Mr Tim Irish

Vice Chair

National Institute for Health and Care Excellence

10 Spring Gardens

London, SW1V 2BU

26 March 2019

Dear Mr Irish

**Re: Final Appraisal Determination – Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum - containing chemotherapy [ID1536] (CDF guidance review of TA519)**

Merck Sharp & Dohme (“MSD”) wishes to appeal against the above Final Appraisal Determination, according to which pembrolizumab is not recommended for routine funding once it exits the Cancer Drugs Fund (“CDF”). MSD was disappointed by the Appraisal Committee’s decision and disagrees with many aspects of the Final Appraisal Document (“FAD”). However, the company has not taken the decision to bring this appeal lightly. We appreciate that NICE is often faced with taking difficult decisions. Nevertheless, the Appraisal Committee must act rationally and reasonably in light of the evidence, applying a methodology that is fair and equitable.

MSD requests that: (i) this appeal be determined at an oral hearing; and (ii) if the appeal is successful, the Appraisal Committee reconvenes to reconsider its decision.

**Introduction**

Pembrolizumab is an immune checkpoint inhibitor that binds to the receptor programmed death-1 (PD-1) and blocks its interaction with ligands PD-L1 and PD-L2. Technologies such as pembrolizumab are considered a step forward in the treatment of urothelial, and other, cancers. They are better tolerated and more effective than chemotherapy. NICE acknowledges that pembrolizumab significantly improves overall survival compared to chemotherapy. Clinicians have described it to have *“transformative”* effects on certain patients, a proportion of whom go on to complete remission.

NICE initially reviewed pembrolizumab for urothelial cancer in 2018 (TA519) and considered that the product had the potential to be cost-effective (*i.e.*, that the ICER could potentially fall under £50,000, the threshold for end-of life treatments). In that initial review, Appraisal Committee D identified “*uncertainty around overall survival and [the] continued treatment effect [of pembrolizumab]*” which could affect its cost-effectiveness. NICE therefore recommended the product for use within the CDF. This provided time to collect additional data to try to resolve the uncertainties identified. The purpose of appraisal ID1536 was to review updated data from the KEYNOTE-045 trial and assess whether pembrolizumab was cost-effective.

**Summary of Grounds for Appeal**

The Appraisal Committee has chosen not to recommend pembrolizumab because it considers that the most plausible ICER is likely to be above £50,000. That is based upon various judgements and assumptions the Appraisal Committee has made on key aspects of the evidence-base, in particular to manage uncertainties in the evidence. We submit that many of those judgements and assumptions cannot, by objective standards, be considered reasonable in light of the evidence. The Appraisal Committee has reached conservative and pessimistic conclusions because it has subjected the evidence available to onerous and sometimes impossible requirements, without proper justification. The conclusions reached are inconsistent with the type and quality of the data submitted and the approach taken to similar issues in analogous appraisals, particularly TA525 (atezolizumab for locally advanced or metastatic urothelial carcinoma), despite there being greater uncertainty in the evidence for that product. The Appraisal Committee’s approach is therefore inequitable and unfair, and inevitably results in an unreasonable cost-effectiveness assessment. Because of that, many of the arguments made under Grounds 1a and 2 are interconnected and we have structured the Grounds to demonstrate this as clearly as possible.

We also urge the Appeal Panel not to lose sight of the wider context of this appeal. Pembrolizumab is a life-extending and life-improving immunotherapy. It is one of two immune checkpoint monoclonal antibodies indicated for the treatment of locally advanced or metastatic urothelial carcinoma, both of which block signalling through the PD-1/PD-L1 axis. The other product is atezolizumab, a monoclonal antibody that inhibits programmed death ligand-1 (PD-L1), which was assessed and recommended following TA525. Both products are checkpoint inhibiting immunotherapies. They work through the same overall pathway and are indicated to treat the same patient population. There are also clear parallels in the nature of the data presented during their respective technology appraisals, *i.e.* similarly sized open-label, randomised controlled trials versus the standard of care (*i.e.*, investigators’ choice of vinflunine, docetaxel or paclitaxel). Where they differ, however, is that the data for pembrolizumab are more robust, with a longer duration of follow-up. Moreover, atezolizumab failed to meet its primary outcome in patients with PD-L1 expression ≥ 5%, thus precluding further formal statistical analysis in patients with PD-L1 expression ≥ 1% or the overall study population. As discussed further in this appeal letter, most clinicians therefore prefer pembrolizumab over atezolizumab because the study data for pembrolizumab are of better quality and suggest improved outcomes and survival prospects.

While we understand that NICE is not bound to conduct HTAs in the same way, the Methods Guide requires that Appraisal Committees strive for consistency, particularly in the approach taken to assessing cost-effectiveness. We respect the fact that different Appraisal Committees may choose to take different approaches, or that differences in the quality and robustness of the evidence base sometimes require taking a divergent approach. However, given the similarities between pembrolizumab and atezolizumab, the nature of their evidence bases and the similar questions NICE faced during both assessments, we believe we had every reason to expect a fair and consistent approach on key points impacting the ICER.

We accept that there may be cases where poorer quality evidence introduces greater uncertainty, and that this may mean that an Appraisal Committee needs to make more conservative assumptions. Here, however, the same Appraisal Committee was faced with more robust evidence of effectiveness but has taken a more conservative approach. This is both procedurally unfair and unreasonable.

The benefit of doubt afforded to atezolizumab in TA525, despite the uncertainties inherent in the evidence base for that product, also raises questions about whether NICE has met its obligations under human rights and equalities laws in this appraisal. When appraising life-extending technologies, we recognise that NICE has difficult decisions to make about the allocation of resources. In cases where human rights laws engage, however, Appraisal Committees must take particular care when considering evidence that is material to the survival prospects of patients and take decisions in a manner proportionate to the life-extending nature of the product. They must also act in a non-discriminatory manner. It is difficult to see how the Appraisal Committee can reconcile these obligations with the more conservative approach it has taken in this appraisal, given that pembrolizumab is more effective and is backed by a stronger evidence base than atezolizumab. This infringes key human rights and equalities principles and fails to give proper regard to patients who may benefit from pembrolizumab. On that basis, MSD feels compelled to bring this appeal.

**Detailed Grounds for Appeal**

The summary above shows that the grounds for this appeal concern multiple examples of unfairness, unreasonableness or NICE acting *ultra vires*. However, most are inter-related and it is necessary to view them holistically and in a logical sequence. We have therefore structured the key elements of our appeal in order to reflect this logic, while still categorising the grounds according to NICE convention: NICE has failed to act fairly (Ground 1a); NICE has exceeded its powers (Ground 1b); and unreasonableness in light of the evidence submitted (Ground 2). We hope that this structure will assist the Appeal Board and that NICE will accept our approach. However, we are willing to modify it following initial scrutiny, if the Institute wishes us to do so. We then list a number of additional individual grounds according to NICE convention.

