NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from** Merck Serono
   a. Response form
   b. Appendix

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Action Bladder Cancer UK
   b. Fight Bladder Cancer

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

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 Social Care 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 document (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 and Social Care, 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	Merck Serono	**Page 8: The generalised gamma and log-normal models are both acceptable for extrapolating overall survival data** As in our response to technical engagement, we accept that both the generalised gamma and log-normal are plausible for extrapolating overall survival data with similar AIC/BIC scores for statistical fit. However, we propose that one model should be applied in the base case for decision making purposes. We accept that the generalised gamma may be considered optimistic for the WW arm and note that the estimates of 5- and 10-year OS (15.00% and 6.48%, respectively) are closer to the upper bounds suggested by the clinicians as detailed in the ERG report. Therefore, we propose that the log-normal model is selected to align with ERG's preferred base case as this is the more conservative OS curve for avelumab and predicts 5- and 10-year OS closer to the mid-point of the clinical expert expectations for the WW arm.	Comment noted. Thank you. The Appraisal Committee considered both extrapolation models during the second committee meeting. The discussion is documented in section 3.6 of the final appraisal document. The committee concluded both the generalised gamma and log-normal models were plausible for extrapolating overall survival.
2	Company	Merck Serono	**Pages 9-11: Time to stopping treatment should reflect the trial** We would like to clarify that the TTD assumption in the cost-effectiveness model (95% patients stopping treatment at 2 years) is not a stopping rule and the company did not expect this to be implemented in clinical practice. This model assumption was incorporated following an advisory board and follow-up interviews with UK-based clinicians to best reflect the likely treatment duration that would occur in clinical practice. Clinicians noted that the majority of patients in clinical practice would discontinue treatment by 2 years due to toxicity or patient choice as has been noted for other IO therapies across indications. This approach was also used in the company's submission for avelumab for treating metastatic Merkel cell carcinoma (TA517) (1). The ERG have also agreed with these TTD assumptions and included them in their base case following clinical expert advice. We accept that the TTD assumptions could impact the duration of treatment benefit and this was explored in several scenarios by both the company and ERG. Given that the majority of patients will discontinue treatment before 2 years (median TTD in JB100 was approximately 25 weeks), supported by clinical expert opinion and current use of IO therapies in mUC, we propose the implementation of a 2-year stopping rule for avelumab for maintenance treatment in mUC to help reduce the uncertainty around treatment duration. The cost-effectiveness results with a 2-year stopping rule and 5-year	Comment noted. Thank you. The FAD has been updated to explain this **(**section 3.8 in the final appraisal document). At the second committee meeting, the committee considered the proposal of a 2-year stopping rule. The discussion has been documented in section 3.8 of the final appraisal document. Thank you for noting this drafting error, which we

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
			treatment benefit waning applied are presented in the appendices to this response. We would like to note that the statement in the ACD that *"The committee noted that other NICE technology appraisals of immunotherapies for urothelial cancer have preferred no stopping rules"* is incorrect. In previous technology appraisals for immunotherapies in mUC for atezolizumab (TA525) and pembrolizumab (TA692), the NICE Committee have accepted 2-year stopping rules and included these in final recommendations (2, 3). In the NICE FAD for atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525) it is stated that **"***… the committee recognised that in previous NICE technology appraisals clinicians have highlighted growing concern about using immunotherapies beyond 2 years."* and **"***The committee also recognised that NICE guidance for other immunotherapies for metastatic urothelial carcinoma and other cancers include 2-year stopping rules (1). The committee concluded that it is appropriate to include a 2-year stopping rule in the economic model."* It should also be noted that a 2-year stopping rule was not included in the IMvigor 211 clinical trial for atezolizumab (4).	explained during the committee meeting and documented in the committee slides. We have corrected this in the final appraisal document which now reads "The committee noted that other NICE technology appraisals of avelumab have preferred no stopping rules".
3	Company	Merck Serono	**Page 10 and 11: The committee would therefore like to see the progression-free survival and time to stopping treatment curves presented on the same graph to assess the relationship between the 2 in the trial.** Figures 1 and 2 present the KM curves for TTD and PFS on the same graph, demonstrating that patients did receive treatment beyond progression up until approximately 15 months when the curves cross, from which point it is clear that patients discontinued treatment prior to progression. ***Figure 1: KMs TTD vs PFS (BICR definition) – time in years***  Abbreviations: BICR = blinded independent central review; PFS = progression-free survival; TTD = time to treatment discontinuation	Thank you for providing this information. The committee took this into consideration during its decision-making.

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			Figure 2: KMs TTD vs PFS (investigator-assessed) – time in years  Abbreviations: INV = investigator-assessed; PFS = progression-free survival; TTD = time to treatment discontinuation	
4	Company	Merck Serono	**Page 11: It is not appropriate to include a lifetime treatment effect for people stopping avelumab before disease progression** We have explored duration of treatment effect in several scenarios submitted during technical engagement, however these were excluded from both the company's and ERG's base case due to a lack of available evidence to inform these scenarios as avelumab is the first IO to be used in this maintenance setting. Based on the committee's conclusion we have provided a revised base case in comment 2 of this document with treatment waning applied at 5 years (where there is an instant loss of treatment benefit , HR reverts to 1) in association with a 2-year stopping rule. We have applied treatment benefit waning at 5 years (3 years post treatment stop) to align with feedback from eight consultant oncologists specialising in the treatment of advanced urothelial cancer consulted as part of technical engagement, who agreed there is a sustained benefit for immunotherapy once patients discontinue treatment. This is supported by clinical experts at the committee meeting as stated in the ACD, *"The clinical experts explained that for immunotherapies, it is common for the treatment benefit to continue when treatment stops."* This approach is also in line with previous NICE appraisals of immunotherapies in mUC where treatment waning has been explored in a range of 3-5 years post treatment stopping (TA525).	Comment noted. Thank you. The committee considered the company's revised base case with treatment waning applied. It also considered the ERG scenario analyses. It concluded that since a stopping rule had not been accepted, a treatment waning effect should not be included in the model (see FAD section 3.9).
5	Company	Merck	**Page 13: It is not appropriate to pool health state utilities across treatment arms**	Thank you for providing

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<tr><td></td><td></td><td>Serono</td><td>We note that while there is some evidence to suggest that utilities differ for avelumab patients versus WW patients within the progression-free and post-progression health states, we are aligned with the ERG that it is reasonable for the purpose of informing the model to pool the utility values across treatment arms as per previous HTAs in metastatic urothelial cancer (TA519) (5). The number of patients and records by treatment arm and health state used for the base-case EQ-5D model (including progression but not proximity to death) are presented in Table 1. This shows that there is a smaller number of observations to inform the post-progression utility values for each treatment arm which could explain the lower utility value in the post-progression health state for avelumab.

Table 1: Sample sizes used to estimate progression-free and post-progression utility values<table><tr><th></th><th>Number of patients</th><th>Number of observations</th></tr><tr><td>Progressed – Avelumab + BSC</td><td>196</td><td>722</td></tr><tr><td>Progressed - BSC</td><td>234</td><td>504</td></tr><tr><td>Progression-free – Avelumab + BSC</td><td>311</td><td>2273</td></tr><tr><td>Progression-free - BSC</td><td>282</td><td>1258</td></tr></table>The lower utility seen in the post-progression health state for avelumab may be explained by (1) higher subsequent IO use in the BSC arm and (2) the patients who had progressed at the time of the data cut of the JAVELIN Bladder study. Due to the fact that progression is delayed with avelumab, patients who had progressed at this time are likely sicker patients with potentially lower QoL, compared to healthier patients who would not have progressed yet. Additionally, relating to point 1 above, in the pembrolizumab HTA appraisal for 2nd line mUC (NICE TA692), the NICE Committee agreed with the use of pooled utility values, indicating that there was no utility benefit associated with pembrolizumab versus SoC (3). This suggests that a higher subsequent IO use in the 2L would not provide a higher utility for patients.</td><td>this additional evidence. The committee took this into consideration at the second committee meeting. It acknowledged health state utility values pooled across treatment arms have been accepted in NICE's technology appraisal TA692, but in that appraisal, the same treatments were available to people in both study groups whose disease progressed. The committee concluded it was not appropriate to pool health-state utilities across treatment arms. The committee discussion is documented in section 3.12 of the final appraisal document.</td></tr>
<tr><td>6</td><td>Company</td><td>Merck Serono</td><td>Page 14: It is unclear whether life expectancy for people with urothelial cancer who have not had avelumab is less than 24 months

Life-expectancy should be measured from the point at which the technology under appraisal is used in the decision problem. Therefore, we strongly disagree with the suggestion that life expectancy for patients receiving BSC be measured from the start of chemotherapy as this does not reflect the use of avelumab in the 1L maintenance setting. Life expectancy should instead be measured from the point at which patients with metastatic urothelial cancer are eligible for first-line maintenance treatment with avelumab, which is when they achieve CR/PR/SD following treatment with platinum-based chemotherapy. We refer the Committee to the Final Scope, which asks for a comparison with other maintenance options, not with first-line chemotherapy options. This interpretation is also consistent with the economic modelling carried out by the company and the ERG.

