

- Bihani Kularatne Oncology Medical Affairs Manager,
Pfizer, UK
 - Simon Crabb Associate Professor of Medical
Oncology, University of Southampton
 - Adela Williams Legal representative, Partner, Arnold
and Porter
6. Association of Cancer Physicians were represented by:
- Mark Linch Associate Professor and Consultant
Medical Oncologist, University
College London Hospital
7. British Uro-Oncology Group were represented by:
- Alison Birtle Secretary of British Uro-Oncology Group,
Honorary Clinical Professor and Consultant
Oncologist Rosemere Cancer Centre
8. Fight Bladder Cancer were represented by:
- Lydia Makaroff Chief Executive, Fight Bladder Cancer
 - Anne MacDowell Corporate Partnerships (volunteer), Fight
Bladder Cancer
 - Melanie Costin Support Services Manager and bladder
cancer patient, Fight Bladder Cancer
 - Sana Gilfillan Policy and Communications Manager, Fight
Bladder Cancer
9. Action Bladder Cancer UK were represented by:
- Kevin Gorman Trustee, Action Bladder Cancer UK
10. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

- Lindsay Smith Technology Appraisal Committee D Chair, NICE
- Helen Knight Programme Director, Technology Appraisals and Highly Specialised Technologies, NICE
- Ross Dent Associate Director, Technology Appraisals, NICE
- Giles Monnickendam Technology Appraisal Committee D Member, NICE

11. The panel’s legal adviser Stephen Hocking, DAC Beachcroft LLP, was also present.

12. The following member of the NICE appeal panel for technology appraisal and highly specialised technologies were present as a silent observer throughout the hearing and panel discussions:

- Alina Lourie Non-executive director, NICE

13. Under NICE’s appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

14. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

15. Mark Chakravarty, NICE Lead Non-executive Director for Appeals, in preliminary correspondence had confirmed that Merck Serono Ltd,

Action Bladder Cancer UK, Fight Bladder Cancer, Association of Cancer Physicians, and the British Uro-Oncology Group all potentially had valid grounds for appeal under Ground 2.

16. The appraisal that is the subject of the current appeal providing advice to the NHS was on the use of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy.
17. Avelumab is a checkpoint inhibitor anti-cancer immunotherapy agent that activates immune cells by blocking the PD-L1 receptor on their surface. It is used in patients who have had a good response to first-line chemotherapy for locally advanced or metastatic bladder cancer to prevent disease progression.
18. Action Bladder Cancer UK, Fight Bladder Cancer, the Association of Cancer Physicians, and the British Uro-Oncology Group, were invited by the panel chair to describe the impact of metastatic bladder cancer on patients; although he emphasised that these comments were 'scene setting' for the panel to appreciate the impact of the disease on patients, their families and carers and would not be considered as stand-alone grounds for the appeal. The panel would like to thank the patient representatives and clinicians for their insights into living with metastatic and locally advanced bladder cancer. The panel was left in no doubt about the poor prognosis associated with locally advanced and metastatic bladder cancer, its significant effect on quality-of-life, the impact that it has on the psychological and social well-being of patients and their families and the limitations of existing therapies.
19. Before the appeal panel inquired into the detailed appeal points the following made preliminary statements: Amerah Amin on behalf of Merck Serono Ltd, and Lindsay Smith on behalf of NICE. Action Bladder Cancer UK, Fight Bladder Cancer, the Association of Cancer Physicians, and the British Uro-Oncology Group were invited by the chair to make preliminary statements but did not have additional points

to raise not covered in the statement of Amerah Amin on behalf of Merck Serono Ltd and the patient impact statements previously delivered.

