NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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The following documents are made available to consultees and commentators:

Appeal papers are available on the NICE website:
https://www.nice.org.uk/guidance/indevelopment/gid-ta10466/documents

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy

Decision of the panel

Introduction

1. An appeal panel was convened on 23 June 2020 to consider an appeal against NICE's final appraisal document (FAD), to the NHS, on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. The appeal was conducted via Zoom.

2. The Appeal Panel consisted of:

• Prof Alan Silman	Chair
• Mr Tom Wright	NICE Non-executive director
• Dr Biba Stanton	NHS representative
• Dr Mark Chakravarty	Industry representative
• Mr John Morris	Lay representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered an appeal submitted by Merck Sharp & Dohme (MSD), the company.

5. MSD was represented by:

• Benjamin Bates	Health economics manager, MSD
• Grant Castle	Partner, Covington & Burling LLP
• Dr Simon Crabb	Associate Professor of Medical Oncology, University of Southampton
• Kalpana D'Oca	Team Leader, HTA & OR, MSD
• Keiron Hughes	Head of Strategic Pricing, MSD

6. In addition the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

• Dr Lindsay Smith	Committee Chair TAC D (for this appraisal)
• Nicola Hay	Technical advisor
• Helen Knight	Programme director
• Linda Landells	Associate director

- Prof Gary McVeigh — Committee member
- Daniel Gallacher — ERG representative

7. The appeal panel's legal adviser Stephen Hocking of DACBeachcroft LLP was also present.

8. Two members of the NICE appeals panel (Mr Alan Thomas and Mr Tony Heddon) were present as observers but did not participate in any of the discussions of the appeal panel, or in the decision-making.

9. Under NICE's appeal procedures members of the public are admitted to appeal hearings and several members of the public and NICE staff observed the appeal via Zoom.

10. 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

b) Exceeded its powers.

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

11. The then Vice Chair of NICE (Dr Rima Makarem) in preliminary correspondence had confirmed that MSD had potentially valid grounds of appeal as follows:

- **Ground 1a – NICE has failed to act fairly**
  - Ground 1a.1 – Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural fairness
  - Ground 1a.2 – It is procedurally unfair to have introduced paragraph 3.19 ("The costs of pembrolizumab are likely underestimated in the model") in the FAD at a very late stage, without explanation or any opportunity to respond
- **Ground 1b – NICE has exceeded its powers**
  - Ground 1b.1 – NICE has breached its legal obligations under human rights and equalities laws
- **Ground 2 – the recommendation is unreasonable in the light of the evidence submitted to NICE**
  - Ground 2.1 – The Appraisal Committee's assessment of duration of treatment effect and its effect on cost-effectiveness is illogical and unreasonable*
  - Ground 2.2 – The Appraisal Committee's analysis of evidence from the clinical expert in paragraph 3.15 of the FAD is internally inconsistent

and its conclusions are unreasonable*

- *Agreed as valid points with 2.2 to be taken as an aspect of 2.1

- Ground 2.3 – The Appraisal Committee's decisions that: (i) a range of possible ICERs from £48,518 to £70,520 applies; and (ii) the "most plausible" ICER for pembrolizumab is likely to be above £50,000, are unreasonable in light of the evidence submitted
- Ground 2.4 – The statement that "the costs of pembrolizumab are likely underestimated in the model" lacks meaningful explanation and evidence and it is unreasonable to have taken it into account for the purposes of assessing cost-effectiveness
- Ground 2.5 – The conclusion that new data from KEYNOTE-045 "shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account" results from a flawed and unreasonable interpretation of the evidence

12. The appraisal that is the subject of the current appeal provided advice to the NHS on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy.

13. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Grant Castle on behalf of MSD, and Dr Lindsay Smith on behalf of the appraisal committee.

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly.

Appeal Ground 1a.1: Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural fairness

14. Grant Castle, for MSD, said that the committee had deviated from an established, reasonable approach in the case of this appraisal. In particular, there were clear similarities between this appraisal and the appraisal of atezolizumab (TA525). Therefore, if a different approach were to be taken in this appraisal, it should be clearly justified. He said that the key example of the difference in approach is the different treatment effect duration assumptions used in the two appraisals (3 years from the end of treatment with a two year treatment stopping rule in TA525, 3-5 years from the start of treatment in this appraisal).

15. Mr Castle said that section 6.2.16 of the NICE methods guide suggests that appraisal committees should try to take a consistent approach unless there are differences in the evidence. In this case, pembrolizumab has been shown to have an effect on overall survival, where atezolizumab has not, and there are longer follow-up data available for pembrolizumab. Therefore, the differences in the evidence would be in favour of assuming a longer rather than shorter duration of treatment effect for pembrolizumab.

16. Mr Castle said that MSD had raised this concern at several points throughout the appraisal but had never received a satisfactory explanation.

17. Benjamin Bates, for MSD, explained that with a cap on treatment effect duration at 3 years from the start of treatment, the modelling assumes that for patients still alive on active treatment at this time point their hazard rate suddenly jumps to that of the standard of care arm. The company's position is that the lower chance of dying with pembrolizumab continues past three years.

18. Mr Bates said that the approach taken by the ERG in this appraisal was significantly different from that used in other immune-oncology technology appraisals.

19. Dr Simon Crabb, for MSD, said that the real clinical benefit of pembrolizumab is not the improvement in median survival but that a small group of patients have very long survival, even after stopping treatment. He also emphasised that the clinical trials of atezolizumab and pembrolizumab were extremely similar.

20. Prof Gary McVeigh, for NICE, explained that in 2017-2018 atezolizumab and pembrolizumab were considered in parallel by the committee (in TA525 and TA519) but at that stage the data were extremely immature. At that time there was no evidence for a prolonged treatment effect, and it was impossible to know how many patients might have a prolonged effect from treatment. The committee had agreed that a lifetime effect was not plausible. He agreed that it is not plausible that the benefit of treatment is instantaneously lost at a specific time point for all patients. On the other hand, the data support a waning of the treatment effect over time (even before treatment is stopped). Using a treatment effect duration cap was therefore a compromise. The options presented to the committee in TA525 were either a 5 or 7 year treatment effect duration (3-5 years after a two year stopping rule).

21. Prof McVeigh said that the reason atezolizumab was approved for routine practice, whereas pembrolizumab went into the Cancer Drugs Fund, was due to the commercial offer around atezolizumab's acquisition. With that offer, the range of plausible ICERs for atezolizumab was well within what is considered cost-effective for an End of Life treatment. Because of this, the duration of treatment effect was not a key determinant of the decision.

22. Later in the hearing (during discussion of Appeal Point 2.3) Helen Knight, for NICE, also made the point that one difference between the two appraisals lay that in TA525 the estimated ICERs were well within the range that is considered cost-effective and thus the uncertainties around treatment effect duration in this appraisal (TA519) were more critical to decision making than in TA525.

23. In response to a question from the panel, Prof McVeigh said that he remains convinced that the decision on atezolizumab in TA525 was correct given the evidence available at the time and the value proposition, incorporating the commercial offer, put to the committee.

24. The panel asked whether the committee had considered a more conservative estimate of treatment effect duration of 3 years (1 year after the 2-year stopping rule) in TA525. Prof McVeigh replied that this was not one of the options presented to the committee. They preferred the most conservative of the options presented and noted the huge degree of uncertainty. He also commented that a 3-year treatment effect duration would not have changed the decision because of the value proposition.

25. Prof McVeigh, for NICE, said that in this current appraisal the committee had considered treatment effect durations of 3 or 5 years, and did not have a preference for 3 years. He pointed out that a 5 year effect from the start of treatment (for pembrolizumab) is not exactly equivalent to a 3 year effect after stopping treatment with a stopping rule of 2 years (for atezolizumab) as more than half of patients were already off treatment after 6 months.

26. In response to a question from the panel, Prof McVeigh said that the committee recognised that a small minority of patients may have a prolonged benefit from pembrolizumab.

27. In response to a question from the panel, Prof McVeigh said that it is difficult to compare the decision in this appraisal to that in TA525 because we now have two more years of data. An expectation of consistency was more relevant to the two decisions in TA525 and TA519 because these were taken in parallel.

28. Grant Castle, for MSD, said that he had still not heard an explanation for why a different approach was taken in this appraisal compared with TA525.

29. Benjamin Bates, for MSD, emphasised that the company considered a 5-year treatment effect duration to be conservative and preferred a lifetime treatment effect. Dr Simon Crabb, for MSD, gave a clinical opinion that the plausible duration of treatment effect was five years at a minimum.

30. Dr Lindsay Smith, for NICE, argued that the committee were not inconsistent in their approach. In both instances, they were presented with a range of options by the company and ERG. In both instances, they considered these options. At the time of TA525 there was very little evidence, and they chose the most conservative option of those presented. For the current appraisal, there was longer follow-up data available. But having longer follow-up data does not necessarily mean this data supports a longer treatment effect. The committee considered the options given to it and reached a different decision.

31. Helen Knight, for NICE, emphasised that committees are mindful of the need for consistency, but that NICE procedures do not allow committees to consider models from other appraisals in reaching their decision. The starting point for committees is always the submissions from the company and ERG, which differ between appraisals.

32. The appeal panel concluded that there is a biologically plausible rationale for thinking that the effect of pembrolizumab may continue after treatment is

stopped, but that there is a great deal of uncertainty about the duration of treatment effect.

33. The panel agreed that appraisal committees should ensure, as far as possible, that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals. The panel also noted consistently with its past decisions that this expectation must not be set too high. Ms Knight is correct that the evidence from one appraisal cannot be considered in another (at least, not unless it has been expressly included in that other appraisal). It is also right that any expectation of consistency between very different drugs or in different disease areas may be set only at a very general level. And it is also right that one committee does not bind another, or even itself for future appraisals, and past approaches may be departed from with appropriate reasoning.

34. The panel agreed that the judgement on duration of treatment effect was materially different between this appraisal and TA525, and that duration of treatment effect was one of the key drivers of the decision. The panel felt that the subject of TA525 and this appraisal were sufficiently similar that a meaningful expectation of consistency applied. Indeed the committee papers seemed to support this view, as they referred to past appraisals including TA525, and so expressly brought those points into consideration. Having rightly set out to take account of practice in relevant past appraisals the committee were obliged to do so reasonably.

35. The panel noted that the committee had responded to the company's concerns about the preferred treatment effect duration of 3 years in the ACD. The FAD considered treatment effect durations of both 3 and 5 years in this appraisal, and did not prefer a duration of 3 years, which represented a change in the committee's thinking in response to consultation. Nevertheless, this remained materially different from TA525, where a treatment effect duration of 5 years was preferred.

36. The panel accepted that it was reasonable for the committee not to ask for modelling of a shorter treatment effect duration in TA525 given that the most plausible ICER was comfortably within the range considered cost effective. However, the expectation of consistency means that substantial changes from this approach in similar appraisals would need to be clearly justified.

37. The panel did not judge that the committee had given a clear justification for this difference either in the FAD or during the hearing. The panel judged that even with the longer follow-up data available for this appraisal, there remained very substantial uncertainty about the duration of treatment effect. Whilst accepting Dr Smith's point that longer follow-up data does not necessarily provide evidence of a longer effect, the panel were not convinced that the committee had yet identified anything in the new data to support a material change in approach from the previous appraisal.

38. In summary, whilst the panel judged that a reasonable approach to duration of treatment effect had been taken both in TA525 and in this appraisal (if each were

taken in isolation), there was insufficient justification of why this approach had changed between the two appraisals. This was procedurally unfair given the expectation of consistency set out in the methods guide.

39. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.2: It is procedurally unfair to have introduced paragraph 3.19 ("The costs of pembrolizumab are likely underestimated in the model") in the FAD at a very late stage, without explanation or any opportunity to respond

40. Grant Castle, for MSD, said that the notion that the cost of pembrolizumab may be under-estimated in the model was raised at a late stage in the process. This was mentioned for the first time at the second committee meeting, where MSD did not have a satisfactory opportunity to respond. Following this meeting, MSD contacted NICE to raise their concern. The response from NICE agreed that this was "not ideal" but no attempt was made to address the concern. Whilst this possible underestimation of the cost may not have been a key driver of the decision, it is another factor which had an incremental effect on the committee's thinking.

41. Dr Lindsay Smith, for NICE, stated that this likely under-estimation of the cost of pembrolizumab was not included in the cost-effectiveness estimates in the FAD.

42. Prof Gary McVeigh, for NICE, acknowledged that this issue arose at the second committee meeting. He said that NICE had been contacted the day before the meeting by NHS England to point out that some patients in the trial had been re-treated. At the meeting, when he asked the company how many patients had been re-treated, they were able to reply without hesitation that it was 5%. Prof McVeigh therefore contended that the company must have been aware of this issue prior to the second committee meeting.

43. Kalpana D'Oca, for MSD, acknowledged that the company knew some patients had been re-treated, but said that they had not known this issue was of concern to the appraisal committee. Had they known this, they would have been able to conduct sensitivity analyses to explore its potential impact.

44. Grant Castle, for MSD, said that the Terms of Engagement for this re-appraisal of pembrolizumab did not include this issue. He argued that the fact that this issue is raised in the FAD demonstrates that it did have an impact on the committee's decision.

45. The appeal panel concluded as follows. The possible under-estimation of the cost of pembrolizumab in the model was raised by NICE for the first time at the second committee meeting. Although the company were aware that some patients in the trial had been re-treated, they were not aware until this point that this might be a factor in the decision-making in this appraisal. This is a key point. It is not enough that a company must be aware of a fact. They must also be aware that it is relevant, either (as will usually be the case) because that is self-

evident, or (as needed to be the case here) because that was made clear. The panel judged that they did not have a satisfactory opportunity to address this point before the FAD was published. Whilst this issue was not a key driver of the final decision, the fact that it was mentioned in the FAD means the panel cannot be confident it had no bearing on the decision. It was therefore procedurally unfair for the issue to be introduced so late in the process without an adequate chance to respond.

46. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

Appeal Ground 1b.1: NICE has breached its legal obligations under human rights and equalities laws

47. The appeal panel received legal advice on this appeal point in advance of the hearing from their legal adviser, Stephen Hocking. MSD had a further opportunity to respond to this, and their advice was also available to the panel and was taken into account. The panel were aware that they may take account of advice and submissions but must apply its own mind to the legal questions raised in the appeal to reach its own decision. The panel was aware that it should not give additional weight to the advice prepared by their legal advisor.

48. At the hearing, Grant Castle summarised MSD's position. He said that there was consensus that Article 2 of the European Convention on Human Rights was engaged, and that this requires NICE to carry out a fair and rational balancing exercise between the needs of patients affected by the decision and the community at large. There was also consensus that the appraisal committee benefits from a "margin of appreciation" in conducting this exercise. He went on to argue that Article 2 requires the committee to take positive measures to preserve life, yet in this case the committee consistently exercised its discretion in the opposite direction. At every stage, the committee applied a more conservative, negative approach to pembrolizumab compared with atezolizumab (a product that may not extend life). He said that the company does not expect NICE to take a more indulgent view of the evidence in this appraisal compared with others but does expect a consistent approach.

49. Mr Castle also outlined the company's position on Article 14 and the Equalities Act, set out in more details in their appeal letter and response to the panel's legal advice. He stated that there are obvious differences between this appraisal and TA525 that are manifestly without reasonable foundation. He argued that this must be discriminatory against patients who would benefit from this treatment compared with others.

50. The appraisal committee was given the opportunity to respond to these points at the hearing but did not wish to add anything.

51. The appeal panel concluded that, although Article 2 of the convention was engaged, it did not make a material difference to the approach that would otherwise have to be taken to this decision by NICE. The panel judged that all of NICE's processes are directed towards carrying out a fair and rational balancing exercise between the needs of patients affected by the decision and the community at large. It did not accept the company's argument that life-extending products should necessarily always be given "the benefit of the doubt" (although some NICE processes like the End of Life criteria do indeed do this) or should be subject to special processes or considerations over and above those provided for in NICE's published procedures. The panel judged that standard NICE processes, applied fairly and reasonably, constitute the necessary positive measures to seek to preserve life. The panel did not agree with the company that in this appraisal the committee had always taken the most conservative approach by default. The committee had considered a range of approaches throughout the appraisal and weighed up various sources of evidence to reach its decision.

52. The appeal panel also understood that Article 14 of the convention requires that the enjoyment of the other rights shall be secured without discrimination on any ground. The panel accepted that patients with locally advanced or metastatic urothelial cancer could have a distinct "status" capable of protection under Article 14. Although the appeal panel has judged that specific aspects of this appraisal were indeed unfair or unreasonable, the panel concluded that it did not add anything to see this as discriminatory. Any unfavourable treatment has arisen as a consequence of the otherwise unfair and/or unreasonable decision, rather than as a consequence of or in connection with any particular status. Therefore it would not be correct to hold that discrimination was a cause of any illegality or that the decision was discriminatory.

53. With regard to the public sector equality duty, again the panel judged that standard NICE processes, applied fairly and reasonably, show due regard to the elimination of discrimination and the advancement of equality of opportunity in most cases. Opportunities to raise equality issues are given during the appraisal process and the FAD specifically notes that no equality issues were identified. There may be particular circumstances where NICE does need to adjust its processes to take account of the needs of a group with a protected characteristic, but that did not apply here. The panel concluded that the fact that a group of patients disproportionately includes older people and people with disabilities is not in itself a reason to deviate from standard processes (as this probably applies in the majority of NICE appraisals). In this particular appraisal, the appeal panel could not identify any specific equality issues that arose during the appraisal and the patient group were not unusually defined by a protected characteristic other than, of course, the disability caused by their disease itself, which the committee plainly took into account.

54. The panel also considered MSD's argument concerning section 29(6) of the Equality Act. They contend that indirect discrimination could arise from inconsistency in decision-making that has not been properly justified and which has been applied without taking account of the disproportionate impact on people with protected characteristics. While the panel agreed that such a scenario could

at the least bear investigation as to whether it was compliant with the Equality Act it was not persuaded that it could easily fit within the concept of indirect discrimination. However it was unnecessary to reach a view on this point because although the panel have agreed under Appeal Point 1.1a that this decision was indeed unfair on the grounds of consistency, the panel did not accept that this constituted discrimination of any form, for the reason given above when discussing Article 14.

55. The appeal panel therefore dismissed the appeal on this point.

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

Appeal point Ground 2.1: The Appraisal Committee's assessment of duration of treatment effect and its effect on cost-effectiveness is illogical and unreasonable

56. The discussion on this appeal point at the hearing had some overlap with the discussion under appeal point 1a.1, so this section should be read in conjunction with that section of the decision letter.

57. Grant Castle, for MSD, building on the points raised in the appeal letter, said that MSD had collected unprecedented follow-up data on pembrolizumab which suggested a duration of treatment effect of 5 years or more. He argued that the latest data from KEYNOTE-045 showed clear evidence of benefit at 4 years, and that it was therefore inconceivable that the effect of treatment stops suddenly at 3 years. He argued that a 5-year treatment effect duration is the most plausible. Therefore, the approach taken by the committee in considering treatment durations of both 3 and 5 years simply did not add up.