# **Ground 2 – the recommendation not to recommend pembrolizumab is unreasonable in 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**

A key example of the unreasonable and inconsistent approach the Appraisal Committee took is its assessment of the duration of treatment effect of pembrolizumab. In this case, the duration of treatment effect was a critical factor to whether or not pembrolizumab fell within the cost-effectiveness threshold.

MSD (and the Appraisal Committee’s clinical expert) considers that a proportion of patients treated with pembrolizumab maintain a durable response, likely reaching beyond 5 years, owing to a “tail of the curve” effect. As such, MSD felt that capping the duration of treatment effect at 5 years in this appraisal was an appropriate approach, and most likely a conservative one.

The Appraisal Committee took a different view, though its rationale for this is difficult to understand. It concluded that a 3-year duration of treatment effect “is” plausible and a 3-year to 5-year duration of treatment effect “could be plausible.”[[1]](#footnote-2) However, the Committee also concluded that “*there is no strong evidence to support a 5-year or longer treatment effect.*”[[2]](#footnote-3) The language used suggests – but does not go as far as to say – the Appraisal Committee believed a 3-year treatment effect to be more credible than the company’s submission supporting a 5-year cap. Based on this, though without any further explanation or detail, the Committee applied a treatment effect cap of 3-5 years to calculate its range of possible ICERs.[[3]](#footnote-4) The Committee has not expressed a preference for a particular point in that range, though the clear implication from the language of the FAD is to call into question the company’s preference for the upper end.

We submit the Appraisal Committee’s approach is misconceived and unreasonable.

***Unreasonable requirement for “strong evidence” of a 5-year treatment effect***

The Appraisal Committee calls into question the company’s preference of a 5-year cap by stating there is “no strong evidence” to support it. The requirement for “strong evidence” to support a 5-year cap is plainly wrong. By its nature, this is an exercise in estimation. Requiring technologies to demonstrate “strong evidence” in the present circumstances is an unattainably high standard. The duration of treatment effect is a question that features routinely in technology appraisals for immuno-oncology drugs. Often, the data available are limited and, as in this case, clinical trials are rarely sufficiently powered to provide “strong evidence” of long-term effects. The routine approach is for Appraisal Committees, informed by the ERG, to review a broad range of evidence to estimate the most likely period. Technologies are often given the benefit of doubt so as not to unfairly prejudice the appraisal. We refer to examples under Ground 1a.1, in which NICE has accepted a 5-year cap or higher (from starting treatment), based on a broad assessment of the data. The most notable example is TA525, which we discuss further below.

ID1536 is in many respects unprecedented in that approximately 4 years of data from KEYNOTE-045 are available for review. This is a higher quality of primary evidence than is available for many other technology appraisals for immuno-oncology products, as indeed was the case in TA525. Given this, it is illogical and unreasonable to expect there to be “strong evidence” supporting a 5-year cap for pembrolizumab when that is not the same standard used elsewhere and when the data available concerning the effect of treatment are far stronger than in comparable appraisals.

***Applying a vague 3-5 year range of treatment effect when calculating the most plausible ICER***

When calculating the range of possible ICERs, the Appraisal Committee applied a broad 3-5 year range, though the FAD effectively casts doubt over the upper-end of that range. To do this undermines the company’s position and implicitly favours a treatment effect of less than 5 years (*i.e.*, 3 years). This approach amounts to an unreasonable interpretation of the evidence submitted. That evidence indicates that (i) the lower end of the range (3 years) is unsuitable; and (ii) the most plausible estimate is likely to be at the upper end (5 years). In that respect, the most appropriate cap on treatment effect would most likely be 5 years. All evidence presented within the appraisal process — data from the phase III randomised clinical trial KEYNOTE-045, opinion stated by clinical experts and biological plausibility owing to the mechanism of action of pembrolizumab — firmly suggests a treatment effect of greater than 3 years and that 5 years is therefore the most credible estimate. If the Appraisal Committee considered that it had no choice but to rely upon a range of possibilities, the lower end of the range ought to have been higher than 3 years and/or there ought to have been a significant weighting towards 5 years. We summarise this evidence and the flaws in the Appraisal Committee’s treatment of it below:

* A broad consensus of clinicians and research groups support a long tail of treatment effect for pembrolizumab in this indication. This includes the ERG’s expert clinician, who suggested that “*some sustained long-term benefit could be plausible for patients receiving pembrolizumab.*”[[4]](#footnote-5) The NCRI-ACP-RCP-RCR Research Group (“Research Group”) noted “transformational” effects observed in some pembrolizumab patients and urged the Appraisal Committee to “*permit more ‘benefit of doubt’ to the [company’s] optimistic*” estimate of treatment effect.[[5]](#footnote-6) The Research Group goes on to say that the most recent updated analysis of the KEYNOTE-045 study (which demonstrates that 20.7% of patients are still alive at 36 months and the median duration of response is 29.7 months) “*is consistent with more positive long-term survival estimates than those assumed by the Appraisal Committee.*”[[6]](#footnote-7)
* The most recent data cut from the KEYNOTE-045 trial (November 2018) provides a total of approximately 4 years’ follow-up data from the start of treatment (*i.e.*, over 2 years of additional follow-up data compared with the company’s pre-CDF submission).  The hazard ratio for pembrolizumab versus UK standard of care decreases from 0.74 to 0.64 (2-stage adjusted) and 0.79 to 0.74 (unadjusted) with additional 2-year data.  This supports a sustained treatment effect, beyond 3 years.  A clinical expert consulted by MSD confirmed that some patients respond well and remain in response, progression‐free. Patients who are progression-free after 2-3 years can expect long-term survival and more favourable outcomes; hence a treatment effect of at least 5 years should be considered plausible and even conservative.[[7]](#footnote-8)
* A 5-year duration of treatment effect for pembrolizumab is further supported by the time varying hazard ratio.  These data show that the mean estimate of hazard ratio comparing pembrolizumab to the UK standard of care is continually lower than 1 after week 8 and reaches a plateau of 0.62 from week 170 (~3 years) to at least year 5. MSD discussed this with a clinical expert, who confirmed that the plateau in the hazard ratio beyond 3 years to 5 years is consistent with his clinical experience.[[8]](#footnote-9) The preferred extrapolation curve (log-logistic distribution) produced a hazard ratio trend that was in line with the fitted time-varying hazard ratio based on the maximum follow-up data, supporting a 5-year cap.
* The company’s extrapolation of overall survival does not fit well with a 3-year treatment effect cap and suggests a 5-year cap or higher is more appropriate.[[9]](#footnote-10) The views of the clinical expert cited in paragraph 3.15 of the FAD are consistent with this interpretation. The expert found it plausible that approximately 5% to 10% of patients treated with pembrolizumab might survive to 10 years after starting treatment. Using a preferred log-logistic extrapolation curve: (i) if a 5-year effect is assumed, approximately 5.48% of patients would survive for 10 years; but (ii) if a 3-year cap applies, the 10-year survival rate would be approximately 4.43%. Therefore, even at the lower end of the expert’s prediction, a 3-year treatment effect does not fit; whereas a 5-year effect does.
* The company extrapolated overall survival using the entirety of the follow-up data from KEYNOTE-045, which included a 2-year stopping rule. The follow-up data spanned approximately 4 years. As such, if any treatment effect was observed within the 4-year follow-up data, it would most accurately be reflected within the fitting of the overall survival curves. Therefore, by applying a treatment effect duration shorter than the follow-up period, two issues arise: (i) all pembrolizumab overall survival information conveyed beyond 3 years from the observed data is effectively entirely disregarded; and (ii) manipulating the fitting data within the observed period would potentially double count the treatment waning effect that has already been reflected by the parametric fitting. Taken together, this clearly calls into question why a treatment effect that is shorter than the follow-up period was considered appropriate, when this does not fit with overall survival.
* As discussed in Ground 1a.1, MSD submitted extensive evidence to demonstrate that applying greater than 3-year treatment effect is consistent with clinical trials for pembrolizumab in other indications and other comparable technology appraisals.