All available evidence of life expectancy for patients with metastatic urothelial cancer should be considered and,</td><td>Comment noted. Thank you. The committee considered the short-life expectancy criterion. It considered life-expectancy data from a range of sources during its decision-making, including decisions made in other technology appraisals, real-world evidence and clinical opinions and the mean estimates from the</td></tr>
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			importantly, based on what is currently occurring in clinical practice and preferably including real-world evidence to demonstrate the life expectancy of patients in the UK. It is inappropriate to only consider the modelled mean from the economic model when assessing life expectancy as this is an extrapolation based on the JAVELIN Bladder 100 study, and patients from clinical trials tend to be fitter than patients in clinical practice (who may have a lower life expectancy). The mean in such situations does not represent the experience of the typical patient, as a minority with (thankfully) good outcomes skew the distribution. We therefore disagree that the mean should be used as the only statistic to inform EoL eligibility because of the long tail seen in the OS curve, representing a small number of patients whose disease sustains a durable response to treatment as they do not reflect survival for the majority of patients. In the company-ERG aligned base-case OS analysis, the modelled median survival estimated for the WW arm was 15.98 months, whilst median survival from the JB100 trial for WW was 14.3 months (95% CI: 12.9 to 17.9 months). The log-normal model used to extrapolate OS for the WW treatment arm in the company and ERG aligned base case estimates that only 35.05% of patients live for longer than 24 months. This indicates that approximately one-third of patients on the WW arm are expected to survive beyond 2 years, whereas two-thirds are estimated to have died prior to this landmark, demonstrating that the majority of patients with metastatic urothelial cancer do not survive for longer than 2 years. There is also precedent for consideration of median OS to qualify for EoL criteria from prior UC NICE appraisals: TA658 Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (3), and TA692 pembrolizumab 2L appraisal (latest appraisal in UC) used median OS to determine if EoL criteria were met: *"For people with locally advanced or metastatic disease who have had platinum-containing chemotherapy, data from the company's model and from the literature showed that median overall survival was much less than 24 months for people having treatment with UK standard care. The clinical experts also agreed that they would expect people with locally advanced or metastatic urothelial carcinoma to live for less than 24 months. The committee concluded that the short life expectancy criterion was met"* (4). Table 2 presents a summary of the OS estimates from the literature which provide evidence that the average life expectancy for patients in this setting is < 24 months. This includes the LaMB study discussed by the clinical experts during the Appraisal Committee meeting. This Phase 3 randomised trial, which included UK patients, compared maintenance lapatinib versus placebo in patients who had responded to first-line chemotherapy for metastatic bladder cancer. The study reported a median OS of 11.8 months (95% CI, 10.0, 12.9) from the time of completion of chemotherapy (n=446) (7). As there is little data in the maintenance setting, we have summarised the median survival for studies looking at 1st line chemotherapy. It is important to note that this is approximately 4-6 months earlier than the point at which patients would be eligible for avelumab. Furthermore, whilst these studies do include patients that progress on chemotherapy,	economic model. The committee considered the best estimate of expected survival came from modelling mean life-expectancy based on the trial estimates because the cost-effectiveness results are based on mean quality-adjusted life years and costs. It concluded the short life expectancy criterion had not been met based on the extrapolation of JAVELIN Bladder 100 from the point of randomisation. This discussion is documented in section 3.14 of the final appraisal document.

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the majority of patients achieve disease control with first-line platinum chemotherapy and therefore would be eligible for treatment with avelumab in the maintenance setting (8-10, 15, 28, 29). Phase 3 randomised controlled trials have reported median overall survival (OS) of 12.5–18.0 months for first-line cisplatin-based regimens (8-14), and 9.3 months for first-line carboplatin + gemcitabine (15). Similarly, in a meta-analysis of seven Phase 2 and 3 studies of cisplatin-based chemotherapy in metastatic UC, the median OS was 13.5 months (16). Outcomes in single-arm studies of atezolizumab and pembrolizumab for first-line cisplatin-ineligible patients have been similar to those observed with first-line chemotherapy (median OS of 11.3–16.3 months) (17-19). Furthermore, recent Phase 3 data have failed to demonstrate superiority of atezolizumab or pembrolizumab over first-line chemotherapy in extending OS (20, 21). These studies all provide evidence that suggest that the average life expectancy for patients in this setting is < 24 months.

Table 2: Summary of OS for patients with mUC
<table>
<tr><th>Study / Source</th><th>Population</th><th>Life expectancy</th></tr>
<tr><td>England Standing Cohort Study (22)</td><td>Adult patients in England diagnosed with Stage III–IV UC between 2013 and 2017</td><td>Median OS = 9.5 months</td></tr>
<tr><td>LaMB - Powles et al. 2017 (7)</td><td>Patients with metastatic urothelial bladder cancer - patients with radiologic progression of disease during chemotherapy were excluded</td><td>Median OS = 11.8 months</td></tr>
<tr><td>Bamias et al. 2013 (8)</td><td>Patients with inoperable, metastatic or relapsed urothelial cancer</td><td>Median OS DD-MVAC = 19 months

Median OS DD-GC = 18 months</td></tr>
<tr><td>EORTC Intergroup study 30987 - Bellmunt et al. 2012 (9)</td><td>Gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy</td><td>Median OS = 12.7 months</td></tr>
<tr><td>Sterberg et al. 2001 (10)</td><td>MVAC in Advanced Urothelial Tract Tumors</td><td>Median OS = 14.1 months</td></tr>
<tr><td>Dreicer et al. 2004 (11)</td><td>M-VAC in patients with advanced carcinoma of the urothelium</td><td>Median OS = 15.4 months</td></tr>
<tr><td>Siefker-Radtke et al. 2002 (12)</td><td>M-VAC in patients with Metastatic or Unresectable Urothelial Cancer</td><td>Median OS = 12.5 months</td></tr>
<tr><td>Bamias et al. 2004 (13)</td><td>MVAC With G-CSF in Advanced Urothelial Carcinoma</td><td>Median OS = 14.2 months</td></tr>
<tr><td>Von der Maase et al. 2005 (14)</td><td>GC vs MVAC in patients With Bladder Cancer</td><td>Median OS GC = 14.0 months</td></tr>
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		Median MVAC = 15.2 months
De Santis 2012 (15)	GC vs M-CAVI in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy	Median OS GC = 9.3 months Median M-CAVI = 8.1 months
Galsky et al. 2013 (16)	Patients With Metastatic Urothelial Cancer Treated With First-Line Cisplatin-Based Chemotherapy	Median OS = 13.5 months
KEYNOTE-052 - Vuky et al. 2020 (23)	First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer	Median OS = 11.3 months
IMvigor210 -Balar et al. 2018 (24)	Atezolizumab in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer	Median OS = 16.3 months
IMvigor130 - Galsky et al. 2020 (20)	Atezolizumab with or without platinum-based chemotherapy versus placebo plus platinum-based chemotherapy in first-line metastatic urothelial carcinoma	Median OS atezo + chemo = 16.0 months Median OS chemo = 13.4 months
KEYNOTE-361 – Loriot et al. 2021 (25)	Post hoc analysis of long-term outcomes in patients with CR, PR, or SD to Pembrolizumab or platinum-based chemotherapy as first-line therapy for advanced urothelial carcinoma	Median OS chemo CR/PR = 18.6 months Median OS chemo SD = 11.1 months

In addition to the available evidence in the literature, we undertook interviews with the following eight UK-based consultant oncologists specialising in the treatment of advanced urothelial cancer as part of our technical engagement response:

[redacted]

As part of the interviews, the clinicians were asked about the average life expectancy of patients with metastatic

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			urothelial cancer who respond to chemotherapy and receive current standard of care in the UK. Estimates elicited from the clinical experts ranged from 12-18 months and it was confirmed that there is no evidence currently available which suggests that average overall survival is greater than 24 months in this patient population. These estimates were informed by both their knowledge of the literature and their own experience with patients in clinical practice. The feedback from clinical experts at the Appraisal Committee meeting regarding life expectancy was fully in line with feedback from the eight UK KOLs interviewed and the population in question was clearly defined in those interviews as well as in the Committee meeting on the 14th April. Consequently we do not agree with the Committee's conclusion that the wrong patient group had been considered by the clinical experts: *"The committee was unsure if the overall survival values from existing clinical trials and estimates provided by the clinical experts accurately reflect people who are eligible for maintenance treatment".* In conclusion, KOL opinion, evidence from the literature and RWE support the JB100 median estimates demonstrating life expectancy of mUC patients is less than 24 months, with the extrapolated mean overall survival from the cost-effectiveness model being the only outlier, due to a small number of durable responders.	
7	Company	Merck Serono	**Page 17: Innovation - The treatment benefit from avelumab has been adequately incorporated into the model** Whilst avelumab is a treatment option for other types of cancer, we believe that innovation should be considered by each indication as there are clear differences in clinical outcomes between each tumour type. Avelumab in first-line maintenance treatment for UC is a completely new treatment strategy in urothelial cancer and targets patients who will benefit the most from treatment. There is a substantial unmet need for patients with advanced bladder cancer with no approved active treatment options in this setting, avelumab is the first treatment option licensed for a broad range of patients regardless of PD-L1 status and cisplatin-eligibility for many years and has been demonstrated to extend median OS by 7.1 months versus BSC (26).	Comment noted. Thank you. The committee considered this in section 3.17 of the final appraisal document. It concluded the treatment benefit from avelumab for this indication has been adequately incorporated into the model.
	Consultee	Fight Bladder Cancer	The Appraisal Consultation Document states "Avelumab does not meet NICE's criteria to be considered a life-extending treatment at the end of life. This is because it is uncertain how long people in the NHS who would be eligible for avelumab live for" This is an unreasonable statement. There is enough data to estimate how long people in the NHS who would be eligible for avelumab live for – a median of 14 months, which is well below 24 months. The Javelin Bladder 100 trial demonstrated a median 14.3 months in people who responded to chemotherapy and then had best supportive care alone. An analysis of National Cancer Registration and Analysis Service data looking at patients with locally advanced or metastatic urothelial cancer found a median overall survival of 14.0 months from initiation of first line systemic therapy (https://doi.org/10.1016/j.jval.2020.08.477). "Most people with locally advanced / metastatic urothelial cancer who respond to platinum-based chemotherapy live for a median of 12-18 months, based on trial data from multiple sources including UK trials. Less than 20% longer than 2 years." Dr Simon Crabb, Associate Professor in Medical Oncology	Comment noted. Thank you. The committee discussed whether avelumab met the short-life expectancy criterion. It considered life-expectancy data from a range of sources during its decision-making, including decisions made in other technology appraisals, real-world evidence and clinical opinions and the mean estimates from the economic model. The