58. Mr Castle said that the aim of having pembrolizumab in the Cancer Drugs Fund was to allow new data to inform subsequent decisions. He argued that it was unreasonable for the committee to expect "strong evidence" of a five-year treatment effect because the statistical power of the KEYNOTE-045 trial meant that this was not achievable.

59. Dr Lindsay Smith, for NICE, said that the committee had considered the external validity of a duration of treatment effect of 3-5 years in its decision-making. This is shown in slide 16 from the second committee meeting where treatment effect durations used in other appraisals were noted. Dr Smith also pointed out other appraisals of pembrolizumab (not listed in this slide) which have used treatment effect durations of 3-5 years (e.g. TA531 and TA557).

60. Dr Smith was asked by the panel whether he agreed that the other appraisals considered at the second committee meeting suggested that 5 years was a more typical estimate of treatment effect duration in similar appraisals. He disagreed and said that the slide simply demonstrated that a wide range of estimates had been used.

61. Dr Smith, for NICE, emphasised that the committee did not express a preference for a treatment effect duration of 3 years in the FAD. At the ACD stage, the committee had preferred 3 years based on ERG advice, but they modified their position following consultation. At the time of the FAD, the committee concluded that both 3 and 5 years were plausible. However, it did not accept the company's assertion that 5 years was most plausible. Dr Smith said that the onus would be on the company to provide evidence for this claim and they had not done so.

62. Dr Smith said that the committee recognised that there may be a small group of treated patients with very long survival, and that this was reflected in the modelling, but that there may also be a cohort of patients with long survival in the Standard of Care group. The crucial question is the relative benefit shown by the hazard ratio. The committee had concluded that there was evidence of waning of the treatment effect even before stopping treatment. They had concluded that there was no convincing evidence from clinical trials of benefit beyond 2 years, but they had been persuaded by the evidence of clinical experts to take a less conservative view.

63. Prof Gary McVeigh, for NICE, discussed the argument from the company in their appeal letter that the time varying hazard ratios from KEYNOTE-045 support a treatment effect beyond 3 years. The committee took the view that this data was not reliable because of a small number of events after 3 years.

64. Prof McVeigh stated that some patients in KEYNOTE-045 were re-treated after the 2-year stopping rule (unlike in NHS practice). The company adjusted for treatment switching in the Standard of Care arm but not for re-treatment in the pembrolizumab arm. This re-treatment may have played a particular part in effects seen after longer follow-up.

65. Prof McVeigh said that the ERG concluded that there was no evidence of benefit beyond 3 years because the confidence intervals around the hazard ratio crossed one very early. He therefore argued that the committee had been lenient in deciding to consider a 5-year treatment effect duration.

66. Benjamin Bates, for MSD, said that the hazard ratio confidence intervals are wide because of the small number of patients at risk, not because of an absence of ongoing treatment effect. It would have been unfeasible for KEYNOTE-045 to be powered to detect a treatment effect at >3 years. He argued that the additional data shows that the time-varying hazard ratio seems to plateau, rather than moving towards 1. He acknowledged that there may be waning of the treatment effect and said that this is reflected in the modelling. However, he argued that it is just not plausible that there would be no ongoing treatment effect after 3 years. The company concluded that a 5-year duration of treatment effect was most plausible based on a combination of the data and clinical opinion.

67. Daniel Gallacher, for NICE, explained why the ERG judged a 3-year treatment effect to be the most plausible. He highlighted again that the treatment effect begins to wane as early as 30 weeks, and the confidence intervals for the hazard ratio cross 1 from 60 weeks. This led the ERG to conclude that only a 2-year

treatment effect could be robustly supported. They acknowledged that this was probably too pessimistic, so used a 3-year effect in their preferred model. He said that the apparent plateau in the time varying hazard ration could not be relied upon because of the low number of events.

68. Dr Simon Crabb, for MSD, strongly rejected the idea that a 3-year treatment effect duration could be clinically plausible. He said that in his clinical opinion, 5 years is the minimum that is plausible.

69. As discussed under Appeal Point 1a.1, the appeal panel concluded that there is a biologically plausible rationale for thinking that the effect of pembrolizumab may continue after treatment is stopped, but that there is a great deal of uncertainty about the duration of treatment effect.

70. The issue of consistency with previous appraisals has been considered above under Appeal Point 1a.1, so is not discussed further here. In reaching a conclusion on Appeal Point 2.1, the panel has considered whether the assessment of duration of treatment effect was reasonable in the light of the evidence submitted in this appraisal only (leaving aside the issue of consistency).

71. The appeal panel judged that the committee had given a rationale for concluding that a treatment effect duration of 3-5 years could be plausible which if it was looked at in isolation was reasonable. The committee reached this judgement based on the trial data, alongside expert clinical opinion. The committee acknowledged the likely "tail of treatment" effect and took account of this in their decision-making. The panel did not agree with the company's view that the committee "considered that the most conservative possible estimate must apply by default". That allegation suggested the committee felt bound to be as conservative as possible, whereas the panel felt the evidence showed the committee exercising judgement, being persuaded on some points, and not always taking the most cautious view. In fact, the ERG judged a treatment effect duration of 2 years to have the most robust evidence, but this was not considered by the committee. The committee were responsive to points raised at consultation, in changing their preferred treatment effect duration from 3 years to at least allowing the possibility of 3-5 years. The committee gave clear reasoning for not placing significant weight on the apparent plateau in the time-varying hazard ration in KEYNOTE-045. Given the substantial uncertainty in the data, it was reasonable to consider a range of treatment effect durations rather than a point estimate. It was also clear that the committee had considered the external validity of their duration of treatment effect at the second committee meeting. The panel did not agree with the company's position that there had been an unreasonable requirement for "strong evidence" of a 5-year treatment effect. The committee had indeed considered a 5-year treatment effect, but had reached a judgement about how much weight to place on this that took into account the strength of the evidence. The panel did not consider this unreasonable.

72. The appeal panel noted the different views taken by the company and the committee on the most appropriate duration of treatment effect in the appraisal (in the face of complex and uncertain evidence), but felt that both these views

could be reasonably held. The appeal panel was satisfied that the committee's reasoning for reaching its position looked at in isolation was rational.

73. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.2: The Appraisal Committee's analysis of evidence from the clinical expert in paragraph 3.15 of the FAD is internally inconsistent and its conclusions are unreasonable

74. At the scrutiny stage it was decided to consider this point as an aspect of Appeal Point 2.1. However, at the hearing they were largely considered separately, so this letter also considers Appeal Point 2.2 separately.

75. Grant Castle, for MSD, said that paragraph 3.15 of the FAD mischaracterised evidence given by Dr Simon Crabb, to the detriment of pembrolizumab. The appeal letter said that the statements in paragraph 3.15 that "the clinical expert found it plausible that 5% to 10% of people having pembrolizumab might survive to 10 years after starting treatment" and that "no more than 5% of people treated with pembrolizumab might be alive after 10 years" were inconsistent.

76. Dr Lindsay Smith, for NICE, said that the committee had considered evidence from clinical experts, patient experts and NHS England to externally validate trial data. Ideally the committee would have access to 2 independent experts, but in this case there was only 1 expert (Dr Crabb) who was put forward by the company. In reaching the conclusion that "no more than 5% of people treated with pembrolizumab might be alive after 10 years" they had considered evidence from a patient expert and the Cancer Drugs Fund clinical lead as well as from Dr Crabb.

77. Dr Simon Crabb could not recall exactly what he had said at the meeting in question and felt that this issue was "getting bogged down in detail".

78. The appeal panel concluded that paragraph 3.15 of the FAD was not internally inconsistent and that the committee's conclusion on this point was not unreasonable.

79. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.3: The Appraisal Committee's decisions that: (i) a range of possible ICERs from £48,518 to £70,520 applies; and (ii) the "most plausible" ICER for pembrolizumab is likely to be above £50,000, are unreasonable in light of the evidence submitted

80. Grant Castle, for MSD, said that the committee's range of possible ICERs from £48,518 to £70,520 was unreasonable because it was based on excessively conservative assumptions. He stated that even if this range were correct, it would be unreasonable to assume the most plausible ICER would be >£50,000.

81. Dr Lindsay Smith, for NICE, said that it is usual for committees to consider a range of ICERs based on their preferred assumptions. In this case, there were three key drivers of the ICERs: duration of treatment effect, adjustment for treatment switching, and the choice of overall survival curve. This generated 12 possible scenarios, and in 11 of these the ICER was >£50,000. The committee had four options for the overall survival curve, and the most pessimistic was not considered in these 12 scenarios. With anything other than the most optimistic curve, even a 5-year treatment effect duration would produce an ICER > £50,000.

82. Dr Smith also explained how the End of Life criteria affect cost-effectiveness thresholds. Without the End of Life criteria, NICE considers treatments to be cost-effective if the ICER is less than £20,000-£30,000. The higher end of this range is used when there is less uncertainty in the modelling, a highly innovative therapy, or important quality of life benefits that are not captured in the model. Dr Smith said that none of these apply here, so the starting point would be closer to £20,000. A weighting of up to 1.7 times is then applied when the End of Life criteria are met. In this case, the lack of robustness in the evidence would likely have meant that a weighting of less than 1.7 was used. So, it is likely that the threshold for pembrolizumab to be considered cost-effective in this appraisal, with End of Life Criteria, would be closer to £34,000 than £50,000.

83. Dr Smith, responding to questions from the panel, acknowledged that this had not been discussed in detail during the appraisal. This was because the committee judged the most plausible ICER to be >£50,000 so further consideration of exactly how the End of Life criteria should be applied was not relevant.

84. Benjamin Bates, for MSD, responded to Dr Smith's comment on 11 out of 12 ICERs being >£50,000. He said that was not reasonable to consider alternative overall survival curves. In addition, he said that 3 of these ICERs would be very close to £50,000.

85. Prof McVeigh, for NICE, said that in the company's base case the ICER is verging on the maximum threshold for cost-effectiveness. To accept this ICER, the committee would have to accept that there was no uncertainty about a treatment effect duration of 5 years or the two-stage adjustment for treatment switching. The committee judged that this was simply not tenable and therefore the most plausible ICER must be >£50,000.

86. The panel concluded that it was reasonable for the committee to generate a range of ICERs based on their preferred assumptions and on other plausible scenarios. Whether or not the key assumptions that this range was based on are reasonable is addressed separately in Appeal Points 2.1-2 (on treatment effect duration) and Appeal Point 2.5 (on the use of the 2-stage model versus unadjusted data). These issues are therefore not considered here.

87. Under this ground, the panel has considered the narrower issue of whether it was reasonable for the panel to conclude that the most plausible ICER was likely to be above £50,000.

88. The panel did not rely on Dr Smith's exposition of the weighting to be given to pembrolizumab being less than 1.7, because this is not discussed in the FAD and the panel were not taken to any contemporaneous document in which the issue was raised. The panel accepted that Dr Smith had this consideration active in his own mind, but was not prepared to accept that it formed part of the committee's overall reasoning.

89. The panel was persuaded by the committee's argument that any deviation from the company's base case (whether in treatment effect duration, overall survival curve, adjustment for treatment switching or indeed other factors) would push the ICER beyond the upper end of the range that can be considered cost effective even if the maximum weighting allowed by the End of Life criteria were applied.

90. Further, if it was suggested by MSD that it was enough that one plausible ICER fell below the usual upper level for recommendation under the end of life criteria, the panel disagreed. An appraisal will typically generate a range of ICERs of greater or lesser plausibility depending on the inputs and assumptions used, and a committee should use that range, and its assessment of the plausibility of the values within it, to reach a holistic judgement whether to recommend or not recommend a treatment. How it does so is very much a matter for its judgement in each appraisal and no attempt should be made to lay down prescriptive general rules.

91. The appeal panel therefore dismissed the appeal on this aspect of point 2.3 but refers also to its decision on Appeal Points 2.1-2 and 2.5.

Appeal point Ground 2.4: The statement that "the costs of pembrolizumab are likely underestimated in the model" lacks meaningful explanation and evidence and it is unreasonable to have taken it into account for the purposes of assessing cost-effectiveness

92. At the hearing, the discussion of this Appeal Point overlapped with the discussion of Appeal Point 1a.2, so this section should be read in conjunction with that section of the decision letter.

93. The appeal letter from the company states that the number of patients who were re-treated in the KEYNOTE-045 trial was very small. Therefore, without further analysis, it is impossible to conclude that MSD has materially under-estimated the cost of its product.

94. Grant Castle, for MSD, said that it was unreasonable to consider re-treatment because this would not be done in NHS practice.

95. Prof McVeigh, for NICE, stated that 11 patients in the pembrolizumab arm of the trial were re-treated. The benefits of this were captured in the model, but the costs were not. Prof McVeigh said it was misleading for the company to trivialise this as a small number. Only 24 people were at risk of progression, so a sizeable proportion of those eligible may have been re-treated.

96. The appeal panel concluded that some patients in the trial were re-treated, albeit a relatively small number, and that the benefits but not the costs of this were included in the model. It is reasonable for appraisal committees to consider factors not included in the model that might affect their decision making, particularly when considering how much uncertainty there is about the estimated ICER or range of ICERs.

97. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.5: The conclusion that new data from KEYNOTE-045 "shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account" results from a flawed and unreasonable interpretation of the evidence

98. Daniel Gallacher, for NICE, explained that the 2-stage method is used to adjust for the fact that some patients in the Standard of Care arm of a trial may switch to active treatment when their disease progresses. It works by comparing the survival time of those who switched when their disease progressed to the survival time to those who did not switch when their disease progressed. This estimates an "acceleration factor" which is then applied to those who did switch.

99. Mr Gallacher, asked by the panel whether this is usually considered an appropriate method, said that it is. It is one of a range of methods that can be used, and one of the more commonly used because it is relatively simple.

100. Grant Castle, for MSD, said that the 2-stage method is uncontroversial and well-established. NICE agreed to this method when pembrolizumab entered the Cancer Drugs Fund. The terms of engagement for this review suggested that this was a settled point. In this appraisal, he argued that the committee has done an "about turn" by giving equal weight to unadjusted data, without a clear rationale. This was one of the important factors that led the committee to conclude that pembrolizumab could not be recommended.

101. Dr Lindsay Smith, for NICE, emphasised that the committee had not considered the 2-stage model to be unacceptable. Rather, they decided it was one of two models they would like to consider (the other being the unadjusted data). The committee took the view that the 2-stage model was over-optimistic and the unadjusted data was over-pessimistic, so both were useful in reaching their "best guess".

102. Daniel Gallacher, for NICE, gave a detailed account of the ERG's concerns about the 2-stage model. Firstly, it assumes a uniform effect (that all patients get the same benefit from switching to five different treatments) which is unlikely to be correct. Secondly, the evidence is that these treatments are not effective in the first 4-5 months (even when given to patients with less advanced disease). The 2-stage model assumes that all patients benefit, but the ERG think this is unlikely to be the case in advanced disease where life expectancy can be short, so patients may die before the treatment effect begins. Thirdly, the ERG did not have detailed information on all potentially important differences between those

who switched when their disease progressed and those who did not. This is a "red flag" that the acceleration factor may be capturing the benefit of other prognostic factors rather than the effect of treatment. Fourthly, results were presented without re-censoring, which is not best practice. In addition, there is a wide confidence interval around the acceleration factor.

103. Mr Gallacher, asked by the panel whether the ERG could not have modelled the confidence intervals around the acceleration factor (rather than using unadjusted data) said that this would have been difficult to do.

104. In response to questions from the panel, Mr Gallacher agreed that these issues can result in both "noise" and systematic bias in the estimation of the acceleration factor. He acknowledged that the "true" acceleration factor could be higher as well as lower than the estimate used.

105. Dr Smith was asked by the panel if it was unreasonable to give equal weight to the unadjusted data (which everyone agrees is problematic) and the 2-stage model (which is imperfect but an accepted method). Dr Smith replied that the committee were particularly concerned that two particular issues (the second and third issues described by Mr Gallacher in paragraph102 above) would introduce systematic bias in the acceleration factor and therefore the 2-stage adjusted model was too optimistic.

106. Daniel Gallacher, for NICE, said that his view was that the unadjusted data could be very plausible (if those who switched did not actually receive benefit from treatment, but survived longer because of other prognostic factors).

107. Kalpana D'Oca, for MSD stated that the ERG report acknowledges that the unadjusted data are biased and acknowledges that this bias is likely to be greater than that in the 2-stage model. She also stated that there is still a source of bias in favour of the control arm when the 2-stage method is used (because there are some patients who switched to whom the adjustment is not applied). She commented on the larger magnitude of the acceleration factor in this re-appraisal compared with the original appraisal of pembrolizumab: although the magnitude has increased, it falls within the range of the original confidence intervals, and the confidence intervals have now narrowed so it can be considered more reliable.

108. Ms D'Oca stated that the committee's support for the unadjusted data seemed to rely on comparison with data from a 2013 study by Bellmunt et al. She argued that this comparison was inappropriate as vinflunine is not established in UK clinical practice.

109. In response to this point, Dr Lindsay Smith, for NICE, said that the Bellmunt study was not relied upon in the final decision, and was not mentioned in the FAD.

110. The appeal panel concluded as follows. There was general acceptance during the hearing that the unadjusted data was biased. At the time of the original appraisal of pembrolizumab in this indication (TA519) the ERG also

judged that the unadjusted model was the least appropriate. The panel understood the limitations of the 2-stage model, as set out by Mr Gallacher, and appreciated that these could cause bias as well as imprecision in estimating the acceleration factor. Nevertheless, these same limitations were known at the time of TA519 and the 2-stage model was judged the most appropriate. The committee did not seem to have considered other approaches to dealing with potential biases in the 2-stage model, such as modelling a range of acceleration factors. The panel was not persuaded that it was necessarily unreasonable to give any consideration to the unadjusted data. However, the FAD suggests that the committee gave equal weight to the unadjusted data and the 2-stage model in their decision-making. The panel judged that it was not reasonable to give equal weight to a method that was previously agreed to be the least appropriate, without a clear reason based on new evidence.

111. The appeal panel therefore upheld the appeal on this point.

Conclusion and effect of the appeal panel's decision

112. The appeal panel therefore upholds the appeal on the grounds that
- Ground 1a.1 – Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural fairness
- Ground 1a.2 – It is procedurally unfair to have introduced paragraph 3.19 ("The costs of pembrolizumab are likely underestimated in the model") in the FAD at a very late stage, without explanation or any opportunity to respond
- Ground 2.5 – The conclusion that new data from KEYNOTE-045 "shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account" results from a flawed and unreasonable interpretation of the evidence

113. The appeal is dismissed on all other grounds.

114. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address these points. In particular, the committee should take into account the expectation of consistency with previous appraisals and whether this should influence their approach to estimating the treatment effect duration. To be clear, the panel does not consider that there is a tension between its conclusions on grounds 1a.1 and 2.1-2. Notwithstanding that the Committee's approach can be regarded as reasonable looked at in isolation, the fact that different approaches have been taken in past relevantly similar appraisals means that, if a different approach is now to be taken, that departure from past approach or practice must be explained, and not only the reasons for the decision in isolation. This requires additional and specific discussion, at least in this case. The panel considers that the committee might be assisted by considering how its processes and its guidance would be seen by patient groups or clinicians, or other stakeholders, and what degree of additional reasoning they would expect to see so that they can understand and have confidence in the Institute's work.

