Dr Rima Makarem

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Dear Dr Makarem

Thank you for your detailed consideration of MSD’s Appeal Letter, particularly at such a difficult time for everyone involved in supporting the Health Service. MSD is grateful for the opportunity to respond to the Initial Scrutiny Letter. Below is a summary of our responses, followed by more detailed observations.

# **Summary of Responses**

* We welcome that you consider that Grounds 1a.2, 2.1, 2.4 and 2.5 are admissible and have no further comments on those Grounds, save for 2.5 for which we provide some additional detail below.
* Regarding Ground 1a.1, we are very grateful for the addition of the FAD from TA525 to the bundle for this appeal. Inconsistency with previous appraisals is a pervasive point in this appeal and we raised this issue during the consultation process. During consultation and in our Appeal Letter, we referred to certain documents from appraisals TA525 and TA520 to show how this appraisal had taken a different approach. As such, we feel it would benefit the Appeal Panel to have those documents first-hand and we may need to refer to them during the Appeal Hearing. We have listed these below and respectfully request that you consider also adding these documents to the appeal bundle.
* We strongly believe that this appraisal raises substantive human rights arguments, which are central to this Appeal. We feel these are issues that the Appeal Panel could only address adequately under a standalone appeal ground under the legality/exceeding powers Ground 1b. We provide detailed responses to your observations to Ground 1b.1 below and request that this Ground is referred to the Panel as originally particularised.
* We have reflected upon your comments on Ground 2.2 and would not object to the Appeal Panel addressing this point as part of an expanded Ground 2.1, on the assumption that there will be an opportunity to discuss the clinical expert’s comments in broad terms.
* MSD respectfully disagrees with amalgamating Ground 2.3 into Ground 2.1. They concern different issues and subject matter and are separate and distinct points of appeal. Ground 2.3 raises methodological questions about how the Appraisal Committee arrived at the “most plausible ICER” based on a range of possible ICERs. Treatment effect, the subject of Ground 2.1, was one of the inputs that contributed to the range but there were several others. We do not see how the methodological points raised under Ground 2.3 could be properly addressed if they were blended into a discussion that primarily concerns treatment effect.
* Lastly, we welcome that you consider Ground 2.5 to be a valid appeal point and therefore admissible. We thank you for your guidance on Ground 2.5. We offer some clarification to our arguments below.

# **Detailed Responses**

***Ground 1(a): In making the assessment that preceded the recommendation, 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**

We are conscious of the challenges that the Appeal Panel faces when assessing questions of inconsistency with other appraisals without access to all of the papers from those appraisals. We appreciate your efforts to provide the Appeal Panel with sufficient context to address meaningfully our submissions on inconsistency. We are very grateful that the FAD from TA525 is to be added to the appeal bundle and agree that this would benefit the Appeal Hearing. However, as our Appeal Letter suggests, inconsistency is a pervasive point in this appeal and was an issue we had raised in our communications with NICE and the ERG during consultation. Much of that only becomes clear when one compares the documents that contributed to the FAD in TA525 against those in this appraisal, as these show the approach taken to the evidence submitted. The TA525 FAD ultimately shows the conclusions the Appraisal Committee reached with a summary of the methodology. On its own, it is insufficient evidence to demonstrate many of the inconsistencies that are central to this Ground.

In particular, in this appraisal, ERG introduced uncertainty around how we had understood treatment effect to be implemented in the economic modelling for TA525. That called into question our view that NICE’s approach in this appraisal was inconsistent with that in TA525. In our response to the ACD, we pointed to a body of evidence that underlined our understanding of TA525 and supported our view that NICE had taken a divergent approach in this case. We also emphasised that our base case assumptions concerning the duration of treatment effect were clearly based on principles and methods that the Appraisal Committee had considered to be acceptable in past appraisals. To validate our point, Comment 12 of our response to the ACD made reference to certain documents from TA525 (the 3rd set of committee papers) and TA520 (the 1st set of committee papers). Comments 3 and 12 of our response to the ACD also referred to how the Appraisal Committee in TA525 had looked to appraisals of immunotherapies in other indications where a stopping rule applied to inform its estimate of the treatment effect for atezolizumab. The 3rd set of public committee slides in TA525 shows this succinctly and is important evidence for Ground 1a.1 (particularly the sub-section entitled “Rejection of Precedent from Other Immuno-Oncology Technology Appraisals”).

