AIMED ALLIANCE
Alliance for the Adoption of Innovations in Medicine

September 16, 2016

Steven Pearson, MD
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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 places a disproportionate emphasis on their prices. Existing studies 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 ("AEs") occur less often with immunotherapies than with docetaxel, and table 15 shows that there are far fewer tier four and five AEs with immunotherapies than with docetaxel. Yet, ICER combines all the AEs 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, current evidence 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

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 prohibiting the Patient-Centered Outcomes Research Institute ("PCORI") from using QALYs as a threshold for determining coverage, reimbursement, or incentives in Medicare. The ban reflected a long-standing concern in the U.S. that the approach would lead to

[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).

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 U.S. Court of Appeals for the Ninth Circuit stated "[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. 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.

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, ICER should 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

[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).

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 is 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 seeks 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

The following statement was issued by the Bonnie J. Addario Lung Cancer Foundation (ALCF) in response to the scoping document evaluating certain lung cancer drugs released by the Institute for Clinical Economic Review (ICER):

In concert with our partners in the Lung Cancer Action Network (LungCAN), we are submitting our concerns with the ICER Draft Evidence Report evaluating certain lung cancer drugs. As a patient focused organization founded by a Stage 3b lung cancer survivor we have additional concerns that must be addressed in terms of ICER's mission and the lack of transparency, the patient's role in the process, and the unintended consequences of a one-sided approach to evaluating "value" and "cost".

ICER's stated mission is to conduct analyses to determine whether a new drug's benefit is worth its cost. In other words – it puts a price on the value of a patient's life. If assessing value to patients, why were so few included in the assessment? Did you ask patients the value of living three more months to see your baby turn one-year-old? Seeing your child graduate from college? Getting married? Ask any patient and they will tell you those moments are priceless.

Treatment options for patients should not be determined based on perceived costs by payers. This method does not allow for weighing the value of medications to the overall health care system. And interestingly, ICER has determined the majority of drug treatments it has reviewed to date are too expensive, yet they do not take into account offsets within the health care system.

Patients treated with the most innovative treatment options actually drive down the cost of health care by reducing the number of doctor visits, ER trips, drug failure costs, related palliative care, etc. It appears that ICER was created to provide the health insurance industry a third party expert to exclude treatments from coverage, which may even create disincentives to new drug development, and create price controls.

We know that personalized medicine is extending the lives of lung cancer patients and the quality of those years. At ALCF we work with patients who are alive today because of this groundbreaking research. I can't imagine how many of them wouldn't be here today if a payer used information from ICER to deem their treatment not worth the cost. Although the survival rate after 5 years has only increased by 3%, the survival rate between 1 and 5 years is increasing daily and preparing to burst through that 5-year barrier. Now is not the time to put the brakes on it, it is time to accelerate the process.

We are on the cusp of innovative medical research that will redefine cancer treatment in the coming years with immuno-oncology being a prime example. We must not prematurely review these therapies when this science is in its infancy and already shows such promise. Data is still being developed and new combinations are in the works as physicians and clinicians on the front lines are determining which patients respond best to which combination. Nothing must stall this remarkable research as new drug development is crucial for the lung cancer community. We know that treatments eventually fail patients, and it is imperative to have multiple lines of therapy available.

ICER's report goes in the complete opposite direction and ignores the transformative, cumulative nature of Personalized Medicine. It moves us back to a one-size-fits-all approach, based on cost of treatment that did not serve patients well.

Finally, we believe that ICER's assessments must be peer-reviewed in the future by outside experts and information should be made public related to their modeling and methodology. Case in point, the data used to evaluate the TKIs was old data sometimes involving solely Asian populations. There are thousands of expert clinicians on the front lines who could provide additional information to ICER in order to develop a more accurate assessment.

The war on cancer was launched in 1971, by President Richard Nixon, but in most ways the war on lung cancer is just beginning. Vice President Joe Biden's Cancer Moonshot is a call to action for the entire cancer community – patients, physicians, biopharmaceutical companies and NIH-funded researchers to come together to accelerate the race to treat and cure cancer – to save lives. Lung cancer patients deserve this focus. They have been stigmatized and ignored for too many years. They deserve better.

About the Bonnie J. Addario Lung Cancer Foundation
The Bonnie J. Addario Lung Cancer Foundation (ALCF) is one of the largest philanthropies (patient-founded, patient-focused, and patient-driven) devoted exclusively to eradicating Lung Cancer through research, early detection, education, and treatment. The Foundation's goal is to work with a diverse group of physicians, organizations, industry partners, individuals, patients, survivors, and their families to identify solutions and make timely and meaningful change and turn lung cancer into a chronically managed disease by 2023. The ALCF was established on March 1, 2006 as a 501c(3) non-profit organization and has raised nearly $30 million for lung cancer research and related programs. For more information about the ALCF please visit www.lungcancerfoundation.org or follow us on Facebook or Twitter.

September 16, 2016

Steven D. Pearson, MD, MSc
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Dear Dr. Pearson:

The American Lung Association appreciates the opportunity to submit comments with regard to the Treatment Options for Advanced Non-Small-Cell Lung Cancer: Effectiveness and Value, Draft Evidence Report.

The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease through education, advocacy and research. The organization represents lung disease patients, their families, loved ones and caregivers. Our organization is committed to defeating lung cancer and ensuring that patients have access to best lung cancer treatments and that the tremendous innovations of lung cancer treatments continues.

The impact of lung cancer is enormous. During 2016, an estimated 224,390 new cases of lung cancer are expected to be diagnosed.[1] The majority of patients diagnosed do not survive the first year.[2] In 2014, there were 155,610 deaths due to lung cancer; 84,910 in men and 70,700 in women.[3] The five-year survival rate for lung cancer is only 17.7% and is among the lowest of all types of cancer.[4]

Innovation with new therapies is providing hope to patients with 6 new drug approvals in the 2015. These new targeted therapies are extending life - often without some of the side effects of chemotherapy such as – fatigue, nausea, vomiting, and diarrhea, which severely limit productivity and quality of life. These new therapies allow patients to lead more active and productive lives while in treatment. This reduces the burden of their disease on their families and caregivers and improves their overall quality of life.

Lung cancer patients place a high value on quality of life and the opportunity of innovation to extend their lives. We are dismayed that the ICER review fails to recognize the importance of these improvements in their everyday lives that are the result of using these new targeted therapies.

Putting the Patient First

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) defines itself as: "a core program of ICER and| provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of **all stakeholders**. (**emphasis added**)" However, the input of all stakeholders is actually not included in your recommendations. "Inputs Gained from Discussions with Patients and Patient Groups" are mentioned only on a page and a half of the 185 page document. These brief anecdotal comments are never mentioned again, and absent from the final analysis.

Additionally, although the issue of financial toxicity is mentioned, the context of this toxicity versus the potential positive impacts of increased patient survival is not addressed. Financial toxicity is not contextualized properly - the expenditure might not be an issue for the patient who wants to survive another three months to participate in their child's wedding or witness the birth of their grandchild.

Other areas important to patient quality of life, including symptom relief, are not considered in the analysis of drug cost and effectiveness. In fact the ICER analysis itself explains that the "costs and effects that might be relevant from a societal perspective, such as productivity, transportation of caregiver costs" were not incorporated in this analysis. Certain drug therapies, in particular targeted therapies, have changed the way we fight and live with serious diseases. These positive differences on the lives of those living with lung cancer are absent from adequate consideration.

Overall, actual patient value, and the impact of these considerable improvements on patient lives, are under appreciated and under recognized in the analysis.

Payers Not Patients

In addition to assessing cost-effectiveness of these drugs without understanding the actual patient impact, the report attempts to ascertain the "potential budgetary impact of each regimen over a 5 year time horizon". This analysis further demonstrates ICER's cursory examination of patient impact, and theorizes a health care payment model which does not currently exist. Dollars that are unspent on lung cancer care are not then miraculously transformed to be used for other health care issues that ICER may think have greater societal value. Does the ICER approach appreciate the realities of the disease progression of lung cancer and that only 17.7% of lung cancer patients survive five years?

Taking the Precision out of Precision Medicine

We have witnessed tremendous gains in lung cancer treatment over the last 10 years. Discovery of biomarkers and the impact of targeted therapy has been fueled by a concomitant increase in diagnostic testing. The surge and improvements in these developments help put the "precision" into "precision medicine" and are the basis of important developments. The President's Precision medicine initiative states that "Through advances in research, technology and policies that empower patients, the PMI will enable a new era of medicine in which researchers, providers and patients work together to develop individualized care."[5] ICER's analysis runs counter to the leadership needed to bolster and build on these important advances. As our ability to increasingly identify and target specific somatic changes, the one-size-fits-all analysis by ICER will quickly become outdated.

Immunotherapy

As stated in our comments on the draft scope, we strongly believe that any conclusions on the effectiveness and value of immunotherapy are premature. Many scientific questions remain about the patient population that can receive the greatest benefit from immunotherapy. We believe the data available at this juncture, are not consistent enough to form a robust model of final conclusions and overall effectiveness. As more data become available, the likelihood is that the population identified to receive these medications will be further defined and the benefits within these populations will become more evident. The current data available for many of these drugs are based on the drug approval trials, and do not contain the impact of these drugs in practice, or reflect any changes in practice that might be seen after initial drug approval.

Innovation

The premature analysis of the patient populations studied to date undermines the potential advances that can be achieved through further development of targeted therapies. As the science of personalized medicine expands, so should the body of available therapies. ICER's recommendations will discourage innovation in this important new area of drug development. The ICER analysis ignores these important advances, by grouping populations together, rather than analyzing the success of the drugs differently than traditional medications.

Public Comments

We thank ICER for extending the review period for the Draft Evidence Report. However, we continue to believe that to receive more comprehensive input from patients, ICER should provide a minimum of 60 days. We also strongly recommend that ICER should produce a document that includes a written response to all comments it receives similar to the response to comments that federal agencies provide to comments received in rulemakings conducted under the

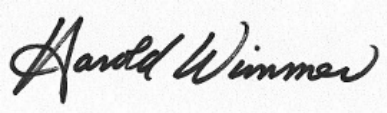
Administrative Procedure Act. This will demonstrate that ICER has considered the comments and provide transparency for all stakeholders on the process.

Conclusion

Although we understand drug pricing may be an important issue, the Lung Association is concerned about the impact these analyses will have on patient treatment and survival, particularly since the perspective of the patient and the practicing oncologist are not included in these analysis. In essence, ICER has created a process which can be used to undermine the positive innovations we have seen in lung cancer survival, and in doing so, undervalues the positive personal impact many of these drugs have made on the lives of patients. We believe that those perspectives were not adequately incorporated into the final report and as such, any measures of effectiveness and importance are incomplete.

Thank you for the opportunity to comment.

Sincerely,



Harold P. Wimmer
National President & CEO

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[2] U.S. National Institutes of Health. National Cancer Institute: SEER Cancer Statistics Review, 1975-2013.

[3] Centers For Disease Control And Prevention. National Center For Health Statistics. CDC WONDER On-Line Database, Compiled from Compressed Mortality File 1999-2014 Series 20 No. 2T, 2016

[4] U.S. National Institutes of Health. National Cancer Institute: SEER Cancer Statistics Review, 1975-2013.

[5] https://www.nih.gov/precision-medicine-initiative-cohort-program, accessed on 9/16/2016

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Ms. Khan,

Thank you for the opportunity to comment on the CEPAC/ICER draft report "Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value". Below please find our comments to your health economic assessment of tyrosine kinase inhibitors (TKIs), including IRESSA® (gefitinib), which is approved as a first-line treatment in patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

While we have limited comments on the review of TKIs within the context of the NSCLC draft report, we do continue to have concerns around other aspects of ICER's methodology and the limited level of transparency around the models used by ICER. Outside of our current comments, we will continue to engage with ICER to further the discussion around appropriate mechanisms to effectively evaluate emerging therapies.

1. **Recommend removing scenario 1 from analysis**

We have concerns regarding the scenario analysis utilizing overall survival (OS) estimates from a network meta-analysis (NMA) of trials with crossover from the chemotherapy doublet arms to TKIs post-progression. As presented in Table C3, crossover from chemotherapy doublet to TKIs was reported in 9 out of 11 studies that were included in the NMA. The crossover rates of chemotherapy doublet treated patients receiving TKI after progression range from 48.4% in LUX-Lung 6 to 93% in NEJ002. Due to limitations in reporting, it is not possible to quantify the impact of crossover on OS.

The comparative efficacy derived from this analysis does not properly represent the survival benefit of TKIs versus chemotherapy doublet in first-line treatment. Instead, it represents the comparative efficacy between different treatment pathways, and in both pathways TKIs have contributed to the OS.

The draft report acknowledged in page 24 that "… assessing the true survival benefit of an emerging therapy can be difficult when study participants are permitted to cross over to receive the alternative study treatment after tumor progression and the key studies included in the sample set for this review had high levels of crossovers". In light of this, we would recommend that this analysis be omitted from the final report due to the specific limitations of the supporting data. If included, it has the potential to add more confusion to clinical practice and a negative impact to patients. In our opinion, this approach provides limited usefulness to the public.