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			"Most people with locally advanced / metastatic urothelial cancer who respond to platinum-based chemotherapy live for an average of around 14 months." Prof Alison Birtle, Consultant Oncologist	committee considered the best estimate of expected survival came from modelling mean life-expectancy based on the trial estimates because the cost-effectiveness results are based on mean quality-adjusted life years and costs. The discussion is documented in section 3.14 of the final appraisal document.
9	Consultee	Fight Bladder Cancer	The Appraisal Consultation Document states that "it is important for the committee to consider the mean survival" In determining whether survival is 'normally less than 24 months' for 'End of life', we submit that failing to rely on median survival was unreasonable in this context. The patient community has a legitimate expectation that median survival is a more appropriate measure in determining whether or not survival is 'normally less than 24 months', rather than mean. This is due to the small number of long-term survivors in this population that unreasonably skew the distribution. The NICE criteria make no explicit reference to use of either median or mean survival. There is precedent for using median life expectancy (e.g. TA541).	Comment noted. Thank you. The committee considered further evidence regarding median life expectancy at the second committee meeting. It acknowledged decisions made in previous technology appraisals during its discussion. In these appraisals, both median and mean overall survival was less than 24 months. This was also true in TA541. The committee considered the best estimate of expected survival came from modelling mean life-expectancy based on the trial estimates because the cost-effectiveness results are based on mean quality-adjusted life years and costs. The discussions

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				are documented in section 3.14 of the final appraisal document
10	Consultee	Fight Bladder Cancer	If NICE still does not consider the End of Life criteria to be met, and still chooses to use mean overall survival, we submit that, given that "the ERG's [Evidence Review Group's] base case predicted a mean overall survival of 27.82 months and a median of 15.6 months", any committee decision to utilise any lower threshold other than the maximum available to a treatment not meeting end of life (£30,000 per QALY gained) would be unfair and unreasonable in the context of treatments close to End of Life.	Comment noted. Thank you. The committee considered the cost-effectiveness estimates during its decision-making. The technology appraisals methods guide does not require the committee to consider life expectancy as a modifier of the ICER threshold if it concludes that the end of life criteria have not been met (see Guide to the methods of technology appraisal, 2013). Both the company and ERG ICERs were considerably higher than what is normally considered to be cost effective. (Please see section 3.15 of the final appraisal document).
11	Consultee	Fight Bladder Cancer	The Appraisal Consultation Document states that "the ERG's [Evidence Review Group's] base case predicted a mean overall survival of 27.82 months and a median of 15.6 months". This fails to account for the fact that patients in clinical trials are often healthier than the population that would be eligible for treatment in general clinical practice, and it is unreasonable of NICE to just use extrapolation from an economic model to determine overall survival.	Comment noted. Thank you. The committee considered evidence from a range of sources during its discussions around overall survival. Extrapolations from economic models are often used to determine expected survival. Importantly extrapolations from economic models are almost always used to

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				determine the quality-adjusted life years (based on mean survival) and costs of treatments in order to assess cost-effectiveness. The discussion is documented in section 3.14 of the final appraisal document.
12	Consultee	Fight Bladder Cancer	The Appraisal Consultation Document states “Avelumab is not suitable for use within the Cancer Drugs Fund because it is unlikely to be cost effective and further data collection is not an option” We submit that this statement is unreasonable. If NICE does not wish for this drug to be available via routine commissioning, we suggest that the drug could be used within the Cancer Drugs Fund. We suggest to NICE that National Cancer Registration and Analysis Service data could then be used to resolve uncertainty around the 2 year stopping rule (discussed below), as well as the effects on cost and effectiveness regarding the recommendation to not use atezolizumab as a second line treatment in real world practice (in contrast to Javelin Bladder 100).	Comment noted. Thank you. To be considered in the Cancer Drugs Fund, a technology needs to have shown plausible potential to be cost effective which the committee did not consider avelumab to have done. The committee considered whether avelumab would be suitable for use within the Cancer Drugs Fund. This discussion is documented in section 3.16 of the final appraisal document.
13	Consultee	Fight Bladder Cancer	The Appraisal Consultation Document states that the committee “was concerned that it would be difficult for patients to accept that they would no longer be able to have treatment after 2 years if they were free from disease and they may fear losing treatment benefit.” We submit that this is an unreasonable concern. We have spoken to bladder cancer patients about this issue. Patients shared with us that, as long as they were informed of the 2 year stopping rule at the beginning of treatment, as well as the mechanism of action of the treatment, they would be comfortable with a 2 year stopping rule. We also remind NICE that there is currently no maintenance immunotherapy available as part of routine commissioning for this population of bladder cancer patients.	Comment noted. Thank you. The committee considered further evidence surrounding a 2 year stopping rule at the second committee meeting. It concluded there was no clear evidence to support a stopping rule because JAVELIN Bladder 100 did not include one and the setting and

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
				population in this appraisal is different to other appraisals in this disease area where stopping rules have been considered. The committee concluded that time to stopping treatment should reflect the trial evidence and a stopping rule should not be included in the model. The committee discussion is documented in section 3.8 of the final appraisal document.
14		Fight Bladder Cancer	We also submit that the committee meeting on Wednesday 14 April 2021 was procedurally unfair, as there was insufficient patient input. Patient Experts have a right to be heard, and we submit that Patient Experts were not given enough opportunity to speak during the committee meeting. We submit that the Chair of the meeting failed to act fairly by discouraging Patient Experts from giving their input. The Patient Experts also did not have the opportunity to present all the information in their written Patient carer organisation submission. This meant that there was a failure to properly consider the input of Patient Experts.	Comment noted. Thank you. We apologise your representative thought there was a failure to consider their input during the committee meeting. The submissions are made available to the committee to consider in advance of the meeting. It is not possible for all of the material included in the patient expert submission to be presented in full at the committee meeting. Submissions need to be summarised to ensure the meetings focus on outstanding key issues. Similarly, the chair focuses questions to both the clinical and patient experts in relation to the key issues

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
				presented to the committee.
15	Consultee	Action Bladder Cancer UK	**Recommendations: Section 1.1** We are disappointed by the committee's decision not to recommend avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after chemotherapy. We note that the committee include as a contributing reason their conclusion that patients in this group do not meet NICE's criteria for life-extending treatment at the end of life, because it is uncertain how long such people may live. We think that there is sufficient evidence that the criteria is met, and that NICE has previously accepted that this group meet end of life criteria.	Comment noted. Thank you. The committee considered a range of evidence surrounding end of life criteria. The discussion is documented in section 3.14 of the final appraisal document.
16	Consultee	Action Bladder Cancer UK	**Time to stopping treatment should reflect the trial : Section 3.8** As a charity representing patients, we would prefer that immunotherapies such as avelumab were made available without a stopping rule. However, we also recognise that it is possible longer term use of avelumab might be thought too expensive under NICE affordability criteria. In these circumstances, we would prefer to see a stopping rule in place if the alternative was to deny access to avelumab for this small but very poorly served group of patients. This is also my own personal view as a urothelial cancer patient, and, in so far as we have been able to discuss this with other urothelial cancer patients, they agree.	Comment noted. Thank you. The committee considered the proposal of a 2-year stopping rule at the second committee meeting. The discussion has been documented in section 3.8 of the final appraisal document.
17	Consultee	Action Bladder Cancer UK	**It is unclear whether life expectancy for people with urothelial cancer who have not had avelumab is less than 24 months: Section 3.14** We are surprised that the committee does not accept that this group falls within the NICE end of life criteria. The committee focused on the lack of clarity on life expectancy from the javelin trial data and the difficulty in extrapolating that data to fit UK clinical practice. However, we believe that there is sufficient real world data from UK clinical practice to show that the end of life criteria is met. This was, we thought, confirmed by the clinical experts. The committee has chosen to measure survival from the beginning of chemotherapy treatment. We do not understand the logic of this. From a patient perspective, it seems odd to point to an earlier stage of disease, and believe survival should be calculated from the commencement of treatment with avelumab. In para 3.11 the committee refer to the findings from the guidance on pembrolizumab (TA692) for the same group of patients, ie those with advanced or metastatic urothelial cancer after treatment with platinum based chemotherapy. That appraisal accepted that this group of patients meets the end of life criteria: "For people with locally advanced or metastatic disease who have had platinum-containing chemotherapy…….median overall survival was much less than 24 months for people having treatment with UK standard care……..The committee concluded that the short life expectancy criterion was met" (para 3.29 of TA692).	Comment noted. Thank you. The committee considered additional real-world evidence of life-expectancy for this group at the second committee meeting, taking into consideration life-expectancy estimates as eligibility from the start of having treatment with avelumab. The discussions around the short-life expectancy criterion are documented in section 3.14 of the final appraisal document
18	Consultee	Action Bladder Cancer UK	**The ICER using committee's preferred assumptions: Section 3.14** We do not think the chosen assumptions necessarily reflect UK clinical practice, for example on the use of subsequent immunotherapies where the committee has chosen to include the cost rather than remove the benefit. We accept that it may be difficult to extrapolate data from within Javelin, but we are concerned that the committee's chosen assumptions may have resulted in a cost base which may be artificially high.	Comment noted. Thank you. The committee considered the cost-effectiveness estimates during its decision-

