LUNGEVITY
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September 15, 2016

Steven, D. Pearson, MD MSc, FRCP
President, Institute for Clinical and Economic Review
Boston, MA 02109

Dear Dr. Pearson,

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit, that funds research, provides education and support, and builds communities for the 224,390 Americans diagnosed with lung cancer each year and the over 400,000 Americans living with the disease, we appreciate the opportunity to respond to the request for comments on ICER's draft report for non-small cell lung cancer.

LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are three-fold: (1) to accelerate research to patients that are meaningful to them; (2) to empower patients to be active participants in their care and care decisions; and (3) to help remove barriers to access to high quality care. We have the largest lung cancer survivor network in the country and actively engage with them to identify, understand and address unmet patient needs. We also have a world class Scientific Advisory Board that guides the programs and initiatives of the organization. Additionally, we collaborate with other lung cancer patient advocacy groups, and organizations such as the American Lung Association and CHEST, who serve the lung cancer community.

In this era of unprecedented scientific advancements for the treatment of lung cancer, particularly personalized medicine and immunotherapy, we recognize the importance of balancing innovation with higher costs of medicines while ensuring that patients have access to life-saving therapies. We appreciate the work and the desire to create tools to facilitate the conversation between healthcare providers and patients around treatment options. We also recognize the incredible responsibility of ensuring that ALL stakeholders – ***especially patients*** – are fully represented in developing these tools and the utmost importance of including robust data that represents how the therapies are used in practice.

We are concerned that ICER's report on non-small cell lung cancer does not adequately incorporate ALL stakeholders' views – especially those of patients and practicing lung cancer clinicians – nor does it include adequate data, and therefore reaches conclusions that can be misleading. Our concerns and comments, which include input from members of our esteemed Scientific Advisory Board, are outlined below.

In summary, our five concerns are:

1. The ICER model is in direct contrast to an increasingly individualized approach to lung cancer care.
2. There is a lack of transparency in the development of the ICER model from both a methodological and end-user perspective.

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3. The expert clinician perspective and the patient perspective seem to be lacking in the report.
4. The use of aggregate metrics such as QALYs do not capture patient-level data.
5. The data utilized is not robust.

These are discussed in greater detail below.

Discussion

1. **The ICER model is in direct contrast to an increasingly individualized approach to lung cancer care.**
Lung cancer is benefiting from advancements in precision medicine: clinicians working to match the right patient to the right treatment at the right time. We know that lung cancer is not a single disease, but rather a collection of rare diseases. Since the discovery of the first epidermal growth factor receptor (EGFR) mutation in lung cancer in 2004 [1-3], at least 10 driver mutations in adenocarcinoma have been identified (EGFR, ALK, ROS, RET, ERB2/HER2 mutations, ERB2/HER2 amplifications, MET amplifications, MET mutations, TRK, BRAF, and KRAS) [4, 5].

The model developed by ICER raises two important questions:

- Should cost-effectiveness analysis of drugs meant to be used in selected populations be evaluated through aggregate data that does not take into consideration individual patient-specific factors such as age, stage of diagnosis, histology, and ethnicity?

- In an era when combination treatments are being increasingly used, how can aggregate data be used to understand the effectiveness of different combinations and the sequence of these combinations with other therapies?

The model also proceeds to use population-level data to make patient-level predictions. Such a model is incongruous with the basic tenets of precision medicine and will be detrimental to the lung cancer survivor community. The progress we have seen in lung cancer treatment in the past decade should not be denied to the patient/survivor.

2. **There is a lack of transparency in the development of the ICER model from both a methodological and end-user perspective.**

Methodological transparency: We understand and appreciate the effort ICER has put in toward building a robust cost-effectiveness model and respect the proprietary nature of the effort; however, the lack of transparency calls into question its validity. Oncology value frameworks such as the ASCO Value Framework [6] and Memorial Sloan Kettering Drug Abacus [7] have made their methodology transparent, and we would encourage ICER to do the same.

Given the rapid evolution of lung cancer therapies (there were seven new FDA approvals for lung cancer in 2015 [8]), we encourage ICER to be fully transparent about the selection process of the drugs being evaluated, specifically, why are drugs that have not even been approved yet being included in the model? Furthermore, there needs to be transparency about the expert clinicians who are advising on

the real-world use of the therapies, the model inputs and how the model will be used. At a minimum, we encourage that the models be peer reviewed by disease state experts.

End-user transparency: ICER has maintained that the models developed are end-user-neutral and will not be used to make reimbursement or payment decisions. However, according to the Federal Register / Vol. 81, No. 48 / Friday, March 11, 2016 /Proposed Rules, Medicare payment model under section 1115A of the Social Security Act (the Act), CMS states, "We propose to use indications-based pricing where appropriately supported by published studies and reviews or evidenced-based clinical practice guidelines, such as the ICER reports, to more closely align drug payment with outcomes for a particular clinical indication."

ICER must recognize the impact of their models and ensure that they are created in a robust, evidence-based and patient-centric manner and recognize how their model may be used in practice. We encourage ICER to be much more transparent.

3. **The expert clinician perspective and the patient perspective seem to be lacking in the report.** Though ICER has solicited survivor and clinician input, the incorporation of this critical feedback is not evident from the draft NSCLC report. It is vital to include the patient/survivor perspective in any value assessment.