2. **Recommend clarifying that blinded independent review of CT scans cannot control for time evaluation bias in LUX Lung 7 on page 35 of draft report**

We would like to comment on a limitation of the LUX-Lung 7 trial known as evaluation time bias, which can occur in a non-blinded trial even when an independent review of scans is performed. In LUX-Lung 7, tumors were assessed by CT (preferred) or MRI scan after 4 and 8 weeks of treatment, then every 8 weeks until week 64 and every 12 weeks thereafter until permanent discontinuation of study treatment. We notice that several progression-free survival (PFS) events occurred between scans in the gefitinib arm, while fewer PFS events occur in the afatinib arm between scans, which is illustrated in the difference between the Kaplan-Meier curves. This is a well-known phenomenon in open-label trials where investigators may be more tempted to organize an unscheduled scan for their patients randomized to the control arm which is expected to perform poorer than the experimental arm. This has been described in the literature as "evaluation-time bias" and leads to a biased hazard ratio and p-value.[1,2] To evaluate the magnitude of this bias, the results must be compared to a sensitivity analysis using the date of the next scheduled scan for all progressive disease detected in an unscheduled scan. This analysis was not presented for the LUX-Lung 7 data. Since the NMA includes LUX-Lung 7 in estimating relative PFS, we wanted to propose that this is addressed as a limitation.

Again, thank you for the opportunity to provide comments, and we trust you will consider the points raised above in your final determination. We look forward to continuing the discussions on cost effectiveness and while remaining focused on patient care.

Yours sincerely,

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References:

[1] Panageas KS, Ben-Porat L, Dickler MN et al. When you look matters: the effect of assessment schedule on progression-free survival. *J Natl Cancer Inst* 2007; 99(6): 428–432.
[2] Niimi M, Yamamoto S, Fukuda H et al. The influence of handling censored data on estimating progression-free survival in cancer clinical trials (JCOG9913-A). *Jpn J Clin Oncol* 2002; 32(1): 19–26.

September 16, 2016

Institute for Clinical and Economic Review
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RE: Draft Evidence Report – Treatment Options for Advanced Non-Small-Cell Lung Cancer: Effectiveness and Value

Dear Dr. Pearson,

On behalf of Boehringer Ingelheim Pharmaceuticals, Inc., we are pleased to submit comments on ICER's draft evidence report for its assessment of treatment options for advanced non-small cell lung cancer (NSCLC). Through scientific innovation and collaboration, Boehringer Ingelheim (BI) is committed to discovering and developing novel cancer treatments for patients in areas of high unmet medical need. While ICER's assessment may provide directional value assessments for different drug classes, we strongly believe that it is inadequate in its comparison of value within a drug class, in particular amongst the tyrosine kinase inhibitor (TKI) agents, given several fundamental issues with the methodological approaches undertaken in the comparative value analysis.

Conflation of chemotherapy comparators

ICER had selected the platinum-based chemotherapy doublet of cisplatin plus pemetrexed as the primary baseline comparator to the TKIs in the treatment of first-line EGFR+ NSCLC, with the acknowledgement that "this was likely the most effective platinum doublet option". However, despite different chemotherapy comparators being used in the TKI clinical trials, the network meta-analysis (NMA) was conducted with the assumption of equivalent efficacy across the different platinum doublets, and any efficacy differences were only acknowledged and explored between the cisplatin-based and carboplatin-based doublets. This assumption is not supported by the published evidence, as illustrated below.

The *LUX-Lung 3* and *LUX-Lung 6* trials compared afatinib with platinum-based chemotherapy, and were nearly identical in study design except for the chemotherapy comparator – cisplatin plus pemetrexed was used in *LUX-Lung 3* while cisplatin plus gemcitabine was used in *LUX-Lung 6* (Sequist, 2013; Wu, 2014). Despite both chemotherapy comparators being cisplatin-based doublets, the risk of disease progression, as indicated by the progression-free survival (PFS) hazard ratio (HR) for the common EGFR mutation (Del19 and L858R) population in *LUX-Lung 3* (HR: 0.47; 95% CI: 0.34-0.65) was almost twice that in *LUX-Lung 6* (HR: 0.25; 95% CI: 0.18-0.35). These results clearly demonstrate that efficacy differences exist even

between chemotherapy doublets with the same platinum backbone-agent. Therefore, applying the NMA results directly to the base case PFS and overall survival (OS) curves for the cisplatin plus pemetrexed regimen, without adjusting for efficacy differences among the platinum doublets, artificially inflates the efficacy of erlotinib and gefitinib as these TKIs have not been studied against the more efficacious cisplatin plus pemetrexed doublet.

BI strongly recommends that the NMA takes into account the efficacy differences across the different chemotherapy doublets by creating a full network of treatment options that includes every individual TKI and platinum-based doublet, especially given that the cost-effectiveness analysis results are most sensitive to the PFS and OS HR parameters.

Assumption of a common 8.9-month increase in median OS for all TKIs

Although a NMA was conducted for the OS data from the different TKI trials, ICER chose not to apply the results from this analysis and instead applied a common 8.9-month increase in median OS to all three TKIs citing that these "RCTs had high rates of crossover and showed no OS benefit for TKIs compared with a platinum-based chemotherapy doublet". Similar to the previous assumption of efficacy equivalence across the chemotherapy doublets, this assumption is not consistent with accepted economic evaluation methodology or with the published evidence, and raises several concerns and issues that compromise the usefulness of the cost-effectiveness analysis.

Firstly, the approach of relying on statistical inferences is irrelevant in economic evaluation, which by its nature is performed to inform decision-making in conditions of uncertainty. As emphasized by Claxton (1999), "decisions should be based only on the mean net benefits irrespective of whether differences are statistically significant or fall outside a Bayesian range of equivalence." Instead, point estimates of the data should be incorporated into the economic models with the uncertainty around the results characterized through sensitivity analyses. This view is widely accepted and endorsed by practitioners of health economic evaluations worldwide (Drummond et al., 2015; Ramsey et al., 2015).

Secondly, the statement that "RCTs had high rates of crossover and showed no OS benefit for TKIs compared with a platinum-based chemotherapy doublet" is incorrect. Statistically significant OS benefit was demonstrated in the combined analysis of the OS data for the common EGFR mutations population in *LUX-Lung 3* and *LUX-Lung 6* (HR: 0.81; 95% CI: 0.66-0.99. Yang, 2015), and this was acknowledged in Figure E1 of the draft evidence report. In addition, significant OS benefit was observed in the EGFR Del19 mutation populations in both *LUX-Lung 3* (HR: 0.54; 95% CI: 0.36-0.79) and *LUX-Lung 6* (HR: 0.64; 95% CI: 0.44-0.94).

Next, as highlighted in previous correspondence, the OS results from the *LUX-Lung 7* study comparing afatinib with gefitinib suggests that there are differences in OS benefit among the two TKIs (HR: 0.87; 95% CI: 0.66-1.15. Park, 2016). Furthermore, while ICER had rated this study "good" in its review of the comparative clinical effectiveness of the TKIs, *LUX-Lung 7* was omitted from the list of studies included in the NMA for OS (Figure D1, and Tables D1 and D3

from the draft evidence report). As a result of assuming differentiated PFS benefit but identical OS benefit across the three TKIs, a perverse scenario arises where patients treated with gefitinib are being accorded with a disproportionate benefit in progression life years (1.19 years) as compared to those treated with afatinib or erlotinib (0.98 and 1.02 years, respectively; Table 18a). As the costs associated with progressed disease are relatively lower than those associated with progression-free disease, this could explain the lower incremental cost-effectiveness ratio for gefitinib as compared to that for afatinib and erlotinib, despite its poorer PFS benefit (median PFS of 8.5 months versus. 10.6 and 10.2 months for afatinib and erlotinib, respectively; Tables 18a and 18b). Such results can be easily misunderstood by readers who are less familiar with the nuances of cost-effectiveness analyses, and may mislead healthcare decision makers in their interpretation of the relative value of these three TKIs.

Finally, the estimation of the 8.9-month OS benefit from the *IPASS* study raises some concerns. BI acknowledges that the crossover rates in many of the trials make estimating the OS benefit challenging and appreciates ICER's attempts to adjust for this issue. However, as recognized by ICER, the positive EGFR mutation status of NSCLC patients is associated with improved survival, and therefore an approach comparing OS data from EGFR mutation-negative patients in the carboplatin plus paclitaxel chemotherapy arm with that from EGFR mutation-positive patients in the gefitinib arm is likely an imperfect solution. In addition, by applying this 8.9-month OS benefit directly to the cost-effectiveness analyses, the differences in efficacy of carboplatin plus paclitaxel versus the cisplatin plus pemetrexed comparator are again ignored. Furthermore, by applying the 8.9-month OS benefit, ICER's cost-effectiveness model estimates the median OS for each TKI to be 21.4 months (Table 18a), which is several months lower than the median OS data reported in chemotherapy arms of almost all of the studies that were considered in this value assessment (Table 3). This observation highlights that the 8.9-month OS benefit assumption grossly underestimates the OS benefit of the TKIs in the treatment of EGFR mutation-positive NSCLC patients.

We recognize the challenges faced in estimating the OS benefit of the TKIs, and we do find ICER's assumption that gefitinib improves median OS by 8.9 months compared to carboplatin plus paclitaxel to be a reasonable starting point. However, efficacy differences that exist among the chemotherapy doublets, as well as the TKIs, must be taken into account in the cost-effectiveness analysis. BI recommends that ICER updates the base case results of the NMA by considering the relative efficacies to each of the chemotherapy doublets and TKIs individually, and to then apply the revised OS HR estimates (including data from *LUX-Lung 7*) from the NMA to that for gefitinib versus carboplatin plus paclitaxel to derive differentiated OS estimates for each TKI versus the primary baseline comparator – cisplatin plus pemetrexed. Such an approach would retain ICER's approach to estimating the OS benefit for gefitinib versus carboplatin plus paclitaxel, utilize all of the relevant clinical data, better allow for differences in efficacy to be incorporated and make the analysis more consistent with the principles of good health economic evaluation.

Differences in patient populations across clinical studies

All three TKIs included in the value assessment are similarly indicated for the first-line treatment of NSCLC patients whose tumors have EGFR Del19 or L858R mutations (i.e. common EGFR mutations). Therefore, the evidence presented in the comparative clinical effectiveness and comparative value sections of the assessment should be specific to the common EGFR mutation population whenever this information is available. With reference to Table 3 of the draft evidence report, we note that the median PFS and OS data presented for *LUX-Lung 3* and *LUX-Lung 6* are those associated with the intent-to-treat population that included EGFR mutations other than Del19 and L858R, for which none of the TKIs are currently indicated. These data are also inconsistent with those reported for the majority of studies listed in the table, which are specific to the common EGFR mutation population (i.e. *LUX-Lung 7, WJTOG3405, First-SIGNAL, EURTAC, ENSURE, and OPTIMAL*). We also recommend that the remaining three studies for which common EGFR mutation specific data is unavailable be highlighted in Table 3, so that readers are aware of the patient population heterogeneity that exists across these clinical studies.

The relevant data that should be presented for the common EGFR mutation population is provided below. The PFS and OS data inputs into the NMA should also be updated, as well as the any corresponding tables and figures throughout the evidence report.

- *LUX-Lung 3* (Sequist, 2013; Yang, 2015)
    - Median PFS – Afatinib: 13.6 months versus Cisplatin+Pemetrexed: 6.9 months
    - Median OS – Afatinib: 31.6 months versus Cisplatin+Pemetrexed: 28.2 months
- *LUX-Lung 6* (Wu, 2014; Yang, 2015)
    - Median PFS – Afatinib: 11.0 months versus Cisplatin+Gemcitabine: 5.6 months
    - Median OS – Afatinib: 23.6 months versus Cisplatin+Gemcitabine: 23.5 months

Inconsistencies in efficacy data presented

We would like to highlight a few inconsistencies in the report that should be corrected. Firstly, page 30 and Table D6 of the evidence report state that the PFS HRs for afatinib, gefitinib, and erlotinib are 0.38, 0.45, and 0.30, respectively. However, Table F1 presents PFS HRs of 0.40, 0.53, and 0.42 for afatinib, gefitinib, and erlotinib, respectively. Furthermore, the median PFS presented in Table 18a and Figure F1a (10.6 months, 8.5 months, and 10.2 months for afatinib, gefitinib, and erlotinib, respectively) suggest that the PFS HRs cannot be those listed on page 30 and Table D6.

Next, we noted a mistake in Figure 6 where the bar lines for the *LUX-Lung 3* and *LUX-Lung 6* studies are identical. As mentioned in the previous section, this figure should be corrected to reflect the relevant data for the indicated common EGFR mutation population.