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
				making. Because of confidential discounts for subsequent therapies, the cost-effectiveness results cannot be reported directly. (Please see section 3.15 of the final appraisal document).
19	Consultee	Action Bladder Cancer UK	**Proposed date for review of guidance: Section 3.19** We would welcome an earlier review of 12 months, in recognition of the rapidly increasing data from using immunotherapies for cancers, and the desperate need of this poorly served group of patients.	Comment noted. Thank you. The 3-year period is the time normally given for the review period. However, the Technology Appraisal process guide says: "Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations. NICE is keen to hear about any new evidence that becomes available before the time of review (please send information to nice@nice.org.uk). NICE will assess the likely impact of the new evidence on the recommendations and will propose an update to the published guidance if needed" (from Guide to the processes of technology appraisal 2018, section 6.2).
20	Web comment	Public responder 1	**Has all of the relevant evidence been taken into account?** *"Yes there is little evidence / research for maintenance therapy for bladder cancer"*	Comment noted. Thank you
21	Web	Public	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	Comment noted. Thank

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
	comment	responder 1	“Most patients who progress through first line treatment would not survive for longer than 24 months.”	you
22	Web comment	Public responder 1	**Are the recommendations sound and a suitable basis for guidance to the NHS?** “Given the paucity of options for metastatic bladder cancer, and the limited number of drugs having maintenance therapy for this group of patients would be an important therapeutic strategy. This is the best evidence we have to date.”	Comment noted. Thank you
23	Web comment	Public responder 1	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** “No”	Comment noted. Thank you

References

1. National Institute for Health and Care Excellence. Avelumab for treating metastatic Merkel cell carcinoma. 2018. https://www.nice.org.uk/guidance/ta517
2. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525]. https://www.nice.org.uk/guidance/ta525
3. National Institute for Health and Care Excellence. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [TA658]. https://www.nice.org.uk/guidance/ta658/documents/final-appraisal-determination-document
4. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA692]. https://www.nice.org.uk/guidance/ta692
5. Clinicaltrials.gov. A Study of Atezolizumab Compared With Chemotherapy in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor211]. https://clinicaltrials.gov/ct2/show/NCT02302807
6. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA519]. https://www.nice.org.uk/guidance/ta519/documents/final-appraisal-determination-document
7. Powles T, Huddart RA, Elliot T, et al. Phase III, Double-Blind, Randomized Trial That Compared Maintenance Lapatinib Versus Placebo After First-Line Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 1/2–Positive Metastatic Bladder Cancer. Journal of Clinical Oncology. 2017;35(1):48-55.
8. Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol. 2013;24(4):1011-7.
9. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13.
10. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001;19(10):2638-46.
11. Dreicer R, Manola J, Roth BJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer. 2004;100(8):1639-45.
12. Siefker-Radtke AO, Millikan RE, Tu SM, et al. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. J Clin Oncol. 2002;20(5):1361-7.
13. Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol. 2004;22(2):220-8.
14. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23(21):4602-8.

NICE National Institute for Health and Care Excellence

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Thursday 27 May 2021** 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):	Merck Serono Ltd / Pfizer Ltd Alliance
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:	N/A

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NICE National Institute for Health and Care Excellence

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

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Dear Appraisal Committee members,

Merck Serono Ltd and Pfizer Ltd welcome the opportunity to comment on the NICE Appraisal Consultation Document (ACD) for avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735].

Merck and Pfizer are disappointed with the draft decision; however, we remain committed to working with NICE to achieve access to avelumab for patients with mUC in England and Wales. We have summarised our key concerns with the conclusions from the committee below.

- End of Life criteria – Whilst we welcome the Committee's acknowledgement that avelumab meets the life extension criteria we wholly disagree with the Committee's conclusion that the life expectancy for patients with metastatic urothelial cancer is more than 24 months.

- Time-to-discontinuation assumptions – The TTD assumptions included in the company's and ERG's base case model did not represent a stopping rule for implementation in clinical practice, but instead were incorporated to reflect the expected treatment duration in clinical practice. Considering clinical expert opinion on treatment duration and the current NHS treatment practices for IO therapies in mUC and other indications, we have presented scenarios which include a 2-year stopping rule and 5-year treatment waning effect for the committee's consideration.

Following your review of the evidence addressing each of our concerns in the table below, we hope the committee revisit their position on the degree of uncertainty associated with long term treatment benefits and the current life expectancy of patients with metastatic UC.

Finally, as demonstrated in the JAVELIN bladder 100 trial data, and the unmet need in this patient population, avelumab in the 1L maintenance setting represents a paradigm shift in the existing UC treatment pathway.

Yours sincerely,

[redacted]

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Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

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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.
1 **Overall survival extrapolations**	**Page 8: The generalised gamma and log-normal models are both acceptable for extrapolating overall survival data** As in our response to technical engagement, we accept that both the generalised gamma and log-normal are plausible for extrapolating overall survival data with similar AIC/BIC scores for statistical fit. However, we propose that one model should be applied in the base case for decision making purposes. We accept that the generalised gamma may be considered optimistic for the WW arm and note that the estimates of 5- and 10-year OS (15.00% and 6.48%, respectively) are closer to the upper bounds suggested by the clinicians as detailed in the ERG report. Therefore, we propose that the log-normal model is selected to align with ERG's preferred base case as this is the more conservative OS curve for avelumab and predicts 5- and 10-year OS closer to the mid-point of the clinical expert expectations for the WW arm.
2 **Treatment duration**	**Pages 9-11: Time to stopping treatment should reflect the trial** We would like to clarify that the TTD assumption in the cost-effectiveness model (95% patients stopping treatment at 2 years) is not a stopping rule and the company did not expect this to be implemented in clinical practice. This model assumption was incorporated following an advisory board and follow-up interviews with UK-based clinicians to best reflect the likely treatment duration that would occur in clinical practice. Clinicians noted that the majority of patients in clinical practice would discontinue treatment by 2 years due to toxicity or patient choice as has been noted for other IO therapies across indications. This approach was also used in the company's submission for avelumab for treating metastatic Merkel cell carcinoma (TA517) (1). The ERG have also agreed with these TTD assumptions and included them in their base case following clinical expert advice. We accept that the TTD assumptions could impact the duration of treatment benefit and this was explored in several scenarios by both the company and ERG. Given that the majority of patients will discontinue treatment before 2 years (median TTD in JB100 was approximately 25 weeks), supported by clinical expert opinion and current use of IO therapies in mUC, we propose the implementation of a 2-year stopping rule for avelumab for maintenance treatment in mUC to help reduce the uncertainty around treatment duration. The cost-effectiveness results with a 2-year stopping rule and 5-year treatment benefit waning applied are presented in the

	appendices to this response. We would like to note that the statement in the ACD that *"The committee noted that other NICE technology appraisals of immunotherapies for urothelial cancer have preferred no stopping rules"* is incorrect. In previous technology appraisals for immunotherapies in mUC for atezolizumab (TA525) and pembrolizumab (TA692), the NICE Committee have accepted 2-year stopping rules and included these in final recommendations (2, 3). In the NICE FAD for atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525) it is stated that **"***… the committee recognised that in previous NICE technology appraisals clinicians have highlighted growing concern about using immunotherapies beyond 2 years."* and **"***The committee also recognised that NICE guidance for other immunotherapies for metastatic urothelial carcinoma and other cancers include 2-year stopping rules (1). The committee concluded that it is appropriate to include a 2-year stopping rule in the economic model."* It should also be noted that a 2-year stopping rule was not included in the IMvigor 211 clinical trial for atezolizumab (4).

