Mr Tim Irish

Vice Chair

National Institute for Health and Care Excellence

10 Spring Gardens

London SW1B 2BU

01 October 2020

Re: Final Appraisal Determination - Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell (NSQ NSCLC) lung cancer [ID1572] (CDF review TA848)

Dear Mr Irish,

Bristol Myers Squibb (“BMS”) wishes to appeal against the above Final Appraisal Determination (“FAD”), which recommends funding for nivolumab in NSQ NSCLC patients with PD-L1 expression at 1% or higher (which we refer to as “PD‑L1 positive”) but not the whole population that the product is indicated to treat (*i.e.*, all NSQ NSCLC patients). The recommendation for PD-L1 positive patients is an important advance for the NHS and is not under appeal here. Rather, this appeal concerns NICE’s decision not to review nivolumab in line with its marketing authorization and the Scope of the appraisal; specifically the decision to exclude patients with PD-L1 expression of less than 1% (“PD-L1 <1% patients”) or inconclusive or unquantifiable PD-L1 status.

BMS has great respect for NICE and the work it does, but the company is compelled to bring this appeal on fundamental points of principle and in the interests of patients. This technology appraisal and Cancer Drugs Fund (“CDF”) exit review were designed from the outset to appraise nivolumab for the NSQ NSCLC population as a whole, irrespective of PD-L1 expression. This is clear in the original 2015 Scope, and is restated in the 2019 Scope. The latter applies specifically to the CDF review.

The FAD departs from both Scopes and does not give consideration to PD-L1 <1% and inconclusive PD-L1 patients. Patients will find that difficult to accept, given the clinical data submitted to NICE show that nivolumab improves overall survival, regardless of PD-L1 expression. NICE and/or the Appraisal Committee have refused to review that evidence because, according to NICE, the CDF recommendation has a limiting effect such that NICE must reject any data that does not concern PD-L1 positive patients. That appears to be an internal NICE position. It is wholly incorrect. It has no basis in the Methods Guide or any other procedural document. In fact, the Methods Guide and the FAD itself both say NICE should do exactly the opposite.

It is a position that seems to have developed during the course of this CDF review, without proper consultation or communication. Conducting appraisals in this manner lacks transparency, is procedurally unfair and breaches basic public law principles. It also undermines the key objective of the CDF, which is to allow time to gather the most up‑to-date evidence to resolve uncertainty. Throughout this appraisal — including during the CDF period — BMS, clinicians and patients expected NICE to review the most up-to-date clinical data for the whole NSQ NSCLC population. Such an expectation was fully justified and supported in the Methods Guide and within the data collection agreement. NICE has fallen short of that expectation by unilaterally changing the terms of its review as that review progressed. It has arbitrarily distinguished between patients based on PD-L1 expression, which has been shown to be an imperfect biomarker for this drug class. This leaves PD-L1 <1% patients disenfranchised and without access to treatment that is proven to be life-extending.

BMS requests that: (i) this appeal be determined at an oral hearing; and (ii) if the appeal is successful, the Appraisal Committee reconvenes to evaluate the data BMS has submitted for the whole NSQ NSCLC population.

# **Background**

Opdivo (INN nivolumab) is a monoclonal antibody that targets the PD-1 receptor, working on the immune checkpoint pathway. Its marketing authorization encompasses a number of oncology indications. This includes use as a “*monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer [NSCLC] after prior chemotherapy in adults.*”

***NICE Appraisals of nivolumab in NSCLC***

In 2015, NICE began two technology appraisals of nivolumab in NSCLC: TA483 and TA484. The former related to the use of the product for the squamous (“SQ”) histology; the latter related to the non-squamous (“NSQ”) histology.

The parameters of each appraisal aligned with the marketing authorization of the product. This was clear in the original Scope published for TA484 in 2015 (“2015 Scope”), which stated the appraisal would encompass the NSQ NSCLC population as a whole, irrespective of PD-L1 status.

In 2017, in both appraisals, NICE recommended interim funding through the CDF. In TA483, NICE made this recommendation regardless of the PD-L1 status of SQ NSCLC patients.

In TA484, however, the Appraisal Committee considered that according to the clinical evidence presented to it at the time, nivolumab had not shown a “*convincing overall-survival benefit*” in PD-L1 <1% patients.[[1]](#footnote-1) The Committee therefore recommended its use within the CDF only for PD-L1 positive patients.

At the time, the Committee was concerned with uncertainties in the available evidence, including the level of clinical effectiveness according to PD-L1 expression, long-term overall survival and the duration of therapy.[[2]](#footnote-2) The intention was that during the CDF period, BMS would generate further evidence to resolve those uncertainties. In particular, the data collection arrangement would allow the Appraisal Committee to explore efficacy and hence cost-effectiveness at different PD-L1 expression levels. The primary source of data collection was the ongoing CheckMate 057 Phase III trial, in which a 5-year data cut was expected in June 2019. That trial was of nivolumab vs docetaxel for the treatment of patients with metastatic NSQ NSCLC with progression on or after platinum-based chemotherapy. The primary endpoint was overall survival (“OS”) with efficacy according to tumour PD‑L1 expression level as one of the secondary endpoints.

