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 14 sets of stakeholder comments submitted in response to the initial draft Midwest CEPAC report on treatment options for relapsed or refractory multiple myeloma that was posted on April 7th, 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

- The ICER report was criticized as failing to recognize that multiple myeloma is not a single disease with perfectly homogeneous patient populations. We fully concur that patients with multiple myeloma have many different combinations of clinical characteristics, genetic profiles, and personal values regarding risks for different side effects and the trade-offs involved in considering different treatment options. In some ways this is true of any medical condition. But we still believe that examination of the best existing evidence can provide insights that will prove useful to patients, clinicians, and payers. We have provided further clarification and context on this issue in the report. In addition, we have emphasized that we always seek evidence for key patient subgroups, and we hope our report will add further weight to calls for new evidence that can elucidate the treatment regimens that are appropriate for specific types of patients.

- We received several comments suggesting that the review should have focused not on the most appropriate regimen to use for relapsed or refractory disease, but the sequence in which available regimens should be applied. We agree that this is an important evaluation to make and look forward to the receipt of future evidence to support such comparisons.

- Our review was also criticized as premature, stating that more data are required before definitive analyses can be made. We recognize that there are gaps in currently-available
evidence and that more data are likely to emerge over time, but patients, clinicians, payers, and other stakeholders also need to make decisions now, based on the best available evidence.

- The report was criticized as lacking detailed input about the patient experience. ICER’s process includes formal outreach to patient groups and advocacy organizations for input, beginning with the scoping process and continuing through report generation and the public meeting. For this topic, we have benefited from specific patient input on the most important outcomes, other benefits and disadvantages of new treatment options, and the current context around management of multiple myeloma, including the important advances in survival seen with the introduction of new treatment options. We have updated the report to clarify these considerations where relevant.

- Several groups recommended that we consider other dimensions of care important to patients, such as valuation of quality of life over its length and consideration of low-grade, chronic side effects. We have added further context to the report to address these concerns and have juxtaposed them against what is measured in the available evidence.

- Our report was criticized as being at odds with the idea of personalized medicine—that treatment pathways should be customized to an individual patient’s needs and clinical profile. Our approach to evidence analysis included identification of data that might demonstrate superior clinical benefits for a particular type of patient. Unfortunately, this information is largely lacking in the existing evidence. We look forward to the generation of new evidence that can support the implementation of more customized treatment.

- Commenters also noted a lack of clarity around how ICER arbitrates dissenting votes of its public panels as well as the extent to which dissent occurs. Our final report includes a chapter summarizing the votes taken (including dissenting votes), panel members’ stated rationale behind both positive and negative votes, and a summary of the roundtable discussion and key recommendations.

**Comparative Clinical Effectiveness**

- Several commenters challenged our use of two-drug regimens (i.e., lenalidomide or bortezomib in combination with dexamethasone) as comparators to the newest regimens, stating that three-drug regimens are now preferred for second- and third-line treatment. We recognize that therapy continues to evolve beyond FDA-indicated treatments; however, the comparators in our evaluation represented those employed in the Phase III trials of the regimens of interest, and
continue to be listed as preferred regimens with category 1 evidence in NCCN guidelines. We welcome the opportunity to review head-to-head evidence comparing the newest three-drug regimens when such data are made available.

- Our evidence rating for pomalidomide+dexamethasone (“promising but inconclusive”) was criticized, as the commenter felt the same rationale for excluding it from our network meta-analysis (more advanced disease in the trial population relative to other regimens) should have been used to withhold an evidence rating. However, our rationale for the rating was based on our judgment of a modest net health benefit as well as a comparator regimen not in current use, so the rating remains unchanged.

- The evaluation of panobinostat+bortezomib+dexamethasone was found to be confusing by some, given that the Phase III trial was conducted in a broader population than the subgroup that ultimately received FDA approval. We have updated the report to clarify these distinctions. Our evidence rating for this regimen was also challenged given that we rated the Phase III study to be of good quality. However, the ICER evidence rating is based on a judgment of the overall strength of evidence, not solely on the quality of the underlying studies.

- The use of log-transformed hazard ratios as well as older lenalidomide+dexamethasone data in our network meta-analysis was criticized as methodologically inappropriate and inaccurate. We have added sensitivity analyses to address these concerns for both the evidence review and the cost-effectiveness model. For the evidence review specifically, we followed the methods of Ouwens and colleagues, using all available data from progression-free survival curves and developing time-dependent hazard ratios. We also conducted a separate version of this analysis using only lenalidomide-dexamethasone data from the newest trials of carfilzomib, elotuzumab, and ixazomib. In all cases, findings did not materially differ from those of our original analyses, and therefore did not trigger any changes in evidence ratings.