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3 **Progression-free survival and Time to treatment discontinuation**	**Page 10 and 11: The committee would therefore like to see the progression-free survival and time to stopping treatment curves presented on the same graph to assess the relationship between the 2 in the trial.** Figures 1 and 2 present the KM curves for TTD and PFS on the same graph, demonstrating that patients did receive treatment beyond progression up until approximately 15 months when the curves cross, from which point it is clear that patients discontinued treatment prior to progression. ***Figure 1: KMs TTD vs PFS (BICR definition) – time in years***  Abbreviations: BICR = blinded independent central review; PFS = progression-free survival; TTD = time to treatment discontinuation

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	Figure 2: KMs TTD vs PFS (investigator-assessed) – time in years  Abbreviations: INV = investigator-assessed; PFS = progression-free survival; TTD = time to treatment discontinuation
3 **Duration of treatment benefit**	**Page 11: It is not appropriate to include a lifetime treatment effect for people stopping avelumab before disease progression** We have explored duration of treatment effect in several scenarios submitted during technical engagement, however these were excluded from both the company's and ERG's base case due to a lack of available evidence to inform these scenarios as avelumab is the first IO to be used in this maintenance setting. Based on the committee's conclusion we have provided a revised base case in comment 2 of this document with treatment waning applied at 5 years (where there is an instant loss of treatment benefit , HR reverts to 1) in association with a 2-year stopping rule. We have applied treatment benefit waning at 5 years (3 years post treatment stop) to align with feedback from eight consultant oncologists specialising in the treatment of advanced urothelial cancer consulted as part of technical engagement, who agreed there is a sustained benefit for immunotherapy once patients discontinue treatment. This is supported by clinical experts at the committee meeting as stated in the ACD, *"The clinical experts explained that for immunotherapies, it is common for the treatment benefit to continue when treatment stops."* This approach is also in line with previous NICE appraisals of immunotherapies in mUC where treatment waning has been explored in a range of 3-5 years post treatment stopping (TA525).
4	**Page 13: It is not appropriate to pool health state utilities across treatment arms**

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<table>
<tr>
<td>Health state utilities</td>
<td>
We note that while there is some evidence to suggest that utilities differ for avelumab patients versus WW patients within the progression-free and post-progression health states, we are aligned with the ERG that it is reasonable for the purpose of informing the model to pool the utility values across treatment arms as per previous HTAs in metastatic urothelial cancer (TA519) (5). The number of patients and records by treatment arm and health state used for the base-case EQ-5D model (including progression but not proximity to death) are presented in Table 1. This shows that there is a smaller number of observations to inform the post-progression utility values for each treatment arm which could explain the lower utility value in the post-progression health state for avelumab.

Table 1: Sample sizes used to estimate progression-free and post-progression utility values
<table>
<tr><th></th><th>Number of patients</th><th>Number of observations</th></tr>
<tr><td>Progressed – Avelumab + BSC</td><td>196</td><td>722</td></tr>
<tr><td>Progressed - BSC</td><td>234</td><td>504</td></tr>
<tr><td>Progression-free – Avelumab + BSC</td><td>311</td><td>2273</td></tr>
<tr><td>Progression-free - BSC</td><td>282</td><td>1258</td></tr>
</table>

The lower utility seen in the post-progression health state for avelumab may be explained by (1) higher subsequent IO use in the BSC arm and (2) the patients who had progressed at the time of the data cut of the JAVELIN Bladder study. Due to the fact that progression is delayed with avelumab, patients who had progressed at this time are likely sicker patients with potentially lower QoL, compared to healthier patients who would not have progressed yet. Additionally, relating to point 1 above, in the pembrolizumab HTA appraisal for 2nd line mUC (NICE TA692), the NICE Committee agreed with the use of pooled utility values, indicating that there was no utility benefit associated with pembrolizumab versus SoC (3). This suggests that a higher subsequent IO use in the 2L would not provide a higher utility for patients.
</td>
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<td>5

End of Life Criteria</td>
<td>
Page 14: It is unclear whether life expectancy for people with urothelial cancer who have not had avelumab is less than 24 months

Life-expectancy should be measured from the point at which the technology under appraisal is used in the decision problem. Therefore, we strongly disagree with the suggestion that life expectancy for patients receiving BSC be measured from the start of chemotherapy as this does not reflect the use of avelumab in the 1L maintenance setting. Life expectancy should instead be measured from the point at which patients with metastatic urothelial cancer are eligible for first-line maintenance treatment with avelumab, which is when they achieve CR/PR/SD following treatment with platinum-based chemotherapy. We refer the Committee to the Final Scope, which asks for a comparison with other maintenance options, not with first-line chemotherapy options.
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	This interpretation is also consistent with the economic modelling carried out by the company and the ERG. All available evidence of life expectancy for patients with metastatic urothelial cancer should be considered and, importantly, based on what is currently occurring in clinical practice and preferably including real-world evidence to demonstrate the life expectancy of patients in the UK. It is inappropriate to only consider the modelled mean from the economic model when assessing life expectancy as this is an extrapolation based on the JAVELIN Bladder 100 study, and patients from clinical trials tend to be fitter than patients in clinical practice (who may have a lower life expectancy). The mean in such situations does not represent the experience of the typical patient, as a minority with (thankfully) good outcomes skew the distribution. We therefore disagree that the mean should be used as the only statistic to inform EoL eligibility because of the long tail seen in the OS curve, representing a small number of patients whose disease sustains a durable response to treatment as they do not reflect survival for the majority of patients. In the company-ERG aligned base-case OS analysis, the modelled median survival estimated for the WW arm was 15.98 months, whilst median survival from the JB100 trial for WW was 14.3 months (95% CI: 12.9 to 17.9 months). The log-normal model used to extrapolate OS for the WW treatment arm in the company and ERG aligned base case estimates that only 35.05% of patients live for longer than 24 months. This indicates that approximately one-third of patients on the WW arm are expected to survive beyond 2 years, whereas two-thirds are estimated to have died prior to this landmark, demonstrating that the majority of patients with metastatic urothelial cancer do not survive for longer than 2 years. There is also precedent for consideration of median OS to qualify for EoL criteria from prior UC NICE appraisals: TA658 Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (3), and TA692 pembrolizumab 2L appraisal (latest appraisal in UC) used median OS to determine if EoL criteria were met: *"For people with locally advanced or metastatic disease who have had platinum-containing chemotherapy, data from the company's model and from the literature showed that median overall survival was much less than 24 months for people having treatment with UK standard care. The clinical experts also agreed that they would expect people with locally advanced or metastatic urothelial carcinoma to live for less than 24 months. The committee concluded that the short life expectancy criterion was met"* (4). Table 2 presents a summary of the OS estimates from the literature which provide evidence that the average life expectancy for patients in this setting is < 24 months. This includes the LaMB study discussed by the clinical experts during the Appraisal Committee meeting. This Phase 3 randomised trial, which included UK patients, compared maintenance lapatinib versus placebo in patients who had responded to

first-line chemotherapy for metastatic bladder cancer. The study reported a median OS of 11.8 months (95% CI, 10.0, 12.9) from the time of completion of chemotherapy (n=446) (7).

As there is little data in the maintenance setting, we have summarised the median survival for studies looking at 1st line chemotherapy. It is important to note that this is approximately 4-6 months earlier than the point at which patients would be eligible for avelumab. Furthermore, whilst these studies do include patients that progress on chemotherapy, the majority of patients achieve disease control with first-line platinum chemotherapy and therefore would be eligible for treatment with avelumab in the maintenance setting (8-10, 15, 28, 29). Phase 3 randomised controlled trials have reported median overall survival (OS) of 12.5–18.0 months for first-line cisplatin-based regimens (8-14), and 9.3 months for first-line carboplatin + gemcitabine (15). Similarly, in a meta-analysis of seven Phase 2 and 3 studies of cisplatin-based chemotherapy in metastatic UC, the median OS was 13.5 months (16). Outcomes in single-arm studies of atezolizumab and pembrolizumab for first-line cisplatin-ineligible patients have been similar to those observed with first-line chemotherapy (median OS of 11.3–16.3 months) (17-19). Furthermore, recent Phase 3 data have failed to demonstrate superiority of atezolizumab or pembrolizumab over first-line chemotherapy in extending OS (20, 21). These studies all provide evidence that suggest that the average life expectancy for patients in this setting is < 24 months.