20. The appeal panel chair proposed that given the similarity of the two appeal points raised by each of the five appellants under ground 2, that the appeals under each point should be heard together. No objections were raised by any participant.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Merck Serono Ltd appeal point 1a.1: The Committee's conclusion that a stopping rule is inappropriate for avelumab is inconsistent with previous appraisals for immunotherapies (IOs) in metastatic urothelial cancer (mUC)

Action Bladder Cancer UK appeal point 1a.1: Rejection of a stopping rule was unfair in light of past practice and the evidence of patients and clinicians

Association of Cancer Physicians appeal point 1a.1: A stopping rule was rejected but one has been proposed in past appraisals without difficulty

British Uro-Oncology Group appeal point 1a.2: The failure to allow for a stopping rule was not consistent with TAs 525 and 492 (atezolizumab) or TA 692 (pembrolizumab)

21. (Whilst initially raised on Ground 1a, Mark Chakravarty, NICE Lead Non-executive Director for Appeals, during initial scrutiny, considered these appeal points more appropriately related to whether the NICE appraisal committee had acted reasonably. Consequently, these appeal points were considered by the panel under Ground 2)
22. Bihani Kularatne, on behalf of Merck Serono Ltd, stated that the decision of the appraisal committee not to apply a stopping rule was inconsistent with the decisions of appraisal committees previously. She stated that whilst the JAVELIN Bladder 100 trial did not include stopping rules this was also the case for the other trials on which previous technology appraisals that included stopping rules were based. She stated that these prior technology appraisals relate to the

same patient population, the only difference being that maintenance immunotherapy with avelumab is brought forward in the treatment pathway. As the same population of patients have accepted a stopping rule for immunotherapy in other appraisals, it should be assumed that they will accept a stopping rule for immunotherapy no matter what its place is in the care pathway. She stated that the committee did not explain why evidence relating to atezolizumab, also a second line immunotherapy agent, was not relevant to this technology appraisal.

23. Bihani Kularatne stated that the committee also did not consider the evidence from patient groups and clinical experts, who all felt that application of a stopping rule in clinical practice would be accepted.
24. Bihani Kularatne concluded by stating that the guidance was inconsistent with previous appraisals with no proper explanation offered and therefore unreasonable.
25. Simon Crabb, on behalf of Merck Serono Ltd, stated that in the patient population under consideration the only option was immunotherapy, and the question was whether to give it now (i.e., maintenance) or to give it later (i.e., “rescue” after progression). There is no evidence from atezolizumab, where a decision was made to implement a stopping rule in order to allow access to this immunotherapy, that there were practical problems in implementing a stopping rule in this patient population. He stated that experience from applying the stopping rule for the past three years is that patients understand the rationale for the stopping rule and find it acceptable provided it is explained in advance.
26. Simon Crabb stated that patients do not find it acceptable to have access to effective therapies denied. He stated that he did not recognise the assertion by the appraisal committee - made in the preliminary statements of this appeal - that the understanding of patients’ attitudes to stopping rules may have changed in the intervening period since the application of stopping rules in previous appraisals. He stated that he felt patients would find a stopping rule for

immunotherapy just as acceptable in the context of a maintenance therapy, as for a second line therapy given when there was disease progression. In response to questioning from the panel chair he stated that he accepted that patients would find it difficult to accept a stopping rule if they were told after two years of therapy that it had to stop. However, if it was explained to patients before the medication was started that it would be stopped at two years, and the rationale, in his experience, patients found this acceptable. He also stated in response to questioning from the panel chair that he did not think that application of a stopping rule in the context of a maintenance therapy would be any different from a second line therapy given for disease progression. He stated that in this situation patients would understand that a stopping rule would apply if they received immunotherapy for disease progression and therefore would accept that it should apply in the context of maintenance therapy.

27. Anthony Eccleston, on behalf of Merck Serono Ltd, stated that application of a stopping rule would reduce and give certainty to the modelled cost of avelumab, and that different scenarios for treatment effect waning could be modelled, as had been undertaken in previous technology appraisals.
28. Lydia Makaroff, on behalf of Fight Bladder Cancer, described how in her organisation's weekly team meetings she heard stories of patients who had died in the last week. She stated that the NICE decision not to apply a stopping rule was inconsistent with the approach taken for atezolizumab.
29. Lydia Makaroff stated that the assertion by NICE that a stopping rule could not be applied in practise for avelumab was inconsistent with evidence from both clinicians and patients heard by the appraisal committee. She stated that she believed that patients would accept a stopping rule if they were told about it in advance.

30. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that the assumption that all patients would currently have second line therapy if they experienced disease progression was false. She stated that when disease progression was recognised, only 30% would be fit enough to be started on second line therapy. She also stated that less than 5% of patients taking avelumab would be on therapy at two years, and therefore the assumption that all patients would be receiving avelumab at two years was false.
31. Alison Birtle stated that if patients were told prior to starting therapy about a stopping rule, and the reason for the rule, then application of a rule would be acceptable. Finally, she stated that application of a stopping rule would be entirely consistent with immunotherapy technology appraisals in this disease area. She stated that the examples cited by the appraisal committee to explain their concerns about the practical application of stopping rules (Merkel cell carcinoma and renal cell carcinoma) related to different diseases and patient populations and therefore were not relevant in this case.
32. Mark Linch, on behalf of the Association of Cancer Physicians, explained that he had discussed stopping rules extensively with fellow cancer clinicians and their attitude to stopping rules depended on how the discussion was framed. He stated that whilst many clinicians would prefer not to have stopping rules, they would readily apply stopping rules if this was the only way to have access to an effective therapy. He stated that it was not a difficult conversation to have with patients at the start of their treatment with avelumab. Thus, if they were to survive for two-years on therapy then this would be a very good outcome, compared to their normal life expectancy with current standard of care, for metastatic or locally advanced bladder cancer. He stated that it would not be a difficult discussion to have with patients at two years to stop avelumab, as they would have enjoyed two years of quality of life that they would not have had without avelumab. In response to questioning from the chair he stated that a conversation about stopping

therapy following two years of therapy was not without challenge. However, many aspects of clinical medicine were challenging, and this is the type of conversation that he and his colleagues have with patients frequently.

33. Mark Linch stated that immunotherapies were intended to train the patient's immune system to fight cancer and therefore the effect of the immunotherapy was often maintained following cessation of therapy. This was supported by Alison Birtle, speaking on behalf of the British Uro-oncology group, who stated that the treatment effect was durable and that some patients maintained a good response despite stopping immunotherapy. Giles Monnickendam, on behalf of NICE, later challenged this stating that there was no evidence from any clinical trial of a prolonged effect of immunotherapy following cessation of therapy and the only trial to investigate this effect had been negative.
34. Mark Linch stated that CheckMate153 was not relevant to the appraisal of avelumab as the response of metastatic non-small cell lung cancer to therapy was entirely different to metastatic or locally advanced bladder cancer.
35. Kevin Gorman, on behalf of Action Bladder Cancer UK, stated that whilst stopping rules were logical, they could be difficult to explain to patients with bladder cancer. Patients with bladder cancer had a strong preference for receiving some therapy, even for a limited period, rather than not having access to therapy at all. He would find the current FAD hard to explain to patients.
36. Melanie Costin, on behalf of Fight Bladder Cancer, stated that patients would accept a stopping rule. She stated that it was less unfair for patients to have a stopping rule imposed on them than to have no access to avelumab at all.
37. Simon Crabb, on behalf of Merck Serono Ltd, stated that patients would have a choice whether to start maintenance therapy with a

stopping rule or to not start therapy in the hope of receiving second line immunotherapy. He stated that patients were capable of understanding and making this choice.

38. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that the discussion about whether to have immunotherapy now or later with a stopping rule was not a difficult discussion to have with patients. All treatment had a duration. In response to a question by the appeal panel chair about whether patients who were having maintenance immunotherapy would have access to other therapies, should they have disease progression; she said that they were options in the context of clinical trials. She added however only a fraction of patients were still taking maintenance therapy at two years either because of disease progression or toxicity.
39. Lindsay Smith, on behalf of NICE, stated that the proportion of patients in the JAVELIN bladder 100 trial that were still taking avelumab was [REDACTED] at two years rather than 5%. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that the proportion of patients taking therapy at 2 years was [REDACTED]. Helen Knight, on behalf of NICE stated that when censored data was accounted for using a Kaplan-Meier estimation it was [REDACTED] which was the correct way to estimate the number of patients still taking avelumab. Amerah Amin, on behalf of Merck Serono Ltd stated that when estimated using the Kaplan-Meier method it was [REDACTED], however most clinicians felt that in practice this would be approximately 5%. Amerah Amin, stated in response to questioning from the panel chair that this was because patients in the JAVELIN bladder 100 trial were fitter than other patients with metastatic and locally advanced bladder cancer. Bihani Kularatne, on behalf of Merck Serono Ltd, subsequently stated that this was often the case with clinical trials.
40. Lindsay Smith, on behalf of NICE, stated that in the FAD no reference was made to any difficulty that clinicians may have in applying a

stopping rule. He stated that the appraisal committee have every confidence that clinicians had the appropriate communication skills and training and would be able to apply a stopping rule. He added however that the concern of the appraisal committee was whether patients would accept a stopping rule at two years. He stated that patient experts had said they would not be happy to accept a stopping rule at two years. Mark Linch, on behalf of the Association of Cancer Physicians, subsequently challenged Lindsay Smith's statement about the FAD, drawing the attention of the panel to section 3.8.

41. Helen Knight, on behalf of NICE, stated that different approaches were required for different immunotherapies. She stated that the general approach to stopping rules had changed as the government had received petitions from patient groups that were not happy to accept a stopping rule at two years. She added that the appraisal committees had been asked to be mindful about the application of stopping rules.
42. Lindsay Smith, on behalf of NICE, in response to questions from the panel chair, stated that that there was a combination of reasons behind the decision not to implement a stopping rule for avelumab. He said a significant number of patients would be affected by a stopping rule, and that ■■■ of patients would have to be salvaged with second line therapy. Thus, if a stopping rule was used it would be difficult to apply in clinical practice. He stated that avelumab was different from atezolizumab as patients tolerated the former treatment better. He stated that there was no evidence from similar populations that a stopping rule could be applied to avelumab. In response to questioning from the panel chair he said that it was an important factor that the JAVELIN bladder 100 trial did not have a stopping rule. He added therefore there was no clinical trial evidence to justify a stopping rule. He stated that there was no clinical justification for a stopping rule, the only rationale was to reduce the uncertainty around the cost of avelumab. He said that whilst in 2017 a stopping rule was justified on cost grounds for atezolizumab, patients felt increasingly unhappy about

being asked to stop therapy for economic reasons and that the appraisal committee did not have this experience when TA525 was formulated.

43. Simon Crabb on behalf of Merck Serono Ltd, challenged the assertion in Lindsay Smith's evidence that the patient population in the technology appraisal of avelumab was different to the population in atezolizumab (TA525). He therefore questioned the justification for not applying a stopping rule in the case of avelumab.
44. Helen Knight, on behalf of NICE, stated that TA492 (Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable) did not have a stopping rule. Bihani Kularatne, on behalf of Merck Serono Ltd, later challenged this.
45. Adela Williams, on behalf of Merck Serono Ltd, stated that the fact that the SmPC (Summary of product characteristics) does not include a stopping rule (which was mentioned in the FAD) is an irrelevant consideration. The European Medicines Agency which agreed the SmPC is primarily concerned with safety, emphasising factors such as toxicity and side-effects whereas NICE is concerned with economic evaluation. NICE therefore would have a different rationale for applying a stopping rule. She stated that this was a relevant matter as whilst the content of the SmPC may not have been a major factor, it was a factor in the appraisal committee's decision making. Ross Dent, on behalf of NICE, stated that the absence of a stopping rule in the SmPC was not the reason why the appraisal committee chose not to include a stopping rule.
46. The appeal panel concluded as follows:
47. The panel acknowledge that there is no obligation for an appraisal committee to adopt the same approach that previous committees have used to appraise a technology. However, patients, clinicians and industry can reasonably expect that a broadly consistent approach

should be adopted in technology appraisal. This is so that all key stakeholders are aware of the criteria required for NICE to recommend adoption of a technology, or, where an inconsistent approach is adopted, that adequate and rational reasons will be given.