***Data Generated During CDF Period***

During the CDF period, BMS increased the quality and depth of its evidence base. Data from the CheckMate 017 (SQ) and 057 (NSQ) trials demonstrated that, over the longer term, nivolumab significantly improved overall survival across the whole 2L NSCLC patient population. In CheckMate 017, the proportion of patients treated with nivolumab alive at 5 years was XXXX% compared to XXX% with docetaxel. In CheckMate 057, the proportion of patients treated with nivolumab alive at 5 years was XXXX% compared to XXX% with docetaxel.

Updated 5-year Kaplan Meier curves from CheckMate 057 demonstrate:

* + For baseline PD-L1 positive patients, the proportion treated within nivolumab alive at 5 years was XX.X% compared to X.X% with docetaxel.
  + For baseline PD-L1 <1% patients, the proportion treated within nivolumab alive at 5 years was X.X% compared to X.X% with docetaxel.
  + For patients with unquantifiable PD-L1, the proportion treated within nivolumab alive at 5 years was XXXX% compared to XXX% with docetaxel.

Irrespective of PD-L1 expression, treatment with nivolumab at least xxxxxxx overall survival rates compared to docetaxel. These survival rates are considerably higher than those taken into account at the time of the CDF recommendation; xxxxxxxxx the figures the Evidence Review Group (“ERG”) estimated at the time.

***The CDF Review***

In July 2019, NICE began the “CDF exit” process for TA484 (*i.e.*, ID1572). For this, it published an updated Scope for the CDF review (“2019 Scope”). The 2019 Scope confirmed that the relevant patient population for the CDF review remained the same as in 2015, *i.e.*, the whole patient population, irrespective of PD-L1 expression. On that basis, BMS submitted clinical data to NICE for the whole NSQ NSCLC population.

Around the same time, however, NICE provided BMS with non-binding terms of reference for the CDF review (“Terms of Engagement”). The purpose of the document was to set out the Appraisal Committee’s preferred assumptions and provide context. The Terms of Engagement state the Committee’s preference to focus on PD-L1 positive patients.

In subsequent correspondence, NICE representatives made clear: “*[the] PD-L1 <1% population data will not be considered by committee as part of the CDF review.*”[[3]](#footnote-3) NICE has refused to consider any data that concerns PD‑L1 <1% (or inconclusive PD-L1) patients. That was despite the fact that BMS’ submissions include such data; and that the ERG has included the whole patient population in its review.

The Appraisal Committee’s position is that the 2017 CDF recommendation precludes any further consideration of PD-L1 <1% patients. In other words, in August 2019, NICE adopted an internal approach by which the CDF recommendation would supersede the 2015 and 2019 Scopes. As a result, the FAD limits itself to considering only the evidence for the PD-L1 positive sub-group and limits the recommendation to this sub-group.

# **Summary of Appeal Grounds**

In BMS’ view, the decision to restrict the CDF review to PD-L1 positive patients gives rise to multiple grounds for appeal. Specifically: (i) the CDF review process was procedurally unfair (Ground 1(a)); (ii) the review breaches NICE’s human rights and equality obligations (Ground 1(b)); and (iii) NICE has reached unreasonable conclusions in light of the evidence submitted (Ground 2).

**Procedural Unfairness — Ground 1(a)**

* By focusing on PD-L1 ≥1% patients alone, the CDF review undermines both the 2015 and 2019 Scopes. Both Scopes encompass the whole NSQ NCLSC patient population. NICE must at the very least consider evidence for the whole population. NICE has not provided clear and adequate reasons to justify this departure from the Scope. To have done so is procedurally unsound and breaches the Methods Guide.
* The Appraisal Committee has incorrectly assumed that a CDF recommendation narrows the remit of the CDF review. The Methods Guide does not say this or suggest it. The Methods Guide says that no changes to the Scope may be considered during a CDF review. The Appraisal Committee’s approach lacks any procedural basis and is inappropriate and unfair. Particularly so, given that the 2015 and 2019 Scopes, the Methods Guide, as well as other documents created the legitimate expectation that the CDF review would consider the clinical evidence generated in all patients, regardless of PD-L1 expression.
* NICE’s approach breaches numerous public and administrative law principles. In its review, the Institute has failed to take relevant evidence into account. It has undermined BMS’ right to a fair hearing. The Institute has unjustifiably fettered its own decision. NICE has failed to explain or justify its decisions.

