AIMED ALLIANCE
Alliance for the Adoption of Innovations in Medicine

September 16, 2016

Steven Pearson, MD
Institute for Clinical and Economic Review
2 Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine (Aimed Alliance) is a tax-exempt, not-for-profit organization that improves health care in the United States by expanding access to evidence-based treatments and technologies. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the Draft Evidence Report, entitled "Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value" ("Draft Report") published by the Institute for Clinical and Economic Review ("ICER").

Real-Life Costs and Benefits

Patients must have a meaningful role in the discussion of value. The value of treatment should account for the unique situation of the individual patient and not be based on price alone. The Draft Report downplays the personal benefits of programmed death 1 receptors and their ligands (referred to herein as "immunotherapies") and placed a disproportionate emphasis on their prices. While there are few studies available, those that do exist all conclude that all three immunotherapies have provided significant advances over the first-line therapy (*i.e.*, docetaxel), including better overall survival, response rate, and progression-free survival.[1]

The Draft Report's table 13 shows that adverse events occur less often with immunotherapies than with docetaxel, and table 15 shows that there are far fewer tier four and five adverse events with immunotherapies than with docetaxel, including infections, leukopenia, neuromotor, and neutropenia. Yet, although adverse events differ significantly among the three immunotherapies, ICER combines all the adverse events resulting from immunotherapies together in its calculations, creating a distortion.

Moreover, the Draft Report states that the existing evidence was inadequate to evaluate improvements to quality of life. It states that only one in the four trials it analyzed had evaluated quality of life. Nevertheless, it acknowledges that even with uncertainties about the duration of benefit with immunotherapies and affect patients to varying degrees, the current evidence base provides high certainty that a substantial number of patients with non-small cell lung cancer ("NSCLC") do respond to the treatment and achieve important gains in overall survival (providing a rating of "A").

Although the Draft Report acknowledges that immunotherapies improve survival overall compared with docetaxel, it questions the statistics available. The Draft Report also states that there is insufficient evidence on symptom control. If ICER is not willing to trust the existing evidence, then it should wait until more evidence emerges before assessing the value of immunotherapies rather than distorting or denigrating current data.

QALYs are Discriminatory

[1] Abstract, Gaetan Des Guetz, et al., Anti PD-1 (nivolumab, pembrolizumab) or anti PD-L1 (atezolizumab) versus docetaxel for previously treated patients with advanced NSCLC: A meta-analysis. J. Clin Oncol. 34, 2016 (abstr e20555); Gregory A. Masters & Dhaval Shah, *Immunotherapy in Lung Cancer Treatment: Current Status and Future Direction*, ASCO (June 3, 2016), https://am.asco.org/immunotherapy-lung-cancer-treatment-current-status-and-future-directions; Michael Smith, *ASCO: Immunotherapy Ups Survival in Non-Small Cell Lung CA*, MedpageToday (May 29, 2015), http://www.medpagetoday.com/meetingcoverage/asco/51847.

The use of quality-adjusted life-years ("QALYs") is inconsistent with American values and public policy. Recognizing that value-based frameworks can result in an inappropriate rationing of care, Congress added language to the Patient Protection and Affordable Care Act that prohibited the Patient-Centered Outcomes Research Institute ("PCORI") from using QALYs as a threshold for determining coverage, reimbursement, or incentives in the Medicare program. The ban reflected a long-standing concern in the U.S. that the approach would lead to discrimination on the basis of age and health status, unfairly favoring younger and healthier populations. Patients with a health condition are valued at less than whole, and QALYs do not adjust for remission. Therefore, despite long-term stability without disease progression, patients are never valued as whole.

QALYs put a price tag on the value of a human life that merely reflects the individual's diagnosis and deems those with chronic, debilitating, and rare conditions, such as NCSLC, as being worth less than the rest of the population. They treat individuals' lives and health as a commodity and ignore the patients' and practitioners' individualized concept of the value of treatment. Therefore, the QALY should not be used to set a threshold for a large population of individuals with one-of-a-kind life narratives across a complicated health care system.

Patients Access to Options

To ensure patients receive adequate care, quality and choice of treatment options should not, by default, be sacrificed for cost-saving measures. The United States Court of Appeals for the Ninth Circuit has stated that "[f]aced with such a conflict between financial concerns and human suffering . . . the balance of hardships tips decidedly in [the patients'] favor."[2] Given the chance of recurrence of NSCLC and the tendency for the body to build a resistance to previous treatments, patients must have access to all treatments available to them.

Moreover, competition will drive down drug prices. Currently, there are two immunotherapies on the market, and a third coming soon. As with hepatitis C medications, competition provides pharmacy benefit managers with leverage to negotiate lower prices. Both pharmaceutical companies and insurers approve of such a system.[3] Yet, health care rationing in the form of insurers implementing take-it-or-leave-it price caps precludes prescriber discretion and consumer choice among medically necessary treatments.