Table 2: Summary of OS for patients with mUC

Study / Source	Population	Life expectancy
England Standing Cohort Study (22)	Adult patients in England diagnosed with Stage III–IV UC between 2013 and 2017	Median OS = 9.5 months
LaMB - Powles et al. 2017 (7)	Patients with metastatic urothelial bladder cancer - patients with radiologic progression of disease during chemotherapy were excluded	Median OS = 11.8 months
Bamias et al. 2013 (8)	Patients with inoperable, metastatic or relapsed urothelial cancer	Median OS DD-MVAC = 19 months Median OS DD-GC = 18 months
EORTC Intergroup study 30987 - Bellmunt et al. 2012 (9)	Gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy	Median OS = 12.7 months
Sterberg et al. 2001 (10)	MVAC in Advanced Urothelial Tract Tumors	Median OS = 14.1 months
Dreicer et al.	M-VAC in patients with advanced	Median OS = 15.4

2004 (11)	carcinoma of the urothelium	months
Siefker-Radtke et al. 2002 (12)	M-VAC in patients with Metastatic or Unresectable Urothelial Cancer	Median OS = 12.5 months
Bamias et al. 2004 (13)	MVAC With G-CSF in Advanced Urothelial Carcinoma	Median OS = 14.2 months
Von der Maase et al. 2005 (14)	GC vs MVAC in patients With Bladder Cancer	Median OS GC = 14.0 months Median MVAC = 15.2 months
De Santis 2012 (15)	GC vs M-CAVI in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy	Median OS GC = 9.3 months Median M-CAVI = 8.1 months
Galsky et al. 2013 (16)	Patients With Metastatic Urothelial Cancer Treated With First-Line Cisplatin-Based Chemotherapy	Median OS = 13.5 months
KEYNOTE-052 - Vuky et al. 2020 (23)	First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer	Median OS = 11.3 months
IMvigor210 - Balar et al. 2018 (24)	Atezolizumab in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer	Median OS = 16.3 months
IMvigor130 - Galsky et al. 2020 (20)	Atezolizumab with or without platinum-based chemotherapy versus placebo plus platinum-based chemotherapy in first-line metastatic urothelial carcinoma	Median OS atezo + chemo = 16.0 months Median OS chemo = 13.4 months
KEYNOTE-361 – Loriot et al. 2021 (25)	Post hoc analysis of long-term outcomes in patients with CR, PR, or SD to Pembrolizumab or platinum-based chemotherapy as first-line therapy for advanced urothelial carcinoma	Median OS chemo CR/PR = 18.6 months Median OS chemo SD = 11.1 months

In addition to the available evidence in the literature, we undertook interviews with the following eight UK-based consultant oncologists specialising in the treatment of advanced urothelial cancer as part of our technical engagement response:

[redacted]

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

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	[redacted] As part of the interviews, the clinicians were asked about the average life expectancy of patients with metastatic urothelial cancer who respond to chemotherapy and receive current standard of care in the UK. Estimates elicited from the clinical experts ranged from 12-18 months and it was confirmed that there is no evidence currently available which suggests that average overall survival is greater than 24 months in this patient population. These estimates were informed by both their knowledge of the literature and their own experience with patients in clinical practice. The feedback from clinical experts at the Appraisal Committee meeting regarding life expectancy was fully in line with feedback from the eight UK KOLs interviewed and the population in question was clearly defined in those interviews as well as in the Committee meeting on the 14th April. Consequently we do not agree with the Committee's conclusion that the wrong patient group had been considered by the clinical experts: *"The committee was unsure if the overall survival values from existing clinical trials and estimates provided by the clinical experts accurately reflect people who are eligible for maintenance treatment".* In conclusion, KOL opinion, evidence from the literature and RWE support the JB100 median estimates demonstrating life expectancy of mUC patients is less than 24 months, with the extrapolated mean overall survival from the cost-effectiveness model being the only outlier, due to a small number of durable responders.
6 **Innovation**	**Page 17: Innovation - The treatment benefit from avelumab has been adequately incorporated into the model** Whilst avelumab is a treatment option for other types of cancer, we believe that innovation should be considered by each indication as there are clear differences in clinical outcomes between each tumour type. Avelumab in first-line maintenance treatment for UC is a completely new treatment strategy in urothelial cancer and targets patients who will benefit the most from treatment. There is a substantial unmet need for patients with advanced bladder cancer with no approved active treatment options in this setting, avelumab is the first treatment option licensed for a broad range of patients regardless of PD-L1 status and cisplatin-eligibility for many years and has been demonstrated to extend median OS by 7.1 months versus BSC (26).

Insert extra rows as needed

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References

1. National Institute for Health and Care Excellence. Avelumab for treating metastatic Merkel cell carcinoma. 2018. https://www.nice.org.uk/guidance/ta517
2. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525]. https://www.nice.org.uk/guidance/ta525
3. National Institute for Health and Care Excellence. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [TA658]. https://www.nice.org.uk/guidance/ta658/documents/final-appraisal-determination-document
4. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA692]. https://www.nice.org.uk/guidance/ta692
5. Clinicaltrials.gov. A Study of Atezolizumab Compared With Chemotherapy in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor211]. https://clinicaltrials.gov/ct2/show/NCT02302807
6. National Institute for Health and Care Excellence. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA519]. https://www.nice.org.uk/guidance/ta519/documents/final-appraisal-determination-document
7. Powles T, Huddart RA, Elliot T, et al. Phase III, Double-Blind, Randomized Trial That Compared Maintenance Lapatinib Versus Placebo After First-Line Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 1/2–Positive Metastatic Bladder Cancer. Journal of Clinical Oncology. 2017;35(1):48-55.
8. Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol. 2013;24(4):1011-7.
9. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13.
10. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001;19(10):2638-46.
11. Dreicer R, Manola J, Roth BJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer. 2004;100(8):1639-45.
12. Siefker-Radtke AO, Millikan RE, Tu SM, et al. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. J Clin Oncol. 2002;20(5):1361-7.
13. Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol. 2004;22(2):220-8.
14. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23(21):4602-8.

15. De Santis M, Bellmunt J, Mead G, et al. 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. 2012;30(2):191-9.
16. Galsky MD, Krege S, Lin CC, et al. Relationship between 6- and 9-month progression-free survival and overall survival in patients with metastatic urothelial cancer treated with first-line cisplatin-based chemotherapy. Cancer. 2013;119(16):3020-6.
17. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389(10064):67-76.
18. ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (MK-3475-052/KEYNOTE-052) 2020 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT02335424.
19. Vuky J, Balar AV, Castellano DE, et al. Updated efficacy and safety of KEYNOTE-052: A single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol. 2018;36(15_suppl):4524.
20. Galsky MD, Arija JAA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10236):1547-57.
21. Merck & Company Inc. Merck Provides Update on Phase 3 KEYNOTE-361 Trial Evaluating KEYTRUDA® (pembrolizumab) as Monotherapy and in Combination with Chemotherapy in Patients with Advanced or Metastatic Urothelial Carcinoma 2020 [Available from: https://investors.merck.com/news/press-release-details/2020/Merck-Provides-Update-on-Phase-3-KEYNOTE-361-Trial-Evaluating-KEYTRUDA-pembrolizumab-as-Monotherapy-and-in-Combination-with-Chemotherapy-in-Patients-with-Advanced-or-Metastatic-Urothelial-Carcinoma/default.aspx.
22. Knott C, Health Data Insight CIC. Observational cohorts of patients with advanced or metastatic cancer in England (MS100070-0027). 2019.
23. Vuky J, Balar A, Castellano D, et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Cancer. Journal of Clinical Oncology. 2020;38(23):2658-2666.
24. Balar AV, Dreicer R, Loriot Y, et al. Atezolizumab (atezo) in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer (mUC): Long-term efficacy from phase 2 study IMvigor210. Journal of Clinical Oncology. 2018;36(15):4523-4523
25. Loriot Y, Alva A, Csószi T, et al. Post hoc analysis of long-term outcomes in patients with CR, PR, or SD to Pembrolizumab or platinum-based chemotherapy as first-line therapy for advanced urothelial carcinoma in KEYNOTE-361. Genitourinary Cancers Symposium. 2021
26. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-30.
27. Von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study. Journal of Clinical Oncology. 2000;17(17):3068-3077.
28. Dogliotti L, Carteni G, Siena S, et al. Gemcitabine plus Cisplatin versus Gemcitabine plus Carboplatin as First-Line Chemotherapy in Advanced Transitional Cell Carcinoma of the Urothelium: Results of a Randomized Phase 2 Trial. European Association of Urology. 2006;52:134-141.

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Single technology appraisal

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Technical Engagement

Additional Evidence Appendices

February 2021

File name	Version	Contains confidential information	Date
ID3735_Avelumab_UC_ACD_appendices_FINAL_27May21_ACIC	1.0	Yes	27 May 2021

Contents

List of tables

1. Time to stopping treatment

Given that the majority of patients will discontinue treatment before 2 years (median TTD in JB100 was approximately 25 weeks), supported by clinical expert opinion and current use of IO therapies in mUC, we propose the implementation of a 2-year stopping rule for avelumab for maintenance treatment in mUC to help reduce the uncertainty around treatment duration. The cost-effectiveness results with a 2-year stopping rule and 5-year treatment benefit waning effect applied are presented in Table 1. This revised base case results in an ICER of £29,263 when considering the Committee's preferred assumptions for the other issues detailed in the ACD (LN OS curves, Gen gamma TTD curve, BICR PFS, JB100 Subsequent treatment proportions, IO treatment after avelumab).

Table 1: Cost-effectiveness results with 2-year stopping rule

Treatment	Total Costs	Total QALYs	Total LYG	Incremental Costs	Incremental QALYs	ICER
Avelumab	[redacted]	[redacted]	[redacted]			
WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,263

Table 2 presents the cost-effectiveness results of scenario analysis with a [redacted] assumed range used for the atezolizumab PAS to support the Committee's decision making.