It is clear the ERG had a preference for a 3-year cap. It points to the relatively low number of events (*i.e.*, deaths) in the standard of care population beyond 3 years as evidence that data generated beyond this point is unlikely to be meaningful.[[10]](#footnote-11) Again, this overlooks the fact that KEYNOTE-045 was not powered to demonstrate long-term treatment effect. Given the powering and the likelihood of mortality in this indication, it is unsurprising that there are low numbers of events in the comparator arm after 3 years. It is illogical to conclude that the statistical powering of the study means that a 3-year cap on treatment effect must apply by default. Nor does it undermine the company’s evidence in support of a 5-year cap.

The ERG also refers to the 95% confidence interval for the hazard ratio crossing “one” within the first 2 years of follow-up, which according to the ERG suggests a potential waning effect and “considerable uncertainty” in using this parameter.[[11]](#footnote-12) While MSD acknowledges this observation, it would be highly speculative to conclude from this alone that there is no treatment effect beyond 3 years.

While the differences between MSD’s and the ERG’s positions may be technical, it is important for the Appeal Panel to recognise that this appeal Ground is not simply a matter of technical disagreement. Our submission is that the demands placed upon the company’s evidence by the ERG and the Appraisal Committee were self-evidently unrealistic and unattainable given the powering and structure of KEYNOTE-045. The Committee’s position seems all the more unreasonable when one considers that the Committee would have been well aware of the structure and limitations of KEYNOTE-045 from the outset. This was the trial that informed NICE’s decision to fund pembrolizumab through the CDF, and the trial that NICE had agreed would form the basis for this reassessment as per the agreed Data Collection Arrangement (which formed part of the Managed Access Agreement at the time of the publication of TA519).

The Appraisal Committee appears to have decided that the most conservative possible estimate of treatment effect must apply by default. That is despite the fact that other products have not been subject to such an approach, including in TA525. Based on the above, NICE’s approach is 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**

Paragraph 3.15 of the FAD concerns the duration of treatment effect and the overall survival prospects of patients treated with pembrolizumab. The Appraisal Committee reached two conclusions: “*there was no strong evidence to support a 5-year or longer treatment effect [and] no more than 5% of patients treated with pembrolizumab might be alive after 10 years.*” The Appraisal Committee’s analysis of the evidence is confused and internally inconsistent.

The Appraisal Committee took that advice of its clinical expert and noted that: “*[t]he clinical expert found it plausible that 5% to 10% of people having pembrolizumab might survive to 10 years after starting treatment (with a 2-year stopping rule).*” The Appraisal Committee then refers to evidence from the CDF clinical lead and a patient expert that there was uncertainty about how long people might survive after having pembrolizumab. The evidence cited directly contradicts the conclusion that “*no more than 5% of patients treated*” would be alive after 10 years. Nor does the evidence disprove a 5-year or longer treatment effect. Rather, as discussed under Ground 2.1, a 5% survival rate at 10 years (the lower end of the clinician’s range) would in fact support the company’s modelling of a 5-year effect of treatment.

MSD raised this inconsistency during the ACD consultation phase and the Appraisal Committee did not substantively respond to it.[[12]](#footnote-13) As such, the Appraisal Committee has not explained why it has in effect overruled the evidence of the nominated clinical expert, to the detriment of pembrolizumab.

Treatment effect and survival rates are central considerations in assessing the most plausible ICER. As the FAD currently stands, the conclusions reached in paragraph 3.16 of the FAD are unsupported by the evidence cited.

## **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**

In paragraph 3.22 of the FAD, the Appraisal Committee concludes that there is a range of possible ICERs and, based on that range, the “most plausible” ICER is likely to be above £50,000. MSD submits that both of these assertions are unsound and the result from an unreasonable assessment of the evidence.

***Range of Possible ICERs from £48,518 to £70,520***

The range is structured upon certain parameters that the Appraisal Committee considered to be uncertain and therefore variable. These include: (i) a 3-5 year treatment effect; and (ii) taking adjusted and unadjusted figures into account for treatment switching[[13]](#footnote-14) (see Ground 2.5 below).

The credibility of the ICERs depends on whether the Appraisal Committee correctly accounted for treatment effect and treatment switching. Our submission in Grounds 2.1, 1a.1, 2.2 and 2.5, is that NICE made errors with both of these inputs. The 3-5 year range of treatment effect is overly broad and ought, at a minimum, to be weighted in favour of 5 years. In addition, there was no justifiable basis to include unadjusted figures for treatment switching (as discussed below). If those errors were corrected, the range of possible ICERs would consequently become narrower, moving towards the lower end (*i.e.*, £48,518). In other words, because the input variables are wrong, the range of ICERs that NICE relies upon not to recommend pembrolizumab is necessarily unreliable and prejudices against MSD.