115. If the Committee conclude that a different approach is needed from that taken in previous appraisals this should be clearly justified. The company should be given a chance to respond to the committee's concern that the costs of pembrolizumab may have been under-estimated in the model. The company's response should be considered in reaching a final decision. The committee should re-consider how potential biases in the 2-stage method could be addressed and re-consider the relative weight given to the 2-stage method versus other models in their decision-making.

116. 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.

MSD

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07 October 2020

Dear Linda,

ID1536: Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519)

Please find herewith MSD's response to the request from NICE received on 19 August 2020 for further analyses and information to support the NICE Committee's decision making, following the outcome of the appeal hearing which took place on 23 June 2020.

This response addresses three main areas:

- Duration of treatment effect concerning the appropriate approach and aligning with TA525
- Consideration of the impact on the ICER estimate when introducing the cost of retreatment with pembrolizumab
- Further scenario analyses concerning the 2-stage method, used to adjust for subsequent therapy use in the UK SoC arm in KEYNOTE-045.

These areas address the three upheld appeal grounds (1a.1, 1a.2 and 2.5 respectively). The analyses are presented in more detail on the following pages.

In addition, we present the grounds by which pembrolizumab should be assessed against the £50,000 end-of-life threshold for the indication under consideration, by applying the end-of-life modifier to the £30,000 threshold, appropriate to innovative, life-saving treatments such as this.

[redacted]
which has been incorporated into the updated base case analysis resulting in a deterministic ICER estimate, for MSD's preferred base case, of £46,774 per QALY gained. The probabilistic estimate is £47,052 per QALY gained, demonstrating pembrolizumab is a cost-effective treatment option, compared to UK SoC, at the £50,000 per QALY threshold applicable to end-of-life technologies (see Section B).

MSD reports the results of six scenario analyses exploring the impact of key model assumptions for the three areas described above, see Table 1. This analysis suggests that the results of the economic model are stable, plausible and consistently below the £50,000 threshold associated with end-of-life technologies. The scenarios assuming a three-year treatment effect (two years on treatment plus one year of maintained effect) go marginally over the £50,000 threshold. However, as it has already been

acknowledged in this appraisal that treatment duration lies at minimum between 3 and 5 years, it is reasonable to assume the true ICER for this indication is below threshold.

Table 1:Results from the scenario analyses versus trial UK SoC (discounted price)

Description	Pembrolizumab vs UK SoC
	ICER (£)
MSD Base Case: 2-stage adjustment (no re-censoring), 5-year treatment effect (TE) duration	£46,774
CE Scenario 1: 2-stage adjustment (no re-censoring), 3-year TE duration	£51,692
CE Scenario 2: 2-stage adjustment with lower CI as AF (no re-censoring), 5-year TE	£48,277
CE Scenario 3: 2-stage adjustment with re-censoring, 5-year TE	£44,395
CE Scenario 4: 2-stage adjustment with lower CI as AF (no re-censoring), 3-year TE	£54,638
CE Scenario 5: 2-stage adjustment with re-censoring, 3-year TE	£49,988
CE Scenario 6: 2-stage adjustment (no re-censoring), 5-year TE, retreatment	£48,848

Following the conclusion from the NICE appeal panel regarding 1) fundamental differences and inconsistent methodologies in the consideration of evidence [ground 1a.1]; 2) procedural unfairness [ground 1a.2]; and 3) the flawed and unreasonable interpretation of the evidence submitted [ground 2.5], we request a balanced and fair examination of the information presented.

We believe that we have addressed all the requests from NICE and in doing so report ICER estimates, with a degree of certainty that suggests pembrolizumab is an innovative treatment meeting the end of life criteria.

Should any clarification be required please do not hesitate to contact us.

Best regards,

Kalpana D'Oca
Team Leader – HTA & OR

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SECTION A – MSD Responses concerning the three upheld grounds following appeal

A1. Duration of Treatment Effect

Relating to Upheld Ground 1a.1: Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural fairness

To be consistent with the methodology applied in TA525, in which the final Technology Appraisal Guidance (TAG) includes a 2-year stopping rule, the duration of treatment effect that should be applied for pembrolizumab is five years.

MSD welcomes the Appeal Panel's decision to uphold the appeal on Ground 1a.1- *"Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural unfairness*". MSD agrees with the Appeal Panel's conclusion that there is an expectation of consistency set out within the methods guide and we are unaware of any justification for deviating from the approach taken in TA525.

The published response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)[1] details the Committee's response to MSD's concerns surrounding the lack of consistency with TA525. Comment 7 reads:

> "*Comment noted. The committee was aware of a number of differences between the company submissions for atezolizumab and pembrolizumab. There was no 2-year stopping rule in the trial of atezolizumab or its summary of product characteristics and the modelling of duration of treatment presented to the committee was different to the modelling presented in this appraisal of pembrolizumab. Considering the company's new evidence, the committee agreed that a 3- to 5-year treatment effect from the start of pembrolizumab treatment could be plausible. See FAD section 3.18. The range of treatment effect durations was taken into account in the committee's consideration of the cost-effectiveness estimates. See FAD section 3.22."*

MSD does not agree with this rationale. Although the absence of a 2-year stopping rule was a key difference between the IMVIGOR 211 and KEYNOTE-045 study designs, there is no material difference that can be attributed to the lack of a 2-year stopping rule within IMVIGOR 211 due to the imposed stopping rule. This is reinforced by the maximum follow-up of this trial which, at the time that TA525 was appraised by NICE, was 24.5 months. An imposed 2-year stopping rule is also reflected in the recommendation from TA525[2] which states the following:

"Atezolizumab is recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- *atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses*
  and
- *the company provides atezolizumab with the discount agreed in the patient access scheme*."

Secondly, NICE state that:

> "*the modelling of duration of treatment presented to the committee was different to the modelling presented in this appraisal of pembrolizumab."* [1]

MSD queries the evidence base upon which this statement is based. During ACD consultation, MSD outlined in detail (within comment 12 of the company response) the rationale for why the modelling of treatment effect duration within TA525 and ID1536 should be considered equivalent. Following extensive examination of the two submissions, we stand by our interpretation that the modelling of treatment effect duration is equivalent between the two appraisals.

Pembrolizumab and atezolizumab are both immune checkpoint monoclonal antibodies indicated for the treatment of locally advanced or metastatic urothelial carcinoma, both acting upon the PD-1/PD-L1 axis. KEYNOTE-045 had a stopping rule of 35 cycles (2-years) of treatment with pembrolizumab. NICE imposed a 2-year stopping rule on treatment with atezolizumab within TA525. As there is no material difference between TA525 and the current appraisal, ID1536, MSD considers that the same approach to duration of treatment effect should be maintained.

A2. Costs of Retreatment

Relating to Upheld Ground 1a.2: It is procedurally unfair to have introduced paragraph 3.19 ("The costs of pembrolizumab are likely underestimated in the model") in the FAD at a very late stage, without explanation or any opportunity to respond

Based on the November 2018 data cut of KEYNOTE-045, there are 10 patients in the pembrolizumab arm who were retreated with pembrolizumab (as permitted in the study protocol). Updated cost-effectiveness analysis showing the impact of retreatment with pembrolizumab is presented in Section B. This shows that the impact of retreatment on the base case ICER is an increase to £48,848.

As detailed in the Final Appraisal Document (FAD) for ID1536[3], patients in the pembrolizumab arm who stopped taking pembrolizumab because they had a complete response or after the 2-year stopping rule, could subsequently restart pembrolizumab for up to 1 year, if their disease progressed.

Having now had the opportunity to investigate this issue in more detail, MSD can confirm that 10 patients in the pembrolizumab arm were retreated with pembrolizumab, based on the November 2018 data-cut which informs ID1536 (please note that in the committee meeting which took place in February 2020, MSD incorrectly stated that 11 patients had been retreated).

Of these 10 patients who were retreated with pembrolizumab, eight had completed the initial treatment course, one had a complete response and one had unknown reasons for discontinuing their initial course of pembrolizumab treatment. The median number of retreatment cycles received by the 10 patients concerned was 10.0 cycles (minimum 3.0; maximum 18.0).

Updated cost effectiveness analyses showing the impact of retreatment with pembrolizumab is detailed in Section B (pages 18-20).

A3. Using the 2-stage method to adjust for subsequent anti-PDL1/PD-1 therapy use in the UK SoC arm

Relating to Upheld Ground 2.5: The conclusion that new data from KEYNOTE-045 "shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account" results from a flawed and unreasonable interpretation of the evidence

Adjustment for subsequent anti-PDL1/PD-1 therapy use in the UK SoC arm is important in order to adjust for the use of therapies in the third-line setting which are not part of the treatment pathway in England. It is inappropriate for equal weighting to be given to both adjusted and unadjusted analysis for the purpose of decision making.

MSD's base case remains unchanged with respect to the appropriateness of the previously implemented 2-stage model. In order to address the request from NICE, further analyses have been provided, including alternative approaches to dealing with potential biases in the 2-stage method, in order to assist the Committee's decision-making on adjusting for subsequent therapy use in the UK SoC arm of KEYNOTE-045

Updated cost-effectiveness analysis incorporating the scenario analyses based on the 2-stage model are provided in Section B (pages 18-20). The associated ICER estimate is £46,774, and different scenarios are associated with £48,277 and £44,395 per QALY, when implementing the 2-stage adjustment using the lower CI as the acceleration factor and 2-stage adjustment with re-censoring, respectively.

Purpose of adjusting for subsequent therapy usage:

The purpose of adjusting for subsequent therapy usage in the UK SoC arm, is to adjust for therapies which are not part of the treatment pathway in England. Patients with urothelial cancer do not receive 3L immunotherapies following 2L chemotherapy in clinical practice in England according to the current treatment pathway. Therefore, the pathway experienced by patients who switched in the UK SoC arm represents an implausible scenario. Consequently, adjustment for subsequent anti-PDL1/PD-1 therapy use in the UK SoC arm is necessary to address the bias that would otherwise exist in favour of the UK SoC arm.

During the NICE appraisal process for ID1536, the ERG report and technical report stated that not adjusting the data, *"introduces bias which favours the control arm"*, and the ERG report additionally stated "*this bias may be potentially stronger than any biases associated with the using the 2 stage method*"[4].

For these reasons, it is methodologically inappropriate for equal weighting to be given to the adjusted and unadjusted analysis for the purpose of decision making. This view was reflected in the appeal panel's decision which stated the following:

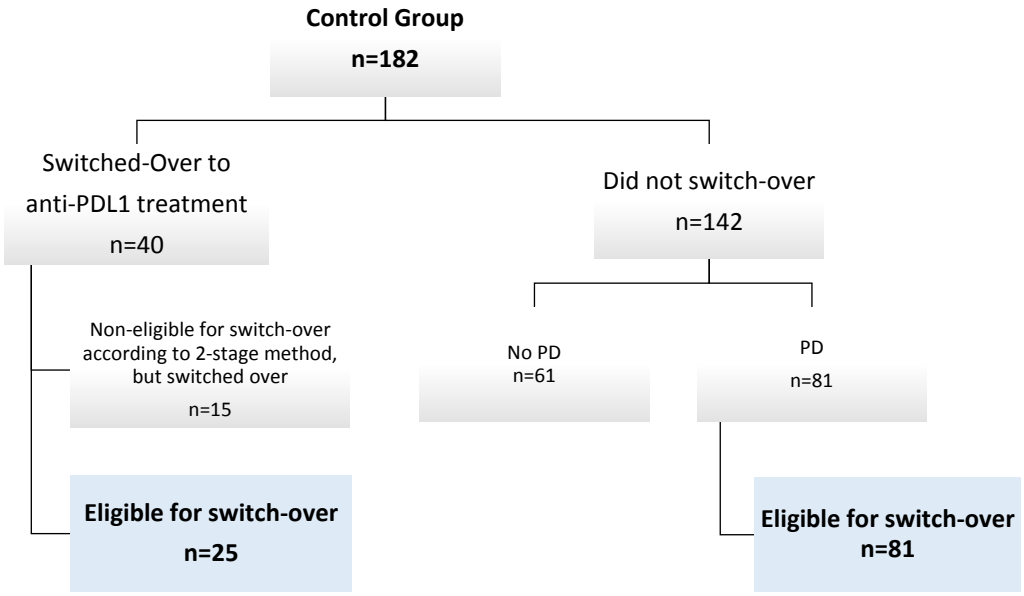
> *"… the FAD suggests that the committee gave equal weight to the unadjusted data and the 2-stage model in their decision-making. The panel judged that it was not reasonable to give equal weight to a method that was previously agreed to be the least appropriate, without a clear reason based on new evidence."*

Methods

In the 2-stage model, OS is defined similarly as in ITT, but the survival time of the UK SoC arm subjects receiving subsequent therapy (anti-PD-1/PD-L1 treatment) is adjusted. Disease progression (defined centrally by RECIST 1.1) is the timepoint used as a "secondary baseline" under the assumption that all patients are at a similar stage of disease at the point of disease progression[5]. Patients who received subsequent therapy after disease progression and therefore met the secondary baseline criteria were considered to be 'eligible' to receive subsequent therapy; for such patients, the survival time after the secondary baseline (time of progression) is adjusted multiplicatively by an acceleration factor determined in stage 1, using a regression model applied to post progression survival data.

The breakdown of the disposition of patients in the UK SoC arm of KEYNOTE-045 is depicted in Figure 1. This shows that among 40 control patients who received subsequent anti-PDL1/PD-1 treatment, 25 of these patients were considered 'eligible' for subsequent therapy on the basis they switched-over following disease progression.

Figure 1: Breakdown of disposition of patients in the UK SoC arm



Results

Results using the 2-stage method (with no re-censoring) to adjust for subsequent anti PD-1/PD-L1 treatment (previously presented as Table 4 and Figure 1 of the original submission of ID1536 in July 2019) are replicated and presented in the Appendix (Table 1 and Figure 1) for the subgroup of subjects pre-assigned to UK SoC. This shows an acceleration factor of **5.370 (3.231,10.094). MSD stands by this method of adjustment as providing the most appropriate results for decision making.**

- Among 40 control patients who received subsequent anti-PDL1/PD-1 treatment, 25 patients met the eligibility criteria to receive subsequent therapy (i.e. they experienced progressive disease); therefore, the survival times of these 25 patients were adjusted accordingly. For the

remaining 15 patients who switched, but were classified as non-eligible (due to not meeting the secondary baseline criteria of switching following disease progression defined centrally by RECIST 1.1), their survival times were not adjusted; instead their unadjusted survival times were used in all analyses.

- **As 15 of the 40 switchers (38%) did not have survival times reduced, the consequence of this is that the overall survival results for 8% (15/182) of the UK SoC arm remain biased in favour of the control arm. The ERG had already acknowledged that by not adjusting, it introduces bias which favours the control arm[4], and during the appeal hearing it was also confirmed that the Committee consider the unadjusted data to be *"over-pessimistic".***

As reiterated throughout the CDF guidance review process (ID1536), MSD considers that the acceleration factor of 5.37 based on the November 2018 data-cut of KEYNOTE-045 is a more precise and reliable estimate of the acceleration factor than that generated at the time of the original appraisal of TA519 (3.86), for the following reasons:

- In our CDF guidance review submission, when the 2-stage method was applied to the November 2018 data-cut using this standard approach, the calculated acceleration factor was 5.37. Importantly, the 2-stage method was applied to the November 2018 data-cut using the same methodology as previously employed in the original appraisal of TA519 when it was deemed by both the ERG and NICE Committee as the most appropriate method to use, and appropriate for decision making[6].

- The acceleration factor was 5.37 (95% confidence interval [CI] 3.23 to 10.09) (based on 25 patients) after the November 2018 data cut, compared with 3.86 (95% CI 1.79 to 11.68) (based on 14 patients) using previous data. It is unsurprising that the very small sample size used in the original 2017 appraisal (n=14) resulted in a smaller acceleration factor (3.86) and a wider confidence interval (difference between upper and lower confidence interval = 9.89). It is recognised that any statistical inference applied to such small sample sizes may produce uncertain results, therefore the width of the confidence interval is not surprising.

- Based on the November 2018 data-cut which informs the CDF guidance review, the acceleration factor is higher in magnitude (5.37) but the confidence interval generated is narrower as compared to that generated in the original submission (November 2018 data-cut difference between upper and lower CIs = 6.86). **It is noteworthy that the confidence interval obtained using the November 2018 data-cut (3.23 to 10.09) is not only narrower, but also falls entirely within the range of the confidence interval of the original acceleration factor based on the previous data cut at the time of the original appraisal (1.79 to 11.68).**

Scenario Analyses to assist NICE decision making: Methods and Results

Following the outcome of the appeal, NICE has requested that MSD provides further analyses that would assist the committee's decision-making on adjusting for crossover in KEYNOTE-045, including alternative approaches to dealing with potential biases in the 2-stage method (e.g. using a range of acceleration factors).MSD is therefore providing the following scenario analyses, described in more detail below. The cost-effectiveness results associated with these scenario analyses are presented on page 20:

1) 2-stage method using the lower 95% confidence limit of the acceleration factor taken from original model based on the November 2018 data cut (3.23) as the acceleration factor for this model
2) 2-stage model based on original acceleration factor (5.37) from ID1356, *with* re-censoring

In addition, the following two previously provided scenario analyses are presented again for the Committee's consideration:

3) Calculation of acceleration factor when including vinflunine patients in the comparator arm
4) Application of acceleration factor to all 40 patients in UK SoC arm who switched to subsequent anti PD-1/PD-L1 therapy

For each scenario, a summary of the acceleration factor applied and resulting hazard ratios (with 95% CIs) for pembrolizumab versus adjusted UK SoC, are summarised in Table 2 below. Full results presented in the Appendix (Tables 1-3, Figures 1-3). These scenarios are discussed in more detail in turn below:

Table 2: Summary of adjustment scenarios

	Comparison pembrolizumab versus UK SoC - adjusting for treatment switch in SoC arm using 2-stage analysis	
	Acceleration factor	**Hazard Ratio (95% CI)**
MSD Base case 2-stage analysis; no re-censoring; acceleration factor of 5.37	5.370 (3.231,10.094)	0.64 (0.49, 0.81)
Adjustment Scenario 1 2-stage analysis with acceleration factor of 3.23 (no re-censoring)	3.231	[redacted]
Adjustment Scenario 2 2-stage analysis with re-censoring, based on original acceleration factor (5.37)	5.370 (3.231,10.094)	[redacted]
Adjustment Scenario 3 2-stage analysis: calculation of acceleration factor when including vinflunine patients	5.32 (3.44, 8.446)	0.62 (0.50, 0.76)
Adjustment Scenario 4 2-stage analysis: application of acceleration factor of 5.37 to all 40 patients in UK SoC arm who switched to subsequent anti PD-1/PD-L1 therapy	5.370 (3.231,10.094)	0.55 (CI 0.41, 0.69)

1. 2-stage method using a reduced acceleration factor

As stated in the above sub-section, the acceleration factor generated when running the 2-stage model (with no re-censoring) based on the November 2018 data cut, resulted in an acceleration factor of 5.37 (95% confidence interval [CI] 3.23 to 10.09).