Survivor input:
With progress in lung cancer treatment, survivors are living longer. It is imperative to incorporate the survivor perspective rather than make generalized statements about all people with lung cancer as the patient/survivor populations can be very different. Contrary to popular belief, lung cancer is becoming a disease of the young and the non-smoker [9]. A young, 30-year-old, stage IV survivor may value benefits from a treatment regimen very differently than a 70-year-old survivor. These nuances would be captured through patient preference studies and quality of life metrics which are often not included in existing clinical trial data.

An example of types of generalized statements that the report makes can be found on page 16:

> "With TKI therapy in particular, there can be heightened anxiety around adverse events and reporting these events…This may affect the frequency of adverse events reported in the published literature."

This is in direct contrast to feedback we have received from the survivor and clinician community who have experience with these therapies. According to lung cancer clinicians, survivors invariably report on rashes in response to TKIs and, in fact, often ask their doctors about the use of skin protectants such as sunscreens and emollients to control them. We encourage ICER to prioritize survivor input in any of their models.

Clinician input: The report does not seem to include the experience of clinicians familiar with prescribing the drugs described in the model, nor their real-world observations that have resulted in changes in practice behavior. These real-world observations can only be obtained by incorporating the input from disease-expert clinicians, as it often differs from the published clinical trial data.

Below are two such examples provided by lung cancer clinicians that we consulted:

1. In the description of Population 3 on Page 9, ICER states that "P3) Have a tumor without a driver mutation that has progressed after first-line treatment with a platinum-based chemotherapy doublet (e.g., cisplatin+paclitaxel, carboplatin+gemcitabine, etc.).

   According to lung cancer clinicians, all of the references to platinum doublet need to also note that for some patients, chemo + biologic (e.g. bevacizumab), is now the first line treatment, and would be the choice that the clinician is making. Their observation confirms that even a traditional treatment modality such as chemotherapy has become increasingly personalized, based on the individual patient's characteristics.

2. In the immunotherapy summary on Page 43, ICER states that "[B]ecause of the limited follow-up in the existing studies, we are uncertain of how large the benefit is for the minority of patients who do respond to these agents."

   Our clinician experts have pointed out that they have patients on their 4th year of immunotherapy, reiterating the point that while we are uncertain of how large the benefit can be, we do know that the magnitude of benefit can be immense in those survivors who show a response to immunotherapy.

4. The use of aggregate metrics such as QALYs do not capture patient-level data.

QALYs or quality-adjusted life-years have long been used by economists to forecast healthcare financial decisions. While the QALY is easy to use, a recent article in the *New England Journal of Medicine* points out that the QALY value typically used by healthcare economists in fact underestimates the impact of a drug [10]. Also QALY is an aggregate metric—it does not capture patient-level data in making economic predictions. An ideal model is one that includes patient-level metrics that can customize a prediction to an individual patient, in line with the tenets of precision medicine.

Furthermore, unlike other diseases where QALYs may have some applicability, lung cancer is not a singular disease. Rather, it is a continuum where stage of diagnosis, presence or absence of actionable mutations, recurrence, and end-of-life care would impact a patient's decision about a treatment option. Using QALYs may not adequately capture what different patients value along the lung cancer continuum [11].

As an alternative to QALY, patient-reported outcomes and quality of life metrics can be used to accurately capture the differences in patient perspective along the lung cancer continuum. As pointed out by ASCO in their value framework discussion, inclusion of PROs makes their model more robust [6]. We encourage ICER to take into account PROs and QoL metrics.

5. The data utilized is not robust.

We encourage ICER to assess evidence once a drug has been used in practice for a significant amount of time to accurately capture the impact a drug has made on the survivor community. In the present

report, ICER has analyzed two groups of lung cancer drugs – one that has been in use for over a decade, and the other for less than 2 years. It is still unclear why this selection was made due to the lack of transparency of the selection process.

Immunotherapy was first made available in 2015, and atezolizumab, which is included in the analysis, has not received FDA approval for use in lung cancer patients, nor have any of the PD1 drugs been approved in a first line setting (population/treatment P2).

It is also too early to make assessments about the use of PD-1 immunotherapy in patients with EGFR+ tumors. In the report, it is stated that, "… *given our estimation, as discussed below, that PD-1 immunotherapy may have no benefit in patients with EGFR+ tumors*." (page 53). However, given the limited evidence of the efficacy of immunotherapy in EGFR+ populations, this statement is premature and may have potentially dangerous implications for EGFR+ patients who have progressed on EGFR TKIs and may actually derive benefit from immunotherapy.

Conclusion

LUNGevity sincerely thanks you for the opportunity to comment on ICER's draft report for advanced non-small cell lung cancer. We look forward to additional opportunities to contribute to ICER's ongoing work, and encourage the Institute to provide more opportunities for stakeholder input into its process for developing and refining its value assessment framework.

As stated, the areas of concern that we have outlined above can be actively discussed with my staff, myself, and LUNGevity's Scientific Advisory Board, which is made up of some of the world's leading experts in lung cancer biology, practice management, access to innovative medicines, and overall patient care. I encourage you and ICER to access our expertise.

I can be reached at 240-454-3100 or aeferris@lungevity.org if you have any questions or would like to engage in further dialog.

Thank you for your attention to this very important matter.

Sincerely,

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