**Breach of Human Rights and Equalities Laws — Ground 1(b)**

* NICE’s decision to exclude PD-L1 <1% and inconclusive PD-L1 patients from the review deprives those patients of a life-extending treatment. That decision was unreasonable and procedurally incorrect. It is an unjustifiable interference in those patients’ fundamental human rights, including the right to life and to fair and equal access to life-extending treatment. NICE has failed to uphold its legal obligation to protect those rights. NICE’s decision creates an artificial and unreasonable distinction based on PD-L1 status. This amounts to unjustified and unlawful discrimination.

**Unreasonable Conclusions in light of the Evidence — Ground 2**

* The FAD is founded upon an unreasonable assessment of the evidence submitted because the Appraisal Committee refused to assess the totality of BMS’ submissions. The assertion made in the FAD that the Appraisal Committee reviewed the data submitted is plainly wrong. It is illogical to conclude, as the FAD effectively does, that nivolumab is clinically and cost effective for PD-L1 patients but not for the rest of the patient population, if the Appraisal Committee has only looked at the evidence base for one of those groups.
* The recommendation arbitrarily distinguishes between patients based on their PD-L1 status. PD-L1 is a limited and imperfect biomarker. It is variable, both over time and because of the heterogeneity of tumours. Moreover, the most up-to-date data show that nivolumab is effective regardless of PD-L1 status. To rely upon PD-L1 expression to determine which patients do or do not receive treatment in this case is illogical.

# **Detailed Appeal Grounds**

## Ground 1(a) — NICE has failed to act fairly

### **Ground 1(a).1 — NICE has unjustifiably departed from the 2015 and 2019 Scopes and the Methods Guide**

The Scope is a critical component of any appraisal, including where that includes a CDF review. According to the Methods Guide, the Scope “*sets out what questions the potential appraisal will address … and focus[es] the appraisal.*”[[4]](#footnote-4) That includes identifying the patient population for whom the technology will be appraised.[[5]](#footnote-5) More broadly, the Scope sets expectations for patients and other stakeholders (including the Secretary of State, who signs off the document) about what the eventual recommendation will and will not cover.

In this case, the 2015 Scope states the patient group under review to be “*people with previously treated locally advanced or metastatic non-squamous non-small cell lung cancer.*” That encompasses the whole patient population in line with the product’s marketing authorization. It also says: “*[i]f the evidence allows, consideration will be given to subgroups based on biological markers.*”

The 2019 Scope - issued specifically to manage the product’s exit from the CDF - is materially identical to the 2015 Scope. Put together, both set a clear and consistent trajectory for the CDF review. The CDF review is to address all NSQ NSCLC patients; any sub-group recommendations must be evidence‑based.

In reality, after issuing the 2019 Scope, NICE performed an about-turn. The FAD departs from both Scopes, by concentrating on one sub-group within the patient population. NICE has not provided any evidence-based reasons for doing this. It is difficult to see how any evidence-based reasons exist, given the Appraisal Committee has refused to consider the totality of the evidence, which must clearly be a pre-requisite to providing those reasons.

The only conclusion to draw is that NICE has narrowed the 2019 Scope and done so unjustifiably. NICE’s Appeal Panel has upheld previous appeals for precisely these reasons. For example, the Appeal Panel has previously concluded:

“*In every appraisal,* ***the starting point to define the question put to the Committee is the same: the scope****….* ***Unless a scope specifies otherwise,*** *the Appeal Panel considers there is* ***a soft presumption that the starting point for any Committee should be consideration of the whole patient group as one, with a view to making one recommendation for that group.*** *Where different recommendations are made for different groups of patients, the reason for departing from one recommendation should be* ***clear and adequate***” (emphasis added).[[6]](#footnote-6)

In this CDF review, the Appraisal Committee has not considered the population as a whole, nor sought to make a holistic recommendation. Its reasons for issuing a sub-group-focused recommendation are neither clear nor adequate. The Committee has, in effect, pre-determined the sub-group for which it intends to recommend the product and refused to review any data that does not relate to that sub-group.[[7]](#footnote-7) In these respects, the Committee has clearly breached the Methods Guide.

All of the above is particularly surprising since the FAD acknowledges the principle that a CDF review should not differ from the original scope. Section 3.2 of the FAD considers whether the fact that other potential comparators are now authorized and NICE-recommended could result in a different choice of comparator in the CDF review. The answer was clear: “*In line with NICE’s methods guide for technology appraisals, the original scope was not changed for this CDF review*.”