Methodologically, it is inappropriate to run the model using randomly selected acceleration factors; so instead, to address the request from NICE, MSD is providing the results of running the 2-stage model (again with no re-censoring applied, as per the MSD base case), **using the lower 95% confidence limit of the acceleration factor taken from original model based on the November 2018 data cut (3.23) as the acceleration factor for this model**.

- MSD considers an acceleration factor of 3.23 to be the most reasonably conservative scenario possible, given this represents the lower bound of the 95% CI of the acceleration factor point estimate of 5.37.

- Notably, an acceleration factor of 3.23 is lower than that generated when the 2-stage model was run based on the previous data cut (i.e. 3.86) which informed the original appraisal of TA519, and was at that time considered by the ERG and NICE committee to be appropriate for decision making.

The full results from running the 2-stage model using an acceleration factor of 3.23 (i.e. the lower 95% confidence limit of the original acceleration factor based on the November 2018 data-cut) is provided in the Appendix (Table 2 and Figure 2). Cost-effectiveness scenario analyses using results based on this acceleration factor is provided on page 20.

2. 2-stage model with re-censoring, based on original acceleration factor (5.37) from ID1536

MSD's decision to implement the 2-stage model without re-censoring, was highlighted during the appraisal of ID1536 as a possible source of bias in the implementation of the 2-stage method. This is despite the ERG report for ID1536 stating that it "*must be noted that re-censoring can lead to a loss of information and may not always be beneficial to the analysis*"[4].

MSD considers that our approach to the implementation of the 2-stage method in ID1536 is a standard approach, aligned with previous pembrolizumab submissions to NICE, and also reflecting the ERG's preferred approach at the time of the original appraisal of TA519[6]. However, to address the ERG's concern, with this response we are providing the results when running the 2-stage model ***with*** re-censoring.

The results of the analysis of OS adjusting for subsequent therapy including Kaplan-Meier estimates of OS and estimation of treatment effect with the re-censoring procedure applied are provided in the Appendix (Table 3 and Figure 3). With re-censoring, the number of events in the control arm [redacted] with person-time [redacted]. In contrast, without re-censoring (MSD base case), the number of events in control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (Appendix 1: Table 1 and Figure 1).

The full results from running the 2-stage model with re-censoring is provided in the Appendix (Table 3 and Figure 3). Cost-effectiveness scenario analyses using results based on this method is provided on page 20.

3. Calculation of acceleration factor when including vinflunine patients

During the clarification question phase of the CDF guidance review, the ERG had requested that MSD estimates the acceleration factor when also including vinflunine patients in the SoC arm (i.e. full ITT population), in an attempt to reduce uncertainty. The results of this analysis (provided in our response to clarification questions) were deemed "*consistent"*[3] with the original analysis presented by the Company (i.e. acceleration factor = 5.32, confidence intervals: 3.44, 8.446). **Thus, even by increasing the sample size to assess variability and check for accuracy of the generated acceleration factor, the results were stable**.

4. Application of acceleration factor to all 40 patients in UK SoC arm who switched to subsequent anti PD-1/PD-L1 therapy

As mentioned above, the 2-stage method only applies an adjustment to overall survival estimates for patients in the UK SoC arm who were 'eligible' to switch on the basis of having a secondary baseline of disease progression (defined centrally per RECIST1.1). The acceleration factor was not applied, and consequently survival time was not reduced for the 15 patients whose switch to subsequent therapy was not based on documented disease progression.

In paragraph 3.5 of the ACD, the ERG had raised a specific concern which stated "*The acceleration factor was not applied to the overall survival time of 15 patients who switched at different times. It is not known how including these 15 patients in an adjustment would have affected the estimated incremental cost-effectiveness ratio (ICER)."* To address this concern, sensitivity analysis was conducted by MSD to show the results of the 2-stage adjustment when applying the same acceleration factor of 5.37 to all 40 switchers; i.e. including the 15 patients who switched at a time other than documented disease progression defined centrally by RECIST 1.1[1].

- The results showed that with the inclusion of these 15 patients, the hazard ratio for the comparison of pembrolizumab versus UK SoC is 0.55 (CI 0.41, 0.69)[1].
- **This improved hazard ratio shows that MSD's original approach, of not including these 15 patients in the 2-stage adjusted analysis, is a more conservative approach: it results in the survival times of fewer patients in the UK standard of care arm being adjusted downwards, and therefore a less favourable hazard ratio for the comparison of pembrolizumab with UK SoC.**.

Conclusion

MSD stands by our original base case in ID1536; that is, the adjusted analyses using the 2-stage model (with no re-censoring) provides the most appropriate results for decision making.

MSD reiterates that the November 2018 data-cut and the analyses provided to date demonstrate robustness in the generated acceleration factor of 5.37. Based on the rationale described above, we consider this point estimate to be more precise and reliable than the acceleration factor generated at the time of the original appraisal of TA519.

The 2-stage method only adjusts within-trial overall survival for the 25 patients in the UK SoC arm who switched following disease progression (secondary baseline). This means that even with the adjustment to the UK SoC arm using the 2-stage method, there remains bias in favour of the control arm, given 15 patients in the UK SoC arm did not meet the secondary baseline criteria and hence did not have their survival times adjusted; instead their within-trial survival times were used in all analyses.

MSD's response to other concerns raised by the ERG during the course of appraisal ID1536 about the appropriateness of the 2-stage method:

Uniformity of Effect

During the appeal hearing, the ERG representative stated that one of their concerns was that the 2-stage model assumes a uniform effect (i.e. that all patients get the same benefit from switching to five different treatments) which they stated was unlikely to be correct. We consider this to be somewhat misleading without also providing additional context about the calculation of the acceleration factor, as explained in more detail here. The 2-stage model assumes an average adjustment for eligible subjects receiving subsequent therapy. The average adjustment estimates an average of the effect and benefits seen in some patients, equally balanced by including those patients who benefitted less from switching. Therefore, patients who benefitted less or not at all from switching therapy are included in the 2-stage model, which better reflects clinical practice.

The ratio of those patients considered as 'eligible' to switch to subsequent therapy on the basis of having a secondary baseline of disease progression (n=25) versus those who were 'eligible' but did not switch (n=81) is used to generate the acceleration factor; specifically, the calculation of the acceleration factor includes those patients who would have benefited more as well as those who would have benefited less from switching to subsequent therapy. The acceleration factor is then applied uniformly as a multiplicative factor to eligible switchers. This is a known and recognised inherent feature of the 2-stage method.

There are currently no known alternative approaches whereby certain patients could have survival times individually adjusted according to their particular circumstances.

Duration of Subsequent Therapy Received

The Appeal Panel's decision document states "*the evidence is that these treatments are not effective in the first 4-5 months (even when given to patients with less advanced disease). The 2-stage model assumes that all patients benefit, but the ERG think this is unlikely to be the case in advanced disease where life expectancy can be short, so patients may die before the treatment effect begins."*

MSD acknowledge that there is an early crossing of KM curves; however this is not an unusual occurrence in trials featuring immunotherapeutic agents versus chemotherapy (with some rationale being a longer time to immune activation via IO versus the relatively immediate cytotoxicity of chemotherapy), and does not alter the overall results of the study. The KM curves clearly show that the study arms separate from months 4-5 onwards, with pembrolizumab demonstrating superior efficacy versus UK SoC (Appendix - Figure 1).

Table 3**Error! Reference source not found.** below details the duration of subsequent therapy for UK SoC patient who switched to anti-PD-1/PD-L1 treatment. This shows that the mean duration of subsequent anti-PD-1/PD-L1 treatment is >6 months; so beyond the initial 4-5 months duration during which the ERG question the efficacy of such treatment.

Table 3: Duration of Subsequent Anti-PD1/PD-L1 Therapy - Subjects Pre-assigned to UK SoC

KEYNOTE-045	Control
Duration of Subsequent Anti-PD1/PD-L1 Therapy (Days)	
N	40
Mean (SD)	197.6 (235.8)
Median [Min; Max]	119 [1.0; 953.0]
Subsequent therapy end date taken as documented end date of subsequent therapy where available, else earliest of Overall Survival censoring date; death date; data cut-off date. *Duration of subsequent therapy in days defined as End Date - Documented Subsequent Therapy Start Date + 1* *(Database Cutoff Date: 30NOV2018).*	

MSD also disagrees with the statement that pembrolizumab is "*not effective in the first 4-5 months*" – this is not accurate. Patients who received a clinical benefit in the pembrolizumab arm (defined as CR, PR or SD) all did so within that time frame. Patients were scanned ~9 weeks after randomisation and then again 6 weeks after the first scans; so, most patients should have had at least 2 sets of imaging before 4 months on study. This means that all those patients who did not progress on those 2 sets of imaging did experience a clinical benefit from pembrolizumab within the first 4 months on study. Ultimately, the pembrolizumab arm offered patients a better chance at longer survival and durable responses compared with UK SoC, as clearly demonstrated by the KEYNOTE-045 study results.

Subject Characteristics: UK SoC subjects eligible to receive subsequent therapy

A known limitation of the 2-stage model is the requirement that there be no unmeasured confounders. The variables included in the 2-stage model have been consistent for each model run on the KEYNOTE-045 data, for all data-cuts and sub-populations: the same variables (age, gender, ECOG at secondary baseline [0, ≥1], time to progression, liver metastases, time from last prior chemotherapy [<3 vs. ≥3 months], haemoglobin at secondary baseline and site of primary tumour) have been used as per the original submission. During the appeal hearing, the ERG representative acknowledged that the variable considered were a "fairly comprehensive list".

A4. Cost-effectiveness threshold used by NICE in ID1536

> The threshold against which this technology should be assessed is £50,000 per QALY gained, representing the end-of-life modifier applied to the usual threshold of £30,000, accepted for an innovative treatment associated with a confidence in the efficacy data

MSD was concerned to learn during the appeal hearing that an ICER threshold of less than £50,000 per QALY gained had been a consideration. This had not been apparent at any point during the appraisal process. Such a lack of transparency makes it impossible for pharmaceutical companies to successfully conclude a NICE STA process.

Point 82 of the appeal decision letter outlines the consideration that a £34,000 per QALY gained threshold was more appropriate. Neither the ACD nor FAD documents make reference to an ICER threshold of £34,000. The heading for section 3.18 of the ACD and section 3.22 of the FAD both read "*£50,000 per quality-adjusted life year gained"*. If the NICE committee were considering a lower threshold within ID1536, MSD considers the non-transparency around this very important issue to have very significant consequences for the pharmaceutical industry's trust in NICE following due process. Specifically, it has the direct consequence of preventing a company estimating what is cost-effective for this indication.

MSD recognises that it is within the remit of the NICE committee to alter the ICER threshold according to different factors. Section 6.3.3 of the Guide to the Methods of Technology Appraisal states a number of factors that should be accounted for by the NICE committee when assessing technologies with ICERs above £20,000 per QALY gained, including the following[7]:

- *The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.*

- *The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.*

- *The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life' (see section 6.2.10).*

MSD considers pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy to fulfil these three criteria:

- The latest data-cut (November 2018), which was conducted beyond the pre-specified final analysis of KEYNOTE-045, in order to meeting the requirements of the NICE CDF guidance review ID1536, confirms the improvement in OS seen within TA519 and provides more certainty surrounding the ICERs produced.

- Pembrolizumab is considered a highly innovative therapy within a patient population that has not seen advancement in treatments for in excess of a decade. As the CDF guidance review ID1536 should adhere to the same scope as the original appraisal of TA519, there were no alternative immunotherapy options available for this patient population – only standard chemotherapy (atezolizumab is not a relevant comparator in this appraisal).

- As established within sections 3.23 and 3.24 of the 1st FAD[3], pembrolizumab within this indication meets the end of life criteria. Furthermore, Section 6.2.10 of the Guide to the Methods of Technology Appraisal stipulates 2 further criteria for satisfying end-of-life criteria[7]:

    - *the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and*

    - *the assumptions used in the reference case economic modelling are plausible, objective and robust.*

MSD believes that both criteria are met through extensive discussion surrounding the subsequent-line adjustments and assumptions used to inform the economic model. The committee have outlined that a QALY gain of 0.63 to 0.72 is most plausible. MSD hence believe a maximum weight of 1.7 should be applied to the £30,000 per QALY threshold to establish a £50,000 per QALY gained threshold. MSD would also like to highlight that this is in line with all therapies meeting end of life criteria being assessed by NICE within recent years[8,9,10,11,12,13,14]. In each of the referenced TA's, end-of-life criteria were met and the only ICER threshold mentioned within the FAD referred to £50,000 per QALY.

SECTION B: UPDATED COST-EFFECTIVENESS ANALYSES

MSD's Base-Case

Since the second appraisal committee meeting (ACM), there has been an updated Patient Access Scheme (PAS) [redacted] therefore 200 mg administration of pembrolizumab will cost [redacted]. This has been incorporated into the updated analysis provided with this response. Table 4 below presents MSD's preferred base-case deterministic results. MSD's preferred base-case is based on the following assumptions:

- Two-stage adjust for treatment switching (no re-censoring)
- 5-year treatment effect cap
- OS cut-off point at 24 weeks with log-logistic distribution for extrapolation
- PFS cut-off point at 21 weeks with Weibull distribution for extrapolation (updated following 2nd ACM)
- Weibull and Generalised Gamma distributions for ToT of pembrolizumab and UK SOC
- Pooled utility values based on health state approach

Table 4: Deterministic results for MSD base-case (discounted)

TECHNOLOGIES	TOTAL COSTS (£)	TOTAL LYG	TOTAL QALYS	INCREMENTAL COSTS	INCREMENTAL QALYS	ICER (£) VERSUS BASELINE (QALYS)
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	£33,507	0.72	£46,774
ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYS, Quality-Adjusted Life Years						

Additional Analysis

To address the issues outlined by the Committee as a result of the appeal decision, MSD has conducted further scenario analyses surrounding the subsequent line adjustment and retreatment of patients within the pembrolizumab arm.

- **Subsequent line adjustment - modelling overall survival**

Please see Section A.3 for further details of the adjustment methods used. These scenarios have been incorporated into the economic model, with extrapolations being fitted at different cut-off points; however, only a 24-week cut-off point has been presented as per the committee's preference[3]. Table 5 below details the statistical fit of the log-logistic, log-normal and generalised gamma parametric distributions for the pembrolizumab arm in addition to different UK SoC subsequent line adjustment methods. These distributions were the committee's preference[3].

Table 5: Summary of goodness-of fit qualities of OS models for pembrolizumab and UK SoC, at 24 week cut-off, with different adjustment methods

Fitted Function	Pembrolizumab		UK Soc (2-stage adjustment)		UK Soc (2-stage adjustment- with re-censoring)		UK Soc (2-stage adjustment- lower CI as acceleration factor)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Llogistic	**1365.3**	**1371.7**	**664.1**	**669.0**	186	190.9	683.7	688.7
Lnormal	1366.4	1372.7	664.3	669.2	**185.1**	**190.0**	682.5	687.5
GenGamma	1369.8	1379.3	665.7	673.1	186.9	194.3	**680.4**	**687.9**

For each arm, the statistical fit criteria show minimal differences between the distributions. The log-logistic distribution is the best fitting for both the pembrolizumab arm and the UK SoC 2-stage adjustment arm, the log-normal the best fit for the UK SoC 2-stage adjustment with re-censoring arm and the generalised gamma being the marginally best fitting curve for the UK SoC 2-stage adjustment lower CI arm.

Section 3.20 of the 1st FAD stated that clinical expert opinion established a 5-year survival rate for the UK SoC arm to be between 2% to 3%[3]. Table 6 below shows the 5-year survival estimates for the different SoC arm subsequent therapy adjustments, fitted with the log-logistic, log-normal and generalised gamma functions. For each of the different adjustment scenarios the generalized gamma function produces optimistic 5-year overall survival estimates for UK SoC, and therefore considered less plausible.

Table 6: 5-year Overall Survival estimates for the UK SoC arms

Parametric distribution	UK Soc (2-stage adjustment)	UK Soc (2-stage adjustment- recensored)	UK Soc (2-stage adjustment- lower CI as AF)
Llogistic	3.27%	2.13%	3.11%
Lnormal	3.19%	3.20%	2.89%
GenGamma	3.99%	8.48%	5.14%

MSD's preference for modelling overall survival is to use the log-logistic distribution regardless of adjustment scenario; it should be noted that the base case for the company, ERG and committee implemented the log-logistic curve at a 24-week cut-off. This is because the overall survival estimates of the log-logistic and log-normal distributions for UK SoC are both in-line with clinical expert opinion, however the better fitting curve for the pembrolizumab arm is the log-logistic distribution; alongside the MSD base-case for UK SoC using the 2-stage adjustment (without recensoring).

- **Retreatment**

Please see section A2 for details surrounding the retreatment of patients in the pembrolizumab arm within KEYNOTE-045.

MSD has investigated the impact of retreatment on the cost-effectiveness results within further scenario analyses. It is important to note that retreatment is not permitted within UK clinical practice, and therefore this scenario is not fully reflective of UK clinical practice.

The costs incurred by the proportion of patients who are re-treated with pembrolizumab in the pembrolizumab arm are applied using a one-off approach, where a total one-off cost is calculated and applied at the start time in the cost-effectiveness model.

To ensure the appropriate discount was applied to the upfront cost, continuous discounting approach was applied. To calculate the discounted cost at the model start time for costs accrued between two

discrete time points, the following formulae was used. First the instantaneous discount rate (iDR) was calculated from the annual discount rate:

$$iDR = \ln(1 + DR)$$

Using the iDR, the discounted number of life-years between two discrete time points could then be calculated:

$$Discounted\ number\ of\ years = \frac{e^{(t_{new\ event} - iDR)} - e^{(t_{previous\ event} - iDR)}}{-iDR}$$

$t_{previous\ event}$ represents the starting time of re-treatment and $t_{new\ event}$ represents the end time of re-retreatment (start time + duration of retreatment).

The discounted life-years was then applied to the annual cost of pembrolizumab drug acquisition and administration costs to estimate the discounted cost of pembrolizumab re-treatment per patient. This cost was then multiplied by the proportion of patients who had re-treatment resulting in the total one-off discounted cost of pembrolizumab re-re-treatment applied at model start time for the pembrolizumab arm.

Within the economic model the retreatment cost was assumed to start at 24 weeks. MSD consider this to be conservative considering 80% of patients started retreatment after completing 2-years of treatment.

SCENARIO ANALYSIS

- **Scenario 1:** 2-stage adjustment (no re-censoring), 3-year treatment effect duration
- **Scenario 2:** Using the 2-stage adjustment with the lower confidence interval as the acceleration factor, 5-year treatment effect duration
- **Scenario 3:** Using the 2-stage adjustment with re-censoring for the UK SoC arm, 5-year treatment effect duration
- **Scenario 4:** Using the 2-stage adjustment with the lower confidence interval as the acceleration factor, 3-year treatment effect duration
- **Scenario 5:** Using the 2-stage adjustment with re-censoring for the UK SoC arm, 3-year treatment effect duration
- **Scenario 6:** Using the 2-stage adjustment (no re-censoring), including the cost of retreatment, 5-year treatment effect duration

Table 7:Results from the scenario analyses versus trial UK SoC (discounted price)

Description	Pembrolizumab		UK SoC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case: 5-year treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	£33,507	0.72	£46,774
Scenario 1: 2-stage adjustment (no recensoring), 3-year TE duration	[redacted]	[redacted]	[redacted]	[redacted]	£32,508	0.63	£51,692
Scenario 2: 2-stage adjustment with lower CI as AF, 5-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£33,182	0.69	£48,277
Scenario 3: 2-stage adjustment with recensoring, 5-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£34,040	0.77	£44,395
Scenario 4: 2-stage adjustment with lower CI as AF, 3-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£32,031	0.59	£54,638
Scenario 5: 2-stage adjustment with recensoring, 3-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£32,776	0.66	£49,988
Scenario 6: 2-stage adjustment (no recensoring), retreatment	[redacted]	[redacted]	[redacted]	[redacted]	£34,992	0.72	£48,848

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis is presented below, incorporating the updated CAA.

