Mr Tim Irish

Vice Chair

National Institute for Health and Care Excellence

10 Spring Gardens

London, SW1V 2BU

22 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 TA484)

Dear Mr Irish,

Thank you for your Initial Scrutiny Letter, dated 8 October 2020. We are grateful for your review of our Appeal Letter and for your initial view that all of the Appeal Grounds are admissible.

**Submission of Data**

Your letter asks us to clarify that the company did submit “all the data from CheckMate 017 (SQ) & 057 (NSQ) re PD-L1 positive patients, PD-L1 <1% patients, and unquantifiable PD-L1 patients, and if so when.”

BMS submitted evidence from CheckMate 017 in squamous (SQ) NSCLC patients for another appraisal (TA483). Those submissions covered all PD-L1 patient types. In that appraisal, NICE accepted and reviewed the evidence submitted and recommended nivolumab for the whole SQ patient population. We are happy to provide more detail on our submissions in TA483, if that would help. However, their relevance to this appeal is not immediately clear to us, as TA484/ID1572 concerns non-squamous (NSQ) NSCLC patients only.

In ID1572, BMS collected clinical data from CheckMate 057 for the whole NSQ NSCLC treatment population (i.e., for PD-L1 positive patients, PD-L1 <1% patients, and unquantifiable PD-L1 patients). BMS submitted these data to NICE at the beginning of the CDF review. We continued to re-submit these data throughout the review process (despite NICE maintaining its position that it would not accept clinical data concerning PD-L1 <1% and unquantifiable PD-L1 patients). As the Appeal Letter mentions, the ERG — unlike the Appraisal Committee — examined the data in full, such that the Appraisal Committee had every opportunity to appraise the product for the whole indicated NSQ NSCLC population.

Table 1, at the end of this letter, sets out the evidence we submitted and the dates of those submissions. We trust that these confirmations are helpful and that the Initial Scrutiny Letter can stand as the Final Scrutiny Letter. We are happy to provide further information, if this would help you and/or the Appeal Panel.

**Structure and Approach of Appeal Hearing**

We note and agree with your observation that there is an overarching issue in this appeal, namely NICE’s refusal to consider the totality of the evidence that BMS submitted and was therefore available to NICE. We agree that this gives rise to a question of principle, namely whether NICE should consider all available evidence in the context of a CDF review; or whether a CDF recommendation requires NICE to take a more limited approach (and thereby effectively limit a company’s right and duty to submit all relevant evidence to NICE). We welcome the opportunity to discuss that question at the Appeal Hearing, and agree that it would be beneficial to do so in a structured way. We will obviously defer to the Chairperson’s views of the best approach to achieve this. One option might be to allocate a period of time at the beginning of the Hearing for the parties to make submissions on this question, and for the Panel to explore those submissions, before addressing each Appeal Ground in order.

For the avoidance of doubt, however --and we do note that your letter does not say this-- we would disagree with any suggestion that the Appeal Grounds can ultimately be reduced to that single question of principle or that the Appeal Grounds are adequately addressed by focusing on that question alone. This is not the sum total of this appeal. In fact, we consider that the opposite is true. To address the question of principle fully will require the examination of a variety of legal, ethical and procedural issues. That includes, for example:

* the ultimate purpose of the CDF and how that purpose affects the overall review of a technology, both as it enters the CDF and also on CDF exit. In our submission, it is clear that the CDF was established to provide an opportunity for patients to access new, innovative cancer therapies while further evidence is gathered to: (i) enable a fuller assessment of a technology; and (ii) resolve any outstanding uncertainties. The CDF was not designed to have a limiting or narrowing effect on that assessment, or change the fundamental basis for, or nature of the assessment.
* whether it is procedurally sound and fair for a CDF recommendation to foreclose the possibility of reviewing further data and thereby pre-judge the outcome of guidance;
* whether, given NICE’s fundamental statutory and public law duty to consider “all available evidence” in an appraisal, there can ever be legitimate reasons not to fulfil that duty, and (if so) whether such reasons existed in this case; and
* whether NICE’s decision not to consider “all available evidence” is fair and equitable to patients and whether, in making that decision, NICE respected their human rights and/or discriminated against a subgroup of patients whose data NICE would not review.

With respect, these factors (along with others) are not simply different ways of expressing the same question. They are key questions in their own right, and are key parts of this appeal.

