

April 20, 2016

Steven Pearson, MD  
President  
Institute for Clinical and Economic Review

Dear Dr. Pearson:

The American Society of Hematology (ASH) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft report on drugs for multiple myeloma in preparation for the May 26 Meeting of the Midwest Comparative Effectiveness Public Advisory Council (CEPAC). ASH represents more than 15,000 physicians, researchers, and medical trainees, who are committed to the study and treatment of blood and blood-related diseases, such as leukemia, lymphoma, and myeloma; non-malignant conditions, including anemia and hemophilia; and congenital disorders, such as thalassemia. Because of the very short turnaround time associated with this review, ASH's comments are brief. The Society intends to have representation at the upcoming Midwest CEPAC Meeting, and ASH will also make a statement regarding the work that is presented at the meeting.

In recent years, the science of treating myeloma has advanced considerably. A number of new drugs were approved by the Food and Drug Administration (FDA) in 2015, which increased the number of therapeutic options available for individuals afflicted with this difficult disease. Clinical experience has shown some indication that the new drugs have better tolerability for certain patients. In addition, there is now increasing knowledge of the variable risk associated with individual biological features of this disease, including specific genetic factors. The availability of these new drugs, in combination with the increasing understanding that myeloma is a heterogeneous disease, has improved the treatment of patients with this disease, but has also made their care more complex.

ASH understands why ICER would like to determine the comparative effectiveness of the various drugs used in the treatment of myeloma, given the expense of the many new agents. Unfortunately, the scope of ICER's analysis is far too narrow because it does not represent the realities of clinical practice. As such, ASH believes that the type of analysis has only limited value in determining the just price and utility of novel drugs and drug combinations in this rapidly advancing field.

Specifically, the most important limitation of ICER's analysis is its comparison of drug combinations and regimens that do not reflect current clinical practice. The important clinical question is not which drug regimen to use, but determining the sequence in which to provide multiple drug combinations. Because of limited available data, these difficult questions about which drug combinations to use, and which order to use them, cannot be addressed by only a cost-effectiveness analysis. Ideally, these drugs could be addressed by further comparative effectiveness research.

For example, the ICER analysis compares the FDA-approved combinations of novel drugs to historical treatment, such as using lenalidomide plus dexamethasone. In clinical practice,

patients who are prescribed new agents have typically already failed the historical standard treatment, making this comparison irrelevant. Clinicians have gained considerable experience in how to choose among the novel agents, and how to sequence their use based on clinical factors, such as risk profile, previous response, and tolerance of side effects. Furthermore, clinicians understand that a patient who is elderly may respond differently to a certain drug combination than younger patients, who were included in the clinical trials of the drugs. Clinical judgment – clinical experience combined with a rapidly developing knowledge of myeloma, including genetic factors and their association with risk and prognosis – has resulted in better clinical outcomes. ICER's analysis focuses on the information from clinical trials and ignores the necessary element of experience that has followed. Clinical trials are a fundamental part of drug development and improvements in therapy, but clinical knowledge continues to be gained even after trials are completed. Therefore, if the ICER analysis is applied, it will constrain clinical practice, and it risks setting back the important improvements that have been made in caring for patients with this disease.

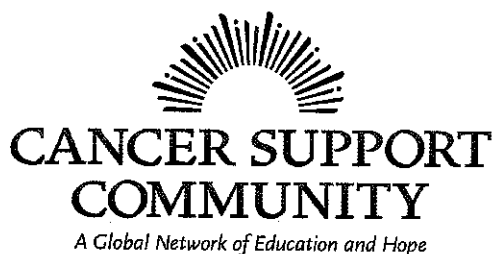
ASH is concerned that ICER's analysis will be used to limit the options for patients in receiving the best possible treatment for a very difficult and complicated disease. ASH strongly encourages other efforts to measure the comparative effectiveness of new myeloma drugs, such as comparative effectiveness trials, or the development of clinical data registries.

ASH appreciates the opportunity to offer comments on this process. If you have any questions or wish to discuss this further with ASH experts, please contact Brian Whitman, Senior Manager of Policy and Practice at [bwhitman@hematology.org](mailto:bwhitman@hematology.org) or (202) 292-0264.