Lastly, in reviewing the PFS and OS data for the key TKI studies listed in Table 3, it was noted that some of the data presented was not the most recently available. For example, the median OS data for the *NEJ002* study in Table 3 was based on the publication by Maemondo et al. (2010),

although updated OS data are available in the publication by Inoue et al. (2013). It is important for ICER to revise the data presented in Table 3, and to ensure that the NMA is based on the updated data so that the clinical evidence reviewed is current and informative to readers.

Transparency and rigor

BI supports constructive and informed dialogue among patients, physicians, payers, and manufacturers about the value of new innovative drugs and medical technologies, and welcomes the opportunity to participate. However, in order for such conversation to be productive and objective, these value assessments must be underpinned by methodologically sound and robust analyses that holistically and objectively consider the breadth of evidence available for health care decision-making. BI therefore strongly urges ICER to thoughtfully consider the comments and recommendations that have been presented in this letter.

Please feel free to contact me if you have any questions or need additional information.

Sincerely,

(SENT ELECTRONICALLY)

Martina Flammer MD, MBA
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Response to ICER's Draft Report on Non-Small Cell Lung Cancer

Bristol-Myers Squibb (BMS) believes the value in healthcare should be measured by longer, healthier lives of patients. We are pleased to see that nivolumab received a superior ('A') rating as acknowledgment of the value it provides to patients, their families and caregivers. However, we continue to challenge the ICER approach to evaluating transformational and innovative medicines and its lack of transparency. Furthermore, we disagree with many aspects of this draft report as well as the focus of ICER's framework on an arbitrary budget impact threshold and care rationing.

BMS is committed to a comprehensive, evidence-driven approach to value that incorporates patient priorities, real world data, total health system value, multi-stakeholder input and the most up-to-date clinical science. With this in mind, we are providing comments in response to the "Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value" draft report.

An evidence-driven approach to measuring treatment value is critical as BMS and other stakeholders continue to tackle challenging diseases with the highest unmet need, like non-small cell lung cancer (NSCLC), where the science is progressing rapidly. BMS has identified six key areas of concern with the PD-1 inhibitor sections of the report and is providing recommendations to ensure that disease complexity, patient experience, and the full value of innovation are incorporated to produce a more appropriate assessment of value. We strongly urge ICER to incorporate the data we have previously submitted and to revise the final results based on the points that follow.

I. ICER does not clearly define a clinically relevant research question

A. ICER analyses fail to acknowledge the need to account for complexity and heterogeneity of lung cancer and response to therapies.

The National Comprehensive Care Network (NCCN) recommends different treatments and treatment sequences for non-squamous (NSQ) and squamous (SQ) patients.[1] In the ICER analyses, the populations considered across PD-1 inhibitors are not sufficiently comparable due to the distinct natural history and biology of NSCLC in terms of histology. Cross-trial comparisons in second-line EGFR negative patients should reflect consistent and relevant patient populations to ensure that trials included in the network meta-analysis (NMA) be sufficiently comparable.[2-4] Therefore, any meta-analysis should consider whether the intent-to-treat populations are comparable in terms of histology and biomarker testing, which may affect the relative efficacy of the interventions.

There is insufficient evidence to determine whether histology is an effect modifier based on two trials that present the NSQ and SQ histologies individually (CheckMate trials may have study level differences and cannot be included in such an assessment). ICER's conclusion that histology is not an effect modifier is inappropriate given clinically relevant differences and a lack of power to refute this; therefore pooling patients to assess clinical measures (i.e. overall survival) is not appropriate and overlooks key clinical differences.[1]

BMS Recommendation: ICER should conduct their analysis separately by histology given differences in clinical pathways and NCCN guidelines across these populations.

B. ICER analyses fail to account for the role of PD-L1 expression in the non-squamous (NSQ) population.

The role of PD-L1 appears to be specific to histology, which supports the need to assess histology separately. For NSQ patients, the NMA and cost-effectiveness analysis (CEA) have to account for PD-L1

expression given its role as a potential treatment effect modifier and clear differences observed in the distribution of PD-L1 thresholds across the trials for different interventions. To ensure the validity of the NMA, comparisons can be assessed at the PD-L1 ≥1% for all trials based on either histology (CheckMate trials and POPLAR) or intent to treat population (KEYNOTE-010). For SQ patients, since the role of PD-L1 expression is not as clear, the NMA and CEA could be performed based on the ITT population for all trials (see Goeree et al (2016))[5].

BMS Recommendation: *In addition to splitting the analysis by histology, the ICER analysis should correctly incorporate the role of PD-L1 expression into the NSQ component of the NMA and CEA by comparing treatments at the PD-L1 ≥1% threshold.*

C. ICER includes treatments and dosages in their review which have not been FDA approved

Both atezolizumab and the 10mg dosing of pembrolizumab have not received FDA approval for NSCLC, making it premature to consider them in this report. Both nivolumab and pembrolizumab (2 mg dosing) have different labeled indications, and it is unknown what the label population might include for atezolizumab, if/when approved. Beyond limitations regarding available early evidence, ICER has drawn conclusions regarding cost-effectiveness based on an indication for atezolizumab (i.e., PD-L1 ≥1%) that has not been established during the review process or public comment period.

Although pembrolizumab 2mg has received FDA approval, ICER has pooled the 2mg and 10mg populations from the KEYNOTE-010 trial in the comparative clinical effectiveness section and NMA, whereas the CEA does not take into account the 10mg dose of pembrolizumab.

BMS Recommendation: ICER should wait until atezolizumab is approved and the label indication is finalized, and then should update the report with the correct population based on the label. At a minimum, ICER should clearly state throughout the report that atezolizumab is not FDA approved for NSCLC and that ICER is making assumptions regarding the future label indication. Additionally, Figure 3 should not include atezolizumab with the other FDA approved therapies. Furthermore, there should be consistency in the evaluation of the pembrolizumab doses in the clinical effectiveness and care value model sections.

II. ICER fails to utilize the most relevant data available

A. The analyses fail to compare treatments using patients with similar PD-L1 levels

The immuno-oncology therapies reviewed by ICER used different PD-L1 expression inclusion criteria in the clinical trials that are the basis for the current FDA indications or ongoing FDA submissions. Although differing patient populations makes a comparison across treatments challenging, ICER failed to consider an analysis for the PD-L1 ≥50% expression subpopulation across all PD-(L)1 inhibitors despite BMS providing this overall survival subgroup data. ICER excluded this data from the analysis as well as from Table 8. Selectively excluding relevant data led to the false conclusion that "PD-L1 expression levels were not comparable because investigators provide different cutoffs," resulting in a missed opportunity to assess comparative efficacy of PD-(L)1 inhibitors based on a comparable threshold.

BMS Recommendation: ICER should add the PD-L1 ≥50% expression data from CheckMate 057 to Table 8 (as well as any other data provided by manufacturers) and conduct a NMA based on subgroup data for all PD-(L)1 inhibitors in the report. Additionally, ICER should remove the statement which says PD-L1 expression levels were not comparable because investigators used different cut-offs.

B. ICER fails to account for the patient perspective by omitting quality of life (QoL) data from the RCTs used in the efficacy analysis of the NMA and CEA for second-line EGFR negative patients.

Although ICER mentions the QoL data collected from the CheckMate trials, they do not utilize these data in their CEA. Rather, ICER utilizes QoL estimates from Nafees (2008).[6] The choice of QoL data is inferior for several reasons: 1) CheckMate QoL data is derived using EQ-5D whereas Nafees et al. is based on direct elicitation; 2) CheckMate QoL data is based on NSCLC patients (including US sites, thereby patients) whereas Nafees et al. is based on the general public in the UK setting.[6] Novel treatments in NSCLC not only provide increased efficacy when compared with prior standards of care, but also offer additional benefits such as increased symptom reduction and lower toxicity.[7-10] Such benefits are less likely to be accurately represented by QoL data from a general population, making patient reported QoL data more relevant in this context.

Finally, the EQ-5D utility from CheckMate 017 has been used in the base case economic model by Goeree et al (2016).[5] This study identified that results were sensitive to utility values, reinforcing the importance of incorporating these utility estimates.[5] Using the lower pre-progression utility by Nafees et al. has the most impact on a treatment that improves progression-free survival the most (nivolumab), which does not align with the value patients assign to remaining progression-free.[6]

BMS Recommendation: ICER should incorporate the QoL data from the CheckMate trials into their CEA in the base case. Nafees (2008) utility estimates post-progression could be assessed as scenario analysis given drop outs over time in QoL data from Checkmate trials (Goeree 2016).[5,6]

III. ICER's report is not transparent and does not provide sufficient detail to justify their methodological approach.

The general lack of transparency and detail provided in the report is a major issue. Lack of information surrounding the methodology, assumptions, and data in the report precludes the ability to have valid scientific discussion or critique of the report, and makes accurate interpretation of the results findings difficult. These limitations would likely prevent publication of these results in a peer-reviewed journal, undercutting their scientific validity.

The lack of transparency in the report surrounding the data, methodology, and assumptions used in the NMA and CEA make interpretation difficult. At a minimum, the report should include the following information with respect to methodology and modeling approach:

- The KM curves used in the NMA and CEA analyses (including references and figure numbers, specified population, and follow-up duration)
- Methods used to generate time-varying hazard ratios for NMA and CEA
- Alternative models considered for NMA (Weibull and Gompertz are mentioned)
- Model used for meta-analysis of docetaxel for each PD-(L)1 inhibitor
- Justification for the method used to extrapolate time-varying hazard ratios ("flattening of curves") in CEA
- Rationale for the inconsistent methods for hazard ratios in NMA and CEA
- Rationale for the model choices in NMA and CEA
- Systematic exploration of proportional hazards assumptions
- Specific references for the costs of routine care pre- and post-progression and end of life

Further, greater transparency should be included around the presented results:

- Model fit statistics for all NMA models as well as all models assessed (not just those presented in report for the meta-analysis of docetaxel)
- Parameters for NMA and hazard ratios *at all time points* for NMA and CEA
- Lack of clarity of which results were synthesized in NMA and which were incorporated in CEA

<u>BMS Recommendation:</u> ICER should provide detailed information related to the above points, and provide adequate support (published references) for each of their model choices and assumptions. In cases where published support does not exist, ICER should conduct sensitivity analyses around each assumption and present results in the updated report, particularly in cases where parameters are found to be a key driver of results such as overall survival hazard ratios. We additionally recommend that ICER utilize Bremner (2015) coupled with the CMS Physician Fee Schedule as the source for costs of routine care.[11-12] Moreover, ICER should provide the CEA model, or additional details that allow for full understanding of the analysis in line with peer-review journal requirements.

IV. <u>Elements of ICER's analysis in all population settings are premature</u>

A. ICER should assume a consistent treatment duration in the 2nd line EGFR- population for all PD-(L)1 inhibitors.

The CEA should consider how treatments are likely to be administered in real-world clinical practice. For instance, it is unclear whether patients will receive a PD-(L)1 inhibitor 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-(L)1 inhibitors. Both nivolumab and pembrolizumab are currently indicated for continued treatment until disease progression or unacceptable toxicity, of patients with metastatic NSCLC in the second line setting.[13-14] Some Health Technology Assessment (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 example, the maximum treatment duration was assumed to be a maximum of 96 weeks).[15] Therefore, in light of the lack of 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-(L)1 inhibitors.

<u>BMS Recommendation</u>: The final report should continue to assume all treatments are administered until progression in the base case and explore the impact of a stopping rule that is consistent for all PD-(L)1 inhibitors until real world data is available.

B. ICER considers PD-(L)1 inhibitors for the first line EGFR- population in the report.

Although ICER states that 'patients are already being treated with first-line PD-(L)1 immunotherapy in the absence of evidence from randomized trials', FDA approval has not been granted and there is no reference or data to support this statement (which may encourage inappropriate off-label use). ICER's inclusion of this population is premature, and could lead to inappropriate conclusions on the basis of limited evidence.

<u>BMS Recommendation</u>: ICER should remove the first line EGFR- population and nivolumab should not be included in this analysis.

C. ICER considers PD-(L)1 inhibitors for the second line EGFR+ population in the report.

PD-(L)1 inhibitors in the second line EGFR+ population are not currently recommended by the NCCN guidelines in the second line setting, and the clinical evidence base is limited. Despite this fact and the rating of 'I' (Insufficient evidence) in this population, ICER makes a strongly worded statement that "we feel that PD-(L)1 immunotherapy should be avoided in this setting" despite the lack of evidence refuting or supporting this statement.

<u>BMS Recommendation</u>: ICER should remove the second line EGFR+ population from the PD-(L)1 inhibitor section of the report. At a minimum, ICER should remove all statements related to this population since insufficient evidence exists to draw any conclusions.

V. ICER's budget impact framework is inappropriate

A. ICER's budget impact approach is not evidence-based and establishes arbitrary budget caps, which fundamentally ignore the value of innovation in healthcare.