We feel it is important to be able to refer to these documents first-hand during the Appeal Hearing, so that the Appeal Panel can fully understand the differences in the Appraisal Committee’s approach to the two appraisals and assess whether the Appraisal Committee was correct, following the ACD consultation, to reject our submissions around consistency. It would be impossible to do this without an opportunity to review the underlying documents that we highlighted during our engagement with the Appraisal Committee. Therefore, we respectfully ask you to consider adding the additional documents below to the appeal bundle (together with MSD’s comments in response to the ACD, if not already included):

* TA525 – 3rd set of committee papers (in particular, the additional analyses submitted by the company);
* TA520 – 1st set of committee papers (in particular, pages 112-113 of the ERG report); and
* TA525 – 3rd set of committee slides (in particular, slides 15-17).

We appreciate that some of these documents are lengthy and are happy to provide the Appeal Panel with a precis or excerpts of the key passages, if that would assist. However, the sections identified to be most relevant within those documents are relatively short and we do not believe their inclusion, added to the FAD in TA525, would substantially increase the Appeal Panel’s burden of review. Given that we had already referred to these documents (or their content) during the consultation process, we do not believe that their addition to the appeal bundle introduces new evidence at this stage.

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

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

The Initial Scrutiny Letter states that, subject to further review, you are not minded to refer Ground 1b.1 to the Appeal Panel. Your preliminary view was that: (i) our submissions under Article 2 of the Convention had merit but they would be better addressed under other Grounds concerning unfairness and unreasonableness; and (ii) the Appeal Letter did not raise a specific issue of discrimination.

Having carefully considered your observations, we continue to feel strongly that our submissions under Ground 1b.1 raise substantive and weighty questions concerning human rights and equalities laws.

***Article 2 of the Convention***

We welcome your acknowledgement that, in principle, Article 2 is engaged in this case. We also agree with your general characterization of our submission (*i.e.*, that “*the argument is not that Article 2 compels a positive recommendation per se, but rather it compels a particular approach to the evidence or it narrows the range of otherwise reasonable conclusions*”). However, we respectfully disagree that this does not give rise to a standalone 1b appeal ground and that the arguments we raise are best assessed as examples of unreasonableness or procedural unfairness. As you suggest in the language above, Article 2 compels a particular approach and/or narrows the range of options. Without this stand-alone ground for appeal there is a risk that the Appraisal Committee may be afforded greater flexibility and health economic discretion than the law would otherwise permit.

NICE’s Process and Methods Guide for Appeals makes clear that “*NICE is a public body…*[and] *undertakes its work in accordance with public law…*” As such “*[a]n appellant may appeal on the ground* [*i.e.*, Ground 1b] *that NICE has acted outside its remit or has acted unlawfully*.”[[1]](#footnote-2) As such, a 1b appeal ground arises if an appellant presents an arguable case for a breach of NICE’s public law obligations. We believe our submissions concerning Article 2 of the Convention clearly present such an arguable case.

Article 2 is essentially the right to have life protected. In certain contexts, this right obliges States to take positive measures to preserve life. Case law concerning Article 2 has contemplated the obligations of a State to fund treatments that are essential in order to save lives.[[2]](#footnote-3) It is generally accepted in cases concerning Article 2 and state-funded healthcare “*regard must be had to the fair balance that has to be struck between the competing interests of the individual and the community as a whole*.”[[3]](#footnote-4) In other words, when Article 2 is engaged, NICE must conduct a balancing exercise between the needs of particular patients and the wider community.

That is a free-standing obligation. It is not discharged by demonstrating that the appraisal process was procedurally sound or that the Appraisal Committee considered the evidence before it reasonably. Rather, the effect is to compel the Appraisal Committee to appraise the product in a manner that respects patients’ right to life and fairly weighs the interests of affected patients against those of the wider community. As such, even if the Appraisal Committee could successfully demonstrate that its approach was objectively fair and its evaluation of the evidence was reasonable, Article 2 would require ensuring that the decision fairly weighed the interests of patients against those of the wider community. As your letter suggests, this does require taking a particular approach to reviewing evidence and may narrow the range of conclusions available to the Appraisal Committee.

To clarify, MSD’s position in this Appeal is that, in addition to conducting an unfair and unreasonable assessment (Grounds 1a and 2, respectively), the Appraisal Committee’s approach and conclusions failed to respect the right to life or balance competing interests fairly.

We believe that in order to conduct a fair balancing exercise, the Appraisal Committee had a duty to address and accommodate for a number of critically important factors. These include: (i) the unique circumstances the patients faced; (ii) the potential benefits to their life prospects that pembrolizumab offers; (iii) the ramifications of a decision to refuse to fund treatment, particularly as some patients may have poorer life prospects; and (iv) the risk of failing to respect the right to life in those circumstances. We are unaware of any evidence that the Appraisal Committee considered or gave appropriate weight to these issues.