Table 2: Scenario analysis with 2-year stopping rule

Gradual waning effect	[redacted] Avelumab PAS
[redacted] Atezolizumab PAS	[redacted]
[redacted] Atezolizumab PAS	[redacted]
[redacted] Atezolizumab PAS	[redacted]
[redacted] Atezolizumab PAS	[redacted]
[redacted] Atezolizumab PAS	[redacted]

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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]
Comment number	**Comments**

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	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	**1.1 Recommendations** We are disappointed by the committee's decision not to recommend avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after chemotherapy. We note that the committee include as a contributing reason their conclusion that patients in this group do not meet NICE's criteria for life-extending treatment at the end of life, because it is uncertain how long such people may live. We think that there is sufficient evidence that the criteria is met, and that NICE has previously accepted that this group meet end of life criteria.
2	**3.8 Time to Stopping Treatment** As a charity representing patients, we would prefer that immunotherapies such as avelumab were made available without a stopping rule. However, we also recognise that it is possible longer term use of avelumab might be thought too expensive under NICE affordability criteria. In these circumstances, we would prefer to see a stopping rule in place if the alternative was to deny access to avelumab for this small but very poorly served group of patients. This is also my own personal view as a urothelial cancer patient, and, in so far as we have been able to discuss this with other urothelial cancer patients, they have agreed with this position.
3	**3.14 Life Expectancy** We are surprised that the committee does not accept that this group falls within the NICE end of life criteria. The committee focused on the lack of clarity on life expectancy from the javelin trial data and the difficulty in extrapolating that data to fit UK clinical practice. However, we believe that there is sufficient real world data from UK clinical practice to show that the end of life criteria is met. This was, we thought, confirmed by the clinical experts. The committee has chosen to measure survival from the beginning of chemotherapy treatment. We do not understand the logic of this. From a patient perspective, it seems odd to point to an earlier stage of disease, and believe survival should be calculated from the point of eligibility for treatment with avelumab. In para 3.11 the committee refer to the findings from the guidance on pembrolizumab (TA692) for the same group of patients, ie those with advanced or metastatic urothelial cancer after treatment with platinum based chemotherapy. That appraisal accepted that this group of patients meets the end of life criteria: *"For people with locally advanced or metastatic disease who have had platinum-containing chemotherapy…….median overall survival was **much less than 24 months** for people having treatment with UK standard care……..The committee concluded that the short life expectancy criterion was met"* (para 3.29 of TA692).
4	**3.19 Review Date** The use of immunotherapies in cancer treatments is still relatively new, but is

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	increasing rapidly. With the steady stream of published papers outlining real world results in addition to the trial data presented to the committee, we would urge an earlier review date in 12 months time. We hope that more evidence would become available within that time showing the efficacy of avelumab in treating the desperate need, accepted by the committee, of those with advanced urothelial cancers after chemotherapy.
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Fight Bladder Cancer
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]

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1	The Appraisal Consultation Document states "Avelumab does not meet NICE's criteria to be considered a life-extending treatment at the end of life. This is because it is uncertain how long people in the NHS who would be eligible for avelumab live for" This is an unreasonable statement. There is enough data to estimate how long people in the NHS who would be eligible for avelumab live for – a median of 14 months, which is well below 24 months. The Javelin Bladder 100 trial demonstrated a median 14.3 months in people who responded to chemotherapy and then had best supportive care alone. An analysis of National Cancer Registration and Analysis Service data looking at patients with locally advanced or metastatic urothelial cancer found a median overall survival of 14.0 months from initiation of first line systemic therapy (https://doi.org/10.1016/j.jval.2020.08.477). "Most people with locally advanced / metastatic urothelial cancer who respond to platinum-based chemotherapy live for a median of 12-18 months, based on trial data from multiple sources including UK trials. Less than 20% longer than 2 years." Dr Simon Crabb, Associate Professor in Medical Oncology "Most people with locally advanced / metastatic urothelial cancer who respond to platinum-based chemotherapy live for an average of around 14 months." Prof Alison Birtle, Consultant Oncologist
2	The Appraisal Consultation Document states that "it is important for the committee to consider the mean survival" In determining whether survival is 'normally less than 24 months' for 'End of life', we submit that failing to rely on median survival was unreasonable in this context. The patient community has a legitimate expectation that median survival is a more appropriate measure in determining whether or not survival is 'normally less than 24 months', rather than mean. This is due to the small number of long-term survivors in this population that unreasonably skew the distribution. The NICE criteria make no explicit reference to use of either median or mean survival. There is precedent for using median life expectancy (e.g. TA541).
3	If NICE still does not consider the End of Life criteria to be met, and still chooses to use mean overall survival, we submit that, given that "the ERG's [Evidence Review Group's] base case predicted a mean overall survival of 27.82 months and a median of 15.6 months", any committee decision to utilise any lower threshold other than the maximum available to a treatment not meeting end of life (£30,000 per QALY gained) would be unfair and unreasonable in the context of treatments close to End of Life.
4	The Appraisal Consultation Document states that "the ERG's [Evidence Review Group's] base case predicted a mean overall survival of 27.82 months and a median of 15.6 months". This fails to account for the fact that patients in clinical trials are often healthier than the population that would be eligible for treatment in general clinical practice, and it is unreasonable of NICE to just use extrapolation from an economic model to determine overall survival.

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5	The Appraisal Consultation Document states "Avelumab is not suitable for use within the Cancer Drugs Fund because it is unlikely to be cost effective and further data collection is not an option" We submit that this statement is unreasonable. If NICE does not wish for this drug to be available via routine commissioning, we suggest that the drug could be used within the Cancer Drugs Fund. We suggest to NICE that National Cancer Registration and Analysis Service data could then be used to resolve uncertainty around the 2 year stopping rule (discussed below), as well as the effects on cost and effectiveness regarding the recommendation to not use atezolizumab as a second line treatment in real world practice (in contrast to Javelin Bladder 100).
6	The Appraisal Consultation Document states that the committee "was concerned that it would be difficult for patients to accept that they would no longer be able to have treatment after 2 years if they were free from disease and they may fear losing treatment benefit." We submit that this is an unreasonable concern. We have spoken to bladder cancer patients about this issue. Patients shared with us that, as long as they were informed of the 2 year stopping rule at the beginning of treatment, as well as the mechanism of action of the treatment, they would be comfortable with a 2 year stopping rule. We also remind NICE that there is currently no maintenance immunotherapy available as part of routine commissioning for this population of bladder cancer patients.
7	We also submit that the committee meeting on Wednesday 14 April 2021 was procedurally unfair, as there was insufficient patient input. Patient Experts have a right to be heard, and we submit that Patient Experts were not given enough opportunity to speak during the committee meeting. We submit that the Chair of the meeting failed to act fairly by discouraging Patient Experts from giving their input. The Patient Experts also did not have the opportunity to present all the information in their written Patient carer organisation submission. This meant that there was a failure to properly consider the input of Patient Experts.

Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Organisation	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"Yes there is little evidence / research for maintenance therapy for bladder cancer"

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"Most patients who progress through first line treatment would not survive for longer than 24 months."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"Given the paucity of options for metastatic bladder cancer, and the limited number of drugs having maintenance therapy for this group of patients would be an important therapeutic strategy. This is the best evidence we have to date."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"No"

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Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

ERG'S CRITIQUE OF THE COMPANY'S RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT

Produced by **Aberdeen HTA Group**

Authors: Dwayne Boyers[1]
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Date completed: **04 June 2021**

Version: **1.0**

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Strictly confidential: Contains [redacted] information

Overview

The purpose of this document is to provide the ERG's critique of the company's response to issues raised in the Appraisal Consultation Document (ACD) for the assessment of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]. Table 1 summarises the committee preferred assumptions from the ACD, the company's revisions to the base case assumptions in response to the ACD and a summary of the ERG critique and additional scenario analyses provided for the committee's information. This document further critiques remaining issues of disagreement between the preferred committee assumptions from the ACD and the company response to ACD.

Table 1 Summary of company revisions to base case cost-effectiveness assumptions following ACD

Parameter / Assumption	Committee preference (as per ACD)	Company revised base case	ERG critique
Overall survival for avelumab and watchful waiting (WW)	Considered both generalised gamma and log normal to be appropriate for decision making	Prefer LN based on clinical expert opinion.	Agree that LN is appropriate, scenario analysis using generalised gamma provided for the committee's information.
Definition of progression	Preferred blinded independent central review (BICR)	Accepts committee preference	Company based case now aligns with ACD.
Time to treatment discontinuation.	Preferred survival curves fitted to KM data, without additional discontinuation at 2 or 5 years.	Disagree with committee view and revised base case applies a stopping rule at 2 years.	ERG note that stopping rules have some precedence in guidance. Provides TTD curves (generalised gamma) fitted to trial data, without additional discontinuation for the committee's information.
Duration of continued treatment benefit (PFS / OS)	Survival curves fitted to trial data, without additional treatment benefit capping or additional treatment discontinuation.	Company prefers treatment benefit capping with HR of PFS and OS = 1 for avelumab vs. WW beyond 5 years (3 years	Substantial remaining uncertainty regarding the most appropriate treatment benefit capping assumptions in the context of a treatment stopping rule. Several additional scenario analyses conducted to explore uncertainty surrounding treatment benefit capping time-point and whether

Parameter / Assumption	Committee preference (as per ACD)	Company revised base case	ERG critique
		after treatment stopping)	an instantaneous or gradual treatment waning effect is applied.
Post – progression treatment proportions	Considers data from JB100 trial to be more appropriate than the SACT dataset	Accepts committee preference	Company based case now aligns with ACD.
Post progression use of IOs in the avelumab arm	Committee considered it more appropriate to include post-progression IOs as per the JB100 trial to ensure that costs and benefits are considered consistently	Accepts committee preference	Company based case now aligns with ACD.
Health state utility values for pre- and post-progression	Considers treatment specific health state utility values to be more appropriate than utilities pooled across treatment arms	Company disagree and prefers pooled health state utility values	ERG provides analyses with both pooled and treatment specific utilities for the committee's information.