In that light, the obvious departure from the 2019 Scope is difficult to comprehend. One must question why the 2019 Scope was issued if NICE did not intend to adhere to it. In discussions, NICE representatives have suggested to BMS that the 2019 Scope may have been issued in error. In BMS’ view that is not a valid reason. The Committee might also point to the Terms of Engagement (also issued in 2019) to justify the approach it took. However, it is incorrect to suggest that this document could or does amend or supersede the Scope. The 2019 Scope set out the formal parameters of the review, entitled BMS to submit the totality of the data it had collected from the CheckMate 057 and 017 studies and required the Committee to review those data as a whole and with an open mind. The Terms of Engagement did no more than to set out the Appraisal Committee’s preferred assumptions, *i.e.*, that it would prefer to focus on the PD-L1 positive sub-group; but that it was still obliged to review the totality of the data submitted (see below).

### **Ground 1(a).2 — The premise that the 2017 CDF recommendation limits the scope of the 2019 CDF review has no procedural basis, misinterprets the CDF process and falls short of BMS’ legitimate expectations**

#### **The premise lacks a procedural basis**

On 19 July 2019, NICE representatives wrote to BMS as follows:

“*We have been able to clarify that the CDF guidance review (para 6.19 – 6.27 of the Guide to the process of technology appraisal) should be understood as* ***following the original recommendation*** *for the CDF and the terms of the managed access agreement.*”[[8]](#footnote-8) (emphasis added)

Furthermore: “*your evidence submission for a CDF guidance review should provide the committee the additional data requested in the MAA, which relates to their* [original CDF] *recommendation…*[*i.e.*, data relating]***only* [to] *PD-L1 positive patients****.*” (emphasis added)

That is not what the Methods Guide says. At no point do Sections 6.19 – 6.27 (which govern the CDF process) say or even suggest that a CDF recommendation narrows the parameters of the reassessment on exiting the CDF. We cannot see any basis for NICE’s assertions in this regard, nor any basis for disregarding the 2019 Scope.

It is unclear how, and with whom, NICE was able to “clarify” its position; or why this was necessary. The Methods Guide is unambiguous. Section 6.25 states that a “*Cancer Drugs Fund guidance review* ***will take into account the data that have become available since the original appraisal... No changes to the scope of the appraisal will be considered.****”* According to the Methods Guide, the 2015 and 2019 Scopes are unaltered by the CDF recommendation and must be respected. The Committee is unable to reject in-scope evidence.

It appears that NICE has developed its position internally and reactively, as the CDF review has progressed. Such an approach lacks transparency and is procedurally unfair.

#### **The Appraisal Committee has misinterpreted the effect of the CDF recommendation in the technology appraisal process**

ID1572 is not a standalone or new STA; it follows from TA484 and represents the logical end-point of the original appraisal. TA484 sought to ascertain whether nivolumab was suitable for routine commissioning in the whole NSQ NSCLC population. The purpose of the CDF is to provide access to a product while the manufacturer generates and submits the data necessary to complete the appraisal. A CDF recommendation is, in that respect, a statement as to how the technology will be available during that interim period. It does not pre-determine the outcome of that review or set limits on the data that NICE may consider going forwards.

NHS England’s SOP for the CDF says a CDF recommendation is appropriate when “[there is] *plausible potential for a drug to satisfy the criteria for routine commissioning, but where there is currently too much uncertainty surrounding the clinical data and consequently the cost effectiveness estimates to make such a recommendation*”[[9]](#footnote-9) By its very nature, a CDF recommendation is a non-determinative statement based on the plausible potential of a product to be cost effective. It is subject to various unknowns that are yet to be resolved (which in this case include efficacy across different levels of PD-L1 expression).

The CDF SOP continues: “*NICE will schedule the re-appraisal of the drug and* ***this will take account of data available since the original appraisal***” (emphasis added).[[10]](#footnote-10) That is an unqualified statement (it does not, for example, say “*NICE…will take account of those data available that align with the original appraisal”*). The Committee has failed to take into account of the SOP and misinterpreted what the CDF is there to achieve.

#### **BMS had a legitimate expectation that the CDF review would consider data for the whole patient population**

BMS submitted updated clinical data to NICE relating to the whole patient population in good faith, and had every right to expect the Appraisal Committee to consider those submissions in full. The legitimate expectation arises because (amongst other things):

* The 2015 and 2019 Scopes require BMS to submit evidence for the whole population, and for NICE to assess it.
* At the time of the CDF recommendation, there was no indication that PD-L1 <1% patients would be excluded from the review going forwards. The 2017 FAD makes clear that based “*on the clinical evidence presented to it* [*i.e.,* in 2017]*, the Committee considered it reasonable to exclude…* [PD-L1 <1% and unquantifiable patients] *from the cost effectiveness considerations* [*i.e.,* in 2017]*.*”[[11]](#footnote-11) The 2017 FAD does not say that the CDF review must also exclude this sub-group.
* The 2017 Managed Access Agreement points to the Appraisal Committee taking a holistic view of the evidence collected over the CDF period. Section 4.1 states:

*“****While the use of nivolumab within the CDF is available only to those with a PD-L1 expression of at least 1%, different PD-L1 expression level [sic] will therefore be explored as part of the data collection arrangement****. The primary data source will be CheckMate -057 as the protocol for this trial included collecting this data along with other biomarkers at baseline.*  ***PD-L1 expression subgroup analyses using the 5-year follow-up data will be undertaken, including cost-effectiveness analysis, and provided to NICE when the guidance is reviewed****”* (emphasis added).