ICER arbitrarily establishes budget caps for societal expenditures on medical innovations and fundamentally ignores the value of innovation in healthcare. This approach assumes patients subjected to a cancer of high incidence or prevalence are worth 'less' than patients who have a more rare form of cancer, creating disincentives for innovation and healthcare investment. Further, setting budget criteria instead will deter innovators from developing therapies that could benefit a broader patient population. Nevertheless, treatments that provide significant benefits to a large number of patients are exactly the treatments most desired by society. 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. ICER's budget impact threshold focuses narrowly on one component of healthcare costs, with an emphasis on medicines. In essence, this practice implies that spending on new medicines should be frozen based on current patterns of care. These budget caps have not been vetted and endorsed in the scientific, policy and patient communities. Therefore we strongly object to the budget impact framework as a means for deriving value and "value-based price benchmarks".

BMS Recommendation: Remove the budget impact threshold analysis

B. ICER should state explicitly if/how they incorporated the total cost of care into their budget impact analysis

When conducting a budget impact analysis for any treatment, it is important to include not only the cost of the treatment, but also any changes to other medical costs (e.g., reduced hospitalization) in this calculation. ICER does state that it includes cost offsets in its budget impact analysis. The magnitude of these cost offsets and their source are never described in report.

Any offsets that may be included are limited to those affecting medical costs. However, estimates from the National Institutes of Health (NIH) indicate that approximately 78.8% of all lung cancer costs are attributable to lost productivity.[16] Even though ICER points out NSCLC patients are at the highest risk for depression among cancer patients, they have not included productivity or any other indirect costs (such as caregiver burden) in their analysis. Given the NIH estimates, this omission clearly results in an underestimate of treatment benefits.

BMS Recommendation: If cost offsets are included in ICER's analysis, we recommend stating both the size of the cost offsets and the methodology to obtain them in the report. Cost offsets should be defined broadly to include changes in cost due to patient productivity and caregiver burden. If cost offsets are not included, these should be added to both the care value and budget impact analyses.

VI. ICER's care value approach does not take into account patient priorities

ICER's care value model does not fully take into account the patient perspective, both in terms of the components of value included in their value framework and how these components of value are measured. The effect of NSCLC treatments on patient and caregiver productivity, for instance, are not considered even though productivity losses make up a large share of cancer care.[16] Further, although ICER does incorporate survival benefits into their model, their methodology ignores the fact that patients place a high value on treatments that improve survival in the tail of the distribution, above and beyond any improvements in median survival.[17] In contrast to ICER, the America Society of Clinical Oncology's (ASCO) value framework does recognize the importance of long-term survival and awards "bonus points" to treatments that improve survival in the tail of the distribution.[18]

BMS Recommendation: ICER should rely on a patient centric approach to its care value model and incorporate the benefit of treatments on various dimensions of survival, QoL, productivity, and caregiver burden.

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September 16, 2016

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RE: Institute for Clinical and Economic Review non-small cell lung cancer evidence report

Dear Dr. Pearson,

On behalf of the Cancer Support Community, an international nonprofit organization that provides support, education and hope to over 1 million people affected by cancer each year, we appreciate the opportunity to respond to the request for comments regarding ICER's non-small cell lung cancer report. Given the NSCLC report was developed under the current framework, CSC believes it to be flawed in a number of areas and that it should be re-worked to minimally meet the criteria outlined below. As appropriate, we will flag concerns which are heightened given the nature of the patient experience with lung cancer.

As the largest direct provider of social and emotional support services for people impacted by cancer, and the largest nonprofit employer of psychosocial oncology professionals in the United States, CSC has a unique understanding of the cancer patient experience. Each year, CSC serves more than one million people affected by cancer through its network of 44 licensed affiliates - more than 120 satellite locations, and a vibrant online community- and delivers more than $40 million in free, personalized services each year.

Additionally, CSC is home to the Research and Training Institute - the only entity of its kind focused solely on the cancer patient experience. The Research and Training Institute has contributed to the evidence base regarding the cancer patient experience through its Cancer Experience Registry®, various publications and peer-reviewed studies on distress screening, and the psychosocial impact of cancer and cancer survivorship, to name a few. This combination of direct services and research uniquely positions CSC to provide organizations like ICER with feedback based on evidence as well as real world impact.

CSC acknowledges ICER's intent to seek multi-stakeholder input as a part of the process involved in assessing the value and effectiveness of different oncology treatment regimes. Both the conversation on value and multi-stakeholder engagement is at the core of CSC's work on access, and we are eager to work with you to move appropriate solutions forward.

CSC stands by our offer to create a panel of patients and caregivers living with NSCLC cancer to test the concepts and frameworks suggested by ICER.

Dr. Pearson, we remain concerned about several principles of the framework and your engagement requirements.

Unrealistic formatting specifications and response time

On a very basic level, the instructions you give for submitting feedback are limiting in both feedback opportunity and transparency. While encouraging public comment, you specifically limit the length of some submissions to 3 pages and require a font size of 12. Additionally, you require submission in a Word document and indicate that comments **may** be made public.

The two week public comment period does not allow adequate time to review ICER's recommendations and solicit feedback from patients and experts. CSC thanks ICER for extending the time to respond to the NSCLC report and encourages ICER to consider review times that are even more generous in the future.

CSC encourages you to amend these practices to allow the respondent the time and space to provide full and complete feedback on your positions. Additionally, CSC believes you should allow submissions to be in pdf format and that you also make all comments publicly available throughout the entire development and review process.

Inadequate patient representation

CSC acknowledges the attempt to include patients on both the Governance Board and also the regional panels.

CSC encourages ICER to consider the following:

1. There should be a sufficient number of patient representatives to allow an equal share of voice when votes are taken.
2. Patient representation on the Governance Board should include expertise and knowledge that represents the full spectrum of wellness, disease understanding and geography. This board should be expanded to include individuals who can represent or who have access to resources which would allow ICER to benefit from a more comprehensive level of information on the patient experience.
3. There should be patient representation as a part of the evidence report development. As an example, this lung cancer evidence report was developed and approved by a panel exclusive of patients. ICER does note that it received input/feedback from patient groups, including CSC, but it should be noted that CSC did not have access to any of the draft reports prior to or including this "final" draft report being made publicly available.

Lack of clinical expertise

In addition to ensuring patients on your panels have the appropriate level of expertise to fully understand complex clinical scenarios, CSC encourages ICER to require health care professionals serving on voting panels to have relevant and deep expertise in caring for patients with lung cancer. Specifically, CSC would like ICER to mandate that physicians serving on the voting panel for the lung cancer report have board certification in medical oncology and that they are actively treating patients with lung cancer.

Inconsistent methodology

CSC fully recognizes the importance of evidence in setting policy and when making decisions with patients. CSC encourages ICER to consider the following:

1. ICER must be transparent with all resources used in the development of evidence reports.
2. ICER must include a balance of data derived from controlled clinical trials (including observational trials) and real world evidence.
3. ICER must create principles to ensure that the use of data meets a high level of scientific credibility. For example, the use of cross-trial comparisons should be discouraged.
4. ICER must require peer-review by a panel of experts for all evidence reports.

Relevance and timeliness of recommendations

The plan for ICER to update recommendations as new data becomes available is unclear. For diseases with rapidly changing scientific discoveries, any organization making clinical recommendations must be nimble and responsive to the environment. CSC encourages ICER to implement the following:

1. A transparent timeline for review and update of previously published recommendations.
2. A deadline for decision that does not impact the ability of a patient to access a treatment option determined effective for a particular disease.
3. Expertise on the review and voting panel that mirrors the topic of scientific discovery.
4. Full transparency of the data used for decision making.

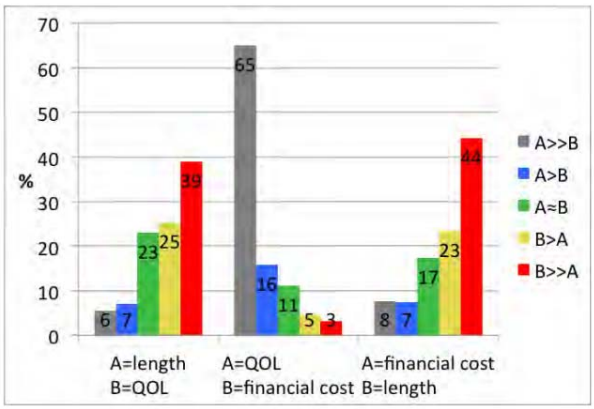
A quick search of clinicaltrials.gov reveals 699 studies listed for EGFR+ NSCLC and 71 studies listed for PD-1 and lung cancer. ICER should be prepared to address new information in rapid fashion as these trials mature.

Lack of consideration of the patient definition of value

CSC understands your use of quality-adjusted life year (QALY) as an endpoint but does not support this as an endpoint which is meaningful to patients. Multiple studies, including CSC's Registry data, show that for patients with cancer and other long-term debilitating illness, there is a delicate balance between quality and quantity of life. In fact, some patients have reported a desire for a shorter overall survival in exchange for quality of life. The QALY framework assigns the exact same score to an individual who lives six months in perfect health and to an individual who lives a full year in a debilitated state. Patients would assign a very different level of value to each of these scenarios.

Data from the Cancer Experience Registry continues to reveal the importance of quality of life as an important indicator of value to patients. This figure, taken from a recent analysis and presentation on patients in the Registry, indicates that quality of life may, in fact, be of greater importance to the majority of patients when making a treatment decision than length of life. Other value models (American Society of Clinical Oncology and the National Comprehensive Cancer Network) have taken similar approaches to assigning higher levels of value to endpoints such as overall survival without a full appreciation and representation to the value patients assign to shorter, incremental gains.

Figure 2. Relative impact of factors A and B when considering a treatment decision



Note: >> much more; > slightly more; ≈about equal

- *44% indicated LoL had much more of an impact on treatment decision than financial cost*
- *65% indicated that QoL had much more of an impact on treatment decision than financial cost*
- *39% indicated that QoL had much more of an impact on treatment decision than LoL*

Additionally, responses collected directly from cancer survivors in an open-ended question about how they define value in their cancer care show quality of life issues and attention to individual preferences and needs emerging as key factors. For example, one respondent wrote: "Value is most meaningful when it is applied to my individual life, and not to an algorithm or statistical fact." Another notable trend is time with the health care team to fully understand all available options and the risk and benefit scenarios (including cost) associated with each. A respondent wrote: "A good team of doctors that works with you, not at you."

Data from CSC's Cancer Experience Registry, presented at the 2015 Association for Value-Based Cancer Care annual meeting demonstrates that in patients with metastatic breast cancer, only 5% of respondents conceived value as having any exchange-based meaning specific to health. As noted in the study, when defining value relative to health care, patients emphasized the importance of their relationship with Health Care Providers (HCPs) rather than the benefit of cost-effective treatment. Although quality, efficiency and cost transparency in value-based care are essential, patients may be more focused on quality care as it relates to the HCP–patient relationship than on value relative to efficiency/cost. While accounting for the clinical merits of a particular therapy is important, the current ICER model represents only a component of the overall care and may overshadow other dimensions of care that are also valuable to patients. CSC would like ICER to utilize a framework which more closely represents the endpoints that are meaningful to patients.

Lack of consideration of low-grade chronic side effects

ICER's value framework does not include consideration of low-grade, chronic side effects. CSC acknowledges concerns regarding the lack of patient reported outcomes as a part of the formal data collection process and CSC sincerely looks forward to working with ICER on a plan to remedy future data collection requirements. The reality for patients is that long-term side effects are a significant part of their overall experience, ranging from quality of life, to financial considerations, to work and family challenges. As documented in the 2014 Index, Elevating the Patient Voice, the top concern people want more help managing is long-term side effects. Given the body of evidence currently available on long-term effects of the vast majority of the "prevailing standard of

care", CSC strongly encourages ICER to incorporate that information as an important component in the calculation of clinical-effectiveness.

Focus on medications acquisition costs

The impact on the individual in terms of personal health care spending is increasing and documented in the literature. Indeed, data from CSC's Insight into Patient Access to Care in Cancer report demonstrates that patients are primarily concerned about costs related to insurance premiums, co-pays for services and co-pays for drugs.

We believe the focus solely on sales or acquisition costs to estimate treatment costs minimizes the reality and attention that should be placed on finding solutions that address the multitude of factors impacting elevated spending. Further, this narrow focus can significantly under-weight aspects of the delivery of care that contribute substantially to a patient's calculation. Aligned with the patient voice, our broader community should focus its attention on creating a system that rewards the provision of comprehensive, quality care inclusive of transparency, shared decision-making and long-term risk/benefit disclosures.

Lack of inclusion of financial toxicity

The causes of financial toxicity in patients with cancer are becoming well recognized and the reality of the rising cost of health care is daunting and not sustainable. Patients report financial distress as more severe than other sources of distress associated with physical, social and emotional functioning (e.g., Delgado-Guay et al., 2015).
The current Value Assessment Framework does little to recognize the impact of the comprehensive nature of financial toxicity. In addition to patient cost sharing for medications and services, it is well documented that patients experience additional expenses related to their cancer treatment. Some expenses are more difficult to measure (parking, housing, etc.), but the framework could allow the capture of additional elements. In particular, ICER could apply some level of consideration to frequency of treatment as a part of the evaluation. Given the high cost of travel and time off work, a regimen that would be administered once per month may be less financially toxic to a patient than one administered every week, as one example. Additionally, this framework does not give consideration to the costs associated with interventions required as a comprehensive part of treatment. For example, supportive care agents needed to manage nausea, steroids required as a part of a treatment regimen, etc.