48. Stopping rules are widely applied in the NICE technology appraisals for systemic cancer therapy, including for comparable therapies for apparently similar populations (Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525], and Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA692]).
49. Whilst there is no obligation for the appraisal committee to apply a stopping rule in the case of avelumab because they have been widely applied previously, it is reasonable to expect that the appraisal committee should fully explain their rationale for not doing so.
50. In the view of the panel this could include an explanation of why application of a stopping rule for avelumab would be flawed based on new information addressing the difficulties in the health service with the practical application of stopping rules in clinical practice, or their theoretical basis, that was not considered during the development of TA525 and TA692.
51. Alternatively, the panel consider that it could be reasonable for the appraisal committee to explain why avelumab represents a sufficiently different technology from atezolizumab or pembrolizumab; that the proposed application in this technology appraisal is different from TA525 and TA692; or that the population is distinct in this appraisal from that envisaged in TA525 and TA692, in order to explain why a stopping rule is not applicable in this technology appraisal.
52. The panel can express no view as to whether any such explanations, if given, would be reasonable.

53. The appeal panel heard evidence that the committee were increasingly aware about the broader difficulty in applying stopping rules in particular the acceptance of stopping rules by patients at two-years following the start of treatment. However, no evidence was presented in the FAD or the documents associated with the appraisal committee meetings to support the reasonableness of a change in approach to the application of stopping rules in NICE technology appraisals. If the reason was patients petitioning the Department of Health and Social Care against stopping rules, then the panel considered that to be irrelevant. NICE is independent of the Department of Health and Social Care. Thus, while NICE can consider if a stopping rule might create practical difficulties in implementation for the NHS, it should not consider other difficulties created for other bodies. Patients may well lobby many bodies for access to many treatments, but that lobbying should not be a factor in a technology appraisal.
54. Finally, the appeal panel accepted that modelling a stopping rule in the case of avelumab is problematic, in particular modelling what if any effect avelumab continues to have after cessation of treatment. However, the panel noted from the slides of the appraisal committee meeting, that it was possible to model a number of different scenarios. Whilst it might be reasonable to adopt a conservative modelling approach in view of the uncertainty, the appeal panel do not feel that it is reasonable to reject a stopping rule only on the basis of the difficulties associated with modelling the effect of avelumab following the cessation of treatment. The appeal panel believe it would have been preferable to have considered the various scenarios and used them to inform a decision.
55. Consequently, the appraisal committee finds that insufficient justification was given in the FAD for adoption of an approach in the appraisal of avelumab that was not broadly consistent with previous comparable technology appraisals, and accordingly this inconsistency is unreasonable.

56. The appeal panel therefore upheld the appeal on these points.

Merck Serono Ltd appeal point 2.1: In considering the application of the end of life criteria, the Committee has misapplied the relevant test and reached a conclusion which does not reflect the balance of the evidence.

Action Bladder Cancer UK appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

Fight Bladder Cancer appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

Association of Cancer Physicians appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

British Uro-Oncology Group appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

57. Anthony Eccleston, for Merck Serono Ltd, stated that there were two key tests for eligibility for the NICE end of life criteria. Firstly, that the life expectancy must be extended by more than three months, and secondly that life expectancy should be normally less than 24 months. He stated that clearly avelumab meets the first criterion because it extends life-expectancy by seven months. He stated that the appellants disagree that the 24-month criterion was not met. He stated that it is not explained how to assess the patient's life expectancy in NICE guidelines. He stated that the committee received 20 estimates of life-expectancy from clinical trials, epidemiological studies, clinical expert testimony. However NICE chose to adopt an estimate from the modelled mean, ignoring the majority of the other evidence. He stated that the mean data does not reflect the real-world patient data. In response to questioning from the panel chair, Anthony Eccleston stated that life expectancy should be measured from the point at which avelumab would be started.