Although CDF funding was limited to PD-L1 positive patients, the Managed Access Agreement expressly contemplates collecting data from CheckMate 057 across different PD-L1 expression levels. In other words, the agreement pointed to exploring clinical efficacy in patients with PD-L1 levels above 0%, as all such patients “express” PD-L1 (in that respect, patients with PD-L1 <1% are called PD-L1 “negatives” as a matter of convenience). The meaning conveyed to BMS and other stakeholders at the time (which is reinforced by the Scope and the Methods Guide) is that data relating to patients expressing PD-L1 <1% would be explored with a view to resolving uncertainty. The Managed Access Agreement does not say or suggest that “*…only PD-L1 expression levels above 1% will be explored…*” This may be what the Committee, in hindsight, wishes that the agreement means. But that is irrelevant when it comes to assessing legitimate expectations created at the time.

BMS has collected and submitted evidence in accordance with the Scope and the nivolumab marketing authorization. BMS legitimately expected NICE to take those data into account.

### **Ground 1(a).3 — NICE’s approach in ID1572 has infringed fundamental public law principles**

As a public body, NICE must act in accordance with public law. Its approach in ID1572 breaches numerous fundamental public law principles.

#### **NICE has failed to take relevant evidence into account**

NICE must accept and appraise all relevant evidence, regardless of any internal positions or preferences. This is confirmed in case law: “*NICE has a duty to obtain and evaluate all relevant evidence.*”[[12]](#footnote-12) Section 3.3.1 of NICE Methods Guide also states:

“***Whatever the sources of evidence available*** *on a particular technology and patient group, they should be integrated into a systematic review.* ***A systematic review attempts to assemble all the available relevant evidence****…*”(emphasis added).

NICE’s approach in ID1572 fails to respect these principles. Clinical data relating to PD-L1 <1% and inconclusive PD-L1 patients was clearly relevant to this review. NICE’s failure to review or even accept those data is a breach of duty.

#### **The approach undermines BMS’ right to a fair hearing**

BMS has a right to a fair hearing. It must be free to submit in-scope information. NICE is duty-bound to review those submissions fairly and in good faith. Ignoring information that has been put before a decision-maker, without examining it, is inconsistent with the right to a fair hearing.[[13]](#footnote-13) Courts have confirmed that it is “*plainly incumbent upon NICE to consider [clinical trial data] …since that had been submitted and relied upon by a consultee.*”[[14]](#footnote-14) In this CDF review, NICE has self-evidently breached these requirements.

#### **NICE has inappropriately fettered its discretion**

If NICE is lawfully able to exercise discretion or make a judgement call, it cannot refuse to do so because of an internal position or policy. That would be an unlawful fettering of discretion[[15]](#footnote-15) Yet, this is exactly what NICE has done in ID1572. According to its statutory remit and its own procedures and policies, NICE had the ability to review and engage with the totality of BMS’ submissions (indeed this was a requirement under the 2019 Scope). It has made a conscious choice not to do this because of an internal position it has decided to adopt. The consequences of this choice are detrimental to BMS and the interests of patients. It is clear that NICE has inappropriately fettered its discretion.

#### **NICE’s failure to explain or justify its approach means that its procedures lack transparency**

NICE’s decisions and processes should be clear and transparent. The Courts have held:

*“The reasons for a decision must be intelligible and they must be adequate. They must enable the reader to understand why the matter was decided as it was and what conclusions were reached on the ‘principal and important issues.’”[[16]](#footnote-16)*

NICE has failed to justify its narrow interpretation of the Methods Guide; or explain why it has deviated from the Scope. No such explanation exists in the FAD. Patients and other stakeholders who read the document would not be able to understand why the recommendation does not cover the whole patient population.

BMS has asked NICE to explain its approach on multiple occasions. Most notably, BMS wrote to xxxxx xxxxxx (Programme Director for Technology Appraisals) on 17 December 2019 to question the “*legal and ethical basis of NICE’s current approach.*” The letter asked for further discussions. BMS received no reply and NICE has failed to provide any reasonable explanation.

## Ground 1(b) — NICE has exceeded its powers

### **Ground 1(b).2 — NICE has breached its legal obligations under human rights and equalities laws**

NICE must respect the obligations imposed on public bodies by the 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”). There are numerous references to this obligation in NICE guidance.[[17]](#footnote-17) 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 subject to those directions. NICE is therefore bound to take into account the State’s obligations under human rights law.