Sincerely,

Charles Abrams, MD  
President  
American Society of Hematology

Kenneth Anderson, MD  
President-Elect  
American Society of Hematology



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April 21, 2016

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

RE: Institute for Clinical and Economic Review (ICER) Assessment of Drug Therapies for Multiple Myeloma

Dear Dr. Pearson,

On behalf of the Cancer Support Community, an international nonprofit organization that provides support, education and hope to more than one million people affected by cancer each year, we appreciate the opportunity to respond to the request for comments regarding ICER's draft report of treatment options for relapsed or refractory multiple myeloma.

As the largest direct provider of social and emotional support services for people impacted by cancer, and the largest nonprofit employer of oncology mental health professionals in the United States, CSC has a unique understanding of the cancer patient experience. Each year, CSC serves people affected by cancer through its network of 44 licensed affiliates - more than 120 satellite locations, a toll free telephone helpline 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. However, we encourage you to seek input earlier in the process and in a more comprehensive way. Both the conversation on value and multi-stakeholder engagement are at the core of CSC's work on access, and we are eager to work with you to move appropriate solutions forward.

Dr. Pearson, we are concerned about several items, which I have outlined below.

#### **Lack of consideration of the patient definition of value**

At the Cancer Support Community, the patient experience drives all aspects of our work: direct service delivery, research and policy. To better understand the needs of people with cancer, we developed the Cancer Experience Registry. The Registry collects survey data that measures all aspects of the cancer experience including, the social, emotional, spiritual and financial effects of cancer on the person diagnosed as well as his or her family. Over 9,300 people have participated so far, sharing almost one million data points about their experience.

Responses collected directly from cancer survivors 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 emerging 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.”

This data from CSC’s Cancer Experience Registry, presented at the 2015 Association for Value-Based Cancer Care 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 from a clinical perspective, the current ICER’s model represents only some components of the overall care and may overshadow other dimensions of care that are also valuable to patients.

### **Lack of patient validated endpoints**

Contrary to the belief that all patients want aggressive treatment at all costs, CSC recently presented data from 935 patients attending psychoeducational workshops (Harvey, et al.) demonstrating that only 33% of patients attributed “most aggressive” to their treatment decision. The patient perspective is not incorporated into the ICER’s value framework, incorporating instead elements that are certainly relevant when exploring the efficacy and safety required for regulatory approval, but absent is the guidance of real world experience and preferences of the patients. 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.

CSC understands your use of 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, 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. 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. 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. However, 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 five concerns people want more help managing are: 1) long-term side effects, 2) emotions related to cancer, 3) short-term side effects, 4) financial impact of cancer and 5) lifestyle changes, such as diet and exercise. One patient went further to state, “I would make sure every patient had some sort of aftercare—that they were given resources on support groups in their area, the ‘real’ long-term side effects of chemo, and most importantly, how to mentally handle being a survivor.” 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.

### **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 collection 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 costs 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.

At the Cancer Support Community, we are acutely aware of the rising costs of treating cancer and support efforts that contain costs while ensuring the provision of truly comprehensive cancer care. We believe that patients 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 report of treatment options for relapsed or refractory multiple myeloma and share the voice of patients living with 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 the Value Assessment Framework.

Please feel free to contact me at (202) 650-5382 or by email at [linda@cancersupportcommunity.org](mailto:linda@cancersupportcommunity.org) for questions or if we can be of further assistance.

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

A handwritten signature in black ink that reads "Linda House". The signature is fluid and cursive, with the first name "Linda" being more prominent than the last name "House".

Linda House, MSM, BSN, RN  
President

Cancer Support Community National Headquarters

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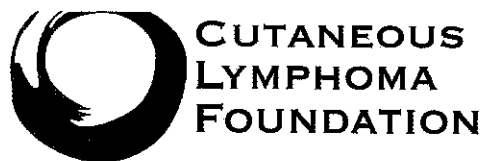
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Steven D. Pearson, MD, MSc, FRCP  
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April 21, 2016

RE: ICER Review of Drug Therapies for Multiple Myeloma

Dear Dr. Pearson:

The undersigned organizations advocate on behalf of Americans with cancer and other life-threatening diseases whose life expectancy and quality of life have significantly improved due to innovative therapies. While we appreciate your efforts to engage in an expanding dialogue around value, in our opinion there is currently no mechanism to calculate the “value” to individual patients of less suffering and longer life. Suffice it to say that for the estimated 14.5 million cancer survivors today, the return on investment from more time with loved ones, a higher quality of life, increased productivity and the ability to work, travel and be active is incalculable.