- It was also mentioned that, since progression-free survival among patients randomized to lenalidomide+dexamethasone varied substantially across trials, heterogeneity in patient populations must have been present. In fact, median progression-free survival for comparator treatment was similar in the trials of elotuzumab and ixazomib (14.9 and 14.7 months respectively), over a median of approximately two years of follow-up. Progression-free survival for lenalidomide+dexamethasone was longer in the carfilzomib trial (median: 17.6 months), but follow-up was also longer (median: 31.5 months). In addition, as described in our original report, we examined baseline characteristics from published studies, conference proceedings,
and FDA submissions, and found that populations were generally comparable along the dimensions available to us. The two exceptions were the pomalidomide+dexamethasone and the daratumumab trials, which involved patients with more advanced disease. We note this in the report and exclude these regimens from quantitative comparisons.

**Comparative Value**

- As noted above, our approach to network meta-analysis, which informed the cost-effectiveness analysis as well as the evidence review, was criticized and a suggestion was made to base our evaluation on head-to-head trial data. We have already noted in the report that, because of our use of a fixed-effects model, the estimates of treatment effect in the model were highly consistent with those observed in each clinical trial. With respect to the use of older comparative data to inform the model as described above under “Comparative Clinical Effectiveness,” we have added a scenario analysis in which progression-free survival with lenalidomide+dexamethasone is adjusted to reflect the data seen in the most recent clinical trials. Model results were similar to those seen in primary analyses.

- Some commenters felt that we underestimated quality-of-life benefits for the newest regimens by not explicitly incorporating differences between these regimens and their comparators in such measures from available clinical trials. As noted in the initial report, quality-of-life data have not been reported for all regimens of interest, which limited our ability to incorporate differential estimates. The model does incorporate different utility values for on- and off-treatment periods in the pre-progression health state as well as a disutility for adverse events. In this way, the average utility score during the pre-progression health state is differential between treatment arms. We have also added a scenario analysis in which we used differential utility scores for triplet vs. doublet regimens in the 2nd line setting based on data from one manufacturer. The incremental results were slightly improved for all triplet regimens but still remained similar to those of the base case. Finally, improvement in quality of life from extending survival without disease progression is already estimated in the model for all regimens, representing a major driver of the gains in quality-adjusted life expectancy that were observed.

- One manufacturer attempted to reconstruct our estimates of life expectancy based on pooled data from the MM-009 and MM-010 trials of lenalidomide+dexamethasone, and reported that life expectancy was underestimated in our model. We have reviewed these comments in detail and have determined that the manufacturer was using progression-free survival data from the
overall pooled sample, while we used data stratified by number of prior lines of treatment (1 vs. >1). We have clarified the citations used for our analyses in the revised report.

- ICER’s use of cost-effectiveness thresholds between $50,000 and $150,000 per quality-adjusted life year (QALY) gained also was challenged as outdated and not reflective of cancer patients’ values. However, a commentary from Neumann and colleagues, while acknowledging the variety of thresholds that have been proposed, argues that, for comparisons of interventions across all disease categories, a single threshold of $100,000 or $150,000 per QALY is reasonable. This also dovetails with World Health Organization guidance that, based on patient preferences and risk attitudes, relevant cost-effectiveness boundaries for any given country/region fall generally in the range of 1-3 times per capita annual income. In the US, this equates to approximately $50,000 - $150,000.

- Common criticisms of the potential budgetary impact analysis included establishment of arbitrary budget “caps” and lack of rationale for uptake assumptions. Regarding the former, our potential budget impact threshold should be considered a “policy trigger” for steps to manage the cost of a new intervention, not as a cap. In terms of the latter, potential budget impact is always presented across the full range of uptake so that readers can assess the impact even if they disagree with ICER’s assumptions.

- The costs of managing adverse events were questioned, as they were lower for two-drug regimens than for the newer three-drug regimens in the initial model. This difference was attributable to two main factors: 1) we have more complete publicly-available data for the older regimens; and 2) random variability, as clinical trials are not powered to assess differences in individual adverse event rates. However, we did revise our estimates for the two-drug regimens using only comparator data from the recent trials of the regimens of interest in our evaluation. These changes had a negligible impact on the incremental results.

- Specific concerns were raised regarding the estimated costs for the regimens of interest in our model. To confirm, costs were based on the combination of wholesale acquisition cost and reported trial data on relative dose intensity for each component of these regimens. Dose-intensity estimates have been adjusted for certain regimens based on recently-available and/or corrected data, and costs have been modified accordingly.

- Several commenters felt that the QALY measure does not adequately capture the full breadth of values that cancer patients consider important. While the QALY is certainly not a perfect
measure, we feel that it represents a consistent and widely-employed method to account for both the quality and length of life. We welcome suggestions for other measures that would appropriately capture these impacts in myeloma patients and other important patient populations. We also acknowledge in all our reports that there may be “other benefits or disadvantages” of a new drug that are not captured in the evidence on comparative clinical effectiveness or incremental cost-effectiveness. We have included some of these potential benefits, such as the benefits to patients and caregivers of receiving oral medication that obviates the need for repeated, extensive IV infusions. We look forward to discussion of this and other potential benefits of different treatment options for multiple myeloma at the public meeting.
References