MSD acknowledges that some of the issues raised under Grounds 2.1 and 2.5 were subject to detailed discussions between the company and the ERG and continued to be areas of disagreement. Notwithstanding that the company and the ERG had differing views, it is the Appraisal Committee’s responsibility to exercise its discretion and make value judgements that produce meaningful conclusions that appropriately reflect the evidence. Unless justified by genuine uncertainty, the Appraisal Committee should not simply summarise areas of disagreement between the company and the ERG and distil these into a range of possible ICERs. We fail to see any such genuine uncertainty here, particularly when less certain data has received a greater benefit of doubt in other appraisals.

***Most Plausible ICER is Likely Above £50,000***

The Appraisal Committee’s conclusion that the “most plausible” ICER is likely to be higher than £50,000 relies on a highly simplistic analysis (*i.e.*, that the most plausible ICER is at the mid-point of the range). The evidence submitted does not support this. If anything, for the reasons discussed above, the most plausible ICER is most likely to be weighted towards the lower end of (or below) the range. Given the evidence, it is unreasonable for the Appraisal Committee not to consider this possibility. On that basis, it is unreasonable to conclude that pembrolizumab is not cost-effective because the £50,000 threshold is below the midpoint in the range.

# **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**

***Principle of Consistency between NICE Appraisals***

MSD appreciates that that Appraisal Committees are not bound by decisions in prior appraisals. We also appreciate that NICE’s recommending atezolizumab in TA525 does not mean that the Appraisal Committee must automatically treat pembrolizumab in the same way. However, principles of procedural fairness require NICE to maintain basic levels of consistency in its methodology, particularly when reviewing similar technologies based on a very similar evidence base, where very similar judgement calls must be made around uncertainty and cost-effectiveness. Previous NICE appeals have suggested that the question is relevant when “*appraisals or their evidence base are sufficiently similar to make consistency a reasonable consideration.*”[[14]](#footnote-15)

Section 6.2.15 of the Methods Guide reflects the general principle:

“*The Appraisal Committee takes account of how the incremental cost effectiveness of the technology being appraised relates to other interventions or technologies currently or potentially applied in the NHS.* ***In addition, as far as possible, the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals***” (emphasis added).

As such, the Appraisal Committee should aim to ensure that it approaches cost-effectiveness judgements in its appraisals in a manner that is not fundamentally and unjustifiably different to other appraisals.

***Principle of Consistency Engaged in this Case***

There are multiple points of similarity between TA525 and ID1536. Pembrolizumab and atezolizumab are both checkpoint-inhibiting monoclonal antibodies that block the PD-1/PD-L1 signaling axis and are indicated to treat same patient population. In addition, both TA525 and ID1536 concern the same indication and patient populations. The primary source of evidence for both came from similarly sized open-label, randomised controlled trials versus the standard of care. There are clear parallels in terms of the type of data available to the Appraisal Committee and similar issues arose concerning uncertainty and extrapolating evidence. In both cases, these issues significantly affected the cost-effectiveness analysis.

The same Appraisal Committee (Committee D) conducted the original (pre-CDF) appraisal of pembrolizumab (TA519) submitted in February 2017, the appraisal of atezolizumab (TA525) in 2018 and the CDF guidance review of pembrolizumab, submitted in July 2019 (ID1536). Therefore, the Committee would clearly have been aware of the similarities of both cases, the relative strengths of the evidence base and the approach taken to managing uncertainties.

***The Approach in the Present Appraisal is Inconsistent with TA525***

The divergences of approach are clearest in the following examples:

* **Approach to Duration of Treatment Effect** – It is important to state at the outset that in TA525, NICE expressed the treatment effect cap of atezolizumab in terms of its effects after stopping treatment; in ID1536, this was expressed differently – *i.e.*, the effect from initiation of treatment. [[15]](#footnote-16) This appears to have caused confusion during consultation. We have tried to clarify this potential confusion as part of the following discussion concerning the significant inconsistencies of approach between the two appraisals.
  + In TA525, the follow-up data in the relevant clinical trial, IMvigor 211, was very limited (a median follow-up of 17.4 months after stopping treatment; and a maximum of 24.5 months). Moreover, the trial did not show that the primary outcome of overall survival in high PD-L1 expressers was statistically significantly higher than with chemotherapy. The Appraisal Committee considered there was insufficient evidence to support a specific duration of treatment benefit for atezolizumab.[[16]](#footnote-17) Despite this, the Appraisal Committee considered it appropriate to apply a 3-year treatment effect cap, following a 2-year stopping rule.[[17]](#footnote-18) In effect, this equates to 5-year treatment effect cap **from the start of treatment**, as established within Comment 12 of MSD’s response to the ACD. This figure fed into NICE’s preferred base case and its calculation of ICERs, as reflected in paragraphs 3.12 and 3.13 of the FAD in TA525.
  + In ID1536, MSD’s base case also assumed a 5-year treatment effect **from the start of treatment**. This was a conservative estimate, particularly because a considerably longer period of follow-up data was available from KEYNOTE-045 compared with the studies used to support TA525 (a median follow-up of 40.9 months from the start of treatment and a maximum of 48.9 months). Despite pembrolizumab having better quality data, the Appraisal Committee disagreed with the company’s proposal of a 5-year cap from the start of treatment. Instead, in the cost-effectiveness assessment for pembrolizumab, the Appraisal Committee assumed a 3-5 year range of treatment effect from treatment initiation, showing preference for the lower end of the range and casting doubt over the upper end.[[18]](#footnote-19) This departs significantly from the latitude afforded to atezolizumab.
  + The cost-effectiveness parameters for the two products are inexplicably different: **(i) for atezolizumab, NICE assumes a treatment effect cap of 5 years from treatment initiation, based on relatively weak follow-up data;[[19]](#footnote-20) (ii) for pembrolizumab, NICE applies a treatment effect cap of 3-5 years (with doubt cast over the upper end) from treatment initiation, based on stronger data**.
  + Throughout the consultation process, MSD questioned this obvious inconsistency in approach. We pointed out the stronger longer term follow-up data for pembrolizumab, which ought to strengthen the company’s assumption of a 5-year treatment effect, rather than put it in a weaker position compared to atezolizumab. In response to ACD consultation, the Appraisal Committee vaguely pointed to a “number of differences” between atezolizumab and pembrolizumab. Specifically, the Committee mentioned the absence of a stopping rule in the atezolizumab study.[[20]](#footnote-21) While the 2-year stopping rule is a difference between the two sets of study data, it is does not explain why the cost-effectiveness parameters (for which a 2-year stopping rule is common) are approached so differently, especially as a 2- year stopping rule has been implemented for TA525, therefore within UK clinical practice the scenarios are identical. The fact that the stopping rule applies to both and reflects clinical practice in the UK goes to the external validity of the data.[[21]](#footnote-22) Given the importance NICE places on taking decisions based on the realities of clinical practice, it is difficult to understand why the cost parameters are so strikingly different.
* **Rejection of Precedent from Other Immuno-Oncology Technology Appraisals** – In TA525, there was insufficient evidence from clinical trial data in that indication to determine the precise duration of treatment effect. In the absence of this, the applicant company suggested, and the Appraisal Committee supported, an approach of estimating the likely treatment effect cap by reference to appraisals of other immunotherapies in other indications where a stopping rule applied.[[22]](#footnote-23) Consistent with this, in ID1536, MSD also supported its evidence and approach with data from pembrolizumab studies in other indications.[[23]](#footnote-24) Inconsistent with the approach it took in TA525, however, Appraisal Committee D did not accept MSD’s other supporting evidence from immunotherapy appraisals in which a greater than 3-year treatment effect was acceptable to the Appraisal Committee (*i.e.*, in TA428, TA600, TA484, TA483, TA578 and TA520).[[24]](#footnote-25) We do not understand how the same Appraisal Committee considered external data to be relevant in one appraisal but not in another.