The key concern in MSD’s submission related to the way in which the Appraisal Committee managed evidential uncertainty and whether that approach was appropriate in circumstances where Article 2 is engaged. Pembrolizumab is acknowledged to be life-extending and life-improving, as evidenced by a volume of clinical data that is robust and unprecedented in terms of longer-term follow-up. The Research Group considers pembrolizumab to be the only product in this indication that has a “level one” evidence-base. Many clinicians and some clinical guidelines prefer treatment with pembrolizumab over alternatives (including) atezolizumab, largely because of stronger evidence of overall survival benefits. These features have a direct bearing on patients’ right to life and the balancing exercise required under Article 2.

As the Research Group suggested, the unique circumstances patients faced and the potential benefits of pembrolizumab over alternatives like atezolizumab ought to have led the Appraisal Committee to give the technology the “benefit of doubt” in situations requiring assumption, extrapolation or the exercise of discretion. The unfortunate reality is that the Committee took the opposite approach in key aspects of its decision-making. The levels of latitude expected in cases where Article 2 is engaged, particularly compared to previous appraisals, including that for atezolizumab, were not afforded to pembrolizumab and in our view cannot represent a fair balance of competing interests.

We appreciate that the unique circumstances of this case mean that there is considerable factual crossover between Ground 1b.1 and some other Grounds. However, this does not mean that an appeal ground under Article 2 ceases to exist in its own right. Article 2 requires the Appraisal Committee to demonstrate that the decisions and approach it took respected the right to life. It also requires the Appeal Panel to hold the Appraisal Committee to account. We believe that the only way to do this is to consider Article 2 under a standalone 1b appeal ground.

***Discrimination under Article 14 of the Convention and the Equality Act 2010***

We believe the Appraisal Committee’s decision amounts to discrimination under Article 14 of the Convention and the Equality Act because (i) it disproportionately and negatively affects the patient population in this indication, who are disabled[[4]](#footnote-5) and are likely to be older people; and (ii) the same patient population, with protected characteristics, has been treated unequally in comparable appraisals. In other words, there are cancer patients who might benefit from a product backed by evidence showing that it increases overall survival who have been disproportionately and negatively disadvantaged because of the approach the Appraisal Committee took.

We respectfully disagree that in order for discrimination to form the basis of an appeal ground, one must identify a comparator group that has been treated more favourably than patients denied treatment. Rather, a policy that applies universally (*i.e.*, a treatment is not recommended full stop) can be indirectly discriminatory if a particular group with protected characteristics finds itself disproportionately disadvantaged. Indirect discrimination falls under the scope of both the Convention and the Act and is only lawful if objectively justified.[[5]](#footnote-6)

The requirement for an objective justification is a specific legal requirement under Article 14 of the Convention and the Equality Act. It means the decision must represent a proportionate means to achieve a legitimate aim. The suggestion in the Initial Scrutiny Letter that “objective justification” equates to reviewing the evidence reasonably and therefore is best addressed as a general matter under Ground 2 is, with due respect, incorrect.

In the Appeal Letter, we discussed Article 14 of the Convention and Equality Act together. This was for the sake of efficiency and we apologise if it led to a lack of clarity. Although there is significant overlap between both, we discuss each separately below.

***Article 14 of the Convention***

The basic principle behind Article 14 is that everyone is entitled to equal access to human rights established under the Convention. People cannot be directly or indirectly denied equal access to Convention rights on grounds of their personal “status” (including age, sex, race, gender or disability). In this case, Article 14 is relevant because Article 2 is also engaged. As such, two key questions arise: (i) whether the Appraisal Committee’s decision is “discriminatory” as to the enjoyment of the right to life; and if so (ii) whether the discrimination is objectively justified.