Table 8: Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
UK SOC	[redacted]	1.07	[redacted]				
Pembrolizumab	[redacted]	2.16	[redacted]	£33,745	1.09	0.72	£47,052
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 2 and Figure 3. The cost-effectiveness acceptability curve shows that there is a 65% probability of pembrolizumab being cost-effective when compared to UK SoC at the £50,000 per QALY threshold applicable to end-of-life technologies.

Figure 2: Scatterplot of probabilistic results (1,000 simulations; results discounted, with updated PAS)

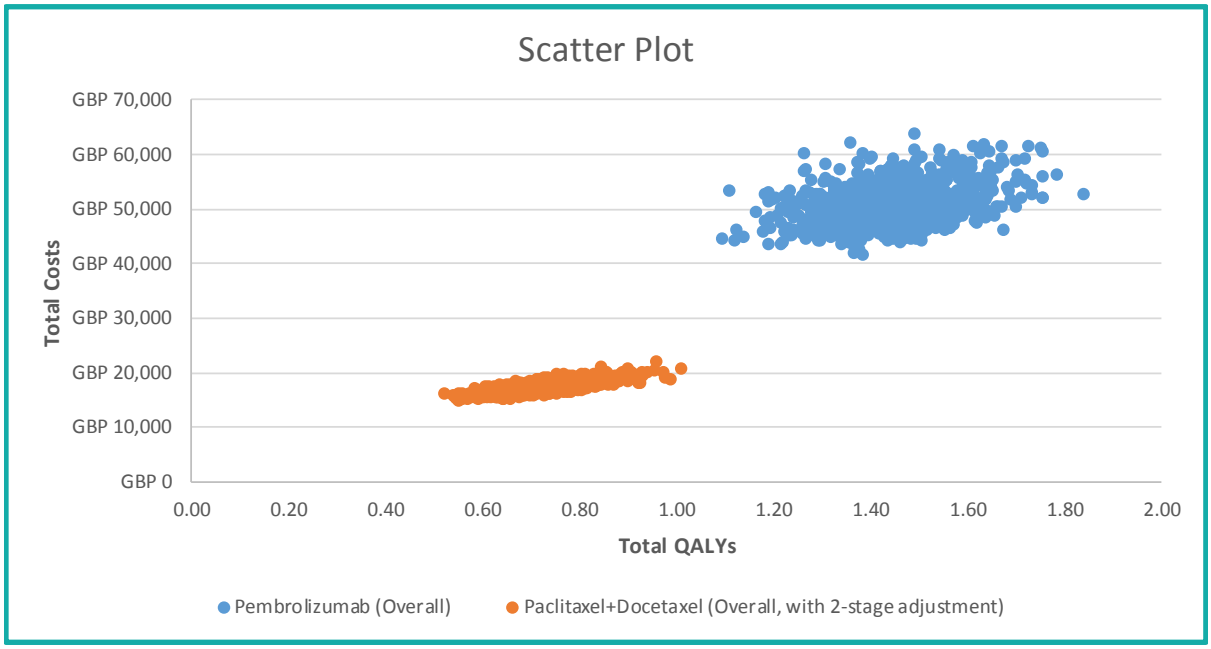
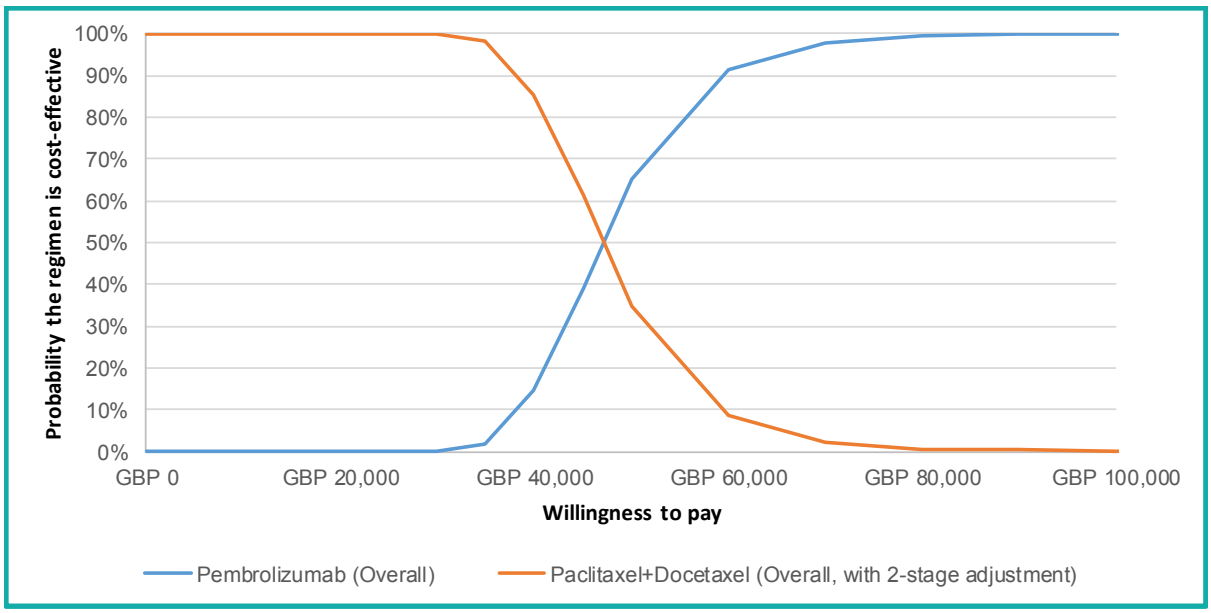


Figure 3: Cost-effectiveness acceptability curve (results discounted, with updated PAS)



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10. NICE Final Appraisal Documentation. Entrectinib for treating NTRK fusion-positive solid tumours TA644

11. NICE Final Appraisal Documentation. Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer TA628

12. NICE Final Appraisal Documentation. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer TA620

13. NICE Final Appraisal Documentation. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer. TA600

14. NICE Final Appraisal Documentation. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. TA584

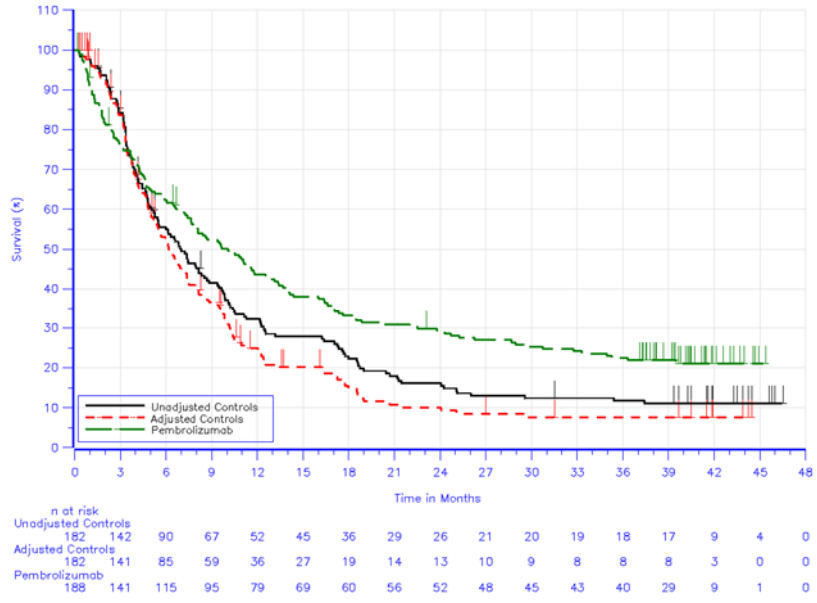
Appendix

Table 1:Analysis of OS | No re-censoring - Subjects pre-assigned to UK SoC - Comparison pembrolizumab versus UK SoC - adjusting for treatment switch to anti-PDL1 treatment in SoC arm using 2-stage analysis

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‖
Control	182	147 (80.8)	2026.2	7.3	7.0 (5.5, 8.7)	32.2 (25.2, 39.4)	---	---
Control, Adjusted ¶	182	147 (80.8)	1559.6	9.4	6.2 (5.2, 7.4)	25.0 (18.6, 31.9)	---	---
Pembrolizumab	188	144 (76.6)	2923.5	4.9	10.1 (7.6, 12.9)	43.5 (36.3, 50.6)	0.64 (0.49, 0.81)	0.0139
Stage 1 model††							**Acceleration factor‡‡**	
§ Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy							5.370 (3.231,10.094)	

¶ Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and haemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.
‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.
†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumour (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and haemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression.
§ Patients were eligible to receive subsequent therapy if they had documented progression.
‡‡ Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy. The 95% CI is based on the same bootstrap samples as for the Cox regression model

Figure 1: Kaplan-Meier (KM) Curves of OS Adjusting for Treatment Switch using 2-stage analysis - No re-censoring - Subjects Pre-Assigned to UK SoC - ITT



(Database Cutoff Date: 30NOV2018)

Table 2: Analysis of Overall Survival | No Recensoring - Subjects Pre-Assigned to UK SoC - Comparison Pembrolizumab versus UK SoC - Adjusting for Treatment Switch to anti-PDL1 treatment in SOC arm using 2-stage analysis with acceleration factor of 3.23

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‖
Control	182	147 (80.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control, Adjusted ¶	182	147 (80.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	188	144 (76.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stage 1 model††	Acceleration factor‡‡
§ Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy	3.231

¶ Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and hemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.

‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.

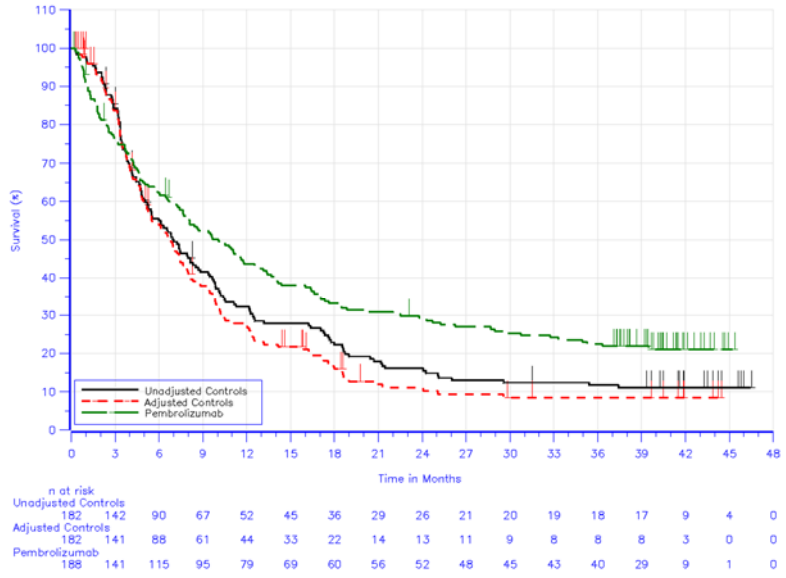
†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumor (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and hemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression. The acceleration factor is the lower limit of the 95% confidence interval around the estimated effect of switch versus no switch.

§ Patients were eligible to receive subsequent therapy if they had documented progression.

‡‡ Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

(Database Cutoff Date: 30NOV2018).

Figure 2: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis with acceleration factor of 3.23 - No recensoring - Subjects Pre-Assigned to UK SoC



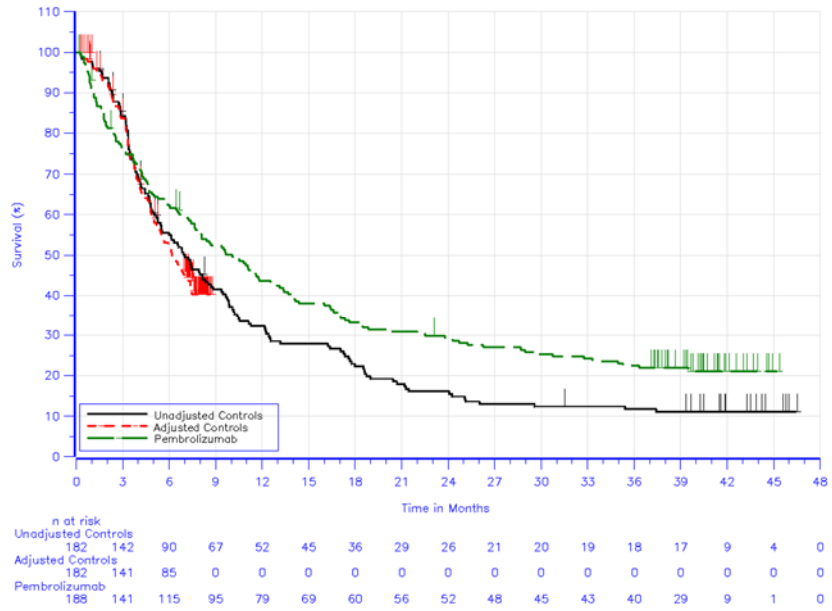
(Database Cutoff Date: 30NOV2018)

Table 3: Analysis of Overall Survival | With Recensoring - Subjects Pre-Assigned to Paclitaxel or Docetaxel - ITT Population - Comparison Pembrolizumab versus Standard of Care (SOC) - Adjusting for Treatment Switch to anti-PDL1 treatment in SOC arm using 2-stage analysis

Treatment	*N*	*Number of Events (%)*	*Person-Months*	*Event Rate/ 100 Person-Months (%)*	*Median OS† (Months) (95% CI)*	*OS Rate at Month 12 in %† (95% CI)*	*Treatment vs. Control*	
							Hazard Ratio‡ (95% CI)‡	*p-Value‖*
Control	*182*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control, Adjusted ¶	*182*							
Pembrolizumab	*188*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 1 model††								***Acceleration factor‡‡***
§ Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy								*5.370 (3.231,10.094)*

¶ Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and hemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.
‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.
†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumor (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and hemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression.
§ Patients were eligible to receive subsequent therapy if they had documented progression.
‡‡ Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy. The 95% CI is based on the same bootstrap samples as for the Cox regression model
(Database Cutoff Date: 30NOV2018).

Figure 3: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis With recensoring -Subjects Pre-Assigned to Paclitaxel or Docetaxel -ITT Population



(Database Cutoff Date: 30NOV2018)

08 December 2020

Merck Sharp & Dohme (UK) Limited
Registered in England No. 233687
Registered Office: 120 Moorgate,
London, United Kingdom EC2M 6UR

Dr Linda Landells
Associate Director, Committee D, NICE

Dear Linda,

ID1536: Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519)

Further to my email of earlier today, please find enclosed an updated version of the cost-effectiveness analyses previously submitted on 07 October 2020.

The updated analyses are being submitted today [redacted]. No further changes have been made to the analyses submitted.

For ease of reference, we enclose the following:

- ***Summary document***: Provides the updated cost-effectiveness analyses (results only)
- ***Appendix 1***: Provides an updated version of the full cost-effectiveness analyses previously submitted on 07 October 2020 (including explanatory text regarding each scenario analysis)

Please let me know should you have any questions.

Sincerely,

[redacted]
Team Leader – HTA & OR

SUMMARY DOCUMENT: UPDATED COST-EFFECTIVENESS ANALYSES

MSD's Base-Case

Since the analysis submitted on the 07 October 2020, there has been an updated Patient Access Scheme (PAS) [redacted] therefore 200 mg administration of pembrolizumab will cost [redacted]. This has been incorporated into the updated analysis provided below. Table 1 below presents MSD's preferred base-case deterministic results. MSD's preferred base-case is based on the following assumptions:

- Two-stage adjust for treatment switching (no re-censoring)
- 5-year treatment effect cap
- OS cut-off point at 24 weeks with log-logistic distribution for extrapolation
- PFS cut-off point at 21 weeks with Weibull distribution for extrapolation (updated following 2nd ACM)
- Weibull and Generalised Gamma distributions for ToT of pembrolizumab and UK SOC
- Pooled utility values based on health state approach

Table 1: Deterministic results for MSD base-case (discounted)

TECHNOLOGIES	TOTAL COSTS (£)	TOTAL LYG	TOTAL QALYS	INCREMENTAL COSTS	INCREMENTAL QALYS	ICER (£) VERSUS BASELINE (QALYS)
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	£30,933	0.72	£43,181
ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYS, Quality-Adjusted Life Years						

SCENARIO ANALYSIS

Please see the response document submitted on the 7th October 2020 for the full description of the scenario analyses presented below.

- **Scenario 1:** 2-stage adjustment (no re-censoring), 3-year treatment effect duration
- **Scenario 2:** Using the 2-stage adjustment with the lower confidence interval as the acceleration factor, 5-year treatment effect duration
- **Scenario 3:** Using the 2-stage adjustment with re-censoring for the UK SoC arm, 5-year treatment effect duration
- **Scenario 4:** Using the 2-stage adjustment with the lower confidence interval as the acceleration factor, 3-year treatment effect duration
- **Scenario 5:** Using the 2-stage adjustment with re-censoring for the UK SoC arm, 3-year treatment effect duration
- **Scenario 6:** Using the 2-stage adjustment (no re-censoring), including the cost of retreatment, 5-year treatment effect duration

Table 2:Results from the scenario analyses versus trial UK SoC (discounted price)

Description	Pembrolizumab		UK SoC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case: 5-year treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	£30,932	0.72	£43,181
Scenario 1: 2-stage adjustment (no recensoring), 3-year TE duration	[redacted]	[redacted]	[redacted]	[redacted]	£29,934	0.63	£47,599
Scenario 2: 2-stage adjustment with lower CI as AF, 5-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£30,608	0.69	£44,532
Scenario 3: 2-stage adjustment with recensoring, 5-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£31,466	0.77	£41,038
Scenario 4: 2-stage adjustment with lower CI as AF, 3-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£29,457	0.59	£50,247
Scenario 5: 2-stage adjustment with recensoring, 3-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£30,202	0.66	£46,063
Scenario 6: 2-stage adjustment (no recensoring), retreatment	[redacted]	[redacted]	[redacted]	[redacted]	£32,278	0.72	£45,060

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis is presented below, incorporating the updated CAA.

Table 3: Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£31,041	1.07	0.71	£43,834

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 1 and Figure 2. The cost-effectiveness acceptability curve shows that there is a 79% probability of pembrolizumab being cost-effective when compared to UK SoC at the £50,000 per QALY threshold applicable to end-of-life technologies.