58. Simon Crabb, for Merck Serono Ltd, stated that the decision by NICE that life-expectancy was greater than 24 months for patients with

metastatic bladder cancer had been met with incredulity by the oncology community. He stated that both median and mean survival are only estimates and that the appraisal committee should evaluate the totality of the data to assess if end of life criteria had been met. He stated that the LaMB trial represented the best long-term estimates of survival in an NHS population, and this suggests that survival would normally be 12 to 18 months. He stated that bladder cancer patients in his clinic often ask him “how long they have got left?”. He stated that his response was that 12 to 18 months is a reasonable estimate of life-expectancy and anyone who told patients that they would normally expect to survive two years would be misleading them.

59. Alison Birtle, for the British Uro-Oncology Group, stated that she was comfortable with the use of 12 to 18 months as an estimate for the normal life expectancy of a patient with metastatic bladder cancer based on data from the LaMB study. She also stated that this was congruent with European and US data.
60. Mark Linch, for the Association of Cancer Physicians, stated that he uses the median to explain likely life expectancy to patients as this is representative of what most patients will experience, but draws the survival distribution and explains the long tail and the hope that the individual patient will be “in the tail”.
61. Adela Williams, for Merck Serono Ltd, stated that the word “normally” in this context could have two meanings. Firstly, that 24 months is not a rigid threshold for application of end of life criteria by NICE. Secondly, that “normally” could refer to the life expectancy that a patient would usually anticipate.
62. Lydia Makaroff, for Fight Bladder Cancer, stated that the mean of 27.8 months fails to account for what the majority of patients will experience, and it is unreasonable to extrapolate from an economic model to estimate life expectancy. Melanie Costin, also on behalf of Fight

Bladder Cancer, confirmed that patients have a reasonable expectation that the median would be used.

63. Lindsay Smith, for NICE, stated that there has been considerable debate over the period that he has been a member of the appraisal committee about whether it would be more appropriate to use the median or the mean and that both have been used in the last two years. It is easier if both the median and the mean are less than two years but more problematic if the mean is greater than two years and the median is less.
64. Lindsay Smith stated that in the other technology appraisals referenced by the appellants in initial scrutiny (TA692 and TA658) both the median and the mean were less than two years. He stated that the appraisal committee has to take into account both the clinical and cost effectiveness. He stated that the appraisal committee fully accepted the clinical effectiveness of avelumab, and the increase in life expectancy was greater than 3 months. He noted that the Office of National Statistics presents means in their survival data. Of more relevance to the committee discussion was the requirement to use the mean, over the median in their preferred approach to the cost-effectiveness analysis.
65. Giles Monnickendam, for NICE, was asked by the panel chair about whether the committee must necessarily use the same analytical framework to assess whether an intervention fulfils the NICE end of life criteria as to perform the economic analysis. Giles Monnickendam stated that life expectancy is currently measured using the mean, as this captures all data. By contrast, in clinical trials the median is often used as there is incomplete follow-up, but this does not take into account the heterogeneity of data. He stated that NICE need to use the same approach, as the mean unlike the median captures the totality of the data for the whole population. He stated that this is why the Office of National Statistics use the mean. He stated that, clinical trials do not

report the mean and only report the median as they generally do not follow-up patients until death, and that is why they are often used in the decision about whether a technology fulfils end of life criteria.