Among these cancer survivors are the more than 88,000 Americans who currently have or are in remission from multiple myeloma (MM), an incurable blood cancer where the introduction of novel treatments has led to dramatic survival gains. In fact, due to innovations in MM therapies, 5-year survival rates increased from 25% in 1975 to 44.9% in 2014. Moreover, with the approval in 2015 of three drugs for relapsed or refractory MM, clinicians now have new weapons to address the ongoing challenge of treatment resistance, which remains the major obstacle to keeping myeloma in remission for longer periods of time.

However, as the tide begins to turn in combatting myeloma, we are concerned that a “one-size fits all” approach to assigning an economic value to different MM drugs will turn back the clock for patients and physicians. Further, as organizations speaking broadly for cancer patients and those with serious conditions, we are also concerned that the Institute for Clinical and Economic Review’s assessment of novel myeloma treatments may be the beginning of a systematic process to restrict access to targeted therapies for many other cancers and hard-to-treat diseases. As such, we have identified specific issues with the design and ultimate impact of ICER’s upcoming report on new therapies for refractory myeloma that we hope can lead to a productive dialogue between ICER and our organizations. Our specific concerns are summarized below.

### **1. The Beneficiaries of ICER’s Value Benchmarks Will Be Payers and Not Patients**

As with other healthcare stakeholders, we are concerned about the rising cost of medical care. However, efforts to limit the utilization of specific medicines based on cost have the potential to harm patients by narrowing available treatment options and impeding physicians’ best clinical judgement. The consequences are especially worrisome for patients with multiple myeloma and other similar cancers, where many patients become refractory to existing drugs and continued survival requires making treatment decisions customized to the circumstances of each patient.

## **2. ICER's Model Does Not Reflect the Reality of Treating Refractory Multiple Myeloma**

As documented in the scientific literature, multiple myeloma is a hard-to-treat blood cancer in which relapses are inevitable. Thus, even as novel therapies have extended survival significantly over the last decade, the reality is that each successive regimen results in a briefer, and less dramatic benefit, reflecting acquired drug resistance. Moreover, refractory MM patients often have comorbidities and difficulties in tolerating certain treatments, limiting the choice among therapies.

For these reasons, in October 2015 the International Myeloma Working Group (IMWG) published updated diagnostic criteria laying out certain treatment decisions based on genetic differences and validating the biological rationale for the use of more precise and accurate targeted therapies with novel mechanisms of action that can be sequenced and used in different combinations to help a majority of patients break through the ceiling and duration of response to treatment. Reflecting this new consensus, the Food and Drug Administration has approved 10 myeloma drugs so clinicians can integrate more novel therapies into the treatment armamentarium. Yet, ICER's assessment fails to take IMWG's criteria into account and instead, uses what we consider to be outdated population-wide data to develop "value-based price benchmarks" that will only make it harder for clinicians to sequence and combine regimens individualized to each patient's characteristics. In our view, this runs counter to quality cancer care and subjects patients to cost control rather than offering them the benefit of potentially more effective therapy.

## **3. ICER's Model Does Not Put Patients at the Center of the Value Equation**

When it comes to assessing the "value" of new multiple myeloma drugs, we are concerned that the use of the cost per quality-adjusted life year (QALY) metric will lead to determinations that limit treatment choices for MM patients and their physicians. This is because the QALY is a rigid measure with many known limitations, especially the inability to assess the value of medicines for rare diseases like refractory myeloma where there are many DNA alterations in myeloma cells that frequently differ from patient to patient.

Therefore, the very nature of myeloma requires models that determine value in terms of the health outcomes achieved from a therapeutic regimen, such as increased survival, improved quality of life and fewer costly hospitalizations. When these health improvements were factored into a recent assessment of new myeloma therapies, a 2015 study published in *Health Affairs* showed that although these agents increased treatment cost by \$72,937 between 2004 and 2009, the improvements in outcomes from these drugs were valued at \$140,800. Thus, the net cost of health actually decreased by \$67,863.