A decision engages Article 14 when it interferes with how persons with protected characteristics exercise other Convention rights.[[6]](#footnote-7) Cancer patients are necessarily a group protected under equalities law. Moreover, as paragraph 3.1 of FAD acknowledges, patients who stand to benefit from pembrolizumab are older and are likely to have significant co-morbidities, including other disabilities. Although the Appraisal Committee’s decision not to recommend pembrolizumab is universal, it disproportionately affects those patients (who have protected characteristics) more than other members of society. The disproportionate effect is amplified here because the decision and approach taken in TA525 treated the same patient population very differently. The decision also interferes with patients’ exercising their right to life in that it blocks their access to a treatment that is life-saving and life-improving. As such, the decision is indirectly discriminatory, in the sense envisaged under Article 14, and would only be lawful if objectively justified.[[7]](#footnote-8)

MSD’s contention is that the Appraisal Committee’s decision was disproportionate in the circumstances and incapable of objective justification. When Courts assess proportionality under Article 14, they examine whether less restrictive policies or approaches were available, the balance the decision-maker struck and the relative weight it attached to the evidence before it.[[8]](#footnote-9) As we mentioned in our Appeal Letter, there may be circumstances where an Appraisal Committee has one or more objective justifications for taking a more restrictive approach or attaching less weight to evidence before it. That might be the case, for example, where there is a lack of quality evidence that gives rise to uncertainties and where the Committee cannot justify certain assumptions, approaches or recommendations. In this case, however, it has eliminated much of the benefit of doubt afforded to atezolizumab in TA525, despite the greater uncertainties inherent in the evidence base for that product. As noted above and in the Appeal Letter, this means that there are abundant examples throughout this appraisal of the Appraisal Committee failing to give proper weight to the particular characteristics of patients and the potential impact of pembrolizumab treatment on their lives. The Appeal Letter also provides examples of disproportionate decision-making, including subjecting pembrolizumab to assessment parameters that were unachievable. Less restrictive approaches were clearly available to the Appraisal Committee, most notably taking an approach that was consistent with TA525.

These examples call into question consistency with Article 14 and a Court considering this issue would not be satisfied with the defence that the authority had acted reasonably (which may be a lower standard). We believe this Appeal must take the same approach.

***Equality Act 2010***

The Public Sector Equality Duty (“PSED”) set out under section 149 of the Equality Act requires NICE to give due regard to eliminating discrimination or victimisation and advancing equality of opportunity between persons who share a relevant protected characteristic and those who do not. “Relevant protected characteristics” include a person’s age and any disabilities (including a cancer-diagnosis). The PSED is broader than Article 14 of the Convention, in that it protects against discrimination in general, rather than specifically with reference to the enjoyment of Convention rights. However, because both protections are based on very similar principles, an allegation that Article 14 has been breached invariably raises a similar issue under the Act. The legal test for objective justification under the Act is essentially the same as under Article 14. Our comments above explain why the Appraisal Committee’s decision fails to meet that test and, for the sake of brevity, we do not repeat them here.

Moreover, courts have emphasised that Section 149 of the Act imposes “*a process, not an outcome duty.*”[[9]](#footnote-10) The duty can be breached by conducting a procedure in a prejudicial or improper manner. The need to have “due regard” to the protected characteristics of people affected by a decision “*requires more than simply giving consideration to the issue, but awareness of the special duties the decision-maker owes in this context.*”[[10]](#footnote-11) The duty may be breached if the decision-maker has failed to meet the expectations of “*a reasonable public authority in the circumstances.*”[[11]](#footnote-12)

Sections 149(3) and 29 of the Equality Act provide further detail on how decision-makers should exercise their equality obligations. Section 149(3) requires having particular regard to: (i) removing or minimising disadvantages suffered by persons who share a protected characteristic; and (ii) taking steps to meet the needs of persons who share a protected characteristic that are different from the needs of persons who do not share it. Under Sections 29(6) and (7), NICE has a duty to make reasonable adjustments in its appraisal to take into account the protected characteristics of the patient population.

The facts of this appraisal point to the Appraisal Committee falling short of meeting these legal obligations, particularly as interpreted by the Courts. The disadvantages suffered by the patient population include the absence of an NHS funded technology that is considered to have “level one” supporting data; and relying on alternative technologies in end-of-life settings that possess a weaker evidence base and may provide poorer life-prospects. Minimizing those disadvantages and making reasonable adjustments in their favour are part-and-parcel of the “special duties” the Appraisal Committee had in the circumstances. Fulfilling these duties would have required applying an appropriate methodology of review, consistent with TA525. We believe that this is the very least that a reasonable public authority would need to achieve in the circumstances. The fact that the Appraisal Committee, inexplicably, took a more conservative approach suggests that barriers and challenges that patients face were exacerbated rather than reduced; in effect working against rather than in favour of the protected characteristics of the patient population. The needs and rights of patients were treated inequitably in comparable appraisals. We do not see how NICE could meet its legal obligations without, at a minimum, providing objective justifications for such inequality.

To conclude, we appreciate that this is a complex and sometimes esoteric legal area and that the Appeal Panel is not a judicial body. Nonetheless, these questions are central to this appeal and, in our view, can only be adequately addressed under a self-contained appeal ground.