66. Giles Monnickendam challenged the assertion by the appellants that the 20 sources of evidence suggesting a survival (mean or median) under 24 months had been rejected by the appraisal committee in favour of using their modelled mean. He stated that 16 of the studies referred to were not in the population of interest. He added that the LaMB study was old and predated the introduction of immunotherapy for metastatic and locally advanced bladder cancer. He further stated that the expert opinions of median survival were entirely consistent with the modelled mean used to assess whether the technology met the end of life criteria.
67. In response to questioning from the panel chair with regards to the report of the ERG in which they stated "...A judgement call is therefore required as to whether avelumab satisfies the first criteria for end of life consideration, but on balance the ERG consider it plausible that criteria 1 is met." Lindsay Smith, on behalf of NICE, stated that it depends on what model to accept, and they were both plausible. He stated that he was not sure whether the ERG in making this statement about the plausibility of end of life criteria being met were referring to the fact that the modelled mean was close to the 24-month threshold, or that the median was less than 24 months.
68. Lindsey Smith stated that it was important to be consistent. You cannot use the median and have the "benefit" of 12 to 18 month life-expectancy to fulfil end of life criteria, and then have the benefit of the mean 2 to 3 year survival from the cost-effectiveness analysis.
69. Giles Monnickendam, for NICE, in response to questioning from the panel chair stated that end of life criteria would have a significant effect on whether the technology was considered cost-effective because the cost-effectiveness threshold would move from approximately

£30,000/QALY to £50,000/QALY. He added however he did not feel this was appropriate as the mean was the most appropriate measure of life expectancy.

70. Giles Monnickendam stated that significant work had been done to assess whether the mean was truly a fair representation of life expectancy and if survival was skewed by a small number of patients in a particularly long tail of the survival curve, then it would not have been used. However as 65% of patients died before two years, he did not feel that the distribution was being disproportionately skewed by a long tail of the survival curve.
71. Giles Monnickendam, stated in response to questioning from the panel chair, that the appraisal committee looked at the estimates from real-world data and clinical expert opinion for the target population and there was no evidence of a lack of generalisability of data from the JAVELIN bladder 100 trial.
72. In response to questioning from the panel chair about “what was in the minds of our masters” about how the word “normally” should be interpreted when the end of life criteria were introduced, Giles Monnickendam stated that as a health economist he understood this to refer to usual mean survival.
73. Helen Knight, on behalf of NICE, stated that she understood the term “normally” was to allow appraisal committees discretion and flexibility around the 24-month timeframe. She stated that it was not unreasonable to use the mean. In response to questioning from the panel chair she stated that flexibility could allow an appraisal committee to use the median.
74. Anthony Eccleston, for Merck Serono Ltd, stated that the life expectancy of a population should be assessed to see if a modifier needs to be applied prior to economic analysis. He stated that the median tells us that the majority survive less than 12 months. He stated

that the ERG felt an estimate of 35 months for the modelled mean was likely to be an overestimate and therefore used 27 months.

75. Simon Crabb, for Merck Serono Ltd, stated that the LaMB study had a median survival of 12 months before immunotherapy was introduced as second line therapy for disease progression. He stated that the atezolizumab trial was a negative study in terms of increasing life expectancy and pembrolizumab only increased life expectancy by three months. He stated that whilst he accepted the LaMB study was an old trial, immunotherapy at most increased life expectancy for participants in that trial by three months. He stated that choice of the estimate of survival should be different for the cost effectiveness analysis and the assessment of whether an intervention fulfils NICE end of life criteria, and this does not undermine the consistency.
76. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that only 30% of patients in LaMB went on to have immunotherapy and only one quarter responded to therapy. She continued that the outcomes following introduction of immunotherapy would not have significantly changed from the LaMB trial. She stated the community could not understand how NICE could have failed to apply the end of life criteria in this appraisal.
77. Anne MacDowell on behalf of Fight Bladder Cancer, stated as a lay person “normally” should mean what the majority of people experience and consequently the median should be the estimate of survival used. She stated that averaging out survival between all patients does not seem right to a lay person.
78. Ross Dent, on behalf of NICE, stated that this is not a new issue. He stated that this has been a subject of previous appeals against NICE appraisals. He stated that in previous appeals, on these grounds the appeal panel had found that the decision to use the modelled mean was not unreasonable.