## **4. Concerns About the Limitations of ICER's Methodology**

In reviewing ICER's proposed scope for evaluating different therapies for relapsed and refractory myeloma, we have also identified a number of problems with the study's design that we believe should be addressed:

- ICER's assessment of new MM therapies involves comparing these drugs against one of two older treatments (lenalidomide or bortezomib in combination with dexamethasone) now widely used as first or second line therapies. Yet, the clinical trials for many of these novel agents involve patients who are refractory to both older drugs. As a consequence, ICER's



value determinations will not reflect the different subpopulations of myeloma patients and the sequencing of therapy approaches based on the configuration of the disease.

- While cost-effectiveness can inform decisions about different therapies, relying solely on this analysis to determine what myeloma treatments should be offered to patients is counter to good clinical practice. Not only does the trajectory of myeloma vary from patient to patient but there are well-known problems with cost effectiveness analysis that may lead to questionable findings – from the quality of the data analyzed to difficulties in generalizing from clinical trials populations to patients in real world settings.
- ICER's methodology does not take into account individual patient characteristics that clinicians must factor into decisions about MM treatment. This includes the frailty and vulnerability of the patient, the specific adverse event profile associated with each treatment and challenges with transportation when patients are unable to drive or live in rural areas.
- We have become aware that ICER will not include several new MM therapies in its review, which suggests that the organization's simulation models to assess the lifetime cost-effectiveness of the new treatment regimens will be incomplete.

Because ICER's purpose is to influence payers decisions about which myeloma treatments should be available to patients and clinicians, we believe the impact of the upcoming report will limit patients' treatment options, make it more difficult for oncologists to practice quality cancer care and stall the progress made in extending the survival of patients with refractory disease. For these reasons, we strongly encourage ICER to confer with leaders in the myeloma and cancer communities and address existing concerns before finalizing a report and pricing recommendations that could have serious and unintended repercussions for myeloma patients.

We appreciate your consideration of the issues raised in this letter, and look forward to a continued discussion on this important matter.

Sincerely,

Alliance for the Adoption of Innovations in Medicine (Aimed Alliance)  
CancerCare  
CancerConnect  
Community Oncology Alliance  
Cutaneous Lymphoma Foundation  
E-Race Cancer  
MDS Foundation  
Myeloma Crowd  
National Patient Advocate Foundation  
Patients Rising  
Patient Services, Inc.

## Introduction

The Multiple Myeloma Research Foundation (MMRF) is a patient-founded, non-profit cancer research and patient advocacy organization that focuses on the best interest of multiple myeloma patients. The MMRF works tirelessly with colleagues in academia, industry, and the government to advance scientific efforts and to improve patient outcomes.

This document is the response of the MMRF to the Institute for Clinical and Economic Review (ICER) Draft Report dated April 7, 2016 entitled “Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value.”

## “Stakeholder” Clarification

In the Draft Report, the MMRF is cited as a “Stakeholder” by ICER; this may be misconstrued and requires clarification. The MMRF responded in March to a direct inquiry from the ICER staff requesting our preliminary thoughts on their effort; that response consisted of an e-mail and a courtesy phone conversation. At that time, the MMRF expressed many of the serious concerns that are outlined in the balance of this letter. The MMRF has no idea whether ICER addressed any of these concerns or ignored them completely. To be clear: the MMRF has not contributed to and in no way endorses, supports, or affirms the views reflected in the ICER Draft Report.

## Serious Concerns About the ICER Draft Report

While multiple myeloma has seen significant improvement in patients’ outcomes in recent years, driven by an explosion of effective, new therapies, there remains a high unmet medical need for a significant segment of patients. Collaborative success has extended the lifespan for many patients; however, multiple myeloma remains a fatal disease and five-year survival remains stubbornly under fifty percent.

The MMRF has a number of concerns regarding the ICER Draft Report including, but not limited to:

- 1) Myeloma is Not One Cancer. Multiple myeloma is a complex, heterogeneous cancer that can and will change as the disease progresses. Based on the MMRF Genomics Initiative, the MMRF CoMMpass® Study, and the work of researchers, we know that there are several sub-types of multiple myeloma based on the specific genetic profile of a patient’s myeloma cells. Characterizing multiple myeloma as a single disease, without taking into account its various subtypes, is a serious flaw in the ICER analysis.