These considerations are particularly important when it comes to differentiating between patient subgroups. Section 5.10.10 of NICE’s Methods Guide provides:

“*When considering subgroups, the Appraisal Committee pays particular attention to its legal obligations on equality and human rights.”*

NICE’s refusal to consider data relating to PD-L1 <1% patients excludes that sub-group from the CDF review in contravention of NICE’s human rights and equalities obligations, specifically under Articles 2 and 14 of the Convention and the Equality Act.

#### **Article 2 of the Convention**

It is important to appreciate that metastatic NSCLC is still a largely fatal disease, despite all the recent advances in treatment. Deaths from lung cancer still exceed those of any other malignancy worldwide.[[18]](#footnote-18) The most recent National Lung Cancer Audit, published in August 2020 (data from 2018), shows that for metastatic (stage IV) disease, the proportion of patients surviving to one year after diagnosis remains low, at 17%, and is unchanged from 2015.[[19]](#footnote-19) A recent observational study from the US found the median OS for metastatic NSCLC patients to still be <1 year.[[20]](#footnote-20) In that context, a treatment that improves overall survival, even by small amounts, is invaluable to any patient who might benefit from it.

Article 2 of the Convention obliges the State to refrain from depriving persons of life intentionally. [[21]](#footnote-21) It is clear from the data submitted that nivolumab is a life-extending treatment in this indication. NICE has acknowledged that nivolumab meets the criteria to be considered a life-extending treatment at the end of life. Article 2 of the Convention is therefore engaged.

BMS 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. Article 2 requires NICE to carry out a fair balancing exercise between the needs of these particular patients and the community at large. The outcome of that balancing exercise must be reasonable. The exercise must, above all, be a rational one that adheres closely to a proper process. It is well established under English public law that a proper process is one which considers all of the relevant material (and no irrelevant material) with an open mind, allowing: (i) proper engagement with stakeholders as the process requires; and (ii) sufficient time for consideration and discussion before a decision is reached.

It is evident from BMS’ submissions under Grounds 1(a) and 2 that NICE has failed to carry out a fair, rational, reasonable and procedurally correct balancing exercise. Specifically, NICE has: (i) not taken relevant material into account; (ii) not had an open mind with respect to the totality of the data; (iii) adhered to a tenuous and incorrect interpretation of the Methods Guide; (iv) applied that interpretation retrospectively, without justification, in contradiction to BMS’s legitimate expectations; and (v) failed to give adequate reasons for this approach. Yet, the most egregious breach of Article 2 results from NICE’s steadfast refusal to consider the evidence that nivolumab improves overall survival for PD-L1 <1% patients, notwithstanding that those patients are clearly within nivolumab’s approved indications (*see* FAD para. 2.1), in scope and, as the FAD acknowledges, the CDF review does not affect this.

The result of NICE’s failure to consider the evidence or conduct a fair balancing exercise, is that the needs and rights of the PD-L1 <1% patients have simply not been taken into account in this appraisal. That is unreasonable and unfair, as set out in the other Grounds. However, there is a particular and material significance for Article 2: namely that the effect of narrowing the review to PD-L1 positive patients is to deprive PD-L1 <1% patients of their right to life. The particular mischief is the change of approach mid-way through the review. Article 2 is breached not only because the process is unsound and unfair but also because of the *way* in which patients, who have a right to life, are left disenfranchised (*i.e.*, even if there were hypothetically a procedural basis for this).

#### **Article 14 of the Convention**

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.[[22]](#footnote-22) Specifically, Article 14 states:

“*The enjoyment of the rights and freedoms set forth in this European Convention on Human Rights* ***shall be secured without discrimination on any ground*** *such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth* ***or other status***” (emphasis added).

In the present case, a sub-group of patients has been denied the possibility to access a life-extending treatment because of its PD-L1 status. Such differential treatment falls within the ambit of Article 14.

BMS acknowledges that whenever a treatment is recommended for one sub-group but not another, certain patients will inevitably be disadvantaged. In such circumstances, a breach of Article 14 is established if NICE’s approach was “*manifestly without reasonable foundation*.”[[23]](#footnote-23) As set out at Grounds 1(a) and 2, not only is there no reasonable foundation for the approach NICE has taken, but the approach is also inconsistent with its own Methods Guide. The approach is procedurally unsound and fails to consider relevant evidence. The approach, therefore, breaches Article 14.

#### **Section 149 of the Equality Act**

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.

Courts have emphasised that the PSED 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.”[[24]](#footnote-24)* ThePSED is breachedif the decision-maker has failed to meet the expectations of “*a reasonable public authority in the circumstances*.”[[25]](#footnote-25)

BMS submits that NICE’s approach discriminates against a sub-group of patients with protected characteristics. By refusing even to consider the relevant data, NICE has not only failed to take into account the special duties it owes to PD-L1 <1% patients; it has simply ignored them. In doing so, it has denied a beneficial treatment to that sub-group on account of their PD-L1 status, notwithstanding the fact that nivolumab is proven to be clinically effective for those patients. Such discriminatory treatment clearly falls short of what is to be expected of a reasonable public authority in the circumstances.

