediction group 3 (exponential, Weibull, Gompertz)	7-14%	0-3%	1-3%	0%

Finally, please could you explain what evidence there is to support your predictions and how this is influenced by variation in response between individuals and also if your view is affected by the outcomes of the phase III IMvigor 211 trial in the 2nd line population.

Response from clinical expert [redacted]

- I agree that patients derive clinical benefit if they do not achieve objective radiological response.
- Yes it is possible to have a higher 5 year survival rate than number of patients achieving objective response rate.
- Prediction group 3. 5 year survival; 7-14%
- Clinical trials data suggest there is a subset of patients who achieve long term response with this drug in advanced metastatic bladder cancer in 2nd line setting. Phase III imvigor 211 continues to show a subset of patients who continue to derive significant benefit in terms of long term disease control that was not seen previously with chemotherapy treatment

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Atezolizumab for treating locally advanced or metastatic urothelial carcinoma: ERG critique of the company's updated analyses for first-line therapy

Appendix to the Evidence Review Group report

Produced by Southampton Health Technology Assessments Centre

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Date completed 25th August 2017

1 Introduction

This document is an appendix to the Evidence Review Group (ERG) report to NICE. It provides the ERG's critique of updated analyses provided by the company for first-line atezolizumab therapy in cisplatin-ineligible patients, in response to the NICE Appraisal Consultation Document (ACD). The company's updated analyses were received by the ERG on 21st August 2018. Unless otherwise stated, analyses presented in this appendix use the company's confidential patient access scheme (PAS) price for atezolizumab.

2 ERG's critique of the company's updated analyses

Overall survival extrapolation

The company disagreed with the ERG's approach regarding the overall survival (OS) extrapolation, citing two reasons:

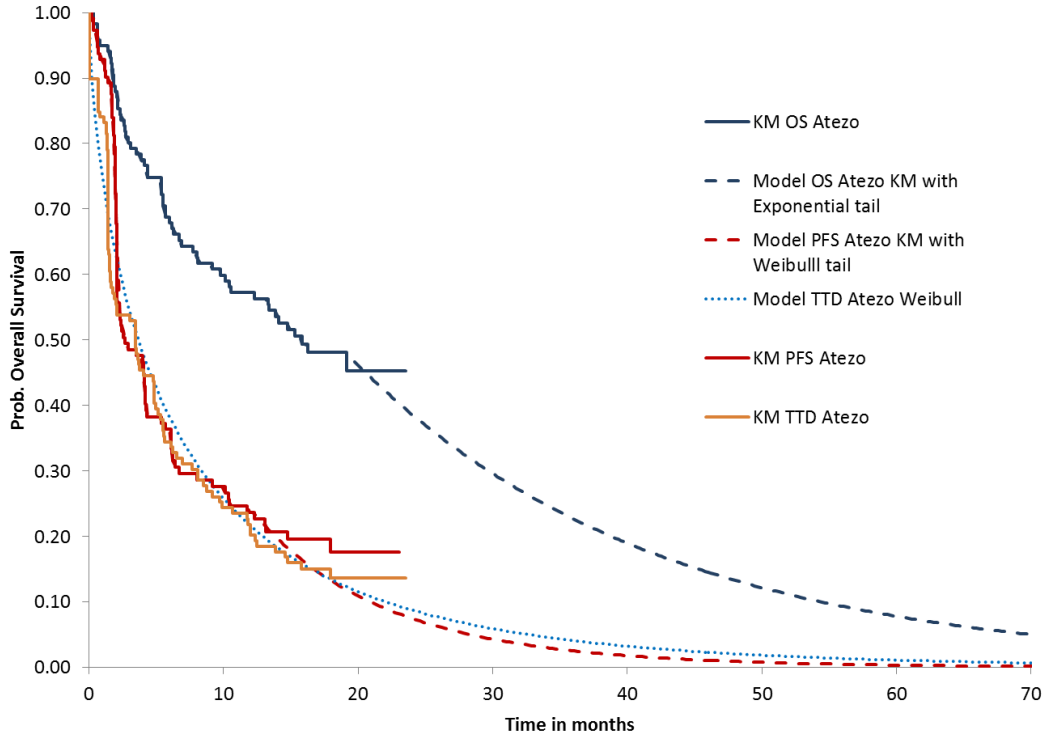
i. The progression-free survival (PFS) and OS curves for atezolizumab meet each other after around 6 years when extrapolating long term data using the ERG's choice of distributions (gamma for PFS; Kaplan-Meier (K-M) + exponential for OS). The company viewed this scenario as clinically implausible as no patient progresses, which is highly unlikely for this patient population. In addition, the company shows in Figure 1 of their response that the PFS and OS curves for the gemcitabine + carboplatin arm cross after 2.7 years (when around 10% of patients are still alive in the model).
ii. The company considers that the survival should be extrapolated based on the atezolizumab arm, rather than based on comparator arms, as the treatment effectiveness of immunotherapies are accepted and proven to be different (i.e. in terms of the durability of the treatment response) compared to standard chemotherapies.