Figure 1: Scatterplot of probabilistic results (1,000 simulations; results discounted, with updated PAS)

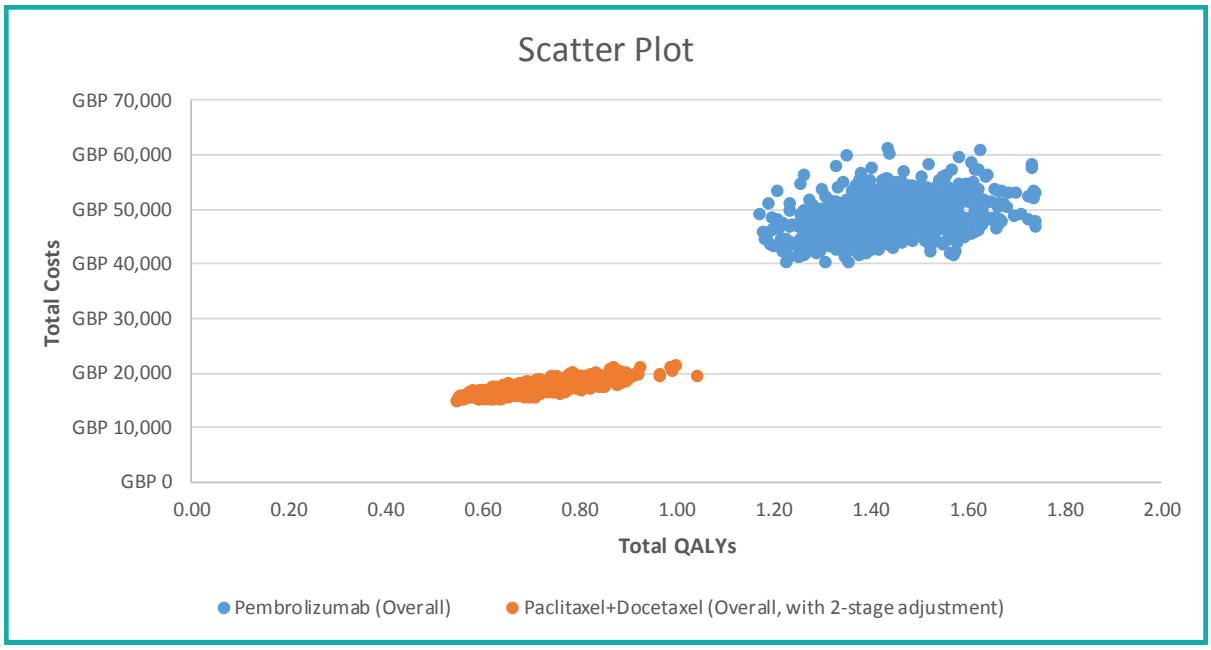
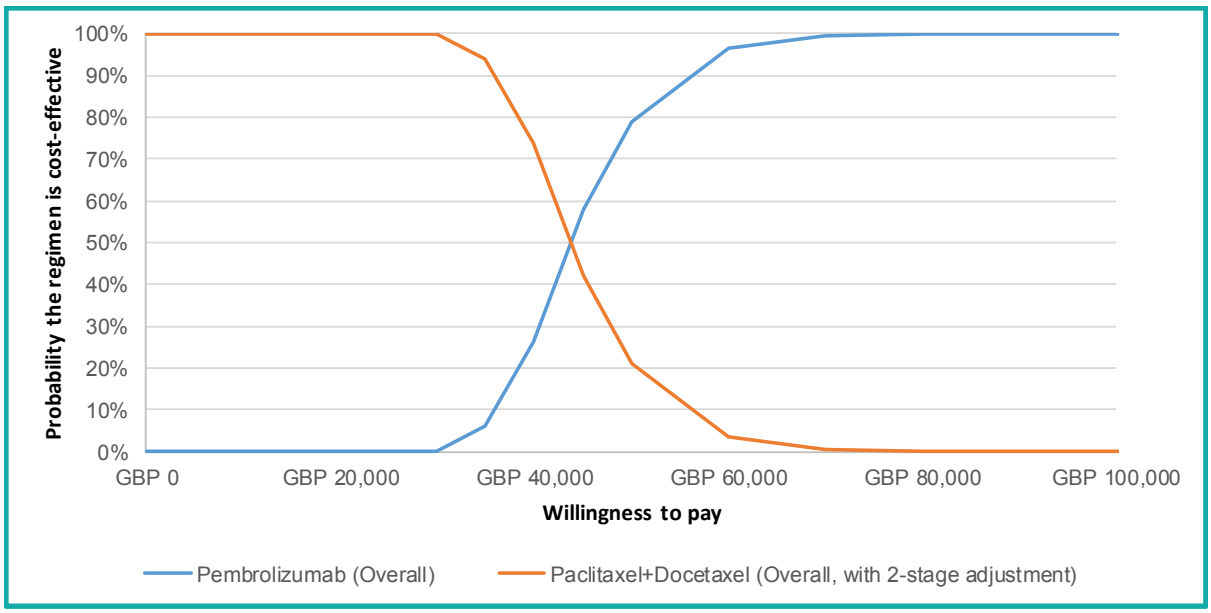


Figure 2: Cost-effectiveness acceptability curve (results discounted, with updated PAS)



References

1. NICE Final Appraisal Documentation. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1536]. 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10466/documents/final-appraisal-determination-document

APPENDIX 1: UPDATED VERSION OF COST-EFFECTIVENESS ANALYSES PREVIOUSLY SUBMITTED ON 07 OCTOBER 2020 (CHANGE TO SIMPLE DISCOUNT ONLY)

MSD's Base-Case

Since the analysis submitted on the 07 October 2020, there has been an updated Patient Access Scheme (PAS) [redacted] therefore 200 mg administration of pembrolizumab will cost [redacted]. This has been incorporated into the updated analysis provided below. Table 1 below presents MSD's preferred base-case deterministic results. MSD's preferred base-case is based on the following assumptions:

- Two-stage adjust for treatment switching (no re-censoring)
- 5-year treatment effect cap
- OS cut-off point at 24 weeks with log-logistic distribution for extrapolation
- PFS cut-off point at 21 weeks with Weibull distribution for extrapolation (updated following 2nd ACM)
- Weibull and Generalised Gamma distributions for ToT of pembrolizumab and UK SOC
- Pooled utility values based on health state approach

Table 4: Deterministic results for MSD base-case (discounted)

TECHNOLOGIES	TOTAL COSTS (£)	TOTAL LYG	TOTAL QALYS	INCREMENTAL COSTS	INCREMENTAL QALYS	ICER (£) VERSUS BASELINE (QALYS)
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	£30,933	0.72	£43,181
ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYS, Quality-Adjusted Life Years						

Additional Analysis

To address the issues outlined by the Committee as a result of the appeal decision, MSD has conducted further scenario analyses surrounding the subsequent line adjustment and retreatment of patients within the pembrolizumab arm.

- **Subsequent line adjustment - modelling overall survival**

Please see Section A.3 of the response document submitted on 07 October 2020 for further details of the adjustment methods used. These scenarios have been incorporated into the economic model, with extrapolations being fitted at different cut-off points; however, only a 24-week cut-off point has been presented as per the committee's preference[1]. Table 5 below details the statistical fit of the log-logistic, log-normal and generalised gamma parametric distributions for the pembrolizumab arm in addition to different UK SoC subsequent line adjustment methods. These distributions were the committee's preference[1].

Table 5: Summary of goodness-of fit qualities of OS models for pembrolizumab and UK SoC, at 24 week cut-off, with different adjustment methods

Fitted Function	Pembrolizumab		UK Soc (2-stage adjustment)		UK Soc (2-stage adjustment- with re-censoring)		UK Soc (2-stage adjustment- lower CI as acceleration factor)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Llogistic	**1365.3**	**1371.7**	**664.1**	**669.0**	186	190.9	683.7	688.7
Lnormal	1366.4	1372.7	664.3	669.2	**185.1**	**190.0**	682.5	687.5
GenGamma	1369.8	1379.3	665.7	673.1	186.9	194.3	**680.4**	**687.9**

For each arm, the statistical fit criteria show minimal differences between the distributions. The log-logistic distribution is the best fitting for both the pembrolizumab arm and the UK SoC 2-stage adjustment arm, the log-normal the best fit for the UK SoC 2-stage adjustment with re-censoring arm and the generalised gamma being the marginally best fitting curve for the UK SoC 2-stage adjustment lower CI arm.

Section 3.20 of the 1st FAD stated that clinical expert opinion established a 5-year survival rate for the UK SoC arm to be between 2% to 3%[1]. Table 6 below shows the 5-year survival estimates for the different SoC arm subsequent therapy adjustments, fitted with the log-logistic, log-normal and generalised gamma functions. For each of the different adjustment scenarios the generalized gamma function produces optimistic 5-year overall survival estimates for UK SoC, and therefore considered less plausible.

Table 6: 5-year Overall Survival estimates for the UK SoC arms

Parametric distribution	UK Soc (2-stage adjustment)	UK Soc (2-stage adjustment- recensored)	UK Soc (2-stage adjustment- lower CI as AF)
Llogistic	3.27%	2.13%	3.11%
Lnormal	3.19%	3.20%	2.89%
GenGamma	3.99%	8.48%	5.14%

MSD's preference for modelling overall survival is to use the log-logistic distribution regardless of adjustment scenario; it should be noted that the base case for the company, ERG and committee implemented the log-logistic curve at a 24-week cut-off. This is because the overall survival estimates of the log-logistic and log-normal distributions for UK SoC are both in-line with clinical expert opinion, however the better fitting curve for the pembrolizumab arm is the log-logistic distribution; alongside the MSD base-case for UK SoC using the 2-stage adjustment (without recensoring).

- **Retreatment**

Please see section A.2 of the response document submitted on 07 October 2020 for details surrounding the retreatment of patients in the pembrolizumab arm within KEYNOTE-045.

MSD has investigated the impact of retreatment on the cost-effectiveness results within further scenario analyses. It is important to note that retreatment is not permitted within UK clinical practice, and therefore this scenario is not fully reflective of UK clinical practice.

The costs incurred by the proportion of patients who are re-treated with pembrolizumab in the pembrolizumab arm are applied using a one-off approach, where a total one-off cost is calculated and applied at the start time in the cost-effectiveness model.

To ensure the appropriate discount was applied to the upfront cost, continuous discounting approach was applied. To calculate the discounted cost at the model start time for costs accrued between two

discrete time points, the following formulae was used. First the instantaneous discount rate (iDR) was calculated from the annual discount rate:

$$iDR = \ln(1 + DR)$$

Using the iDR, the discounted number of life-years between two discrete time points could then be calculated:

$$Discounted\ number\ of\ years = \frac{e^{(t_{new\ event} - iDR)} - e^{(t_{previous\ event} - iDR)}}{-iDR}$$

$t_{previous\ event}$ represents the starting time of re-treatment and $t_{new\ event}$ represents the end time of re-retreatment (start time + duration of retreatment).

The discounted life-years was then applied to the annual cost of pembrolizumab drug acquisition and administration costs to estimate the discounted cost of pembrolizumab re-treatment per patient. This cost was then multiplied by the proportion of patients who had re-treatment resulting in the total one-off discounted cost of pembrolizumab re-re-treatment applied at model start time for the pembrolizumab arm.

Within the economic model the retreatment cost was assumed to start at 24 weeks. MSD consider this to be conservative considering 80% of patients started retreatment after completing 2-years of treatment.

SCENARIO ANALYSIS

- **Scenario 1:** 2-stage adjustment (no re-censoring), 3-year treatment effect duration
- **Scenario 2:** Using the 2-stage adjustment with the lower confidence interval as the acceleration factor, 5-year treatment effect duration
- **Scenario 3:** Using the 2-stage adjustment with re-censoring for the UK SoC arm, 5-year treatment effect duration
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Table 7:Results from the scenario analyses versus trial UK SoC (discounted price)

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	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
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Scenario 2: 2-stage adjustment with lower CI as AF, 5-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£30,608	0.69	£44,532
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Scenario 4: 2-stage adjustment with lower CI as AF, 3-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£29,457	0.59	£50,247
Scenario 5: 2-stage adjustment with recensoring, 3-year TE	[redacted]	[redacted]	[redacted]	[redacted]	£30,202	0.66	£46,063
Scenario 6: 2-stage adjustment (no recensoring), retreatment	[redacted]	[redacted]	[redacted]	[redacted]	£32,278	0.72	£45,060

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis is presented below, incorporating the updated CAA.

Table 8: Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£31,041	1.07	0.71	£43,834
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 1 and Figure 2. The cost-effectiveness acceptability curve shows that there is a 79% probability of pembrolizumab being cost-effective when compared to UK SoC at the £50,000 per QALY threshold applicable to end-of-life technologies.

Figure 3: Scatterplot of probabilistic results (1,000 simulations; results discounted, with updated PAS)

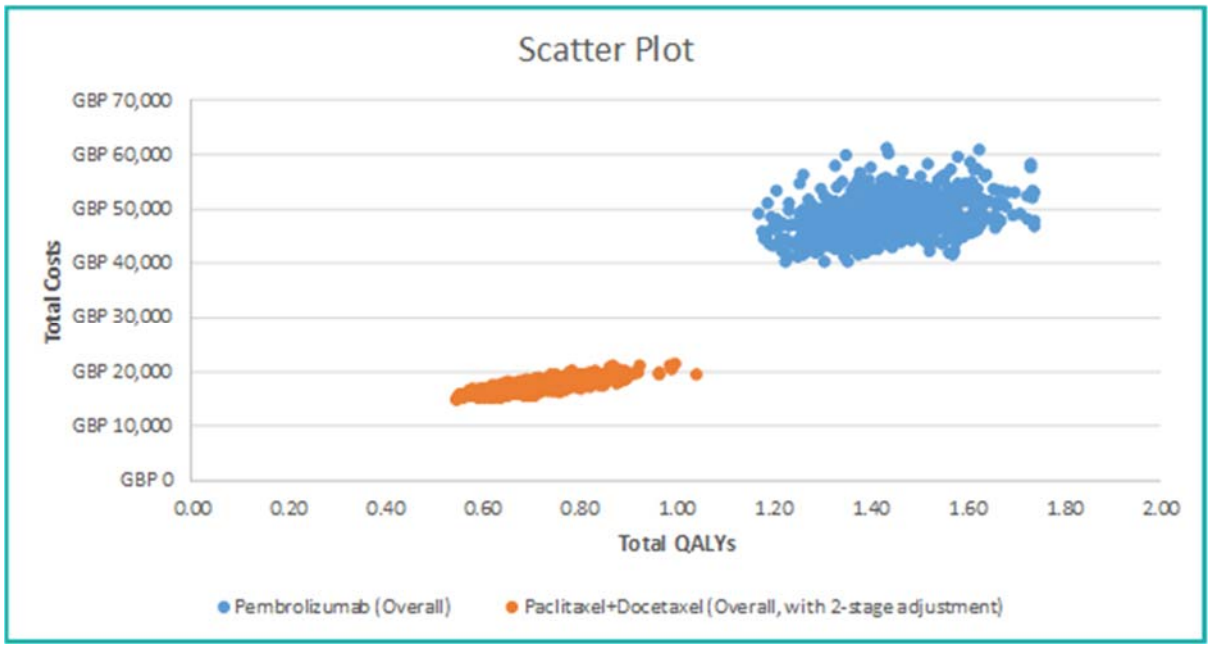
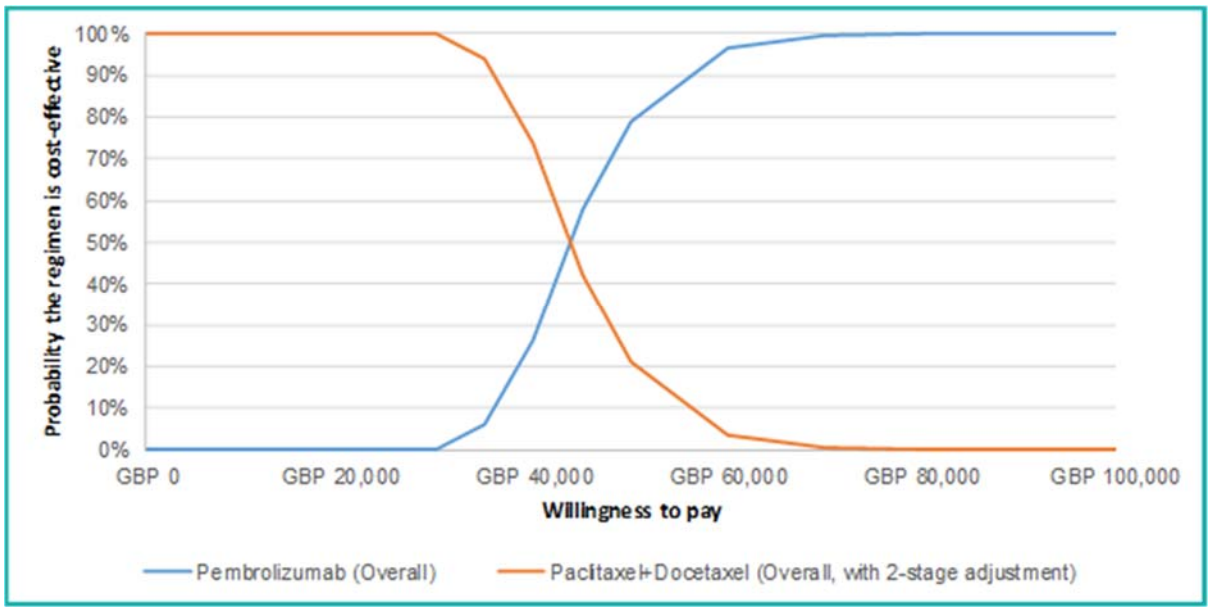


Figure 4: Cost-effectiveness acceptability curve (results discounted, with updated PAS)



References

2. NICE Final Appraisal Documentation. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1536]. 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10466/documents/final-appraisal-determination-document

Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519 - post-appeal work [ID1536]

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Rider on responsibility for report:
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:
Daniel Gallacher (Research Fellow) conducted, reviewed and critiqued the survival and cost-effectiveness analysis and undertook additional analyses; Hema Mistry (Associate Professor) co-ordinated the project and the report, and provided comments on the report.

Contents

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Introduction

This report contains the Evidence Review Group (ERG) summary and critique of the company submission following the appeal hearing on the 23 June 2020.

The company submission is presented as two sections. Section A contains detailed responses on the three main areas of discussion: (i) duration of treatment effect, (ii) the costs of retreatment and (iii) adjustment for treatment switching in the control arm, each of which the ERG will critique below. The company also provide comment on the cost-effectiveness thresholds considered when assessing cost-effectiveness, however this issue is beyond the remit of the ERG.

Appendix 1, which replaces Section B, contains the output from a range of cost-effectiveness analyses. The analyses in Section B include a new PAS discount of [redacted], which was later updated to [redacted] partway through this current appraisal (Appendix 1) and is reflected in the additional analyses presented by the company, whereas in the previous consideration of this appraisal (before the appeal), the PAS discount was [redacted].

All analyses are based on the same data cut from KEYNOTE-045 as in the previous company submission (November 2018). This is disappointing as the availability of additional follow-up would have decreased the level of uncertainty around some of the outstanding discussion points raised in this post-appeal.