Abbreviations: ACD = appraisal consultation document; BICR = blinded independent central review; ERG = evidence review group; JB100 = Javelin Bladder 100 trial; KM = Kaplan Meier; LN = log-normal; OS = overall survival; PFS = progression free survival; SACT = systematic anti-cancer therapy dataset; TTD = time to treatment discontinuation

Issue 1: Overall survival extrapolations

The ERG accepts that either a generalised gamma or log-normal (LN) curve could be used to model OS data as there is little difference in the statistical fits (AIC and BIC) to the Kaplan Meier (KM) data. However, the ERG's clinical expert view was that the LN was more plausible in terms of longer-term extrapolations. The ERG notes that the company also prefers the use of a LN extrapolation for OS in both the avelumab and WW arms of the model. The ERG and company preferred base case assumptions for modelling OS data are now aligned.

Issues 2 & 3: Time to treatment discontinuation (TTD) and duration of continued treatment benefit (PFS and OS) for avelumab following discontinuation.

The ERG notes that the ACD prefers the use of TTD curves fitted to the trial data, without any additional treatment discontinuation at 2 or 5 years. However, the company disagrees with the committee view and have instead amended their original base case analysis (where 95% of patients discontinue treatment at 2 years, with all patients discontinuing at 5 years) to now include a two-year stopping rule, whereby all patients stop treatment at 2 years. The ERG notes that there is substantial uncertainty regarding the most appropriate combination of assumptions regarding treatment discontinuation and duration of clinical (OS and PFS) benefit for use in the economic model. The ERG agrees that a two-year stopping rule reduces the uncertainty surrounding treatment acquisition costs of avelumab, but unfortunately this does not address the uncertainty surrounding the most appropriate assumptions regarding longer term duration of treatment benefit following treatment stopping. The ERG notes that the company has applied a treatment benefit capping at 5 years (3 years post stopping treatment) in their revised base case analysis. The ERG reiterates the concerns raised previously that the true duration of continued treatment benefit with IOs beyond treatment stopping is unknown. To illustrate the magnitude of this uncertainty, the ERG provides several scenario analyses surrounding different plausible treatment benefit capping assumptions, applied to the company's preference for a two-year stopping rule for avelumab. These analyses vary the duration of continued treatment benefit between 0 years (i.e. avelumab HR of PFS and OS set equal to watchful waiting at 2 years) and 5 years (i.e. avelumab HR of PFS and OS set equal to watchful waiting at 7 years). A final analysis applies a gradual loss of treatment benefit between years 2 (treatment stopping time point)

and 5 (3 years after treatment cessation). These analyses serve to illustrate the uncertainty surrounding the most plausible base case ICER.

The ERG also provides an analysis without any treatment stopping or discontinuation rules, with TTD curves fitted to the JB100 trial data as per the committee's preference in the ACD. These TTD curves are fitted using a generalised gamma extrapolation curve. As treatment discontinuation is modelled as per the trial data, no treatment benefit caps are applied to the PFS or OS curves for this scenario.

Issue 4 Health state utilities

In response to technical engagement, the company provided utility data by treatment arm (avelumab and WW) and health state (pre- and post-progression) based on data from the JB100 trial. Pre-progression utilities are slightly higher in the avelumab + BSC arm of the trial ([redacted]), compared to BSC arm ([redacted]), but are somewhat lower for avelumab + BSC ([redacted]) in the post-progression state compared to BSC ([redacted]). Whilst the ERG agrees that many NICE appraisals tend to use pooled health state utilities, and this is generally considered appropriate, it is still relevant to consider any uncertainty that might be introduced by combining health state utilities across treatment arms. The ERG agrees with the company that higher utilities post-progression may be a result of the use of a greater proportion of IOs post progression in the BSC arm of the JB100 trial than in the avelumab + BSC arm. When health state costs are informed by trial data and are treatment arm specific, as in this case, it is reasonable to consider what impact the use of treatment specific utilities would have on cost-effectiveness results, should sufficient data exist. That is because, utility differences may be driven by differences in health state resource use across treatments, as the company have noted in their ACD response. The ERG provides additional scenario analyses exploring the use of treatment specific utilities in the economic model as per the committee's preference from the ACD.

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Issue 5 End of life criteria

The ERG has discussed the arguments for and against the case for avelumab meeting the NICE end of life criteria in previous documentation (ERG's report and critique of response to technical engagement). The ERG reiterates that avelumab clearly meets the life extending criteria. It is however, less clear whether the underlying survival in this population is above

or below 24 months, with a decision on this likely to rest on whether the committee considers the mean or the median to be more appropriate for decision making. The company has provided several additional data sources to support the case for a median survival less than 24 months and the ERG is satisfied that median survival is likely less than 24 months. This is also consistent with the results of the economic model. The ERG accepts the company's argument that median survival is less likely to be skewed by a small proportion of patients who thankfully have longer survival. However, the ERG also note the counter-argument that, from a cost-effectiveness point of view, it is mean life year gains (Lys) that contribute to the estimates of the ICER used for decision making. The economic model projects mean life year gains of 2.32 years using the LN OS extrapolation curve for the watchful waiting arm of the model.

Cost-effectiveness results and additional ERG analyses

The company's revised preferred analysis is based on the following assumptions / data inputs:

1. Use of LN survival curve for the extrapolation of OS data from the JB100 trial
2. BICR PFS with extrapolations based on a 3-knot-normal survival curve.
3. Imposing a stopping rule for avelumab treatment at 2 years.
4. Imposing a cap on the duration of PFS and OS benefit so that the HR of PFS and OS for avelumab vs. WW equals 1 after 5 years, thus assuming a three-year duration of additional continued treatment benefit following the treatment stopping.
5. Subsequent post-progression treatment proportions obtained from the JB100 trial.
6. Inclusion of atezolizumab as a treatment post progression in the avelumab arm.
7. Health state utility values for the pre- and post-progression states pooled across the avelumab + BSC and BSC arms of the JB100 trial.

Analyses 1-7 combined lead to a revised company base case ICER of [redacted]. The ERG has replicated the company's analysis using an earlier version of the model and is satisfied that all amendments have been implemented correctly and as described in the company documentation.

The ERG notes that the remaining areas of disagreement between the ACD and company revised base case relate to assumptions 3,4 and 7. The ERG therefore provides additional

scenario analyses to explore these issues further for the committee's information. The results of these analyses are provided in Table 2. The ERG considers the most important areas of residual uncertainty to be centred around the combination of TTD assumptions and modelled continued duration of treatment benefit. Different plausible combinations of assumptions lead to substantial variation in the ICER. The ERG notes that the use of treatment specific, as opposed to pooled health state utilities leads to only a small increase in the ICER for avelumab. A corresponding table of results applying a confidential PAS price for atezolizumab, used post progression in the model, is provided as a confidential appendix to this critique document.

Table 2. Cost-effectiveness analysis results post ACD

Analysis	Avelumab total			WW total			Incremental			
	Costs	LYs	QALY	Costs	LYs	QALY	Costs	LYs	QALY	ICER
Company revised base case analysis post ACD ([redacted]% PAS avelumab; 0% cPAS atezolizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,263
Scenario analyses conducted by the ERG to align with ACD preferred assumptions										
1. TTD, PFS and OS curves all extrapolated as per JB100 trial without adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,080
2. Apply treatment specific pre- and post-progression utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,152
3. Combined scenarios 1 and 2 (ICER aligned to ACD preferences)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,933
Additional ERG scenarios applied to company revised base case										
4. Generalised Gamma for OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,147
5. 2 year stopping rule + 2-year treatment benefit cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,925
6. 2 year stopping rule + 3-year treatment benefit cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,328
7. 2 year stopping rule + 4-year treatment benefit cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,726
8. 2 year stopping rule + 7-year treatment benefit cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,739
9. 2 year stopping rule + 10- year treatment benefit cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,833
10. 2 year stopping rule + Gradual treatment waning effect between years 2 and 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,390
11.Combinaed scenarios 2 and 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,776

Analysis	Avelumab total			WW total			Incremental			
	Costs	LYs	QALY	Costs	LYs	QALY	Costs	LYs	QALY	ICER
12. Combined scenarios 2,4 and 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,947

Abbreviations: ACD = appraisal consultation document; ICER = incremental cost-effectiveness ratio; LY = life-year; PAS = patient access scheme; QALY = quality-adjusted life year; WW = watchful waiting.