Conclusion

At the Cancer Support Community, we are acutely aware of the rising costs of treating cancer and support efforts that contain cost while ensuring the provision of truly comprehensive cancer care. We believe that patients who have knowledge and experience in the specific topic areas must be fully at the table in discussions about new cancer care models along with providers, payers and other stakeholders. All policy proposals should be evidence-based and promote a rich physician-patient dialogue and care planning that is customized for and with the individual cancer patient. We strongly believe that the process of developing new care models and payment structures and the implementation of those models in practice must be transparent. Patients have a right to know about their full suite of care choices, and the incentives that may influence their providers in terms of treatment recommendations.

In conclusion, CSC sincerely thanks you for the opportunity to comment on ICER's draft evidence report on treatment options for advanced non-small cell lung cancer share the voices of patients living with cancer. We look forward to additional opportunities to contribute to ICER's ongoing work.

Please feel free to contact me at (202) 650-5382 or by email at linda@cancersupportcommunity.org if you have any questions or if we can be of further assistance.

Thank you again for your attention to this very important matter.

Linda House, MSM, BSN, RN
President
Cancer Support Community National Headquarters

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Genentech
A Member of the Roche Group

September 16, 2016

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel:

In response to the public comment period for the ICER draft report titled "Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value", please see the following recommendations on **Tecentriq™ (atezolizumab)**:

Conduct an evaluation of Tecentriq following the publication of the pivotal trial, OAK.

- As previously discussed, it is premature to evaluate Tecentriq in non-small cell lung cancer (NSCLC) since pivotal data have not yet been published.[1]
- To ensure that sufficient scientific evidence is available to support a robust evaluation of appropriate patient populations and therapies, it is critical to conduct a systematic literature review and solicit input from multiple clinical experts.

Provide full disclosure of the modeling approach and the draft cost effectiveness model.

- There are a number of areas where it is unclear how model methods yield the reported results. When following the described methods, Genentech was unable to replicate the efficacy values (Progression-free survival [PFS] and overall survival [OS]), both of which have a significant impact on the cost of treatment and cost-effectiveness results.

Utilize the most current, publicly available trial data to inform the survival curves.

- The primary analysis from POPLAR is currently used to support the evaluation of Tecentriq.[2] Extended follow-up in the POPLAR trial reveals further separation of the OS curves and increased benefit with Tecentriq vs docetaxel.[3] The lack of extended follow-up data may result in misrepresentation and under-estimation of Tecentriq's survival benefit.

Re-evaluate and communicate model assumptions on post-progression costs and therapies.

- Clarification is needed on how the post-progression costs were calculated. The draft report, for example, assumes post-progression treatment with docetaxel after 2L cancer immunotherapy (CIT) is given for three months (p. 60). However, given that the weekly cost shown in Table 17 (p. 61) is only $441 for docetaxel, the post-progression costs shown in Table 19a ($21,571-$25,696) greatly exceed the cost of three months of treatment (p. 65).
- Post-progression therapies should be changed so they are the same regardless of the initial therapy. This will ensure that there is no bias in the third-line (3L) treatment cost

and effectiveness assumptions, and that the focus of the evaluation is on the initial therapy and not on the sequence of therapies.

Remove statements regarding the efficacy of therapies in the absence of direct evidence.

- The draft report states: "We currently have no direct evidence comparing PD-1 immunotherapies with platinum doublet as subsequent-line treatment (after [tyrosine kinase inhibitors] TKIs) of EGFR+ advanced NSCLC" (p. 51). However, on the same page, the following statement is made: "...there are reasons to be concerned that PD-1 immunotherapy could be inferior to a platinum doublet." This is based on a meta-analysis of 2L CIT clinical trials with no pre-specified analysis of the epidermal growth factor receptor-positive (EGFR+) patient population. Statements regarding efficacy that are not supported by evidence, should be removed.

Ensure the model time horizon is long enough to capture all death events in the cost-effectiveness model.

- The time horizon of the cost-effectiveness model has significant impact on the estimates of benefit and the incremental cost-effectiveness ratio. The model time horizon should be long enough to capture 99.9% of deaths according to guideline recommendations.[4] We recommend extending the model time horizon to a maximum of 20 years, clearly reporting the final model time horizon, and including rationale to allow for stakeholder replication and validation.[5,6]

Acknowledge the current approach to modeling survival curves is conservative and other valid approaches may be undertaken.

- The draft report states: "We received a number of comments regarding how to appropriately summarize the effects of PD-1 immunotherapy, as survival curves suggest that the proportional hazards assumption may not be valid, and that there may be a long survival tail among responders to therapy" (p. 49). The model utilizes multiple hazard ratios to estimate survival benefit in order to address issues raised by non-proportional hazards. However, this is a conservative approach since the curve tails remain proportional to docetaxel. We recommend that you acknowledge that the approach taken in the draft report was one attempt to address the non-proportional hazards issue, and that there are other potential survival assumptions (e.g., a cure model) that can be reasonably explored.[7] Furthermore, scenario sensitivity analyses on alternative curves should be undertaken and reported to address this issue.[8]

Provide full disclosure on methods undertaken for the subgroup meta-analysis and clarify results

- There is no description of the methods used to conduct the meta-analysis in Appendix E titled "Subgroup Meta-Analysis Methods and Results" (pp. 139-148).
- Further clarification on the forest plots should be provided, including why some forest plots present fixed and random effects and some only have fixed effects. Figures should also include units.

Correct additional inaccuracies and provide references for statements made in the draft report.

- Stratification of Tecentriq patients by PD-L1 expression should be presented consistently by TC or IC status. PD-L1 expression is defined by TC or IC status in patients treated with Tecentriq, as reported in the POPLAR study.[2] However, Table 8, 11 and F14 report outcomes by PD-L1 percentages (pp. 42, 46, 165).
- The draft report states "For patients with EGFR mutations who have progressed after first-line or first- and second-line TKI therapy, [National Comprehensive Cancer Network] NCCN guidelines recommend treating with a platinum-based chemotherapy doublet" (p. 15). However, the NCCN NSCLC Guideline Version 4.2016 recommends additional first-line (1L) therapy options for adenocarcinoma in this patient population including targeted therapy (e.g. Avastin® [bevacizumab]) in addition to platinum-based chemotherapy.[9]
- There is no reference provided for the following claim: "All of the drugs under review in this report are covered by private insurers for use within their FDA labeled indications" (p. 15). As one pathway is not reflective of all pathways, reporting on placement for one specific pathway (i.e. Anthem) is not appropriate (p. 15).
- Figure F1b is mislabeled and should be corrected to state second-line (2L) survival of anti- programmed death 1s (PD-1s) and anti-programmed death ligand 1s (PD-L1s) (p. 154).
- Please see information in the Appendix for the following Phase III Tecentriq 1LNSCLC trials that were missing from the draft report Appendix H: Ongoing Studies:
    - IMpower 110: Tecentriq vs. pemetrexed/(carboplatin or paclitaxel)
    - IMpower 130: Tecentriq/carboplatin/nab-paclitaxel vs. carboplatin/nab-paclitaxel
    - IMpower 131: Tecentriq/carboplatin/paclitaxel vs. Tecentriq/carboplatin/nab-paclitaxel vs. carboplatin/nab-paclitaxel
    - IMpower 132: Tecentriq/pemetrexed/(carboplatin or cisplatin) vs. pemetrexed/(carboplatin or cisplatin)
    - IMpower 150: Tecentriq/Avastin/carboplatin/paclitaxel vs. Tecentriq/carboplatin/paclitaxel vs. Avastin/carboplatin/paclitaxel

Genentech supports efforts to help patients and healthcare providers better understand their cancer treatment options and ensure patients have access to medicines that may help them fight their disease. Value frameworks like ICER should allow for meaningful dialogue between patients and healthcare providers and account for an individual patient's needs and preferences, without limiting access to potentially life-extending medicines. The over 14.5 million people living with cancer in the United States are relying on continued research to find new breakthroughs that bring us closer to a cure.[10]

FDA Clearance:

Tecentriq is FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

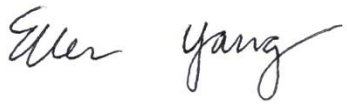
- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please refer to the Tecentriq prescribing information for the full FDA-approved indication and safety information. http://www.gene.com/download/pdf/tecentriq_prescribing.pdf

We welcome the opportunity to provide clarification should ICER have questions on any of these points. Please contact me directly at yang.ellen@gene.com or (440) 292-5535.

Respectfully submitted,



Ellen Yang, Pharm.D.
Senior Scientist, Managed Care Medical Communications
U.S. Medical Affairs, Genentech

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modeling approaches to estimate and extrapolate survival outcomes. J Med Econ 2016; 19(6):630-44.
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APPENDIX:

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
A Phase III Study of Atezolizumab (MPDL3280A) Compared With Cisplatin or Carboplatin + Pemetrexed in Patients With Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)[1] [IMpower110] NCT02409342	RCT	March 2019	-Atezolizumab -Pemetrexed + (carboplatin or cisplatin)	n=570 Key inclusion • 18 years of age or older • PS 0,1 • Treatment-naïve Stave IV non-squamous NSCLC • PD-L1 status • Adequate hematologic and end organ function Key exclusion • CNS metastases • Malignancies (within 5 years) • Autoimmune diseases • History of pneumonitis, IPF, organizing pneumonia • HIV+ • Hepatitis B or C • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 and anti-PD-L1 antibodies • Severe infection	Primary: PFS (investigator assessed) Secondary: ORR, OS, DOR, TTD, PFS (IRF), TIR, PRO, OS at 1 and 2 years, PK analysis, Safety

				• Significant hx of CV disease	
A Phase III Study of MPDL3280A (Anti-PD-L1 Antibody) in Combination With Carboplatin + Nab-Paclitaxel Compared with Carboplatin+Nab-paclitaxel in Patients With Non-Squamous Non-Small Cell Lung Cancer[2] [IMpower 130] NCT02367781	RCT	January 2019	-Atezolizumab + carboplatin + nab-paclitaxel -Carboplatin + nab-paclitaxel	n=550 Key Inclusion: • 18 years of age or older • PS 0,1 • Treatment-naïve Stave IV non-squamous NSCLC • Archival tumor/tissue from biopsy • Adequate organ function Key Exclusion • CNS metastases • Malignancies (within 5 years) • Autoimmune diseases • History of pneumonitis, IPF, organizing pneumonia • HIV+ • Hepatitis B or C • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 and anti-PD-L1 antibodies • Severe infection • Significant hx of CV disease	Primary: PFS (investigator assessed) Secondary: OS, PFS (IRF), ORR, DOR, TTD, PRO, Safety

A Phase III Study of Atezolizumab in Combination With Carboplatin + Paclitaxel or Carboplatin + Nab-paclitaxel Compared With Carboplatin + Nab-paclitaxel in Participants With Stage IV Squamous Non-small Cell Lung Cancer (NSCLC) [3] [IMpower 131] NCT02367794	RCT	February 2023	- Atezolizumab + carboplatin + paclitaxel -Atezolizumab + carboplatin + nab-paclitaxel - Carboplatin + nab-paclitaxel	n=1200 · Key inclusion: • 18 years of age or older • PS 0,1 • Treatment-naïve Stage IV squamous NSCLC • Archival tumor/tissue from biopsy • Adequate organ function Key exclusion • CNS metastases • Malignancies (within 5 years) • Autoimmune diseases • History of pneumonitis, IPF, organizing pneumonia • HIV+ • Hepatitis B or C • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 and anti-PD-L1 antibodies • Severe infection • Significant hx of CV disease	Primary: OS, PFS Secondary: PFS (IRF), TIR, % of patients alive at years 1 and 2, TTD, OR, PRO, DOR, TTR, % patients with anti-therapeutic antibody response, safefacety, PK analysis
A Phase III Study of	RCT	May 2019	-Atezolizumab +	n=568	Primary:

Atezolizumab in Combination With Carboplatin or Cisplatin + Pemetrexed Compared With Carboplatin or Cisplatin + Pemetrexed in Participants Who Are Chemotherapy-Naive and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer[4] [IMpower 132] NCT02657434			platinum (carboplatin or cisplatin) + pemetrexed -Platinum (carboplatin or cisplatin) + pemetrexed	Key inclusion • 18 years of age or older • PS 0,1 • No prior treatment for Stage IV non-squamous NSCLC • 6 mo treatment-free interval after neoadj, adj, or chemoradiotherapy • PD-L1 status • Adequate hematologic and end organ function Key exclusion criteria • EGFR+ or ALK+ • CNS metastases • Spinal cord compression • Leptomeningeal disease • PD-L1 expression from other studies • Malignancies (within 5 years) • Autoimmune diseases • History of pneumonitis, IPF, organizing pneumonia • HIV+ • Hepatitis B or C • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 and anti-PD-L1	PFS (investigator assessed) Secondary: OS, ORR, DOR, TTR, PFS (IRF) PRO, % patients alive after 1 and 2 years, TTD, PK analysis,

				antibodies • Severe infection • Significant CV disease	
A Phase III Study of MPDL3280A (Anti-PD-L1 Antibody) in Combination With Carboplatin + Paclitaxel With or Without Bevacizumab Compared With Carboplatin + Paclitaxel and Bevacizumab in Patients With Stage IV Non-squamous Non-small Cell Lung Cancer[5] [IMpower 150] NCT02366143	RCT	November 2022	-Atezolizumab + carboplatin + paclitaxel -Atezolizumab + carboplatin + paclitaxel + bevacizumab -Carboplatin + paclitaxel + bevacizumab	n=1200 Key inclusion • 18 years of age or older • PS 0,1 • Treatment-naïve Stave IV non-squamous NSCLC • Tumor/biopsy tissue • Adequate hematologic and end organ function Key exclusion • CNS metastases • Malignancies (within 5 years) • Autoimmune diseases • History of pneumonitis, IPF, organizing pneumonia • HIV+ • Hepatitis B or C • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 and anti-PD-L1 antibodies • Severe infection • Significant hx of CV disease	Primary: PFS (investigator assessed) Secondary: ORR, OS, DOR, PFS (IRF), OS at 1 and 2 years, TTD , PRO, Safety

Abbreviations: adj=adjuvant; CNS=central nervous system; CV=cardiovascular; DOR=Duration of response; HIV= human immunodeficiency virus; hx=history; IPF=idiopathic pulmonary fibrosis; IRF=independent review facility; neoadj=neoadjuvant; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PD-1=programmed death 1; PD-L1=programmed death ligand 1; PFS=progression-free survival; PK=pharmacokinetic; PRO=patient-reported outcomes; PS=performance status; RCT=randomized, controlled trial; TIR=Time in response; TTD= time to deterioration; TTR=time to tumor response

Appendix References:

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September 16, 2016

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel:

In response to the public comment period for the ICER draft report titled "Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value", please see the following recommendations on **Tarceva® (erlotinib):**

Include additional comparative data for Tarceva vs. gefitinib in the evidence report.

- There is a phase III, comparative, randomized, controlled trial (RCT) conducted to evaluate the safety and efficacy of Tarceva vs. gefitinib in patients with epidermal growth factor receptor positive (EGFR+) metastatic non-small cell lung cancer (NSCLC) that should be considered for inclusion in the study selection section [abstract enclosed] (p. 21).[1]

Utilize published literature to support scientific statements over expert opinion.

- The draft report states the following regarding ethnicity: "...we received input from various experts that once EGFR status is controlled for, ethnicity does not appear to be an effect modifier for [tyrosine kinase inhibitor] TKI treatment" (p. 35).
- Genentech has provided published references to the contrary on this topic in previous communications [see enclosed].[2-9]
- A thorough review and discussion of both the published literature and expert opinion should be conducted.

Clarify the rationale for selecting the source for adverse event (AE) information.

- In Table 15 of the Comparative Value section, the source of AE inputs varies across the TKIs (p. 59). The Tarceva AE rates were selected from the EURTAC study publication.[10] However, the gefitinib and afatinib AE rates were selected from the USPIs.
- A rationale should be provided for selecting AE rates from various sources.

Re-evaluate model assumptions on post-progression costs and therapies.

- In the post-progression costs shown in Table 17, different subsequent treatments and costs were used for TKIs and the comparator cisplatin-pemetrexed group (p. 61).
- The post-progression therapies should be the same regardless of the initial therapy so that there is no bias in the second-line treatment cost and effectiveness assumptions, and that the focus of the evaluation is on the initial therapy and not on the sequence of therapies.

- A clear rationale in the selection of post-progression therapies that is based on available real-world evidence and is supported by treatment guidelines should be provided.[11]

FDA Clearance:
Tarceva is FDA-approved for the following NSCLC indications:

- First-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test
- Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line therapy
- Treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Tarceva is not recommended for use in combination with platinum-based chemotherapy. Safety and efficacy of Tarceva have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.

Please refer to the product prescribing information for the full FDA-approved indications and safety information: http://www.gene.com/download/pdf/tarceva_prescribing.pdf

Dear Health Care Provider Letter:
http://www.gene.com/medical-professionals/medicines/tarceva

The following enclosures are included for your review (copyright-paid where applicable):

- Yang J, Zhou Q, Yan H, et al. A randomized controlled trial of erlotinib versus gefitinib in advanced non-small cell lung cancer harboring EGFR Mutations (CTONG0901). J Thorac Oncol 2015;10(9 suppl 2):S321.
- Genentech ICER NSCLC Tarceva Communication dated July 22, 2016.

We welcome the opportunity to provide clarification should ICER have questions on any of these points. Please contact me directly at eakle.mary@gene.com or (925) 321-2399.

Respectfully submitted,

Katherine Eakle, Pharm.D.
Managed Care Medical Communications
U.S. Medical Affairs, Genentech

References:

1. Yang J, Zhou Q, Yan H, et al. A randomized controlled trial of erlotinib versus gefitinib in advanced non-small cell lung cancer harboring EGFR exon 19 or 21 mutations

(CTONG0901). Presented at 16th World Conference on Lung Cancer in Denver, CO; September 6-September 9, 2015. WCLC Oral Presentation #16.13.
2. Soo R, Loh M, Mok T, et al. Ethnic differences in survival outcome in patients with advanced stage non-small cell lung cancer. J Thorac Oncol 2011;6:1030-1038.
3. Pilotto S, Maio M, Peretti U, et al. Predictors of outcome for patients with lung adenocarcinoma carrying the epidermal growth factor receptor mutation receiving 1st-line tyrosine kinase inhibitors: Sensitivity and meta-regression analysis of randomized trials. Critical Reviews in Oncology/Hematology 2014;90:134-145.
4. Ahn MJ, Lee J, Park YH, et al. Korean ethnicity as compared with white ethnicity is an independent favorable prognostic factor for overall survival in non-small cell lung cancer before and after the oral epidermal growth factor receptor tyrosine kinase inhibitor era. J Thorac Oncol 2010;5:1185-1196.
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10. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised Phase 3 trial [supplementary appendix appears online]. Lancet Oncol 2012;13:239-246.
11. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer V4.2016. Available at http://www.nccn.org. Accessed on September 16, 2016.

HOPA Hematology/Oncology Pharmacy Association

September 16, 2016

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft Evidence Report: Treatment Options for Advanced Non-Small-Cell Lung Cancer: Effectiveness, Value, and Value-Based Price Benchmarks

Dear Dr. Pearson:

On behalf of the Hematology/Oncology Pharmacy Association (HOPA), I would like to thank you for the opportunity to submit comments on ICER's *Draft Evidence Report: Treatment Options for Advanced Non-Small-Cell Lung Cancer: Effectiveness, Value, and Value-Based Price Benchmarks.* HOPA is a nonprofit professional organization launched in 2004 to help hematology and oncology pharmacy practitioners and their associates provide the best possible cancer care. HOPA's membership includes not just oncology pharmacists, but also pharmacy interns, residents, technicians, researchers, and administrators specializing in hematology/oncology practice. The roles of our membership span from direct patient care, to education, to research. HOPA represents more than 2,500 members working in hundreds of hospitals, clinics, physician offices, community pharmacies, home health practices, and other healthcare settings.

Hematology/oncology pharmacists play an important role in the delivery of care for individuals living with cancer—they are involved with the care of cancer patients at all phases of their treatment; from assessment and diagnosis, to treatment decisions, medication management, symptom management and supportive care, and finally with survivorship programs at the completion of their treatment. Additionally, oncology pharmacists work closely with patients and their families to ensure access to the medications that are part of a patient's treatment plan. As part of this work, oncology pharmacists are often faced with the challenge of helping patients overcome the high cost of many cancer therapies and other medications that are needed for quality cancer care.

The assessment of the appropriate sequence of treatment for non-small cell lung cancer (NSCLC) with newer agents, the role of certain tests to inform treatment decisions, and the management of the costs of these therapies is an important and necessary first step in considering the balance of clinical benefit and financial toxicity when making treatment decisions.

HOPA supports the study's aims and assumptions; the model is reasonable, utilizes trial level data, and recognizes the limitations of the data utilized to achieve the analysis that is needed to conduct more research on treatment options for NSCLC in order to improve patient care. We would like to offer the following comments and recommendations to the Draft Evidence Report:

Section 1: Background

- Future projects should include pharmacist(s) during the development stage.
- The ALK positive and squamous cell carcinoma populations should be factored in because both populations face similar challenges for what to recommend post progression.

Section 2: The Topic in Context

Populations and Therapies of Focus

- There should be an evaluation of the role of immunotherapy in the first line setting, specifically in populations 2 and 4.

Tyrosine Kinase Inhibitors (TKIs)

- The use of Cisplatin/Pembrolizumab to compare to the oral TKIs is appropriate.
- The proportional hazard model is appropriate in this setting of TKIs.
- There appears to be bias towards the clinical benefit of afatinib when compared to gefitinib.
- The impact of the PFS end point is under represented, especially since there is a high crossover rate seen in clinical trials.

PD-1 immunotherapy

- The use of docetaxel to compare to the PD-1 therapy is appropriate.
- Further comment on the RECIST criteria and the limitations of its use due to the delayed response to PD-1 would be beneficial to the document.
- The main bolded comments on overall survival appear to have a negative bias.
- A key missing point in the PD-1 section and analysis is the large (15-20%) proportion of patients who did not have testable tissue for PD-L1 expression in the pembrolizumab studies. The data are more difficult to find with nivolumab and atezolizumab, however, it is likely similar. The effect of this missing data would be to support the conclusion that testing is still of uncertain value. It also feeds into the economic modeling used to include testing.
- For PD-1 antagonism, the critical real world endpoint is OS rather than PFS due to the tail of survival curves and the immune response criteria in trials. The use of an in-house non-reviewed meta-analysis of PFS in EGFR mutated versus unmutated patients holds very little clinical/real world weight or value. Similarly, the use of ORR is clinically challenging for real world decisions for the same reasons. This is a major concern for this document.
- The conclusion that platinum based chemotherapy is preferred to PD-1 antagonism as next therapy in patients who are EGFR mutation positive and have failed TKI treatment is very concerning.

Section 3: Summary of Coverage Policies and Clinical Guidelines
HOPA believes that this is a sufficient summary of current guideline recommendations, but the National Comprehensive Cancer Network guideline descriptions for the four population groups are simplistic and do not provide all current options for second and third line therapies. We believe the report should mention that immunotherapies nivolumab and pembrolizumab are considered category 1 and also mention other available options that are FDA approved in this setting.

Section 4: Comparative Clinical Effectiveness

- HOPA acknowledges that clear criteria for study selection was defined and that the criteria were reasonable and appropriate for the purpose of the guideline.
- The report states that all patients had to submit tumor for PD-L1 expression, however it is important to highlight the percentage of patients that had non-interpretable PD-L1 expression from baseline.
- There are numerous assumptions with the modeling of the PD-1 inhibitors and while the authors account for that in the text, it remains uncertain how it will impact the results and may not be reliable information.

Section 6: Comparative Value

- The assumptions are not clear in how the costs were calculated.
- It would be beneficial to provide a reference to a standard or a baseline in order to compare the estimated cost of the analysis.
- The section on patient and family financial burden is much needed as it is a difficult issue that is rarely discussed or adequately assessed.

We hope that the recommendations above will improve the utility of the report in improving patient outcomes and controlling costs. We truly support the initiative by ICER to begin this important conversation to improve cancer patient care. Thank you very much for your consideration of our comments. If HOPA can be of any assistance to you, please do not hesitate to contact me or HOPA's Health Policy Associate, Jeremy Scott (202/230-5197, jeremy.scott@dbr.com).

Sincerely,

Sarah Scarpace Peters, PharmD, MPH, BCOP
President

P.O. Box 24083, New York, NY 10017 www.LungCAN.org

September 15, 2016

Steven D. Pearson, M.D., M.Sc., FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value – Draft Evidence Report

Dear Mr. Pearson:

The Lung Cancer Action Network (LungCAN), an association of 501(c)(3) nonprofit organizations advocating for and serving the lung cancer community, requests the invaluable patient voice be represented in the evaluation of cancer drugs that may ultimately benefit patients.

Moreover, LungCAN and our member organizations respectfully request that experts in the field of lung cancer be included in that analysis and that the process remains transparent throughout. We specifically request appropriate peer-review by lung cancer specialists (such as oncologists and thoracic surgeons) who are not associated with ICER or the pharmaceutical industry.