These methodological inconsistencies are far from trivial details. Estimating the limits of treatment effect was critical to the cost-effectiveness assessment. We maintain that if the Appraisal Committee had taken a methodological approach that was consistent with TA525, the most plausible ICERs would most likely have fallen below the threshold for recommendation.[[25]](#footnote-26) Adopting inconsistent approaches to managing the same areas of uncertainty in very similar appraisals, without adequate explanation is, by its nature, procedurally unfair.

# **Ground 1b – NICE has exceeded its powers**

## **Ground 1b.1 – NICE has breached its legal obligations under human rights and equalities laws**

NICE is legally obliged to conduct its health technology assessments in accordance with the obligations imposed on public bodies by human rights legislation, including European Convention of Human Rights (“Convention”), as transposed into national law under the Human Rights Act 1998 (“HRA”) and the Equality Act 2010 (“Equality Act”). Further, NICE as a corporate body may only exercise its functions on the direction of the Secretary of State for Health and/or NHS England and is subject to those directions and therefore is bound to take into account the State’s obligations under human rights law.

The benefit of doubt afforded to atezolizumab in TA525, despite the uncertainties inherent in the evidence base for that product, raises questions about whether NICE has met its obligations under these human rights and equalities laws. MSD submits that NICE’s approach in this case breaches the human rights of affected patients and the Equality Act.

***Context of Appraisal***

If pembrolizumab is not available to NHS patients in this indication, the main alternative checkpoint inhibitor is atezolizumab. Atezolizumab is not a comparator in this appraisal. However, in the context of human rights and equalities laws, its existence as the alternative is highly relevant.

Although direct comparisons are difficult to make, NICE’s evaluation of the study data for each product suggests that pembrolizumab has a stronger evidence base for overall survival.[[26]](#footnote-27) NICE has acknowledged that clinicians generally prefer pembrolizumab over atezolizumab because the evidence for pembrolizumab is of higher quality.[[27]](#footnote-28) In our experience, this preference is reflected in clinical practice[[28]](#footnote-29) and independent guidance.[[29]](#footnote-30)

In the ACD consultation, the Research Group pointed out that “*the evidence for [pembrolizumab] remains the only level one evidence for urothelial cancer within the product label.*”[[30]](#footnote-31) The Research Group did not consider the evidence base for atezolizumab to be “level one” evidence. On that basis, the Research Group stated: “*it is undesirable that clinicians may prescribe a drug without level 1 evidence (atezolizumab, docetaxel, paclitaxel) where there is an alternative where such evidence exists (pembrolizumab).”* The Research Group urgedthe Appraisal Committee “*to consider this factor in weighing up other causes of uncertainty in the economic analysis.*”[[31]](#footnote-32)

**Breaches of Human Rights and Equalities Laws**

**Article 2 of the Convention**

Article 2 of the Convention obliges the State to refrain from depriving persons of life intentionally, but also imposes a positive obligation to fund life-saving treatments. The FAD acknowledges that pembrolizumab meets NICE’s criteria to be considered a life-extending treatment at the end of life.[[32]](#footnote-33) Article 2 of the Convention is therefore necessarily engaged.

MSD recognises that public resources are finite, and that Article 2 does not impose an obligation on the State to provide unlimited resources for medical treatment. However, it is clear that pembrolizumab is an exceptional, life-extending treatment that clinicians clearly prefer to other treatments. At a minimum, this requires NICE to give consideration to evidence that is material to the survival prospects of patients and take decisions in a manner proportionate to the life-extending nature of the product. We submit the Appraisal Committee has not done this (or, if it has, it has done so erroneously), in particular by reaching unjustified and overly conservative conclusions concerning the likely treatment effect of pembrolizumab and subjecting pembrolizumab to standards that were not applied in analogous cases (discussed in Grounds 2.1 and 1a.1 respectively).

The direct consequence of NICE’s decision to not recommend pembrolizumab is that, after the failure of chemotherapy, the only checkpoint inhibitor available to patients in this indication is one that clinicians do not prefer because it is not supported by the highest quality (level one) study data. We appreciate that this does not automatically mean that NICE has infringed the right to life by not recommending pembrolizumab, but there is a real risk it could be. Where such a risk exists, authorities must consider the impact of their decisions and, wherever possible, make reasonable adjustments to avoid an infringement of rights. There is no evidence that the Appraisal Committee has met this expectation. In fact, by subjecting pembrolizumab to unattainable standards, far more onerous than those it applied in TA525, NICE has effectively increased rather than decreased the risk of infringing Article 2 of the Convention. In our submission, Article 2 required it to do precisely the opposite.

**Article 14 of the Convention and the Equality Act**

Article 14 prohibits discrimination in the enjoyment of other Convention rights. Accordingly, for Article 14 to be engaged, one of the other Convention rights must be applicable (although not necessarily infringed). For the reasons set out above, Article 2 is engaged, such that Article 14 applies. Where a public body, such as NICE, is providing a public service, it is bound by Article 14 to ensure that it does so in a non-discriminatory fashion.[[33]](#footnote-34)

Similarly, section 149 of the Equality Act also obliges NICE to have due regard to the need to eliminate discrimination. In *R (on the application of Rahman) v Birmingham City Council [2011] EWHC 944* (Admin), the domestic courts noted that limited financial resources did not excuse compliance with the public sector equality duty and indeed there was much to be said for the proposition that in economically constrained times the need for clear, well-informed decision-making when assessing the impacts on less-advantaged members of society was as great, if not greater.