In light of the above reasons, the company has presented AIC and BIC values (Table 1 of the company's response) to ascertain the best choice of distribution for the OS extrapolation (as the company points out, these values are not based on a mix-cure rate model, unlike the AIC and BIC values in CS Table 53). The AIC and BIC values provide a statistical measure for how well a parametric distribution fits observed data. The best goodness of fit was provided by a log-normal distribution, followed by gamma and log-logistic distributions. In Figures 7-9 of the company's response, the company also uses the K-M data and then extrapolates the tail of the survival curves using gamma, log-normal and log-logistic distributions. Results of using these extrapolations are given in Table 3 of the company's

response. The ICER varies between [redacted] and [redacted] per QALY using these distributions for OS.

From visual inspection, all the five extrapolations appear to fit the observed data for the atezolizumab arm. However, the ERG maintains that whilst extrapolating the OS curve using the K-M + gamma distribution may provide the best fit to the observed atezolizumab data, there is still uncertainty associated with the atezolizumab arm due to the small number of deaths and short follow up. We also note that the AIC and BIC values only provide information on the fit to the observed data and do not inform the choice of the extrapolation beyond the trial, which should be based upon clinical plausibility. As stated in the ERG report, we view the OS extrapolation of the comparator arm (gemcitabine + carboplatin) to be more robust due to the availability of long-term data and the alternative scenarios provided in the company's response provide a relatively poorer fit to the observed data in the gemcitabine + carboplatin arm. Furthermore, when using the generalised gamma distribution for OS, the mortality rate for patients after 10 years in the model is less than observed for the general population, which is clinically implausible.

Figure 1: Atezolizumab PFS, OS and time to discontinuation (TTD) curves compared, where K-M + Weibull distributions are fitted to the PFS curves



The ERG considers that the PFS extrapolations are less robust than the OS extrapolations. The ERG's preferred approach is to maintain the extrapolation of OS using the K-M + exponential distribution, based on the rationale given in the ERG report, and to change the

choice of the PFS distribution used in order to avoid the PFS and OS curves crossing. Extrapolating PFS by fitting a K-M + Weibull distribution does not result in the PFS and OS curves crossing. Further, extrapolating PFS using the K-M + exponential distribution also provides a plausible fit. This is shown in Figure 1.

The ICER obtained from the revised ERG analysis is similar to the ICER obtained in the initial ERG analysis, as shown in Table 1 below. Note these differ from the ERG's base case as they only include changes to the survival extrapolations and do not include changes to the utility value.

Table 1: Comparison of the results obtained from the revised ERG analysis

Scenario	Distribution for TTD	Distribution for PFS	Distribution for OS	ICER
Company's base case	Gamma	Gamma	Cure generalised gamma	[redacted]
ERG's analysis	Weibull	Gamma	K-M + exponential tail	[redacted]
ERG's revised analysis	Weibull	K-M + Weibull tail	K-M + exponential tail	[redacted]

The ERG acknowledges there is uncertainty in the OS extrapolation due to immaturity of the OS data. The NICE appraisal committee viewed that the OS for atezolizumab may be more favourable than in the ERG's base case. Conversely, NICE requested the ERG to provide an analysis for a scenario where the treatment benefit was not assumed to persist over the lifetime of the model. They requested this scenario since in the technology appraisal for pembrolizumab for treating non-small cell lung cancer (TA428), and in other appraisals of immunotherapies, the committee was concerned about the clinical realism of this assumption. This uncertainty was explored by setting the OS hazard ratio to a value of 1.0 at 2 years, 3 years and 5 years using the company's base case analysis and shows an increase of between [redacted] and [redacted] per QALY (Table 1 and Table 2).

Table 2: Comparison of the results obtained from changing the duration of the treatment effect

Scenario	Distribution for OS	Year at which hazard ratio set to 1.0	ICER
Company's base case	Cure generalised gamma	2	[redacted]
Company's base case	Cure generalised gamma	3	[redacted]
Company's base case	Cure generalised gamma	5	[redacted]

Time to treatment discontinuation

The company disagreed with the ERG's choice of the Weibull distribution for the time to treatment discontinuation (TTD). The ERG's choice of parametric distribution was based upon the best fit to the observed data for TTD from IMvigor 210. The NICE appraisal committee agreed that it was most appropriate to use the distribution that best fitted the data. The company argued that the choice of distribution should not be based upon the best fit alone but also upon visual examination of the extrapolation and that the generalised gamma distribution is therefore more appropriate.

The ERG disagrees that visual examination shows that the generalised gamma distribution is more appropriate than the Weibull distribution as there is visually very little difference between the curves when fit using the two distributions. The ERG further notes that choosing to use the Weibull distribution, rather than the gamma distribution, only has a small impact on the ICER (a decrease in the ICER of about [redacted] using the company's base case analysis).