We strongly encourage ICER to continue to reach out to stakeholders, particularly patients, advocacy organizations and lung cancer clinicians, as they undergo the process of creating the model and in order to best represent how treatments are being used and what patients value. We are able and willing to assist in this process to help ensure that ultimate recommendations continue to provide access to proper care, based on the unique needs of each patient.

A primary and necessary consideration is the dramatic pace of change in the field of lung cancer diagnosis and treatment. This includes multiple treatments, sequencing of drugs, and combinations in development. The “standard of care” is rapidly evolving, including driver mutations and the use of biomarkers. The evaluation in comparing treatments, must therefore take into account how medicine is being practiced now and in the future. Given the recent introduction of immunotherapy in the treatment of lung cancer, and the

lack of long-term data, it would be premature to conduct a meaningful review, and thus make a value recommendation on this class of agents.

It is also imperative to recognize that lung cancer is not one disease, but rather a collection of many subsets of disease, giving health care providers the ability to tailor and personalize treatment regimens so that patients get the highest value drug for their cancer. Differentiation by histology and subpopulations should be addressed in order to allow for on-going personalized medicine, as well as reflect the changing treatment environment and biology of the disease.

Finally, in addition to quality-adjusted life year, other measures of quality, reflecting patient values and improving care must be considered. LungCAN looks forward to working with ICER to integrate perspectives of patients and families impacted by lung cancer in each step of the analysis to ensure they truly benefit from a more person-centered, affordable and goal-directed care.

Thank you for the opportunity to comment. If you have any questions, please feel free to contact us at info@lungcan.org.

Sincerely,

Bonnie J. Addario Lung Cancer Foundation - www.lungcancerfoundation.org

Caring Ambassadors Program, Inc. -www.caringambassadors.org

Free ME From Lung Cancer -www.freemefromlungcancer.org

Janet Freeman-Daily, lung cancer patient/activist at https://grayconnections.net/

To Dusty Joy Foundation (LiveLung) - www.LiveLung.org

Lung Cancer Alliance -www.lungcanceralliance.org

Lung Cancer Circle of Hope - www.lungcancercircleofhope.org

Lung Cancer Foundation of America -www.lcfa.org

LUNGevity.org - www.lungevity.org

Lung Cancer Initiative of North Carolina -www.lungcancerinitiativenc.org/

Rexanna's Foundation for Fighting Lung Cancer - www.rexanasfoundation.org

Upstage Lung Cancer -www.upstagelungcancer.org

LUNG CANCER ALLIANCE

SAVING LIVES AND ADVANCING RESEARCH BY EMPOWERING THOSE LIVING WITH AND AT RISK FOR LUNG CANCER.

LungCancerAlliance.org

1700 K Street NW, Ste 660
Washington, DC 20006

September 16, 2016

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

On behalf of Lung Cancer Alliance, the leading and most highly rated lung cancer charity in the nation supporting patients, advancing research, elevating awareness and advocating for improvements in our health care system that are responsive to and valued by all those living with and at risk for the disease, I thank you for the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) draft evidence report, *Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value.*

As we have presented in earlier exchanges, lung cancer is experiencing the most exciting scientific progress and groundbreaking developments ever seen in the field and moving at a rapid pace with more drugs approved to treat the disease in the last year and a half than in the previous ten. We know it is critically important to continue evaluating the ever-changing treatment landscape in order for patients to receive the therapies that they will benefit from most.

With the backdrop of this dynamic environment and at a time of rising health care costs, pressure will only increase on care access and affordability. How the value of individual patient care will be judged and whether these judgements will be applied in ways that ignore individual patient differences is of deep concern. Thus it is critically important that ICER's methods and standards used to judge the value of patient care -- be centered on those that are actually valued by patients and their caregivers.

While Lung Cancer Alliance appreciates ICER's attempt to evaluate the health and economic outcomes of certain tyrosine kinase inhibitors (TKIs) and programmed death 1 (PD-1) agents in the treatment of advanced non-small cell lung cancer, we have some concerns regarding the methods and practice of this assessment.

1. ***All recommendations in the above mentioned report regarding PD-1 immunotherapy agents are premature.*** The scientific questions for these agents far outnumber what we know in terms of treating lung cancer. We need to work through those questions before we do any value assessments. The science still needs to identify the right patient population for these drugs, which will, in turn, improve the value. Long term follow-up has not been completed on those who have taken the agents. Tyrosine kinase inhibitors (TKIs) have been approved and in use for over a decade. The same consideration should be given to the PD-1 agents.
2. ***Non-Food and Drug Administration (FDA) approved PD-1 immunotherapy agents, whether it be for a certain indication or as a treatment at all, should be removed from the analysis in the above***

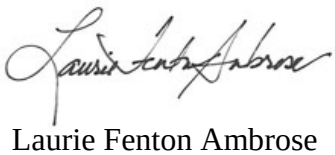
mentioned report. As mentioned above, the data for the PD-1 agents that are approved by the FDA is still too premature to make any recommendations on value and effectiveness. For those PD-1 agents not FDA approved, we do not even have the data needed to make a determination on approval, let alone value.

3. ***The transparency is poor on the assumptions, methods and results for the above mentioned report.*** A key example would be the non-use of figure legends to explain the derivation of the figures throughout the report. In order for the results to be duplicated, the methods need to be made transparent. Because of these gaps and challenges it is important for ICER to consider integrating perspectives of patients and organizations impacted by lung cancer to better reflect and protect the value of patient needs.
4. ***The above mentioned report should be held to the same standards as other clinical research* in the field that determines public health policies and access to care.** The report should be peer reviewed by lung cancer experts independent of ICER who use these drugs on a daily basis. Their scientific knowledge and experience will address some of the issues to promote effective care and outcomes that both patients and the public value.
5. ***At least one, if not more, lung cancer survivors and loved ones should be added to the Comparative Effectiveness Public Advisory Council (CEPAC).*** Modeling and reviewing clinical trials can lead to conclusions, but in many cases, the real life impact of these drugs cannot be ignored as affordability and access to the highest value drug for lung cancer and therefore the perspective from those survivors and loved ones living with lung cancer each and every day should play a critical role in the report findings.

We strongly believe that misapplied assessments and value judgments could set progress back in tripling survivorship of lung cancer and therefore it is most appropriate that care and treatment be left to the patient and their medical provider.

I appreciate your consideration of the views and concerns above and look forward to an open, forthcoming dialogue surrounding your report.

Sincerely,



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LUNGEVITY
Find it. Treat it. Live.

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,

Andrea Stern Ferris
President and Chairman
LUNGevity Foundation

cc:
Sonya Khan
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To: Steven D. Pearson, M.D., M.Sc. FRCP
President, Institute for Clinical and Economic Review

Dear Dr. Pearson,

Merck values the opportunity to comment on ICER's draft evidence report on the cost-effectiveness and value of treatment options for advanced non-small cell lung cancer (NSCLC). We appreciate the effort by ICER to create an evidence report to evaluate the clinical and economic value of different treatment strategies for NSCLC. ICER's report represents an important voice in the discussion of novel agents in NSCLC. Merck welcomes further discussion related to ICER's report, as well as alternative analyses on the cost effectiveness of pembrolizumab, such as this peer-reviewed analysis recently published in the *Journal of Medical Economics*: http://www.tandfonline.com/doi/abs/10.1080/13696998.2016.1230123. We ask that ICER include a discussion of this paper (described below) in its final report.

The value of immunotherapy in cancer should be understood in the context of its approved uses. Pembrolizumab is a programmed death receptor-1 (PD1)-blocking antibody currently approved in the United States for the treatment of: (1) patients with unresectable or metastatic melanoma; (2) patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy; and (3) patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Merck believes strongly in the value of pembrolizumab when used in accordance with FDA-approved uses.

We agree with certain elements of ICER's report. We are encouraged by ICER's acknowledgement of the uncertainty in the estimates of cost effectiveness of PD1 inhibitors, in part driven by uncertainties in the inputs used by ICER. We agree with ICER's suggestion that their report not be used to compare the efficacy of PD1 inhibitors to each other. ICER also acknowledges the lack of comparability of the study populations across PD1 clinical trials reported to date. We would note that there is additional data forthcoming in advanced NSCLC that may further inform the value of immunotherapies, including data in first-line NSCLC.

Although we are encouraged by aspects of the report we do want to raise a number of concerns and suggestions. We believe ICER should:

- Endorse population-based screening of PD-L1 among all patients with advanced NSCLC;
- Separately report a PD-L1 positive (tumor proportion score [TPS]>=50%) population as a main economic analysis, which would be consistent with the pembrolizumab's FDA label for advanced NSCLC;
- Use health-state utilities measured directly from the KEYNOTE 010 clinical trial to better reflect US patient experiences with PD1 inhibitors in NSCLC;
- If combining heterogeneous clinical trials into a single network analysis, ICER should adjust for resulting confounding resulting from differences in demographics and in the performance of the docetaxel control arm across these trials;
- Calculate a value-based price for pembrolizumab that fully accounts for ICER's analyses, including the fact that the budget impact of pembrolizumab is projected to be well below ICER's acceptability threshold.

Biomarker Screening

Non-small cell lung cancer patients often present with advanced disease, and treatment decisions are complex. Pembrolizumab has demonstrated clinical benefit for 2L or later NSCLC patients in patients whose tumors express PD-L1 (pembrolizumab is currently indicated for patients with TPS>=50%). The phase 1B, single-arm, KEYNOTE-001 trial showed that in NSCLC patients previously treated with platinum-based chemotherapy, higher levels of PD-L1 expression correlated with increased overall response rates to pembrolizumab.[1] An update of the KEYNOTE 001 trial by Hui et al., which was recently presented at ASCO 2015, distinguished response rates by PD-L1 status in both previously treated and treatment-naïve patients. The analysis demonstrate an objective response rate (ORR) of 47% (95% CI 23%-72%) in patients with TPS>=50%, 19% (95% CI 8%-38%) in patients with TPS = 1%-49%, and 14% (95% CI 0.4-58) in patients with TPS < 1%. Furthermore, in the phase 2/3 KEYNOTE-010 trial, which randomized NSCLC patients who were PD-L1 positive (TPS >1%) to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel, hazard ratios (HRs) for overall survival improved among patients with higher levels of PD-L1 expression, (HR= 0.71, 95% CI, 0.58–0.88; p=0.0008 for pembrolizumab 2 mg/kg vs. docetaxel) with a median overall survival of 10.4 months with pembrolizumab 2 mg/kg vs. 8.5 months with docetaxel.[2]

Beyond the clinical benefit associated with biomarker screening, a recent peer reviewed manuscript published in the *Journal of Medical Economics* demonstrates the cost-effectiveness of pembrolizumab in a PD-L1 positive (TPS>=50%) population versus doxcetaxel.[3] Like ICER's analysis, this model was a cohort simulation with three mutually exclusive health states: Progression-free state (PF), Progressive disease state (PD) and Death. The model utilized a partitioned-survival approach to estimate progression-free survival (PFS) and overall survival (OS) endpoints. Unlike the ICER analysis, this analysis directly measured cost effectiveness using clinical trial data from KEYNOTE 010, which randomized patients to pembrolizumab or docetaxel. This analysis did not use a network of multiple trials, because this was not necessary to compare pembrolizumab to the comparator of interest, docetaxel. The base case results estimated a mean survival of 2.25 years for pembrolizumab vs. 1.07 years for docetaxel, with quality adjusted life years (QALYs) of 1.71 and 0.76 for pembrolizumab and docetaxel, respectively. The incremental cost per QALY gained with pembrolizumab versus docetaxel was $168,619/QALY, which is cost-effective in the US using a threshold of three times GDP per capita. This is also similar to ICER's published threshold of $150,000/QALY. The findings of this analysis should be acknowledged in the ICER final evidence report.

ICER's draft evidence report also demonstrates the value of biomarker screening. A deterministic sensitivity analysis around a PD-L1 expression threshold of >50% clearly demonstrates the significant role that PD-L1 expression has on producing positive outcomes for pembrolizumab ("near doubling of overall quality-adjusted survival"). By limiting the pembrolizumab model population to a TPS >=50%, the incremental cost effectiveness ratio calculated by ICER was reduced by approximately $30,000/QALY.

Based on the above evidence and the consistent recognition the importance of biomarkers within the ICER report, we ask ICER to do the following:

- In recognition of the improved efficacy, cost effectiveness, and budget impact associated with PD-L1 screening, ICER should endorse population-based screening of PD-L1

among all patients with advanced NSCLC who are being considered for PD1 therapy. While it is up to clinicians and patients to make decisions with respect to treatment, PD-L1 data may lead to more efficient use of health system resources. This is consistent with ICER's stated goals, and is a needed message from ICER, given that a minority of NSCLC patients is currently screened for PD-L1 status at diagnosis or any time in their treatment journey. By doing so, ICER would be taking a leadership role in demonstrating to population-based decision makers how to maximize the value of available treatment options.