Given the importance of these points to the MSD’s Appeal, one option that we would support is to admit Ground 1b.1 as it stands but address it only briefly at the appeal hearing, while referring the issue to the Appeal Panel’s and MSD’s respective legal advisers for resolution or further discussion on an inter-lawyer basis. We understand this has been common practice in previous appeals.

***Ground 2:******the recommendation is unreasonable in the light of the evidence submitted to NICE***

**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**

We welcome your observation that this is a valid appeal point. The reason why we had presented it as a standalone ground was that the evidence from the clinical expert related both to the duration of treatment effect and overall survival, both of which were factors that affected cost-effectiveness (see paragraphs 3.18, 3.20 and 3.22 of the FAD). On that basis, Ground 2.2 is related to but is not the same as Ground 2.1. However, on reflection, we agree that the Appeal Panel may find it helpful to consider this point as part of a broad-based assessment of Ground 2.1, assuming there will be an opportunity to discuss the influence of the clinician’s evidence during the appeal hearing.

**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**

We respectfully disagree with the proposal to incorporate Ground 2.3 into Ground 2.1.

Ground 2.3 is a broad ground concerning the approach the Appraisal Committee took to determining that the “most plausible ICER” was likely to be above £50,000 per QALY gained. As paragraph 3.22 of the FAD makes clear, that conclusion was based on several different inputs: the duration of treatment effect; the 2-stage method for adjusting for switching; the cost of pembrolizumab *etc.* Ground 2.1 only concerns one of those inputs: the duration of treatment effect. Therefore, we do not believe it would be appropriate for the Appeal Panel to consider these under the same Ground. We believe that merging the Grounds risks excluding or undermining a discussion of factors other than treatment effect that contributed to the Appraisal Committee’s assessment of cost effectiveness.

Moreover, MSD’s points under Ground 2.3 are largely methodological. Our submissions under Ground 2.3 are essentially that: (i) the Appraisal Committee did not use the appropriate inputs to establish its range of possible ICERs; and (ii) the Appraisal Committee unreasonably concluded that the “most plausible” ICER would in effect sit at the mid-point of the range of ICERs rather than the lower end. These points concern how the Appraisal Committee reached its decision on the most plausible ICER for pembrolizumab, rather than how the Committee assessed the evidence on treatment effect (which is the focus of Ground 2.1). In our view, the two Grounds pertain to materially different questions and should not be amalgamated into one. We feel that merging them risks making discussions during the hearing unstructured or unclear.

**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**

We welcome that you consider Ground 2.5 to be a valid appeal point. We note your comments and helpful guidance on this Ground. To help clarify, our submission under this Ground is that the 2-stage method was the most appropriate and correct approach to adjust for switching, which was an issue the Appraisal Committee and MSD both acknowledged needed to be managed. Our contention is that the Appraisal Committee’s decision to include unadjusted figures in its analysis was inappropriate and the technical submissions we made in this regard were not properly addressed. As such, the Appraisal Committee’s approach could not be considered reasonably justifiable.

We thank you in advance for considering our further observations and look forward to hearing from you.

Yours sincerely

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1. *Guide to the technology appraisal and highly specialised technologies appeal process -- Process and methods [PMG18]* [↑](#footnote-ref-2)
2. *Scialacqua v Italy* DR 81, 35, *Pentiacova v Moldova* 14462/03 and *NHS Trust A v M* [2001] Fam 348 [↑](#footnote-ref-3)
3. *Pentiacova v Moldova* 14462/03 [↑](#footnote-ref-4)
4. To clarify, a cancer diagnosis in and of itself falls within the definition of a “disability” under the Equality Act (see: <https://www.gov.uk/definition-of-disability-under-equality-act-2010>) [↑](#footnote-ref-5)
5. See, *e.g.*, *R (L and others) v Manchester City Council* [2001] EWHC 707 (Admin) [↑](#footnote-ref-6)
6. *See*, *e.g.*, *Petrovic v Austria* (2001) 33 EHRR 307, 318, 319, paras. 22, 28 [↑](#footnote-ref-7)
7. *See*, *e.g.*, *R (L and others) v Manchester City Council* [2001] EWHC 707 (Admin) [↑](#footnote-ref-8)
8. *Id.*, para. 94 [↑](#footnote-ref-9)
9. *R (otao Rose) v Thanet CCG* [2014] EWHC 1182 (Admin) [↑](#footnote-ref-10)
10. *Id.* [↑](#footnote-ref-11)
11. *Id.* [↑](#footnote-ref-12)