The best treatment for one multiple myeloma patient may not be the best treatment option for another patient. While some efforts were put into trying to look at particular subgroups defined by cytogenetic or other risk markers, the Draft Report acknowledged that they are unable to run a thorough analysis as subgroups are not consistently defined in the available data and/or such information is missing entirely for certain regimens.

- 2) The Study is Premature. In the broad scope of medical research, meaningful multiple myeloma treatments have been developed only in the past twenty years. Patients that were treated in the 1990's were receiving the same treatment as patients in the 1950's. There was little progress, innovation or new drugs.

Fortunately, multiple myeloma has seen an explosion of new, effective therapies. Just last year, there were four new drugs approved by the FDA for multiple myeloma - three within a remarkable two-week period in November. This unprecedented addition to the arsenal of cancer-fighting drugs means that researchers are still learning which of these promising new therapies are the most efficacious for which particular subtype of multiple myeloma. In addition, researchers are studying, analyzing, and learning the most appropriate use (sequence and combination) of these newer regimens.

As noted in the Draft Report, a thorough analysis must evaluate each regimen's performance at different points during the disease course - ideally in head-to-head studies. One of the greatest weaknesses in the report's current comparative net health benefit analysis lies in the lack of truly comparative data across trials. Furthermore, the limited number of available studies as well as the absence of data for certain key subgroups precludes even robust indirect comparisons of the regimens. Finally, the current data for overall survival for the six key studies was limited - with only two reporting final results. More time is absolutely required to allow the data necessary for more definitive analyses to develop; we simply do not know enough to proceed now.

- 3) The Comparisons Are Not Reflective of Current Clinical Practice. The comparators included in the Draft Report are not the most commonly used second and third line treatments. The proposed treatment regimens are quickly changing and evolving as new therapies are introduced and clinical evidence increases. The Draft Report does not incorporate the rapidly changing treatment landscape into the analysis.

ICER states that its reviews seek to provide information on other benefits or disadvantages offered by the interventions that would not be considered as part of the evidence on comparative clinical effectiveness. Sadly, absent in the Draft Report are considerations around ease-of-use as well as management of toxicities and side effects so that patients can enjoy an improved quality of life. There also is a lack of consideration of individual patient experiences such as a patient who is intolerant, but not refractory, to a specific class of treatments or for a patient who has co-morbidities or prior toxicities which would make one treatment less attractive or even potentially dangerous.

- 4) Flaws in the Cost Effectiveness Model. In order to build the cost effectiveness model, ICER made a number of key assumptions; many of these assumptions are incorrect. Most importantly, the trial populations in the data being analyzed are not perfectly homogeneous given the extreme heterogeneous nature of the disease and differences in study populations cited in this document. The treatment received after progression is also not uniform across all comparators. Given those obvious weaknesses, the negative conclusions about the estimated cost-effectiveness of the regimens studied is seriously called into question.

- 5) Going Against Current Trends in Science. The White House is now over one year into its Precision Medicine Initiative, an effort strongly supported by the MMRF. The MMRF is also one of the leaders in this exciting field. The promise of precision medicine is that each patient is unique and will consequently respond to treatment differently based on their particular genetic profile and further understanding of the biology of their disease. Many researchers believe this will be the most efficacious and cost-effective way to treat cancer.

The approach of the Draft Study is not consistent with the current thinking in regard to the future of cancer treatment. The trend is toward more personal, customized approaches to treating patients and not subjecting every patient to the same treatment regimen.

The overarching question is this: why is ICER addressing multiple myeloma right now? Patients are living longer, scientific progress is moving apace and many new therapies are only now available. In this wildly changing, ever-more promising environment, it is not possible to produce a thoughtful, meaningful analysis of the cost effectiveness of the treatments evaluated in the Draft Report. More time is needed as new knowledge is added to our collective scientific understanding every day.

The Draft Report has a number of irreparable flaws, many due to the fast-changing landscape, and it is unclear that any meaningful conclusions can be drawn from this effort.