Critique and Summary of A1 - Duration of Treatment Effect

In this appraisal, the duration of treatment effect refers to the duration of time from the start of the treatment (i.e. start of KEYNOTE-045) for which the hazard rate of overall survival for patients who were randomised to the pembrolizumab arm differs from patients who were randomised to the comparator arm. Beyond either 3 or 5 years, the hazard rate for the pembrolizumab arm is modelled to be equal to that of the UK SOC patient group. In the company's submission A1, their comments focus on the comparison between this appraisal and TA525, which assessed the clinical and cost-effectiveness of atezolizumab for the same indication. In the final appraisal document (FAD) for TA525 the committee considered an analysis where the treatment effect duration was modelled to last for 3 years beyond the end of treatment duration, which was capped at 2 years. This was the shortest treatment effect duration included in the analyses presented within TA525.

There are similarities between these two therapies in that they are both immunotherapies which target the PD-1/PD-L1 pathway. However, the ERG are cautious to accept the 5 year treatment effect duration solely on this basis without considering all of the available evidence. The company state that the maximum follow-up of any patients in the key trials in TA525 was 24.5 months. This suggests that any decision on treatment effect duration in TA525 was not supported by strong evidence from clinical trials. For this present appraisal, we are able to use TA525 as a reference point, whilst also considering the evidence from the extended follow-up of KEYNOTE-045.

As mentioned previously, in KEYNOTE-045 the duration of pembrolizumab was capped at a maximum of 2 years, whilst in IMvigor211, the key phase III trial of TA525, there was no such restriction. Whilst atezolizumab has only been approved for use in the UK subject to a maximum time on treatment of 2 years, this restriction was not present in the clinical trials informing the appraisal, and neither was any formal adjustment made to account for this potential change in the clinical efficacy that may be experienced with the reduced treatment duration. It's unclear how the decision to approve atezolizumab for a maximum of 2 years therapy influenced the committee's

preferred treatment effect duration, but it is possible that the clinical evidence based on the longer treatment duration remained influential.

A second inconsistency between the appraisals, is that pembrolizumab therapy stops immediately upon disease progression. However, section 3.10 of the FAD for TA525 states that patients "for whom atezolizumab remains beneficial would continue treatment after their disease progresses." This reflects the different design of the two trials (KEYNOTE-045 and IMvigor211), where IMvigor211 permitted atezolizumab therapy beyond disease progression under certain circumstances. This would suggest that patients may on average take atezolizumab for longer than pembrolizumab, therefore, more likely receiving a relative benefit for a longer period.

Recalling that this issue is only to relative to patients still alive, a further inconsistency is the proportions of alive patients predicted to be receiving therapy at 2 years. For atezolizumab in TA525, extracting information from the publicly available committee papers, approximately 22.1% of patients were predicted to be alive at 2 years, with 11.5% still on treatment at two years. The latter estimate is taken from a generalised gamma extrapolation, whilst the FAD for TA525 indicates a more optimistic log-logistic extrapolation was actually used for decision making. These reported figures suggest that at least 52% of patients alive at 2 years are still receiving therapy. In contrast, the company's modelling for pembrolizumab predicts that [redacted] of all patients will be on treatment at 2 years, having selected a Weibull curve for extrapolation, and [redacted] patients will still be alive. These estimates suggest that [redacted] of patients alive at 2 years are still receiving therapy. It is not possible to ascertain whether this difference between 52% and [redacted] can be attributable solely to the continuation of atezolizumab therapy beyond progression, or whether there are other contributing factors, however it is undeniable that there is a considerable difference between the populations remaining alive at two years, in terms of their time on treatment.

An examination of the company's preferred Weibull curve suggests that it does not fit well to observed data in the tail of the time-on-treatment curve for pembrolizumab (Figure 1). The log-logistic curve is the best visual fit and predicts [redacted] of total patients to remain on treatment. This is more consistent with the assumptions of TA525, where a log-logistic extrapolation was used, and the ERG present a scenario combining the log-logistic time-on-treatment extrapolation with the 5-year treatment effect duration. Selecting the log-logistic curve results in [redacted] of patients alive at 2 years remaining on treatment.

Figure 1: Time on treatment extrapolations from KEYNOTE-045 data

Ideally, detailed information on treatment response would also be considered, however little information is publicly available, especially for atezolizumab. Median duration of response had not been reached in any of the reported follow-up for pembrolizumab or atezolizumab.

There are also further differences between the populations of the two trials, particularly in the baseline characteristics and the ratio of chemotherapy regimens received in the control arms, all of which may influence the relative efficacy of pembrolizumab/atezolizumab and their respective comparators.

Furthermore, the ERG cannot be confident that the implementation of the fixed duration of treatment effect was uniform across the two appraisals, as it is not described in sufficient detail in the committee papers of TA525.

The ERG have previously presented information based on the follow-up of KEYNOTE-045 which in our interpretation, suggests the relative effect of pembrolizumab over UK SOC is unlikely to be sustained for 5 years.

In conclusion, the ERG do not agree that a 5-year treatment effect duration is the most suitable for this appraisal and maintain that such an assumption is not well justified by TA525. Instead, the ERG prefer the consideration of either a 3 year treatment effect duration used in combination with the Weibull time-on-treatment (TOT) extrapolation, or a 5 year treatment effect duration used in combination with the log-logistic TOT extrapolation for pembrolizumab.

Critique and Summary of A2 - Costs of Retreatment

The company present brief detail on the 10 patients in the pembrolizumab arm who received an additional course of pembrolizumab therapy after their initial treatment. The company report that the median number of cycles received was 10 (minimum 3, maximum 18). This corresponds to a median of 30 weeks (minimum 9 weeks, maximum 54 weeks). The company clarified that these durations were not subject to censoring, and that the patients had completed their retreatment. It is also possible that additional patients have received a second course of pembrolizumab since the

November 2018 datacut.

The ten patients correspond to 3.7% of the original 270 patients randomised to pembrolizumab, to [redacted] of the patients predicted alive at 2 years and [redacted] of patients predicted alive at 3 years. Retreatment also suggests a lack of sustained treatment effect from the first course. Whilst these 10 patients are not a majority in the KEYNOTE-045 trial, they are also not negligible proportions of patients, and have the potential to be influential in the cost-effectiveness analysis. The company present a scenario analysis where the costs of retreatment are included in Section B/Appendix 1.

Critique and Summary of A3 - 2-stage adjustment for treatment switching from control arm

In KEYNOTE-045, 40 patients from the UKSOC population (22%) switched to an anti PD-1/PD-L1 therapy. The company states that these patients received a benefit which should be adjusted out of the analysis to reflect the survival of the population had none of them switched treatments. Their preferred adjustment method is the '2-stage adjustment' where patients who switched at disease progression (n=25) have their post-progression survival times shrunk by an acceleration factor which is estimated by comparing patients who switched at disease progression to those who did not switch. The 15 patients who switched without being considered eligible to be included in the 2-stage adjustment did not have their survival times adjusted. The acceleration factor was estimated to be 5.37 (95% confidence interval: 3.23, 10.09), which means that the post-progression survival time of the 25 patients was divided by 5.37 to obtain their survival time had they not switched.

The company present a series of four scenario analyses exploring the influence of the 2-stage adjustment, some of which are later incorporated into the economic model in Section B.

The first scenario analysis uses as the value of the acceleration factor the estimate of the lower 95% confidence interval (3.23) from the statistical model. This provides a more conservative analysis than the company's base-case analysis.

The second scenario analysis uses re-censoring. The 2-stage adjustment can result in biased analyses when the re-censoring is not performed. The ERG had previously suggested that the company present analysis using re-censoring for completeness. Upon review, the re-censoring has considerably decreased the follow-up and information contained in the control arm to the extent that it is unlikely that this analysis will be very useful to the assessment of cost-effectiveness.

The third scenario analysis includes vinflunine patients in the calculation and implementation of the 2-stage adjustment. These patients were previously excluded from the analysis since vinflunine is not licensed for this indication in England and Wales. This analysis has already been provided by the company at an earlier stage of this appraisal.

The fourth scenario has also been presented previously, where the company apply the acceleration factor calculated from 25 patients who switched onto the full 40 patients who switched. This analysis did not address the concerns raised by the ERG, as the 15 patients who switched but were ineligible for inclusion in the original 2-stage calculation, have still not been included in the calculation of the acceleration factor.

The company conclude that their preference is for the 2-stage adjustment to be implemented applying the acceleration factor of 5.37 to the 25 patients who switched.

The company have not provided the data required for the ERG to reproduce the calculation of the acceleration factor nor details on the patients who switched, which the ERG have previously requested to reduce uncertainty in the suitability of the 2-stage adjustment.

Hence, in order to further investigate the suitability of the 2-stage adjustment, the ERG have recreated the patient level data from the information contained in the economic model for both the adjusted and unadjusted UK SOC population. After comparing the two sets, and removing those that matched, the ERG were able to identify the overall survival (OS) event or censoring times of the 25 patients who were affected by the 2-stage adjustment, with [redacted] experiencing an event, and [redacted] censored. By assuming that within patients progressed in the same order as their event or censoring times, the ERG could generate patient level progression times, and post-progression survival times.

The ERG anticipated that some of the patients who switched may not receive any benefit from switching in terms of life-years, reflecting the behaviour observed in the pembrolizumab arm of KEYNOTE-045, where there are fewer patients alive in the pembrolizumab arm than in the UKSOC arm for a short period. The OS curves only move in favour of pembrolizumab from approximately 4.5 months once 35% of patients in the pembrolizumab arm are expected to have died according to the Kaplan-Meier graph. In contrast, the 2-stage adjustment applied the same average acceleration factor to all 25 patients who switched. It is difficult to compare these periods, as within the trial, pembrolizumab had an active comparator, whereas there was no clear comparator treatment to compare against those who switched treatment from the control arm.
The ERG considered the option of removing the adjustment for patients whose post-progression survival time was less than 4.5 months, whilst leaving the adjustment in place only for patients who may have received life extending benefit. Following a review of the ERG's analysis the company reported that [redacted] died within 4.5 months of switching therapy, meaning it is plausible that at least [redacted] of patients who switched likely received some additional benefit from switching. This is slightly higher than the 65% of patients in the original pembrolizumab arm who were alive at the point that pembrolizumab began to demonstrate superior OS to UKSOC within KEYNOTE-045. The ERG are aware that this apparent difference could partly be explained by the difference in comparator, as pembrolizumab is being compared to active treatment (UKSOC), whilst the switched treatments are not.

Additional information provided by the company suggests [redacted] of the switchers have post-progression survival/censoring times that are in excess of 12 months, compared to a 1-year OS rate of pembrolizumab patients in KEYNOTE-045 of 44.2%. The ERG conclude that the reported experience of the switchers is generally superior to the efficacy observed in the original pembrolizumab arm.

However, the 2-stage adjustment does not attribute all of this post-progression survival benefit to treatment switching, and so the ERG sought to examine the benefit attributed to treatment switching. The ERG conducted an analysis reconstructing the adjusted and unadjusted survival times for the 25 switching patients. The company have had the opportunity to review this analysis and did not provide the actual observed data from KEYNOTE-045, as they did for the previous output from the ERG analysis. The results of the ERG analysis are potentially more reliable as they consider the switchers as a group, rather than as individual patients. However the ERG welcome additional information from the company, if the ERG analysis is inaccurate.

Using the ERG analysis, a comparison of the influence of the two values for the acceleration factor (5.37 and 3.23) presented by the company is shown in Table 1. Table 1 shows what proportion of the post-progression survival is attributed to the treatment switching by each acceleration factor and compares this to the average post-progression treatment duration for the whole UKSOC population. The estimates from the application of the full acceleration factor (5.37) suggest that the switching patients would have had a shorter post-progression survival than the average patient in the UKSOC arm. This supports the ERG's previous view that the acceleration factor was too severe. By comparison, the estimate for using the lower 95% confidence interval of the acceleration factor (3.23) is a close match to the UKSOC average.

Table 1: Comparison of effects of acceleration factors

	Acceleration Factor = 5.37	Acceleration Factor = 3.23	LY Estimate for UK SOC
Mean Post Progression Survival/Censoring time attributed to treatment switching	[redacted]	[redacted]	7.2 months* 7.3 months**
Mean Post Progression Survival/Censoring time not attributed to treatment switching	[redacted]	[redacted]	[Average post-progression survival time for whole arm]

* indicates extracted from company model using company base case

** indicates extracted from company model using company base case but with lower 95% CI estimate for acceleration factor

The ERG maintain their view that the implementation of the acceleration factor (5.37) is likely to over-adjust for the effect of treatment switching, and likely includes apparent benefit not attributable to treatment switching but instead to other factors, with patients experiencing some of this benefit regardless of whether they had switched treatments. The company did attempt to adjust for these factors by including the following covariates in their calculation of the acceleration factor: age, gender, Eastern Cooperative Oncology Group (ECOG) at secondary baseline [0, ≥1], time to progression, liver metastases, time from last prior chemotherapy [<3 vs. ≥3 months], haemoglobin at secondary baseline and site of primary tumour. The company's failure to present the data or output for this statistical model means the ERG are unable to assess the plausibility of the output, it and remains possible that the model has not adequately adjusted for these factors. The ERG's analysis suggests that the adjustment of confounding factors has not been adequate to ensure the acceleration factor is only estimating the influence of treatment switching.

The ERG accept that it is likely that some patients who switched treatments did receive some benefit from switching, however it is not possible to precisely say what proportion of their post-progression survival this should be. The ERG now prefer to use the lower 95% confidence interval for the 2-stage adjustment as the effect of the adjustment appears consistent with the observed data from KEYNOTE-045 and no longer recommend consideration of analyses using the unadjusted control arm.

Critique and Summary of Appendix 1

As Appendix 1 replaces Section B of the company submission, the ERG critique focuses on the most recent analyses.

The company's base-case assumptions remain unchanged from the previous submission, with the changing incremental cost-effectiveness ratio (ICER) reflecting the updated PAS discount. The key assumptions are:

- Two-stage adjust for treatment switching (no re-censoring)
- 5-year treatment effect duration cap
- OS cut-off point at 24 weeks with log-logistic distribution for extrapolation
- PFS cut-off point at 21 weeks with Weibull distribution for extrapolation
- Weibull and Generalised Gamma distributions for time-on-treatment of pembrolizumab and UK SOC
- Pooled utility values based on health state approach

For comparison, the previous ERG base-case assumptions were similar with the following key difference:

- 3-year treatment effect duration cap

The ERG also previously recommended considering the ITT unadjusted analyses alongside the 2-stage adjustment. The ICER resulting from the company's base case can be found in Table 2, and the ERG preferred assumptions in Table 3.

Table 2: Deterministic ICER for company base-case

TECHNOLOGIES	TOTAL COSTS (£)	TOTAL LYG	TOTAL QALYS	INCREMENTAL COSTS	INCREMENTAL QALYS	ICER (£) VERSUS BASELINE (QALYS)
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	-	-	-
UK SOC	[redacted]	[redacted]	[redacted]	£30,933	0.72	£43,181
ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYS, Quality-Adjusted Life Years						

Table 3: Deterministic ICER for previous ERG base-case

	TECHNOLOGIES	TOTAL COSTS (£)	TOTAL LYG	TOTAL QALYS	INCREMENTAL COSTS	INCREMENTAL QALYS	ICER (£) VERSUS BASELINE (QALYS)
2 STAGE ADJUSTED	PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	-	-	-
	UK SOC	[redacted]	[redacted]	[redacted]	£29,934	0.63	£47,599
ITT/ UNADJUSTED	PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	-	-	-
	UK SOC	[redacted]	[redacted]	[redacted]	£26,178	0.46	£57,127
ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYS, Quality-Adjusted Life Years							

The company then present a series of 6 scenario analyses:

Scenario 1: This is identical to the ERG's base-case of using a 3-year treatment effect duration in combination with the 2-stage adjustment.
Scenario 2: This analysis uses the lower 95% confidence interval of the acceleration factor as the acceleration factor in reducing the post-progression survival times of patients who switched therapy in the UK SOC arm. The company maintain a log-logistic extrapolation for OS, however the ERG considers both the log-normal and log-logistic distributions relevant for this scenario, and provide alternative versions of the second scenario in Table 4.

Table 4: Scenario 2 of the company analyses with additional ERG OS extrapolations

Description	Pembrolizumab		UK SOC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 2: 2-stage adjustment with lower CI as AF, 5-year TE, log-logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,608	0.69	£44,532
Scenario 2: 2-stage adjustment with lower CI as AF, 5-year TE, log-normal OS	[redacted]	[redacted]	[redacted]	[redacted]	£29,988	0.64	£47,152
Scenario 2: 2-stage adjustment with lower CI as AF, 5-year TE, gen gamma OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,272	0.65	£46,273
AF, acceleration factor; CI, confidence interval; OS, overall survival; TE, treatment effect							

Scenario 3: In this analysis, the company apply the 2-stage adjustment after applying re-censoring to the adjusted times in the UK SOC population. Recall that re-censoring considerably decreased the information contained in the UK SOC arm, potentially leaving these analyses uninformative. The company prefers the log-logistic extrapolation, however, the ERG consider the log-normal extrapolation also appropriate for this scenario. For both analyses, the quality-adjusted life year (QALY) prediction for UK SOC is lower than in the company base. Results for this scenario are shown in Table 5.

Table 5: Scenario 3 of company analyses with additional ERG OS extrapolation

Description	Pembrolizumab		UK SOC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 3: 2-stage adjustment with re-censoring, 5-year TE, log-logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	£31,466	0.77	£41,038
Scenario 3: 2-stage adjustment with re-censoring, 5-year TE, log-normal OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,384	0.67	£45,288
OS, overall survival; TE, treatment effect							

Scenario 4: This analysis combines the using the lower 95% confidence interval of the acceleration factor in the 2-stage adjustment with the 3-year treatment effect duration. The company again prefer the log-logistic distribution, however the ERG maintain that the log-normal and generalised gamma distributions should not be dismissed. The results are shown in Table 6.

Table 6: Scenario 4 of company analyses with additional ERG OS extrapolations

Description	Pembrolizumab		UK SoC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 4: 2-stage adjustment with lower CI as AF, 3-year TE, log-logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	£29,457	0.59	£50,247
Scenario 4: 2-stage adjustment with lower CI as AF, 3-year TE, log-normal OS	[redacted]	[redacted]	[redacted]	[redacted]	£28,587	0.51	£55,910
Scenario 4: 2-stage adjustment with lower CI as AF, 3-year TE, gen gamma OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,133	0.64	£46,933
AF, acceleration factor; CI, confidence interval; OS, overall survival; TE, treatment effect							

Scenario 5: This analysis combines the implementation of the 2-stage adjustment with re-censoring with the 3-year duration of treatment effect. The results are shown both with a log-logistic and a log-normal distribution for OS (see Table 7).

Table 7: Scenario 5 of company analyses with additional ERG OS extrapolation

Description	Pembrolizumab		UK SoC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 5: 2-stage adjustment with re-censoring, 3-year TE, log-logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,202	0.66	£46,063
Scenario 5: 2-stage adjustment with re-censoring, 3-year TE, log-normal OS	[redacted]	[redacted]	[redacted]	[redacted]	£29,109	0.82	£52,174
OS, overall survival; TE, treatment effect							

Scenario 6: This analysis accounts for the retreatment of 10 patients in the pembrolizumab arm. Ideally the benefit that these patients received would be removed from analysis, imitating the 2-stage adjustment for treatment switching on the control arm. However, the ERG understands that this could be difficult to model accurately, though options include censoring patients at the point of retreatment, or even assuming patients die at the point of retreatment as a worst-case scenario. Instead, the company present an analysis attempting to capture the costs of the retreatment period.