79. Adela Williams on behalf of Merck Serono Ltd, stated that every appraisal is different and because an appeal panel has previously found that it was reasonable to use the modelled mean did not necessarily mean that it was reasonable to use the modelled mean in the case of avelumab.
80. The appeal panel concluded as follows:
81. The appeal panel recognise that there was consensus between the appellants and the appraisal committee that improvement in survival was in the order of seven months, significantly in excess of the three months mandated for application of end of life criteria in technology appraisals.
82. The appeal panel similarly recognise that there was consensus between the appellants and the appraisal committee that median survival was significantly less than 24 months. The appeal panel note however that the modelled mean survival was [REDACTED] [REDACTED] which is entirely consistent with the median survival being [REDACTED].
83. The NICE end of life criteria is applied when, “The treatment is indicated for patients with a short life expectancy, normally less than 24 months”. The appeal panel note that there is no guidance in the NICE Guide to the Methods of Technology Appraisal or from the NICE Decision Support Unit on how the word “normally” should be interpreted and the appeal panel note that historically both the mean and median have been used.
84. The appeal panel note that the NICE end of life criteria are founded on the principles in the NICE guide to the use of Social Value Judgements and the outcomes of the Citizens Council meeting in November 2008.
85. Consequently, the panel feel that the paramount consideration should be what the key stakeholders of NICE: the general public, patients,

clinicians, policy makers and industry would consider a reasonable interpretation of the word “normally”.

86. The appeal panel, therefore, do not accept the argument advanced by the appraisal committee that the mean survival of 24 months must be used as the threshold for application of end of life criteria to maintain consistency with the methodology used to calculate the incremental cost-effectiveness ratio. The appeal panel note that there are a number of other circumstances when policy consideration and social value judgements are incorporated into the technology appraisal framework.
87. The appeal panel felt that the key stakeholders of NICE would consider it unreasonable to state that life-expectancy was not “normally less than 24 months”, even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months.
88. The appeal panel agreed that a totality of the data and analysis have to be looked at when considering if life expectancy is “normally less than 24 months”. It does not wish to suggest there is a general rule that median is preferable to mean or vice versa. The question is it reasonable to conclude that life expectancy is below 24 months, and the mean, the median, and clinical opinion all inform that judgement. Taken in the round the panel did not feel it would be possible to explain to patients or clinicians why it was said these patients would have a life expectancy in excess of 24 months, and therefore this conclusion was unreasonable.
89. The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test that have to be considered on their own terms. If they apply, an appraisal committee still has a discretion as to what level of cost effectiveness it considered acceptable.

90. The panel also agreed that “normally” allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months. Even if it had been correct to use the mean as the main driver of a decision in this case, given that the median and clinical expert opinion was all significantly below 24 months, and the mean was not substantially above 24 months, this was a case where that discretion would have needed to have been discussed.
91. Consequently, the appeal panel concluded that in this case it would be unreasonable to conclude that this end of life criterion was not met.
92. The appeal panel therefore upheld the appeal on these points.

Conclusion and effect of the appeal panel decision

93. The appeal panel therefore upholds the appeal of Merck Serono Ltd on points 1a.1 and 2.1, the appeal of Action Bladder Cancer UK on points 1a.1 and 2.1, the appeal of Fight Bladder Cancer on point 2.1, the appeal of the Association of Cancer Physicians on points 1a.1 and 2.1, and the appeal of the British Uro-Oncology Group on points 1a.2 and 2.1.
94. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address the following issues:
 - a. The appraisal committee should either consider the application of a stopping rule for avelumab or should explicitly detail the rationale for why in contrast to TA525 and TA692 a stopping rule is either methodologically problematic or practically difficult (Merck Serono Ltd point 1a.1, Action Bladder Cancer UK point 1a.1, the Association of Cancer Physicians point 1a.1, and the British Uro-Oncology Group points 1a.2).
 - b. The appraisal committee should appraise the technology on the basis that the NICE end of life criteria applies (Merck Serono Ltd

point 2.1, Action Bladder Cancer UK point 2.1, Fight Bladder Cancer point 2.1, the Association of Cancer Physicians point 2.1, and the British Uro-Oncology Group 2.1).

Whether in light of these recommendations the recommendation will be amended will be a matter for the appraisal committee to consider.

95. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.