#### **Section 29 of the Equality Act**

Section 29(6) applies to NICE and prohibits discrimination in the provision of a public service. Under Section 29(7), NICE must make reasonable adjustments in its processes to take account of the protected characteristics of the patient population.

BMS submits that NICE’s approach in the present case amounts to indirect discrimination. Specifically, NICE has dogmatically adhered to a policy of limiting a CDF review to the terms of the CDF recommendation. That decision, applied rigidly, discriminates against cancer patients, who have been denied a beneficial treatment as a result. Despite this, NICE has failed to make any reasonable adjustment in the circumstances.

## Ground 2 — The recommendation is unreasonable in the light of the evidence submitted to NICE.

### **Ground 2.1 — The FAD is based on fundamentally incorrect assumptions, errors of fact and an unreasonable review of the evidence submitted**

There is an obvious disconnect between: (i) the evidence BMS submitted and the ERG reviewed, which is in line with the Scope; and (ii) the evidence the Appraisal Committee itself reviewed, which formed the basis of its recommendation. The conclusions contained in the FAD are based on the latter and reflect an incomplete assessment of the evidence. Those conclusions are unreasonable in light of the data actually submitted by BMS and available to NICE.

The disconnect means that certain statements and assumptions in the FAD are wrong. For example:

* Section 3 of the FAD states “*[t]he appraisal committee considered evidence submitted by Bristol-Myers Squibb*.” That is only partly true. The Appraisal Committee obviously did not consider all of BMS’s submission.
* The FAD wrongly assumes that PD-L1 positives are the relevant patient population for this review. For instance, when discussing clinical need (at para. 3.1 of the FAD) only PD-L1 positive patients are mentioned, suggesting that this is the patient population under review. That directly contradicts the 2019 Scope.

Moreover, by limiting the recommendation to PD-L1 positive patients, the FAD, *in effect*, says that nivolumab is not clinically or cost effective in the whole patient population. That is incorrect as a matter of fact. The most up‑to‑date clinical data show that, over a 5-year period, nivolumab improves overall survival for these patients, irrespective of PD-L1 expression. Data from CheckMate 057 demonstrate that the 5-year overall survival for PD-L1 <1% patients is more than xxxxx times that of the comparator. This survival rate is xxxx times higher than the rate the ERG took into account in 2017.

### **Ground 2.2 — The Appraisal Committee’s reasons for refusing to consider the totality of BMS’ evidence are perverse**

The Appraisal Committee’s refusal to consider the data submitted for PD-L1 <1% patients is paradoxical and perverse. The approach can, in effect, be summarized as follows:

1. in 2017, nivolumab was not recommended for PD-L1 <1% patients because of uncertainties in the clinical data; and
2. NICE will therefore not review any more up-to-date clinical data, even where those data resolve the concerns identified in 2017.

This is an illogical position. Particularly so, given the evidence-gathering principles behind the CDF. If there are data available that assist NICE with making a well-informed, thorough and up-to-date assessment, it is perverse for NICE to refuse to review them.

### **Ground 2.3 — The recommendation makes an unreasonable and arbitrary distinction based on a patient’s PD-L1 expression states, which is a limited and imperfect biomarker in this population**

Determining PD-L1 status is an important step in the diagnostic pathway. However, PD-L1 remains an imperfect predictive biomarker. Testing methodologies are still being developed and there is no single, standardized test routinely used by the NHS. The tests have a high positive predictive value but a low negative predictive value (*i.e.*, if the patient is positive they are more likely to have a good response, but if they are not positive they may still respond to nivolumab, and may even achieve a complete response).

BMS has been able to demonstrate that patients can benefit from nivolumab regardless of PD-L1 expression in 2L NSCLC. There are also numerous limitations to using PD-L1 expression as a biomarker in this population. These include the following:

* Heterogeneity of PD-L1 expression throughout the tumour, and therefore a biopsy, may not be representative of PD-L1 expression within the whole tumour.
* Unlike tumour driver mutations such as EGFR, protein expression such as that of PD-L1 may vary over time and after prior treatments including chemotherapy. A biopsy at diagnosis may therefore not be representative of PD-L1 expression level at the time of relapse and treatment decision making.
* The level of expression is a continuous variable, and the appropriate threshold for positivity is debated. BMS did not seek to define a “cut-off” for PD-L1 expression level, as we did not consider there was a “cut-off” below which patients should not be considered for treatment with nivolumab in the relapsed advanced metastatic setting. Observed clinical activity in PD-L1 low or non-expressers, suggests that application of stringent PD-L1 cut-offs would likely result in exclusion of patients who would derive benefit from nivolumab treatment.

