June 28, 2016

At Bristol-Myers Squibb, we are committed to putting patients and their families first in their fight against serious diseases. Through our pioneering Immuno-Oncology research, we are transforming the way cancer is treated and expanding our approach to provide meaningful, long-term outcomes across the many stages of the disease. It is essential that the healthcare community continue to foster an environment of innovation in order to fulfill the promise of Immuno-Oncology therapies: longer survival and enhanced quality of life for patients. We appreciate the opportunity to comment on the scoping document “Treatment Options for Advanced Non-Small-Cell Lung Cancer (NSCLC).” We have outlined eight recommendations for ICER to consider when conducting their analysis. We fundamentally disagree with various aspects of ICER’s approach to value assessments.

**Remove P2 Population from Scope; Lack of RCT Data in First-line NSCLC**
This analysis is premature. No PD-1 inhibitors are currently FDA approved for this indication. Randomized clinical trials (RCTs) comparing PD-1 inhibitors to chemotherapy in first-line NSCLC have completed enrollment, but no data have yet been reported. Additionally, the current and planned RCTs are not designed to evaluate treatment sequencing, as was implied within the scope. Therefore, the first-line population (P2) should not be included as part of the scope.

**Evaluation of P3 Population Without Driver Mutation is not Reflective of completed RCTs**
The P3 population is not representative of the intent-to-treat for any of the studies that are subject to this review. All of the studies, and their intent-to-treat analyses included patients with driver mutations and were not powered to look at the mutation subset.

**Separate Assessments by Histology in the P3 and P4 Populations**
The analysis for P3 and P4 should evaluate treatment efficacy and value separately by histology (i.e., squamous vs. non-squamous) to account for differences in responses to treatment and treatment pathways across clinical trial indicated populations for PD-1 inhibitors. The NCCN Guidelines have alternative treatment options for the treatment of squamous and non-squamous NSCLC.
Cross Trial Comparisons in P3 and P4 should Reflect Consistent and Relevant Patient Populations

For all populations of interest, the analysis should ensure that trials included in any network meta-analysis are sufficiently comparable.9-11 Therefore, any meta-analysis should consider whether the intent-to-treat populations are comparable across factors related to efficacy, such as:
  - Histology
    - Analyses should be conducted by histology. Histology was evaluated in the CHECKMATE studies in two separate RCTs, as stated above, but not necessarily broken out in the other studies.3-7
  - Biomarker testing
    - The immunohistochemical stains used in RCTs were not the same. Furthermore, the RCTs assessed different features of the tumor biopsy with testing platforms that are not interchangeable, such as including tumor cells, with or without consideration of tumor infiltrating lymphocytes (TILs). Additionally, the manufacturers ascribe efficacy at different levels of PD-L1 expression.3-7
    - Different studies included different patient populations based on biomarker testing. For example, CHECKMATE and POPLAR included patients irrespective of PD-L1 expression levels (“all comers” studies), whereas the KEYNOTE RCT was conducted in an enriched patient population, including only PD-L1 positive patients above a certain “cut-off”.3-7 As a result, these differences have implications on treatment response.
  - Dose
    - Results should be evaluated based on the data at the approved dose. Dosing in the CHECKMATE RCTs have been consistent in the phase 3 published data and the product label.1,3-4 In contrast, other datasets include pooled data with variable dosing, different from the subsequently approved dose, which may over estimate benefit.5-6

Comparative analyses and interpretations should account for these differences.

Long-term Treatment Duration Assumptions

The cost-effectiveness analysis should consider how treatments are likely to be administered in real-world clinical practice. For instance, it is unclear whether patients will receive PD-1 inhibitor therapy for a fixed treatment duration (at the discretion of the treating clinician) or until progression. Currently, limited evidence is available to assess the treatment duration decision for any of the PD-1 inhibitors. Both nivolumab and pembrolizumab are currently indicated for continued treatment until disease progression or unacceptable toxicity.1-2 Some HTA bodies have recommended against using extrapolations of treatment until progression as the measure of treatment duration in cost-effectiveness analyses, given that their advising clinical experts judged this to be an unrealistic assumption (and in one case assumed treatment duration a maximum of 96 weeks).12 Therefore, in light of the uncertainty around real-world treatment duration, the analysis should apply duration of treatment scenarios in addition to treat to disease progression, and these assumptions should be similar across PD-1 inhibitors.
Include Indirect Measures such as Quality of Life in Assessment
We strongly urge ICER to move away from a strictly payer related focus and move towards including indirect measures into the cost effectiveness analysis. The analysis should capture overall quality of life, such as improvement in disease related symptoms.

Disclosure of Modeling Approach
ICER should be fully transparent in the modeling approach. A citation identifying the pre-existing NSCLC model that will serve as the basis for the study’s model should be provided explicitly in the revised scoping document. Also, additional detail should be provided regarding how “eligible patients” for the budget impact analysis will be defined (e.g. prevalent patients or incident patients) should be provided. Furthermore, sufficient detail related to the modeling assumptions, inputs, and methodology should be provided in the draft report. Given the short two-week timeline to respond to the draft report, ICER should release any available model inputs and methodology details in advance of the report so that external stakeholders can provide more meaningful comments in response to the draft report.

Budget Impact is Not a Measure of Patient Value
We strongly disagree that a budget impact assessment (BIA) should be part of the scope of this review, and recommend that it be excluded from the report. ICER’s budget impact framework arbitrarily establishes budget caps for societal expenditures on medical innovations and fundamentally ignores the value of innovation in healthcare. The framework is inappropriate for measuring value, because it focuses on drug costs, while ignoring benefits to patients, caregivers, and society. As such, utilization of the budget impact framework as a means for deriving value and “value-based price benchmarks” is misleading. Moreover, the focus on a “budget cap” subjects innovative therapies to restrictions based on arbitrary budget thresholds, thus creating disincentives for innovation and healthcare investment. Further, it is fundamentally flawed to assume patients subjected to a cancer of high incidence or prevalence are worth ‘less’ than patients who have a more rare form of cancer.
References:
1. Opdivo Prescribing Information.
2. Keytruda Prescribing Information.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.4.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed 27 June 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.