In this case, the Appraisal Committee’s approach prejudices against patients with locally advanced or metastatic urothelial carcinoma, by taking an approach that is both procedurally unfair, unreasonable and inconsistent, and is therefore discriminatory both against pembrolizumab and patients who would benefit from it.

Moreover, these patients are older and may have comorbidities.[[34]](#footnote-35) NICE is under a legal and moral duty to ensure that its decision is clear and well-informed and does not discriminate against vulnerable members of the patient population. We submit that NICE has not fulfilled this duty. It has been unable to objectively justify its assessment of the evidence and its rejection of many of the fundamental elements of the company’s evidence. Such an approach inevitably disadvantages against patients who could stand to benefit from pembrolizumab (particularly over atezolizumab), who are likely to be older, vulnerable people. The decision amounts to a breach of Article 14 and section 149 of the Equality Act.

In addition, although NICE is entitled to identify clinical priorities and allocate its limited funds accordingly, there are no objective or reasonably justifiable reasons for failing to consider the available data properly or consistently. Accordingly, the decision is not a proportionate means of achieving a legitimate aim and, in addition to the above breaches, infringes section 29(6) of the Equality Act.

# **Further Grounds for Appeal**

As discussed above, the clear inter-relationship between the prior grounds for appeal meant that it made considerable sense to approach them in order. There are, however, a number of other grounds.

## **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**

Paragraph 3.19 of the FAD asserts that the costs of pembrolizumab are likely underestimated in MSD’s modelling because a small proportion of patients in KEYNOTE-045 restarted treatment after having previously stopped therapy following a complete response or completing 2-years’ worth of treatment. This introduces a new point into the Committee’s evaluation. This issue was raised unexpectedly at the second committee meeting; the Appraisal Committee had not raised this issue in the ACD and the company did not have the opportunity to formally respond. The company’s explanations cited in paragraph 3.19 of the FAD come from a wider discussion of treatment benefit and are unrelated to the cost of the product and its effect on cost-effectiveness. The Appraisal Committee has not explained this last-minute addition and it is unclear what weight the Committee gave to it in its overall assessment. However, it clearly had some impact on cost-effectiveness, since the FAD concludes that the added cost would “increase the ICERs.”[[35]](#footnote-36) The introduction of a material point at such a late stage, without explanation or the right to reply during a formal consultation phase of the appraisal process is self-evidently unfair.

## **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 1a.2 addresses how this issue was introduced at the last minute. In addition, we question the appropriateness of taking this point into account during the cost-effectiveness assessment (*i.e.*, because a small number of patients in the KEYNOTE-045 trial had further treatment with pembrolizumab, the ICERs must be higher than those the company submitted). The numbers of patients in question are very small. Without further analysis, it is impossible to conclude that MSD has materially underestimated the cost of its product. We submit that the conclusions that the Appraisal Committee reached in paragraphs 3.19 and 3.22 on this point demonstrate an unreasonable interpretation of the evidence submitted.

## **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**

In order to make a realistic comparison between pembrolizumab and the comparator, it was important to establish the base-case survival rate for the UK standard of care arm in KEYNOTE-045. The complexity here was that in the standard of care arm, patients whose disease progressed could have had subsequent anti-PD-L1 or PD-1 treatment. This included treatment with atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. As such, there was a need to adjust the data in the comparator arm to account for this “treatment switching.” The company proposed a well-established and uncontroversial method to do this – the “2-stage” adjustment method. In the original pre-CDF appraisal for pembrolizumab, the Appraisal Committee considered this to be an appropriate method to adjust for switching, notwithstanding the ERG’s concerns with it.[[36]](#footnote-37) The Terms of Engagement (“ToE”) Document for this CDF guidance review, issued by NICE in advance of the appraisal commencing, did not highlight the 2-stage adjusted analysis as an area which may require deviation from the methodology agreed as appropriate at the time of the original (pre-CDF) appraisal. The ToE clearly stated *“Alternative assumptions should be explored and justified only in the areas where data collection is anticipated to address the committee’s key uncertainties. NICE expects all other committee’s preferred assumptions to remain unchanged at the CDF review.”* The company therefore considered this to be a settled point going into ID1536.

Paragraph 3.6 of the FAD shows that the Appraisal Committee revised its position in light of the updated evidence the company submitted:

“*New KEYNOTE-045 data shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account.*”

The Committee concludes:

“*The committee considered that using the 2-stage adjustment for treatment switching likely underestimated the incremental cost-effectiveness ratios (ICERs) but using no adjustment would overestimate the ICERs.* ***It concluded that the true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment***” (emphasis added).

The Appraisal Committee’s conclusions are significantly influenced by comments from the ERG, which raised concerns with some aspects of the 2-stage method. On that basis, the ERG recommended that the Appraisal Committee should take unadjusted data into account alongside data adjusted pursuant to company’s 2-stage method. The Appraisal Committee followed this recommendation in the FAD and both unadjusted and adjusted data feature in the range of plausible ICERs in paragraph 3.22.

MSD submits that the 2-stage adjustment method has been disproportionately criticised by NICE and the ERG in this appraisal. The 2-stage method is well-established and has been acceptable in numerous previous appraisals. In accommodating adjusted and unadjusted survival rates into the cost-effectiveness assessment, the Appraisal Committee has reached “half-way-house” position that is non-standard and not supported by the evidence. It unnecessarily introduces uncertainty and imprecision into the calculation of the most likely ICER. We further particularise these arguments below:

* It is accepted that adjusting for treatment switching is an issue to be accounted for in the assessment. The 2-stage method is an established and credible approach, which has been followed appropriately by the company. As the company has made clear, more complex methodologies would not work. The company acknowledges that the 2-stage method has its limitations. However, that is scant justification to arrive at a half-way position between a credible approach and unadjusted data. It is illogical to bring an unsound and unsupported methodology into consideration and use this as a basis to inform the calculation of ICERs.
* The updated data from KEYNOTE-045 simply meant that the acceleration factor (a factor applied to the overall survival of chemotherapy patients to adjust for treatment switching) was larger and applied to more patients than that originally generated based on the earlier data-cut from KEYNOTE-045, which informed the original (pre-CDF) appraisal of pembrolizumab. The updated acceleration factor was based on more robust data and a larger sample size than the previous acceleration factor and was therefore more reliable. Although the updated acceleration factor was higher in magnitude, the confidence interval generated was narrower as compared to that generated in the original submission. As highlighted by the company in response to the ACD, it is noteworthy that the confidence interval obtained using the updated 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). In that context, the overall approach remains consistent with what was previously considered acceptable in TA519.
* The Appraisal Committee’s and ERG’s exact concerns with the 2-stage method have not been articulated in a clear, consistent manner throughout the appraisal. It remains unclear what these precisely are and how they are material to its overall assessment, particularly with respect to cost-effectiveness. For example, during the early phases of consultation, the ERG appeared to be specifically concerned with the fact that the higher magnitude of the acceleration factor resulted in the 2-stage adjustment having a greater influence on overall survival than it did in the original appraisal.[[37]](#footnote-38) However, responding to MSD’s comments to the ACD, the ERG expanded their position, stating: “*The magnitude of the acceleration factor is not a concern, but the increased magnitude has amplified the influence of this adjustment, which increased the importance of* *all the other characteristics of the adjustment.*”[[38]](#footnote-39) The Appraisal Committee reflected the ERG’s revised position in paragraph 3.6 of the FAD. The shift of focus to question “*all the other characteristics of the adjustment”* is novel, unclear and lacks meaningful explanation.
* Paragraph 3.6 of the FAD refers to various uncertainties and concerns that the ERG raised about the 2-stage method. The material point is that MSD addressed these in full, with supporting evidence during the ACD consultation process (Comments 4, 5, 6 and 7 of MSD’s Comments on the ACD). However, once it had received the ACD comments, the Appraisal Committee’s response did not materially engage with the company’s submissions (pages 9-18 of NICE’s Responses to Comments on the ACD). On that basis, simply repeating the same points in the FAD makes little sense. The conclusions reached and the related commentary are unfounded, in light of the responses provided by the company during ACD consultation. For example, new uncertainties were seemingly introduced by the ERG and accepted by the Appraisal Committee following ACD consultation.
  + Paragraph 3.6 of the FAD acknowledges that the company provided sensitivity analyses in response to ACD consultation to apply the acceleration factor to all 40 patients who switched (irrespective of whether those patients were “eligible” for switching as defined by the 2-stage method). It is important to note that these analyses were conducted to address a specific concern raised by the ERG in paragraph 3.5 of the ACD, which stated *“The acceleration factor was calculated from the 25 people who switched when progression of their disease was documented. 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).”*
  + Yet upon reviewing the company’s comments on the ACD, the ERG’s response confusingly stated: *“[t]he company present an analysis where the acceleration factor is applied to all 40 patients who switched treatment, and not only to those who switched upon disease progression. Unsurprisingly, reducing the survival time of additional patients in the UKSOC arm makes pembrolizumab slightly better than in the base case analysis.* ***However, the relevance of this analysis is questionable, since the estimation of the acceleration factor is not adjusted in any way****.”* (emphasis added).[[39]](#footnote-40) The ERG’s late shift to focus on the lack of adjustment to the acceleration factor is reflected in the Appraisal Committee’s commentary in paragraph 3.6 of the FAD which states *“…the company provided a sensitivity analysis applying the acceleration factor to all 40 patients. In this, the hazard ratio for pembrolizumab compared with UK SoC was 0.55. However, the calculation of the acceleration factor was not adjusted to include these 15 patients.”*  That criticism of the company’s analysis is wholly unreasonable, given that the sensitivity analysis was to address a specific request from the ERG and its outcome in fact supports the company’s position. To switch attention to the lack of adjustment in the acceleration factor effectively “shifts the goalposts” at a very late stage and is unwarranted and unreasonable. Particularly so, as this introduces uncertainty into the assessment that contributes to the range of ICERs.
* The support for taking unadjusted data into account relies, in part, on the ERG’s use of data from a 2013 study by *Bellmunt et al.* concerning vinflunine[[40]](#footnote-41) as a proxy for results expected to be seen for the adjusted UK standard of care arm of KEYNOTE-045, and hence to validate the results of the 2-stage adjustment. The ERG’s key concern on this point was that the median overall survival in the vinflunine arm of the *Bellmunt et al.* study was closer to the median overall survival from the **unadjusted** UK standard of care arm of the KEYNOTE-045 population. Yet, as clearly highlighted in the company responses to both Technical Engagement and the ACD, the reported 12, 24 and 30 month overall survival from the *Bellmunt et al.* study has better consistency with the results of the **2-stage adjusted** UK standard of care arm from KEYNOTE-045. To fail to take this into account, or even engage with the point, amounts to an unreasonable assessment of the evidence. Notwithstanding this, the company highlighted that reliance on proxy data as a counterpoint to actual study data is highly questionable, especially when, as in this instance, the proxy (vinflunine) is not recommended by NICE and is not considered established in UK clinical practice. The patient populations between the two trials are also considered to be heterogeneous. Consequently, the comparison made between the two studies by the Evidence Review Group – even if it was conducted reasonably – is inappropriate. We submit that such an assessment should not have had any influence over the Appraisal Committee’s decisions.[[41]](#footnote-42)
* The inappropriateness of considering unadjusted data is clear in the context of the implausibility of the long-term overall survival estimates produced when using this method. Section 3.20 of the FAD justifies the selection of the log-logistic curve due to the plausibility of the long-term overall survival estimate at 5 years (3.2%) being aligned to the ERG’s clinical expert’s estimate within the original appraisal (2% to 3%). However, this is referring only to extrapolation based on 2-stage adjusted analysis. When using an unadjusted analysis, the corresponding 5-year overall survival estimate is 5.9%; a vast overestimation compared to that estimated by the ERG’s clinical expert. Consequently, the conclusion reached by the Appraisal Committee stating that the unadjusted method should also be taken into account, directly contradicts Section 3.20 of the FAD, and further exemplifies why only the 2-stage adjusted analyses should be considered appropriate.

It is clear from the above that the Appraisal Committee has not justified why it has arrived at a position where data from an established and well-founded method are considered alongside one that is unsuitable and lacks support. Importantly, this also calls into question relying on both sets of data to derive a range of ICERs, when to do so increases the risk of an uncertain and imprecise cost-effectiveness assessment.

We thank you in advance for considering the company’s submissions in this appeal. We are available to answer any questions you may have or provide further clarifications.