Utility values

The company acknowledged the uncertainty associated with utility values due to the lack of utility data in metastatic urothelial cancer. They stated that whilst phase III data are now available for the second-line in patients who received prior-platinum therapy, utility data from EQ-5D for first-line cisplatin-ineligible patients will be available from the phase III first-line study (IMVigor130) which is likely to finish in July 2020. The available utility values for second-line atezolizumab are not presented for the purpose of this first-line appraisal (reasons are explained in the company's response to the ACD). However, the company presented a range of scenario analyses which included their base case, the ERG's base case and the NICE base case for utilities. Further, they noted that NICE's preferred value of 0.5 for 'off treatment' utility was arbitrary and lower than the values available from the second-line phase III study. However, despite the use of lower utility values, the company claimed that the ICERs obtained were below the acceptable threshold for end-of-life treatment. The company's results are presented below in Table 3

Table 3: Company's results obtained from different utility scenarios

Scenario	Parameter	Value	ICER (without PAS)	ICER (with PAS)

Base case (company)	Utility values	0.75 on treatment 0.71 off treatment	£44,158	[redacted]
ERG scenario	Utility values	0.75 on treatment atezo 0.71 on treatment chemo 0.71 off treatment all	£42,747	[redacted]
		0.75 on treatment all 0.50 off treatment all	£69,252	[redacted]
Committee preferred scenario	Utility values	0.75 on treatment atezo 0.71 on treatment chemo 0.50 off treatment all	£65,842	[redacted]
Committee preferred utility scenario	OS extrapolations	Cure generalised gamma	£65,842	[redacted]
		Gamma	£61,467	[redacted]
		Log-normal	£76,925	[redacted]
		Log-logistic	£77,452	[redacted]
		K-M + gamma	£61,003	[redacted]
		K-M + log-normal	£75,386	[redacted]
		K-M + log-logistic	£75,220	[redacted]

The company's analysis for the ERG scenario differs from that used by the ERG, in that patients have a utility value of 0.75 off atezolizumab treatment and off chemotherapy treatment in the PFS state and all patients have a utility value of 0.71 in the progressed disease state.

We re-ran our analyses using a utility value of 0.5 for progressed disease as shown in Table 4. This increased the ICER substantially.

Table 4: Updated ERG analyses with utility scenarios

Scenario	Distribution for TTD	Distribution for PFS	Distribution for OS	ICER
Company's base case	Gamma	Gamma	Cure generalised gamma	[redacted]
ERG's base case	Weibull	Gamma	K-M + exponential tail	[redacted]
ERG's revised base case	Weibull	K-M + Weibull tail	K-M + exponential tail	[redacted]
ERG's revised base case with PD utility = 0.5	Weibull	K-M + Weibull tail	K-M + exponential tail	[redacted]

PD: progressed disease

Indirect Treatment Comparison

The company conducted a matching-adjusted indirect comparison (MAIC) to validate the results of the simulated treatment comparison (STC) they had previously submitted. The company presented two figures (Figures 10 and 11 in their ACD response) which compared the MAIC predicted atezolizumab K-M curves against the STC predicted atezolizumab K-M curves, for the comparator studies on carboplatin + gemcitabine by Bamias et al. and De Santis et al. The predictions obtained using the MAIC were generally consistent with the STC results presented in the CS, but uncertainty was not reduced by conducting the MAIC (uncertainty was not explicitly quantified). The results of the MAIC were not incorporated into the economic model and as such do not influence the ICERs.

The company provided only very limited information on the MAIC in their ACD response and therefore the ERG is unable to comment on the validity of the approach used. We have several concerns about the uncertainty around the results of both the company's STC and MAIC analyses (including concerns previously stated in the ERG report):

- Only single-arm studies were available, meaning that both STC and MAIC analyses were "unanchored". According to NICE DSU guidance on population-adjusted indirect comparisons (Phillippo et al., 2016, as cited by the company), unanchored comparisons require a very strong assumption that is widely regarded as being very hard to meet (i.e., that absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables, and that all effect modifiers and all prognostic variables are required to be known). No justification to support this assumption has been provided by the company, so the validity of the analytical approach is unclear.
- NICE DSU guidance points out that STC and MAIC "give very considerable leeway to pick and choose variables to be adjusted for". The ERG regards this as a concern given the lack of clarity over the methods employed for the indirect comparisons.
- The NICE DSU guidance also recommends that, for both STC and MAIC, evidence should be provided that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects and an estimate of the likely range of residual systematic error should be presented. Such information has not been provided or discussed by the company.

In summary, the ERG believes the results of the MAIC are highly uncertain. There is likely to be considerably greater uncertainty in the results of the analysis than is captured by the

confidence intervals in Figure 10 and Figure 11 of the company's ACD response, due to systematic error which is not accounted for or discussed.