Short-Term Clinical Evidence

The clinical data used in ICER's analysis of clinical effectiveness, benefits and disadvantages, and comparative value of immunotherapies is premature. Two of the three immunotherapies considered in the Draft Report came to market less than one year ago, and the third has not yet been approved for treatment of NSCLC. Given the recent introduction of these immunotherapies, neither the American College of Chest Physicians nor the American Society of Clinical Oncology has updated its guidelines to include information on these medications.

As such, ICER relied upon only four sources in conducting its analysis and conclusion. These four studies used different thresholds for measuring overall survival, progression-free survival, objective response, and adverse event reporting, making them hard to compare. Additionally, data was combined for both squamous and nonsquamous histologies.

In comparison, tyrosine kinase inhibitors ("TKIs") have been on the market for three years. ICER identified 3,072 potentially relevant studies, 44 of which it used. Evidence came from randomized controlled trials, comparative observational studies, and high-quality systematic reviews. As a result, ICER was able to conduct a more appropriately robust analysis of TKIs.

[2] Lopez v. Heckler, 713 F.2d 1432, 1437 (9th Cir. 1983).
[3] Devon Herrick, *Wholesale Price Disclosure Would Likely Increase Consumers' Drug Costs*, Townhall (June 27, 2016), http://townhall.com/columnists/devonherrick/2016/06/27/wholesale-price-disclosure-would-likely-increase-consumers-drug-costs-n2183885.

Over time, the benefits of immunotherapies will fully emerge. However, if they are deemed inadequately cost-effective now, then the likelihood of third-party payers covering these treatments diminishes, creating barriers to access for patients who need them. Without market uptake, data cannot be collected and analyzed. Therefore, we recommend that ICER refrain from making a determination on the value of treatments until mature data emerges.

Defining Value

Aside from overall survival, objective response rate, health-related quality of life, symptom control, and adverse events, there are other, often subjective, considerations that should be assessed when determining the value of a treatment. For example, the Draft Report notes that ICER sought to "provide information on" the evidence of comparative clinical effectiveness, including (1) methods of administration that improve or diminish patient acceptability and adherence; (2) public health benefits; (3) treatment outcomes that reduce disparities across various patient groups; (4) more rapid return to work or other positive effects on productivity; and (5) new mechanisms of action for treatment of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons.

Additional factors include indirect expenses (*e.g.*, not needing an oxygen tank) and non-health-related quality of life outcomes (*e.g.*, intrinsic value to patient, family, and community). These are important factors in determining value of a treatment, and yet, it unclear as to whether any of them was considered. We recommend that ICER expressly address such considerations in its analyses.

Patient and Practitioner Perspectives

Patients are directly impacted by a report that seek to define the effectiveness and value of their treatment options. Therefore, accounting for how patients define the value of their treatment options should be critical to ICER's analysis. Patients must take an active role in their health care. While we are pleased to see that ICER consulted with patients and patient groups on the topic of NSCLC, is unclear as to whether ICER incorporated patient feedback. For example, the Draft Report states that patient groups discussed benefits that were not captured in clinical trials, such as reductions in distress and anxiety. However, it appears that ICER did not take such feedback into consideration, and instead, focused solely on the data in the clinical trials. If ICER does not intend to consider patients' assessment of the value of a given treatment, it is unclear what the purpose of soliciting comments and feedback from patient populations is.

Additionally, the opinions of health care practitioners are vital in understanding the value of treatment options. Over the course of professional practice, health care practitioners obtain clinical experience with medications and identify emerging clinical trends and best practices. They can employ their practical knowledge to determine which medications are best suited to each patient's individual needs. Therefore, a value assessment is flawed if it lacks practitioners' point-of-view.

While ICER sought external input from at least three physicians, the Draft Report does not specify how these three physicians contributed to the Report's analysis and whether they agree with its methodologies and conclusions. Given that immunotherapies are the standard of care for second-line therapy for patients without a driver mutation who progress on a chemotherapy doublet according to National Comprehensive Cancer Network ("NCCN") and Anthem, it appears inconsistent with clinical practice that the oncologists would agree that all three immunotherapies' cost-effectiveness exceeds the threshold. Therefore, we respectfully request that ICER summarize how it accounted for verbal feedback. Additionally, in the future, we request that ICER publish a record of the discussions with patients and patient groups and report on responsive actions, if any.

Acknowledgement of Comments

Aimed Alliance is pleased that ICER has extended the period to submit comments for the Draft Report. However, we respectfully request that ICER provide additional information regarding ICER's process for reviewing and addressing those comments. We recommend that ICER look to the process used by federal

agencies for proposing a rule. Agencies often respond to comments publicly via the Federal Register when drafting a new regulation or releasing guidance. We recommend that ICER summarize how it accounted for comments. In the future, we recommend that ICER follow the publication and response model of federal executive and administrative agencies.

In conclusion, we offer our assistance in working closely with ICER to address our shared goals of access to high quality health care at a price that accurately reflects public and personal benefits.

Respectfully submitted.

Stacey L. Worthy
Executive Director