These factors are given a voice through the individual Appeal Grounds. Although (as in many appeals) the Appeal Grounds are connected, each is distinct and stands on its own terms. We respectfully argue against amalgamating the Appeal Grounds, reducing them down to a single question and/or subordinating them to a broader point. Each Appeal Ground warrants detailed examination and discussion on a standalone basis, and as particularized in the Appeal Letter. In our view, to do otherwise risks overlooking key issues. This would ultimately hinder, rather than help, answering the fundamental question of principle fully and properly.

Quite apart from the above, some of the Appeal Grounds stand apart from the fundamental question of principle. For example, Ground 1(a).2 (NICE has unjustifiably departed from the 2015 and 2019 Scopes and the Methods Guide) and Ground 2.3 (the recommendation makes an unreasonable and arbitrary distinction based on a patient’s PD-L1 expression states, which is an imperfect biomarker in this population) are unaffected by how one might answer that question of principle. Publishing a Scope in 2019 that contemplates examining data for the whole patient population in the CDF review, but adopting a contradictory position internally, is self-evidently the wrong way to conduct an appraisal (even if there were principled reasons to support that internal position). This further supports giving the Appeal Grounds proper consideration on a standalone basis.

To summarize, we appreciate and agree that there is an overarching question of principle to address at the Appeal Hearing in a structured way. However, we believe the Appeal Hearing must take a systematic approach that gives appropriate time and thought to each Appeal Ground on its own terms. We very much hope that you and the Chairperson understand and agree with our position and are able to take steps to ensure that important points are not lost at the Appeal Hearing.

Yours sincerely

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Table : Submission of 5-year CheckMate 057 data and analyses, prior and during ID1572

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| Document(s) | Context and data included | Date |
| BMS Proposal – Review of nivolumab for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults | Proposal presented by BMS that NICE review the guidance in line with the marketing authorization and the final scope of the original appraisal and that the committee consider all the new evidence available to allow for a change in the recommendation of TA484 to include all NSQ patients as part of the CDF review.  Includes clinical effectiveness data from Checkmate 057 for:   * whole population (regardless of PD-L1 status), * PD-L1 ≥1% patients, * PD-L1 <1% patients, * unquantifiable PD-L1 patients. | 25th July 2019 |
| TA484 Nivolumab in 2L NSQ NSCLC Document D 8 August 2019 | Original company evidence submission for CDF review.  Includes clinical effectiveness data from Checkmate 057 for:   * whole population (regardless of PD-L1 status), * PD-L1 ≥1% patients, * PD-L1 <1% patients, * unquantifiable PD-L1 patients.   Also includes cost-effectiveness analyses for:   * whole population (regardless of PD-L1 status), * PD-L1 ≥1% patients, * PD-L1 <1% patients. | 8th August 2019 |
| TA484 Nivolumab in 2L NSQ NSCLC Document D 14 August 2019  TA484 Nivolumab in 2L NSQ NSCLC Appendix A PDL1 1% analyses 14 August 2019 | Upon request from NICE, amended company evidence submission placing clinical effectiveness data and cost-effectiveness results for PD-L1 <1% patients in the appendix. | 15th August 2019 |
| ID1572 nivolumab (non-squ) company response to clarification questions  Response to ERG clarification questions Appendix on PD-L1 1% analyses | Clarification questions response to ERG questions.  Includes:   * Detailed clinical effectiveness data for whole population (regardless of PD-L1 status) and PD-L1 ≥1% * Kaplain-Meier plots for overall survival by 1%, 5% and 10% PD-L1 subgroups * Additional cost-effectiveness analyses for the whole population and PD-L1 ≥ 1%.   Detailed clinical effectiveness data and cost-effectiveness analyses for PD-L1 <1% patients are provided in the appendix. | 31st January 2019 |
| ID1572 NSQ Nivolumab TE stakeholder response form [ACIC] Final 17 Feb 20  NSQ Tech Engagement Letter AIC 17 Feb20\_AS | Response to the questions for engagement within the technical report  Includes additional cost-effectiveness analyses for the whole population (regardless of PD-L1 status) and PD-L1 ≥ 1%.  Additional real-world evidence on clinical effectiveness data were provided for PD-L1 >1% and PD-L1 <1% patients in the associated letter. | 17th February 2020 |