Treatment Options for Advanced Non-Small-Cell Lung Cancer: Effectiveness and Value

Summary of Public Comments Received on Initial Draft Report and ICER Response

The Institute for Clinical and Economic Review (ICER) values the opportunity to receive and respond to public comment on its work products by interested stakeholders. There were 15 sets of stakeholder comments submitted in response to the initial draft Midwest CEPAC report on treatment options for advanced non-small cell lung cancer that was posted on August 19th, 2016. Below is a summary of the major comments received as well as responses from the ICER team and its research collaborators, including any major changes made to the report.

We also received a number of comments asking for language clarification and/or corrections in our draft report. While not summarized in detail here, we have adjudicated each stated concern and revised our report and analyses accordingly.

Overarching Concerns

- We received multiple comments suggesting that a review of PD-1 immunotherapies is premature. These therapies are available and being prescribed by doctors, administered to patients, and charged for by manufacturers outside of clinical trials. These activities would be ethically questionable if it were not possible to evaluate the comparative effectiveness of the therapies. We agree that over time more information will become available and the drugs may be administered in different ways, including, perhaps, in combinations of immunotherapies. All of ICER's evaluations of therapies recognize that additional information is likely to become available in the future, but patients and doctors are being asked to make decisions based on the evidence that is available right now.
- Several groups questioned the makeup of the Midwest CEPAC panel, requesting that the panel have patients with lung cancer and expert lung cancer clinicians included. The intent of the panel is for a single group to be able to assess multiple therapies and diseases. As such, rather than creating a new panel for each report, input is provided to the panel from domain experts, patient groups, and patients, among others. We also note that our report was peer-reviewed by two individuals with domain expertise in lung cancer and lung cancer modeling.
- We received several comments suggesting that we had not adequately included patient concerns about the side effects of chemotherapy and the benefits of newer regimens. This is incorrect. For example, the rating of evidence for the TKIs reflected the clear evidence of benefit on side effects, despite uncertainties about improvements in OS.

- We received several comments asking how the input from patients about considerations not included in the trial data were incorporated. These were reported in the section "Insights Gained from Discussions with Patients and Patient Groups", and a number were reiterated in the section "Other Benefits or Disadvantages". These will inform the Midwest CEPAC panel's discussion of contextual and other qualitative considerations within the ICER Value Framework.
- We received a number of comments around transparency of the decision model in the interest of reproducibility of results. We agree that model transparency is of utmost importance and have added additional material in the final version of the report. The draft report modeling was subject to change based on concerns raised during the public comment period.

Comparative Clinical Effectiveness

- We received a comment raising concerns about our combining platinum doublets that used pemetrexed with those using other agents. While we agree that there is evidence for the greater efficacy of pemetrexed, we had inadequate evidence to perform an NMA separating these regimens, and given the lack of OS benefit seen in the trials of TKIs, we do not believe this would have affected our ability to assess the relative efficacy of the TKIs.
- We received two comments about the use of bevacizumab in combination with platinum doublet regimens for NSCLC. We had received expert input that this remains an area of controversy, however have added mentions in the report of bevacizumab as an option for some patients with non-squamous NSCLC.
- We received comments that afatinib had shown an OS benefit in a combined analysis of two trials, and that in the Del19 mutation subgroup it showed an OS benefit in each trial. As discussed in the report, had we used these HR assumptions, we would have assumed a smaller OS benefit for afatinib than what was actually assumed for the group as a whole, and would have concluded that afatinib worsens survival in patients with the L858R mutation. We thought both of these were unlikely, and so applied the overall OS effect assumption to afatinib and the other TKIs. We also received comments that given the head-to-head evidence on afatinib vs. gefitinib that we should adjust the OS benefit for afatinib. As discussed in the report, we think, given the PFS results, there are reasons to suspect that afatinib might have additional OS benefits beyond those seen with gefitinib, but the current evidence base is inadequate to estimate the size of this effect, if any.
- We received a request from a manufacturer to perform an analysis of nivolumab at a PD-L1 cutoff of ≥50% based on unpublished evidence they provided from one of the two clinical trials of nivolumab. We have concerns about including evidence from only of the trials, and so have chosen not to perform such an analysis. Even if we had evidence from trials of all three PD-1 immunotherapies at a ≥50% cutpoint, we would not feel the groups were comparable given differences between the assays.
- We received a comment about the proportion of patients who have tumor tissue that cannot be assessed for PD-L1 levels. We have added a sentence about this issue.