- Given that ICER has stated that PD1 inhibitors should only be compared with docetaxel, and not to each other, we ask that pembrolizumab be excluded from ICER's network meta-analysis. KEYNOTE 010 data is sufficient by itself for ICER's stated goal of comparing pembrolizumab's cost effectiveness to docetaxel's. Network meta-analyses should only be employed when attempting to compare agents that were not directly compared within the clinical trial setting.
- Pembrolizumab results should not be reported in the same table as nivolumab and atezolizumab as pembrolizumab is approved in a PD-L1 positive population (TPS>=50%). By including pembrolizumab and nivolumab results within the same table, confusion may be created on whether these drugs are approved in the same patient populations. Atezolizumab is also yet to be approved for NSCLC, and it is not clear at this time if it will be approved with a requirement for a companion PDL-1 biomarker, or if it will be approved in an unselected population, like nivolumab.
- An analysis of pembrolizumab in PD-L1 positive patients (TPS>=50%) should appear separately from other agents, and should be the main analysis for pembrolizumab. Currently, an analysis of this population exists as a sensitivity analysis within the appendix of the evidence report. However, it is reasonable to acknowledge the importance of the regulatory status of pembrolizumab by including this in the main results, given this is the indicated use. ICER should also ensure that the duration of therapy assumed is consistent with the FDA label of pembrolizumab.

Health State Utilities

A number of patient advocacy groups have noted their concerns that utilities may be an imprecise way to measure the full experience of NSCLC. Utilities play an essential role in QALY estimation. If not carefully chosen, utility inputs may lead to an underestimation of the true cost effectiveness of newer interventions. The ICER draft evidence report in NSCLC provides an example of this.

ICER applies utilities for second line therapy in their model from Nafees et al (health state utility of 0.47), which is a widely-used source for NSCLC utilities in the cost-effectiveness literature. However, we would point out that since subsequent to this research, advances in the treatment of advanced NSCLC may have increased the quality of life for patients at baseline. This may affect utility estimation for second line therapy. The research in Nafees et al was conducted before any PD1 immunotherapies were used in NSCLC. Given the differing safety profiles of chemotherapies and immunotherapies in NSCLC, it is reasonable to expect that the patient utilities associated with these agents may not be the same.

Furthermore, Nafees et al derived utilities using data exclusively from non-US populations, which may have affected the outcome of ICER's model, as recent research demonstrates vast variation in utilities for NSCLC by country for "stable disease and no side effects" (0.84 UK to 0.54 Taiwan).[4]

In the KEYNOTE 010 trial, for example, we observed considerably higher baseline utilities in a US population for advanced NSCLC patients, compared to the utilities reported by Nafees et al. In KEYNOTE 010, the EQ-5D questionnaire was administered at treatment cycles 1, 2, 3, 5, 9, 13 and every four weeks, as long as patients were on study treatment, and at both the treatment discontinuation visit and 30-day post treatment safety follow-up visit. The generic health statuses assessed from the EQ-5D questionnaire were converted to population-based utility values using published algorithms. For the base case analysis in KEYNOTE 010, US-based scores were applied to US patients, UK-based scores for UK patients, and EU-based scores for all other patients. Utilities were similar in pembrolizumab and docetaxel treatment groups at baseline, so a pooled approach was used. This approach yielded a utility score of 0.761 for the progression-free and a score of 0.687 for the progressive disease health states, respectively. We have also previously provided treatment-specific utilities to ICER as measured directly in KEYNOTE 010.

The utility evidence from KEYNOTE 010 represents a more recent measurement of advanced NSCLC patients' utility associated with immunotherapy treatment and includes data from US patients. Based on this evidence, we would request that the KEYNOTE 010 utility data be used as we feel it will provide an accurate representation of patient utility in advanced NSCLC.

Network Meta-Analysis

As stated above, we ask that pembrolizumab be excluded from ICER's network meta-analysis. KEYNOTE 010 data is sufficient by itself for ICER's stated goal of comparing pembrolizumab's cost effectiveness to docetaxel's.

Given that a network meta-analysis was performed, we are pleased that ICER emphasizes caution in interpreting its results. ICER states that the "primary interest is on the incremental outcomes, cost, and cost-effectiveness of each PD1 inhibitor in relation to docetaxel not on comparisons between the PD1s themselves.")

We do not believe that ICER adequately addresses the issue of heterogeneity across trials with its network meta-analysis. In ICER's draft analysis, the projected curves for all PD1 inhibitors are modeled from an average docetaxel curve. Thus, if the HRs of docetaxel differ substantially across trials, there is the potential of introducing bias and adjustment methodologies should be employed. Guidelines for network meta-analyses emphasize the importance of evaluating the heterogeneity in the results of different trials.[5] In addition, it has been noted that there was a lower OS for docetaxel (6 mos.) in CHECKMATE 017 vs. historical trials (7.4-8.7 mos.) in second line squamous NSCLC that will impact the results of the network meta-analysis.[3,6-9]

Based on the potential bias associated with the docetaxel HRs, we would like to suggest that ICER consider conducting a sensitivity analysis that uses the constant HR assumption, and that ICER include this sensitivity analysis in the report so that the average docetaxel measure used for comparison in the model is more transparent or adjust for demographic differences in their analyses.

Merck also believes that ICER should acknowledge in its report that the level of evidence incorporated in the network meta-analysis is not the same across immunotherapies reviewed. Phase 2 clinical trials employ smaller sample sizes and often a narrower population selection, where patients may be more likely to respond than in Phase 3 trials. It is possible that network meta-analysis results would be different if the level of evidence incorporated was uniform. This limitation should be acknowledged.

Lastly, while the appendix of the evidence report included multiple curve fitting methods, ICER does not explain how it chose among these curves for incorporation within the network meta-analysis. ICER should provide this explanation in its report, and provide multiple cost effectiveness results based on the use of these different methods. A sensitivity analysis that shows how results would change if different curves are accepted into the model would allow the consumer of the information to better understand the impact of the different methodologies on the model results.

Budget Impact and Value-Based Price Analysis

As detailed in their report, ICER's budget impact model estimates a budget impact of $164.6 MM over 5 years, which is well below the $904 MM per year threshold for a new drug that ICER sets to trigger policy actions to manage affordability. We believe ICER assumes a relatively low uptake of pembrolizumab. We would encourage ICER to compare a scenario where patients are treated with an indicated PD1 inhibitor regardless of PD-L1 status ("all comers") versus a scenario where only PD-L1 positive patients are treated with a PD1 inhibitor ("biomarker enriched".) We believe such an analysis would provide additional supporting evidence for the use of PD-L1 screening in advanced NSCLC.

We would also encourage ICER to consider pembrolizumab's budget impact as a contextual consideration when calculating a value-based price. Budget impact is critical to understanding the affordability of new drugs to health systems. The draft evidence report acknowledges that pembrolizumab's budget impact is well below ICER's established threshold. ICER has stated that its value-based price recommendation is intended to be an integration of both cost-effectiveness and budget impact considerations. We believe that pembrolizumab's budget impact should be incorporated in this recommendation. We also believe that the budget impact results should be a part of the overall summary of the evidence report. Discussion of budget impact should not be confined only to the body of the report.

Summary

Again, we appreciate the opportunity to comment on ICER's draft evidence report for the cost-effectiveness and value of treatment options for advanced NSCLC. We understand that several controversies exist in defining the value of innovative therapies in the United States. We appreciate ICER's efforts in adding their voice to this conversation. We welcome further discussion of these important issues.

Sincerely,
Ravinder Dhawan, Ph.D.
Merck Center for Observational and Real World Evidence (CORE)

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Pfizer Inc
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September 16, 2016

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted via email: publiccomments@icer-review.org

RE: Comments on ICER's draft evidence report for non-small cell lung cancer

Dear Dr. Pearson,

On behalf of Pfizer Inc, I am pleased to submit this letter in response to the call for comments issued by the Institute for Clinical and Economic Review (ICER) with respect to its draft evidence report for non-small cell lung cancer.[1] We appreciate your willingness to solicit feedback from all stakeholders with respect to ICER's framework for value assessment.

As a leading biopharmaceutical company, Pfizer is dedicated to the discovery and delivery of high value therapies across a variety of disease areas. Our scientists have and continue to make significant contributions to medical research, and we strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products.

Pfizer believes it is important to establish a broadly validated approach using the most appropriate methodologies for evaluating the Care Value and Health System Value of any new medicine or device. This is an essential step in increasing the likelihood that results are robust, accurate and can be independently verified. We recommend that presentation of the methodology, inputs, and results of ICER's assessments should follow accepted guidelines (such as CHEERS[2]) to allow appropriate review of the model results; this applies particularly to provision of input parameters and modeling of uncertainty.

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[1] Institute for Clinical and Economic Review. Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value, Draft Evidence Report. Available at: https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_ Draft_Evidence_Report_081916.pdf. Accessed September 14, 2016.
[2] International Society for Pharmacoeconomics and Outcomes Research. Health Economic Evaluation Publication Guidelines (CHEERS): Good Reporting Practices. Available at: http://www.ispor.org/Health-Economic-Evaluation-Publication-CHEERS-Guidelines.asp. Accessed September 12, 2016.

Our specific comments on the draft report focus on the economic evaluation for first-line EGFR-mu patients (referred to in the ICER report as the P1 population).The objective of the evaluation was to assess the cost effectiveness of tyrosine kinase inhibitor (TKI) versus chemotherapy, as represented by the chemotherapy doublet cisplatin plus pemetrexed (CIS-PEM).

In the draft evidence report, ICER appropriately recognizes that the lack of overall survival (OS) gain shown in TKI trials versus chemotherapy is explained to a significant degree by extensive crossover to TKIs in the trials. While we recognize why ICER sought to model an OS gain in order to develop a more robust cost-effectiveness evaluation, use of the modelled results in the base case analysis to assess the cost effectiveness between the TKIs is not a best practice.

The majority of the evidence on efficacy, tolerability and quality of life come from trials comparing TKIs versus chemotherapy, not from trials directly comparing TKIs. Hence, there is uncertainty around the comparative effectiveness of the TKIs. However, the LUX-Lung 7 trial (LL7) provides evidence suggesting that 2nd generation TKIs may be more effective, as an improvement in progression-free survival (PFS) was shown.[3] Overall survival data was not fully available in the LL7 study, but the hazard ratios (HR) in the trial suggested that afatinib offered strong benefits.

We note that meta-analysis results presented in tables D2 and D4 of the ICER report also provide evidence of OS differences between the TKIs.[1] Even though the HRs in the table are not statistically significant, using these estimates in a cost effectiveness model would lead to different results when comparing the cost effectiveness between TKIs as compared to the base case model that assumes a TKI class effect on OS. The class effect assumption artificially cuts OS for treatments with a PFS gain which contradicts a likely positive relationship between PFS and OS.

We also note that the incremental cost-effectiveness analysis shows lowest benefits for gefitninb vs. CIS-PEM compared with the other TKIs (table 18b of the ICER report). However, for gefitinib this is explained by shorter time spent in the progression free health state and as a consequence, lower drug and PFS supportive care costs, while still having the same OS benefit, and therefore life years gained as the other TKIs (table 18a of the ICER report).

The scenario analysis in which the OS benefit of the TKIs is turned off does not provide valid results and significantly underestimates life years, QALYs and the cost effectiveness of TKIs.

ICER provides a scenario analysis (scenario 1a, table F11 in the report) where the class effect gain in OS, equal to 8.9 months, is eliminated. To model OS, it seems ICER used the same survival curve for CIS-PEM as in the base case analysis and OS HRs from the TKI trials that where significantly affected by crossover. Two key issues arise here:

[3] Park K, Tan E, O'Byrne K et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577-89

- The CIS-PEM curve used in the base case analysis is from a trial without any TKIs included, and does not reflect any TKI benefit. The challenges of using the base case CIS-PEM OS curve is seen in the results where the modelled median OS estimates ranges between 10.8-13.4 months – a stark difference against the TKI trials where median OS is close to or beyond 2 years in both the TKI and the CIS-PEM arms. Hence, this assumption underestimates life years and QALYs for all treatment arms including the CIS-PEM arm.

- If an OS curve from one of the TKI trials is used in the scenario analysis, which would be more appropriate, the analysis must also include the drug costs for the share of patients who crossed over to TKIs in 2nd line in the CIS-PEM arm. To not do so would significantly underestimate the cost effectiveness of TKIs compared to CIS-PEM.

In summary, the scenario analysis does not provide reliable results for a comparison of the cost effectiveness of the TKIs versus chemotherapy. As such, the analysis should not be used to explore hypothetical impacts of targeted NSCLC therapy, as intended by ICER.

Closing remarks

We at Pfizer are pleased to have the opportunity to submit these comments for your consideration as part of the NSCLC draft evidence report. We remain very interested in ICER's approach to value assessment, and hope that our comments are useful as the organization seeks to revise its draft report. We would welcome an opportunity to discuss our comments with you in additional detail.

Kind regards,

Sachin Kamal-Bahl, PhD
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