The company apply a one-off additional cost for this period of retreatment, estimating the duration and costs of purchasing and administering the therapy accrued in this period. The company assume a duration of 10.20 treatment cycles, which begins from 0.46 years (24 weeks) in the economic model until 1.05 years. The rationale for the choice of the starting point was clarified by the company to be the earliest point a patient could begin retreatment, following completion of 8 cycles of pembrolizumab. The average duration of re-treatment (10.20 cycles) was as observed in KEYNOTE-045.

The company suggest that this choice of 0.46 years as the beginning of the retreatment period ensures that this is a conservative analysis, because 80% of the retreated patients had completed 2 years of pembrolizumab therapy initially, suggesting the average starting time would be later than

0.46 years. It is unclear why the company has not used the actual average starting time of retreatment for this analysis.

This is conservative in the company's view because they are applying discounting to reflect that this cost occurs later in the model than when it is applied, and that the true discount should be higher than actually applied. The ERG are hesitant to agree to this assumption for two reasons:

Firstly, the company's choice of beginning the retreatment period (0.46 years), means that the vast majority of the retreatment period occurs within the first year of the economic model where no other discounting is applied. The discount rate only begins to have effect after first year has passed. It is unclear why the company apply a discount rate for this period, when this is mostly inconsistent with all other costs captured within this period. However, the ERG acknowledge that it is likely that this start time should be later and present a scenario where the retreatment period begins at 3 years in the economic model.

Secondly, as mentioned earlier in the ERG comment on A2, it is unclear whether any additional patients began retreatment beyond the current data cut off. Hence, the ERG cannot conclude whether this analysis can be considered conservative. Table 8 shows results for scenario 6 plus additional variations on the assumptions.

Note that the formula specified by the company for the discounted number of life years having applied the instantaneous discount rate could be easily misinterpreted, and so the ERG present it again more clearly:

$$Discounted\ number\ of\ years = \frac{e^{(-iDR \cdot t_{new\ event})} - e^{(-iDR \cdot t_{previous\ event})}}{-iDR}$$

Where $t_{previous\ event}$ represents the starting time of retreatment, $t_{new\ event}$ represents the end time of retreatment and $iDR = \ln(1 + DR)$.

The ERG prefer to model the retreatment costs to begin from 3 years. The company states that 8 out of 10 patients completed the full course (2 years) of pembrolizumab. Hence the average retreatment would begin after this point. It then seemed appropriate to allow time for the disease progression to occur, for it to be detected, for the retreatment to be approved by the investigator, and for the treatment to be administered. An average period of a year seemed plausible, but any value beyond 2 years could have been selected. We preferred a year interval, such that the analysis could no longer be considered conservative, and is either fair, or potentially generous to pembrolizumab, in terms of the effect of discounting. However we would welcome the company to provide the actual average start date of retreatment if they are able to share this information. The ERG present different starting times of the retreatment, and the ICER is not very sensitive to this parameter.

Table 8: Scenario 6 of company analyses with additional variations on the assumptions

Description	Pembrolizumab		UK SoC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALY	ICER (£)
Scenario 6: 2-stage adjustment (no re-censoring), retreatment from 0.46 years, log-logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	£32,278	0.72	£45,060
Scenario 6: 2-stage adjustment (no re-censoring), retreatment from 3 years, log-logistic OS	[redacted]	[redacted]	[redacted]	[redacted]	£32,166	0.72	£44,903
Scenario 6: 2-stage adjustment (no re-censoring), retreatment from 3 years, log-normal OS	[redacted]	[redacted]	[redacted]	[redacted]	£31,655	0.67	£46,943
Scenario 6: 2-stage adjustment (no re-censoring), retreatment from 3 years, gen gamma OS	[redacted]	[redacted]	[redacted]	[redacted]	£31,563	0.67	£47,562
OS, overall survival							

In addition, verifying the company's base-case and scenario analyses, the ERG were also able to reproduce the company's probabilistic sensitivity analysis, which when using the company's base-case assumptions suggested a 78% chance of being cost-effective at a threshold of £50,000 per QALY gained. The ERG's 1,000 iterations of the company's base case produced a probabilistic ICER of £44,062.

The ERG consider that additional analyses should also be considered alongside those presented by the company. Table 9 contains the scenario analyses that the ERG deem most relevant, deviating from the company's base-case assumptions. These analyses assume that the log-logistic OS extrapolation is maintained; however, the ICERs for analyses based on log-normal OS extrapolations are also presented in the final column. Previously the ERG preferred considering analyses both with and without the two-stage adjustment applied. Given the most recent information, the ERG now prefer to use the lower 95% confidence interval estimate for the two-stage adjustment, as in E4 and E5.

E1, E2 and E4 each assume a log-logistic TOT, but maintain a 5-year treatment effect duration, aiming for consistency with TA525.

Analyses E2 – E5 all include the costs of retreatment of pembrolizumab patients implemented from 3 years, which does not reflect UK practice, however the analyses would otherwise likely be biased, at least on this issue, in favour of pembrolizumab as they would capture the benefit of retreatment without capturing the costs. It remains unclear whether this adjustment was based on complete or censored data, and so it is possible that this term underestimates the cost of retreatment.

The ERG include analyses based on two options of the adjustment for treatment switching in the control arm. However, the ERG analysis suggests that using the central estimate for the 2-stage adjustment over-adjusts for the benefit of treatment switching. The ERG recommend that scenarios E2-E5 be considered for decision-making purposes.

Table 9: ERG Scenario Analyses

ID	Description	Pembrolizumab		UK SOC		Pembrolizumab vs UK SOC		
		Total costs (£)	**Total QALYs**	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALY**	**ICER (£)**
	Company Base-Case (CBC)	[redacted]	[redacted]	[redacted]	[redacted]	£30,933	0.72	£43,181 [£45,114] {£45,703}
E1	As CBC with log-logistic TOT for pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£33,158	0.72	£46,288 [£48,413] {£49,056}
E2	As CBC with log-logistic TOT for pembrolizumab with retreatment costs applied at 3 years	[redacted]	[redacted]	[redacted]	[redacted]	£34,392	0.72	£48,010 [£50,242] {£50,915}
E3	As CBC with 3-year treatment effect with retreatment costs applied at 3 years	[redacted]	[redacted]	[redacted]	[redacted]	£31,168	0.63	£49,561 [£54,095] {£50,936}
E4	As CBC with log-logistic TOT for pembrolizumab with retreatment costs applied at 3 years and lower 95% CI of acceleration factor.	[redacted]	[redacted]	[redacted]	[redacted]	£34,067	0.69	£49,565 [£52,589] {£51,560}
E5	As CBC with 3-year treatment effect with retreatment costs applied at 3 years and lower 95% CI of acceleration factor	[redacted]	[redacted]	[redacted]	[redacted]	£30,690	0.59	£52,351 [£58,323] {£48,855}

CBC, company base-case; CI, confidence interval; TOT, time-on-treatment
Square brackets [ ] indicate ICER for scenario as described but with log-normal OS distribution
Braces { } indicate ICER for scenario as described but with generalised gamma OS distribution

Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519 - post-appeal work: Appendix [ID1536]

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The ERG were requested by NICE to perform additional analyses based on applying the retreatment costs at different stages in the economic model. The output from these analyses is shown in Table A1 below

Table A1: Extension to Table 9 from ERG report, varying start of retreatment period

ID	Description	Start of retreatment period, if applicable			No retreatment, if applicable
		X = 24 weeks	**X = 2 years**	**X = 3 years**	
	Company Base-Case (CBC)	£43,181 [£45,114] {£45,703}			
E1	As CBC with log-logistic TOT for pembrolizumab	£46,288 [£48,413] {£49,056}			
E2	As CBC with log-logistic TOT for pembrolizumab with retreatment costs applied at X	£48,167 [£50,409] {£51,084}	£48,070 [£50,306] {£50,980}	£48,010 [£50,242] {£50,915}	£46,288 [£48,413] {£49,056}
E3	As CBC with 3-year treatment effect with retreatment costs applied at X	£49,739 [£54,295] {£51,121}	£49,629 [£54,172] {£51,007}	£49,561 [£54,095] {£50,936}	£47,599 [£51,899] {£48,904}
E4	As CBC with log-logistic TOT for pembrolizumab with retreatment costs applied at 3 years and lower 95% CI of acceleration factor.	£49,728 [£52,766] {£51,731}	£49,628 [£52,657] {£51,625}	£49,565 [£52,589] {£51,560}	£47,770 [£50,650] {£49,674}
E5	As CBC with 3-year treatment effect with retreatment costs applied at X and lower 95% CI of acceleration factor	£52,543 [£58,542] {£49,029}	£52,425 [£58,407] {£48,922}	£52,351 [£58,323] {£48,855}	£50,247 [£55,910] {£46,933}

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Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 15 January 2021**using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Duration of treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 3 of the ERG report states: "*The company's main argument is for consistency between this appraisal and TA525, which assessed the clinical and cost-effectiveness of atezolizumab for the same indication.*"	MSD propose the text is changed to: "One of t*he company's arguments attributing to a 5-year duration of treatment effect is for consistency between this appraisal and TA525, which assessed the clinical and cost-effectiveness of atezolizumab for the same indication.*"	MSD have multiple arguments supporting a 5-year treatment effect duration. These include, but are not limited to, Overall Survival data from KEYNOTE-045, OS data from other KEYNOTE trials with longer follow-up data, biological plausibility, clinical expert opinion, the fact that any treatment effect wane would be captured within the fitting of parametric distribution. MSD do not consider the consistency with TA525 argument to be the main justification for a 5-year duration of treatment effect. Please amend the text to reflect this.	The ERG have amended the text to make it clearer we are referring to section A1 of the company's most recent submission.
Page 4 of the ERG report states: "*This would suggest that patients may on average take atezolizumab for longer than pembrolizumab, therefore, more likely receiving a relative benefit for a longer period*"	MSD request this text is removed.	This statement is highly speculative and inaccurate. On inspection of the KM curves (figure 17 of the additional analyses submitted by the company within TA525 committee papers 2) in IMVIGOR211[1], there are approximately 35%, 20% and 15% of patients on treatment at 6 months, 12 months and 18 months, respectively. This is in line with the proportion of patients observed on	The ERG only state this is a possibility. No change necessary.

		treatment at these timepoints within KEYNOTE-045; [redacted] at 6 months, 12 months and 18 months, respectively. Therefore there is no evidence that patients treated with atezolizumab receive more drug than on pembrolizumab. Please remove. *1: NICE. TA525 Committee papers: Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]. 2018 [cited 2021 15 January]; Available from: https://www.nice.org.uk/guidance/ta525/documents/committee-papers-2*	

Issue 2 Costs of retreatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 5 of the ERG report states: "*It is unclear whether these durations are final, or whether these are censored durations with patients potentially receiving therapy for longer periods*. "	MSD request this text is removed.	Clarification on the above point was not previously requested of MSD. However, we can confirm these durations are final; no censoring was involved. Therefore the text is factually inaccurate, please remove.	The ERG have updated the text to reflect this new information.
Page 6 of the ERG report states: "*The ten patients correspond to*	MSD request this text is removed.	MSD consider this statement to be misleading and inappropriate. It is not clear to the reader what the	The ERG's calculations are correct, and may be of interest to the

3.7% of the original 270 patients randomised to pembrolizumab, to [redacted] of the patients predicted alive at 2 years and [redacted] of patients predicted alive at 3 years. ”		proportions mentioned are referring to. It is also questionable whether or not these proportions hold any merit in clinical terms. Therefore MSD request the text is removed to prevent confusion.	committee. No change necessary.
Page 6 of the ERG report states: “*Retreatment also suggests a lack of sustained treatment effect from the first course.* ”	MSD request this text is removed.	MSD consider this statement to be conjecture. MSD also note that this is conflating the issues of treatment effect duration and retreatment. Patients were eligible for retreatment after either progressing post stopping treatment due to a Complete Response or having completed 35 cycles of treatment. The issue of treatment effect duration relates to stopping treatment at 2 years and the time point at which the Overall Survival Hazard Ratio becomes 1. The two issues cannot be considered relatable and to do so is brazen and inappropriate. Please remove the text.	There is likely to be association between disease progression and overall survival. No change necessary.
Page 11 of the ERG report states: “*The company assume a duration of 10.20 treatment cycles.*”	MSD propose the text is changed to: “*The company assume a duration of 10.20 treatment cycles as per KEYNOTE-045.*”	MSD consider the statement to be vague. The assumption of 10.20 retreatment cycles is based on clinical trial evidence. Please amend the text to reflect this.	The ERG have added text to clarify this point, as per the company’s request.
Page 11 of the ERG report states: *“The rationale for the choice of the*	MSD propose the text is changed to:	MSD request the text is changed to the proposal. 24 weeks, or 0.46 years, is based on completing 8	The ERG have amended the text to reflect this new information.

starting point is not made clear but according to a note in the economic model it may be when the first patient began retreatment."	*"The rationale for the choice of the starting point is according to the earliest possible point for retreatment initiation."*	cycles of pembrolizumab treatment, at which point it is possible to achieve a complete response (CR).	

Issue 3 2-stage adjustment for treatment switching

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 6 of the ERG report states: "*This analysis did not address the concerns raised by the ERG, as the 15 patients who switched but were ineligible for inclusion in the original 2-stage calculation, have still not been included in the calculation of the acceleration factor."*	MSD propose the text is changed to: "*In this analysis, the 15 patients who switched but were ineligible for inclusion in the original 2-stage calculation were not included in the calculation of the acceleration factor."*	MSD disagrees with this statement; the request received from the ERG was addressed. The ERG may have an outstanding question, but this is not a request that has been received by MSD at a point in the process which would have allowed us an opportunity to respond. This analysis directly addressed the ERG's concern, as reflected in paragraph 3.5 of the ACD (as seen below): "*The acceleration factor was not applied to the overall survival time of 15 patients who switched at different times. It is not known how including these 15 patients in an adjustment would have affected the estimated incremental cost-effectiveness ratio (ICER)."*	The ERG's statement refers to if it was somehow possible to include the 15 ineligible patients in the calculation and the application of the acceleration factor, which was not well captured in the ACD statement. This could be possible if the baseline data were captured for these other switchers at their point of switching. Hence, these concerns were not addressed in the analysis provided by the company. No change necessary.

Page 7 of the ERG report states: "*The ERG's analysis found only [redacted] adjusted OS times met this criteria to be unadjusted, meaning that [redacted] of patients who switched may have received some additional benefit. The ERG are surprised that this figure is so high, when only 65% of patients in the original pembrolizumab arm appeared to benefit from the therapy when treated with earlier stage disease."*	MSD propose that the ERG's analysis should be revisited and corrected.	Based on our data, MSD can confirm that [redacted] 'eligible switchers who switched' [redacted] died within 4.5 months ***of being randomised***. However, with regards to ***post-progression survival time***, [redacted] subjects ([redacted]) died within 4.5 months of start date of receiving subsequent treatment ('secondary baseline for the 2-stage method'). This means that [redacted] patients ([redacted]) had post-progression survival time of >4.5 months. It is possible the analysis conducted by the ERG used randomisation ('1st baseline') rather than start of subsequent therapy treatment following progressive disease ('2nd baseline').	The ERG welcome the company's additional information on the patients who switched treatment arms. The misalignment between the ERG's analysis and the information reported by the company is unclear but possibly due to the assumption made in the ERG's analysis over the ordering of event/censoring times between the adjusted and unadjusted datasets, with the ERG not having any further information to match between the two groups. The ERG had requested this data previously in clarification B6 of the CDF review, but was told the company were unable to provide this information. The ERG have updated their text and interpretation according to the information provided by the company.
Page 7 of the ERG report states: *"Further examination of the post-progression survival/censoring times of the switchers suggests that*	MSD propose that the ERG's analysis should be revisited and corrected.	Based on our data, MSD can confirm that [redacted] 'eligible' switchers ([redacted]) had post-progression survival/censoring times of greater than 1 year, which	The ERG are grateful to the company for providing this information. It is unclear why there is such a disparity between this and the ERG analysis, as the

[redacted] *are in excess of 12 months, compared to a 1-year OS rate of pembrolizumab patients in KEYNOTE-045 of 44.2%."*		is closer to the 1-year OS rate of pembrolizumab in KEYNOTE-045 as reported above.	company's information is inconsistent with the ERG's analysis. However, the ERG have updated their text and interpretation according to the information provided by the company.
Page 7 of the ERG report states: *"The company have still not provided detailed output from the statistical model used to calculate the acceleration factor…"*	MSD request this text is removed.	The wording in the report suggests that this was something which had been previously requested by the ERG This is factually inaccurate for the following reasons. • At clarification question stage (Question B.6), the ERG had requested MSD to *"Please provide the code and data to allow simple recalculation of the acceleration factor (mentioned in the notes from Table 4 in the company submission)."* The code that was used to provide the acceleration factor for the 2-stage methodology was provided by MSD with our response to clarification questions, and there has been no further request/clarification sought from the ERG for	The ERG have amended the text to better reflect the recorded clarification question.

		output from the statistical model.	
Page 7 of the ERG report states: "*The ERG anticipated that some of the patients who switched would not receive any benefit, reflecting the behaviour observed in the pembrolizumab arm of KEYNOTE-045, where the OS curves only move in favour of pembrolizumab from approximately 4.5 months once 35% of patients in the pembrolizumab arm are expected to have died according to the Kaplan-Meier graph"*	MSD propose the text is changed to: "*The ERG anticipated that some of the patients who switched would not receive any **additional benefit relative to UK SoC,** reflecting the behaviour observed in the pembrolizumab arm of KEYNOTE-045, where the OS curves only move in favour of pembrolizumab from approximately 4.5 months once 35% of patients in the pembrolizumab arm are expected to have died according to the Kaplan-Meier graph"*	MSD considers the comment to be factually inaccurate: we do not agree with the statement here that such patients would not receive **any** benefit prior to the 4-5 month timepoint. MSD had previously provided the below in our post-appeal response: *"MSD acknowledge that there is an early crossing of KM curves; however this is not an unusual occurrence in trials featuring immunotherapeutic agents versus chemotherapy (with some rationale being a longer time to immune activation via IO versus the relatively immediate cytotoxicity of chemotherapy), and does not alter the overall results of the study. The KM curves clearly show that the study arms separate from months 4-5 onwards, with pembrolizumab demonstrating superior efficacy versus UK SoC (Appendix - Figure 1 of MSD's response post-appeal)."* As stated in MSD's response post-appeal, patients who received a clinical benefit in the	The ERG has clarified their statement. Whilst it is plausible that patients can respond well in terms of therapy very rapidly, it is not clear that this is the case for all patients, or that this clinical benefit will always be reflected in patient survival/life years.

		pembrolizumab arm (defined as CR, PR or SD) all did so within the 4-5 month time frame, based on the fact that patients were scanned ~9 weeks after randomisation and then again 6 weeks after the first scans (as per KEYNOTE-045 study protocol); so, most patients should have had at least 2 sets of imaging before 4 months on study. This means that all those patients who did not progress on those 2 sets of imaging did experience a clinical benefit from pembrolizumab within the first 4 months on study.	