Cost-Utility Model

- We received a comment regarding the impact of low-grade and/or low frequency adverse events (side effects) and our decision to exclude them from the analysis. Although this is an appropriate consideration, from a practical standpoint we are limited to modeling the data that are available. As is true for many treatment regimens for a wide array of health conditions, the complete report of adverse events is frequently omitted from publicly available information.[1] Often, only those adverse events that meet an arbitrary cutoff (e.g., occurring in >5% of patients) are reported. Furthermore, the frequency and cost of low-grade and/or low frequency side effects are unlikely to have much if any impact on the overall results, and modeling what is not known adds more speculation to the modeling process. Consistent with the overwhelming majority of decision models in the published literature, we omitted low-grade and/or low frequency adverse events.
- We received a comment that we do not include costs associated with comprehensive treatment, such as supportive care. We do include supportive care costs for both the progression-free/treated and progressed disease health states.
- We received comments that the 8.9 month OS assumption was invalid and should not be included in base case results. The goal for this analysis was to model chemotherapy doublet (without crossover) compared to TKIs. While data-driven estimates are always preferable, the modeling of the comparison between TKIs and chemotherapy doublet was not possible without making this simplifying assumption to address the crossover issue. We have made clear throughout the report that the results derived from this assumption should be interpreted cautiously.
- A number of comments requested that we use the labeled indications for PD-L1 drugs in base case analyses. We agree, although this requires an assumption about what the atezolizumab label will state. The final modeled base case populations are (1) atezolizumab TC2/3 or IC2/3, (2) both PD-L1 negative and positive patients (all comers) for nivolumab, and (3) PD-L1 positive (≥50%) only for pembrolizumab. We have included the subpopulations for (a) atezolizumab 1/2/3, (b) nivolumab PD-L1 ≥10%, and (c) pembrolizumab PD-L1 ≥1% as scenario analyses.
- We received a request from a manufacturer to utilize utilities from their recent clinical trial, stating they were newer and more reflective of a U.S.-based population and of advances in NSCLC treatment. As was pointed out in that comment, the Nafees et al. utilities used in the second-line setting are the most widely-used in NSCLC CUAs. In addition, the Nafees et al. study is specific to second-line patients. To be fair to all of the second-line comparators, we used the same utility estimates regardless of drug, and we believe Nafees et al. to be the most representative choice in this regard. Furthermore, the utility scores from KEYNOTE-010 had internal inconsistencies such as the study's findings that PF disease off-treatment had lower utility than PF disease on-treatment. Also, these second-line utilities more closely resemble the utilities typically used in first-line evaluations. Given these concerns, we opted for the more widely-held approach.
- A manufacturer commented that the issue of heterogeneity was inadequately addressed in the NMA, thus biasing the results versus docetaxel. We have now used the NMA HR from trials as a scenario analysis. For our base-case results, we have directly fitted Kaplan-Meier estimates from the trials with time-varying HRs. Also, our comparison of each PD-1 immunotherapy agent is

with docetexal and not with each other. We have also included a new scenario analysis with the proportional hazard assumption throughout.

- We have added additional details on curve fitting and generation of time-varying hazard ratios. We have also provided illustration of our Kaplan-Meier data digitized from trials along with our curve fits. The current model takes a data-driven approach to fit two-phase proportional hazards models. Of note, we do not think a cure fraction model is appropriate or can be accurately estimated here since long term data, especially post-"kink" in the survival curve, are not available at this point.
- We agree with comments that additional transparency was necessary in our estimation of post-progression treatment costs. We have re-evaluated the approach to post-progression cost and have updated the cost per week in the model. An explanation of the new approach appears in the report.

1. Golder S, Loke YK, Wright K, Norman G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. *PLoS medicine.* 2016;13(9):e1002127.