NICE has attached significance to comments made about PD-L1 in the marketing authorization process. It is important to put this into context. The CHMP assessed the risk-benefit profile of nivolumab to be favourable in all patients, regardless of PD-L1 status. The product is licensed for the whole NSQ NSCLC population, regardless of PD-L1 expression. During the process of marketing authorisation approval, the CHMP requested *post hoc* analyses regarding PD-L1. These *post hoc* results should be interpreted with caution for several reasons: the analysis was retrospective, the subgroup sample sizes are small, and the PD-L1 test was not analytically validated at the 10% or 50% expression levels at the time of the analysis. The information requested by the CHMP has been provided in the SmPC for information, but the licence remains for all patients regardless of PD-L1 expression level.

Given the above, a recommendation that relies upon PD-L1 status to determine whether or not a patient may receive access to a life-extending treatment is illogical. That becomes abundantly clear (if any such clarification is necessary) in light of the most up-to-date clinical evidence that BMS submitted to NICE as part of this review.

For the reasons set out above, BMS submits that the CDF review was procedurally unfair, breached NICE’s human rights and equalities obligations and reached unreasonable conclusions in light of the evidence submitted and that NICE had a duty to assess. We respectfully ask that the above grounds are put before the Appeal Panel for adjudication.

Yours sincerely,

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1. Para. 4.33 of the FAD in TA484 [↑](#footnote-ref-1)
2. Sections 4.1 and 4.2 of the Managed Access Agreement, September 2017 [↑](#footnote-ref-2)
3. Email from xxxxxx xxxxxxxx to BMS, 13 August 2019 [↑](#footnote-ref-3)
4. Section 2.4 of the Methods Guide [↑](#footnote-ref-4)
5. Section 2.4.4 of the Methods Guide [↑](#footnote-ref-5)
6. NICE Appeal on TA282 (Advice on pirfenidone for treating idiopathic pulmonary fibrosis) (appeal date, 2 December 2016), paras. 27 and 28 [↑](#footnote-ref-6)
7. Section 5.10 of the Methods Guide specifically warns against this -- engineering the review of evidence to fit a particular set of recommendations for sub-groups [↑](#footnote-ref-7)
8. Email from xxxx xxxxxx and xxxxxxx xxxxxxxx to BMS, 19 July 2019 [↑](#footnote-ref-8)
9. Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund); A new deal for patients, taxpayers and industry, 8 July 2016, para. 36 (see also para. 56) [↑](#footnote-ref-9)
10. *Id*. para. 99 [↑](#footnote-ref-10)
11. Para. 4.33 of the FAD in TA484 [↑](#footnote-ref-11)
12. *R(otao) Servier Laboratories Ltd v NICE* [2009] EWHC 281 (Admin), para. 171 [↑](#footnote-ref-12)
13. *See* *e.g., R v Manchester Metropolitan University, ex parte Nolan [1990] ELR 380* [↑](#footnote-ref-13)
14. *Supra*, note 12*,* para. 172 [↑](#footnote-ref-14)
15. *British Oxygen Company Ltd v Minister of Technology* [2011] EWCA Civ 462 [↑](#footnote-ref-15)
16. *South Bucks District Council v Porter (No 2)* [2004] 1 WLR 1953 at page 1964, para. 36 [↑](#footnote-ref-16)
17. *See* *e.g.*, Section 1.14 of the Methods Guide, the NICE Equality Scheme and NICE Social Value Judgments principles at paras. 3.1 and 9 [↑](#footnote-ref-17)
18. IARC. Cancer Incidence, Mortality and Prevalence Worldwide GLOBOCAN 2012. Available at: http://gco.iarc.fr/ (accessed Sept 25th 2020) [↑](#footnote-ref-18)
19. Royal College of Physicians. National Lung Cancer Audit (2020). Published August 2020. Available at: https://www.rcplondon.ac.uk/projects/outputs/annual-report-published-2020 (accessed Sept 25th 2020) [↑](#footnote-ref-19)
20. Simeone JC, Nordstrom BL, Patel K, Klein AB. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, US setting. Future Oncol. 2019 Oct;15(30):3491-3502 [↑](#footnote-ref-20)
21. *Osman v United Kingdom* (1997) 29 EHRR 245; *Scialacqua v Italy (1998) 26 EHRR 164* [↑](#footnote-ref-21)
22. *See*, for example, *Belgian Linguistic* Case(No 2) (1968) I EHRR 252 [↑](#footnote-ref-22)
23. *R (DA) v Secretary of State for Work and Pensions* [2019] UKSC 21 [↑](#footnote-ref-23)
24. *R (otao Elizabeth Rose) v Thanet CCG* [2014] EWHC 1182 (Admin) [↑](#footnote-ref-24)
25. *Id.* [↑](#footnote-ref-25)