Yours sincerely

Xxxxx xxxxxxx

Managing Director, UK & Ireland

1. Paragraph 3.18 of the FAD [↑](#footnote-ref-2)
2. Paragraph 3.15 of the FAD [↑](#footnote-ref-3)
3. Paragraph 3.22 of the FAD [↑](#footnote-ref-4)
4. Page 25 of ERG Report for CDF Guidance Review (pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519), 22 August 2019. [↑](#footnote-ref-5)
5. Comment 2 of NCRI-ACP-RCP-RCR Comments on the ACD. [↑](#footnote-ref-6)
6. *Id.* [↑](#footnote-ref-7)
7. MSD’s response to Technical Engagement, at page 14. [↑](#footnote-ref-8)
8. MSD’s response to Technical Engagement, at page 15. [↑](#footnote-ref-9)
9. Page 14 of MSD’s Response to Technical Engagement and Comment 12 of MSD’s Comments on the ACD, respectively. [↑](#footnote-ref-10)
10. Page 7 of the ERG’s Critique of Company Additional Evidence, 9 January 2020. The Appraisal Committee also raises this concern at page 22 of NICE’s Response to ACD Consultation. [↑](#footnote-ref-11)
11. Page 7 of the ERG’s Critique of Company Additional Evidence, 9 January 2020. [↑](#footnote-ref-12)
12. Page 24 of NICE’s response to Consultee, Commentator and Public Comments to ACD. [↑](#footnote-ref-13)
13. Paragraph 3.22 of the FAD. [↑](#footnote-ref-14)
14. Page 4 of the Scrutiny Letter in Osimertinib for untreated EGFR-positive non-small-cell lung cancer [ID1302], 29 July 2019. [↑](#footnote-ref-15)
15. Within section 3.12 of the FAD for TA525, the duration of treatment effect is described as “*3 or 5 years after stopping [the maximum treatment duration of] atezolizumab*” rather than from treatment initiation. In contrast, in TA519, and consequently ID1536, the wording in the FAD refers to treatment effect duration from the *start* of treatment. Section 3.18 of the FAD for ID1536 states “*a 3-year to 5-year duration of treatment effect from the start of pembrolizumab treatment.*” [↑](#footnote-ref-16)
16. Paragraph 3.12 of the FAD in TA525. [↑](#footnote-ref-17)
17. Although the precise economic model is not available to us, the modelling method is outlined Comment 12 of MSD’s response to the ACD. [↑](#footnote-ref-18)
18. Paragraph 3.22 of the FAD. [↑](#footnote-ref-19)
19. Paragraph 3.12 of the FAD in TA525 FAD. [↑](#footnote-ref-20)
20. Pages 6–7 of NICE’s responses to Consultee, Commentator and Public Comments to the ACD. The ERG also highlighted the absence of a stopping rule in the atezolizumab study data. However, it noted that it was not in a position to comment on the effect on cost effectiveness analysis in TA525 (page 3 ERG’s Critique of Company Additional Evidence, 9 January 2020). [↑](#footnote-ref-21)
21. See, for example, Section 3.3.3 of the Methods Guide. [↑](#footnote-ref-22)
22. See: (i) slide 17 of Chair’s Presentation ahead of the 3rd Appraisal Committee Meeting in TA525, 6 February 2018; and (ii) page 28 of the Committee Papers following the ACD in TA525, December 2017. [↑](#footnote-ref-23)
23. See, for example, KEYNOTE-001 (melanoma, non-small lung cancer), KEYNOTE-006 (melanoma) and KEYNOTE-024 (non-small lunch cancer) (see Comment 3 of MSD’s Comments in response to the ACD). [↑](#footnote-ref-24)
24. Paragraph 3.14 of both the ACD and FAD. [↑](#footnote-ref-25)
25. Paragraph 3.22 of the FAD. [↑](#footnote-ref-26)
26. Paragraph 3.4 of the FAD for pembrolizumab states: “*in the latest data cut of KEYNOTE-045, the median overall survival for pembrolizumab was 10.1 months (95% confidence interval [CI] 7.6 to 12.9) compared with 6.2 months (95% CI 5.2 to 7.4) for the UK SoC arm with a hazard ratio of 0.64 (95% CI 0.49 to 0.81). This suggests that pembrolizumab improves overall survival compared with docetaxel or paclitaxel.*” Paragraph 3.4 of the FAD for atezolizumab (TA525) states: “*The primary outcome of IMvigor 211 was overall survival in the group with the highest level of PD-L1 expression (5% or more, n=234). In this group, median overall survival was* ***not statistically significantly higher with atezolizumab*** *(11.1 months) than with chemotherapy (10.6 months, hazard ratio 0.87; 95% CI 0.63 to 1.21)…* ***Median overall survival for the overall population was 8.6 months with atezolizumab and 8.0 months with chemotherapy****, resulting in a similar hazard ratio, 0.85 (95% CI 0.73 to 0.99)…*” (emphasis added). [↑](#footnote-ref-27)
27. Slide 9 of the Chair’s Presentation for the Second Appraisal Committee Meeting, 6 February 2020. [↑](#footnote-ref-28)
28. Data collected from Ipsos’ Global Oncology Monitor shows that, as of the Moving Annual Total ending in September 2019, 39% of reported drug-treated patients in their sample affected with metastatic urothelial cancer in a second-line setting were prescribed with pembrolizumab (following 1st line platinum-containing chemotherapy); this reflects a 17% higher usage share for pembrolizumab compared to atezolizumab (22% patient usage share) among this reported patient sample cohort. [↑](#footnote-ref-29)
29. European Association of Urology – Guidelines on Muscle-Invasive and Metastatic Bladder Cancer (available at: <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=summary-of-changes>, accessed 20 March 2020). [↑](#footnote-ref-30)
30. NCRI-ACP-RCP-RCR Group’s Comments in Response to the ACD, Comments 1-3. [↑](#footnote-ref-31)
31. *Id.* [↑](#footnote-ref-32)
32. Paragraphs 1, 3.23 and 3.24 of the FAD. [↑](#footnote-ref-33)
33. See, for example, *Belgian Linguistic* Case(No 2) (1968) I EHRR 252. [↑](#footnote-ref-34)
34. See, for example, paragraph 3.1 of the FAD. [↑](#footnote-ref-35)
35. Paragraph 3.22 of the FAD. [↑](#footnote-ref-36)
36. Paragraph 3.5 of the FAD. [↑](#footnote-ref-37)
37. Paragraph 3.5 of the ACD. [↑](#footnote-ref-38)
38. ERG Response to Company Comment 4, at page 4 of the ERG’s Critique of Company Additional Evidence, 9 January 2020. [↑](#footnote-ref-39)
39. Page 5 of the ERG’s Critique of Company Additional Evidence, 9 January 2020. [↑](#footnote-ref-40)
40. Bellmunt J, Fougeray R, Rosenberg JE, von der Maase H, Schutz FA, Salhi Y, et al. Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. Ann Oncol 2013;24:1466-72. [↑](#footnote-ref-41)
41. Comment 10 of MSD’s Comments in Response to the ACD. [↑](#footnote-ref-42)