The best interest of multiple myeloma patients must be first and foremost. Despite recent progress, multiple myeloma remains an incurable and fatal form of cancer. Therefore, until there is more data, patients and their doctors need unfettered access to all available therapies in order to improve patients' outcomes, learn the best approach, and, someday, identify cures.

Sincerely,

A handwritten signature in black ink, appearing to read "Paul Giusti", with a stylized flourish extending from the end.

Paul Giusti  
President & Chief Executive Officer

Although I believe as a community consisting of all stakeholders we need to investigate ways to manage the pricing of pharmaceuticals and evaluate the comparative clinical effectiveness and value of therapies for multiple myeloma I don't believe this report has taken the myeloma patient's unique needs into account. Myeloma is a very heterogeneous cancer. No two people present in exactly the same way nor do they respond to treatment in the same manner. I've attended numerous medical conferences where it was stated that researchers have identified 7 sub-types of myeloma and they believe with more refined testing and larger patient populations enrolled in clinical registries more sub-types will be identified. To me this report grouped all myeloma patients into one category, a statistical average. In the age of precision medicine initiatives this can be very dangerous. We are UNIQUE!

The life expectancy of myeloma has more than quadrupled over the last 15 years. I believe the reason for this is two-fold. First new therapies mean new options, but also new therapies mean new combinations that can work in synergy with each other. Some patients may be refractory to a doublet, but when a new drug is added to the combination they will begin to respond. This happened to me. I became refractory to Revlimid/ Dexamethasone after 3 cycles of treatment, but I responded to the combination of Velcade/Revlimid/Dex. When the Revlimid was taken away my response began to dramatically slow down.

With all the new options available we do not know what will work best for individual patients. Some may do well with a doublet where others may need a multi-drug combination, but we don't know who they are yet! The myeloma specialists are only beginning to explore these questions. The data that has been generated and evaluated is too immature. Give the experts time to explore and run comparative trials which identify subgroups of myeloma patients before recommendations are made. If myeloma specialists still don't know what's best for specific subsets of the myeloma population how will a payer be able to decide if a multi-agent combination therapy will be equally as effective as a doublet?

Myeloma is complex. Treatment options are as varied and unique as the patients. Not until more data is generated and myeloma patients are differentiated into groups based on genetic characteristic and head to head comparative trials are conducted are we ready to discuss and evaluate the comparative clinical effectiveness and value of therapies for multiple myeloma.

Cynthia Chmielewski

Myeloma Patient and Advocate - Dx 2008

Board Member of The Philadelphia Multiple Myeloma Networking Group

Twitter- @MyelomaTeacher

Facebook –MyelomaTeacher's Multiple Myeloma Resource Page

RECEIVED FROM ROBERT KANE

Comments on the ICER Draft dated April 7, 2016

Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value

Document is in pdf format – no line numbers

Plan: copy sentences and comment after

“malignant plasma cells that emerge into the bloodstream”

*Not true as stated*

“These agents have been used following treatment with autologous stem cell transplant or as first-line treatment in those ineligible for transplant due to age, frailty, and/or organ dysfunction.”

*Misstated*

“The population of focus for the review included adults with MM whose disease has not responded to at least one previous line of treatment (i.e., refractory) or has relapsed following such treatment...”

*Sentence is backwards in concept*

“In the setting of relapsed and/or refractory disease, further treatment is guided by two major factors: (1) the presence of aggressive disease; and (2) the level and duration of response to prior treatment.”

*There is at least a third factor – patient performance and preference*

“Out-of-pocket expenses for a single new cancer drug are estimated to total \$20,000-\$30,000 annually...”

*More like \$30,000-80,000 or more*

***Response criteria:***

“***Complete response:*** negative for M protein in serum/urine; disappearance of soft tissue plasmacytomas; and <5% plasma cells in bone marrow (normal free light chain [FLC] ratio in patients whose only measurable disease is by serum FLC testing)”

*As you know, since there are several ways to measure the M protein, and CR is an important outcome, I think you make it clearer if you specify “negative by IFE” since there is consensus on this fact. I think it is useful to point out that regulatory science only supports PR or better as a response of clinical interest.*

“***Maintenance treatment:*** use of chemotherapy and/or biologic agents to eliminate residual MM cells during periods of remission.”

*There is no evidence that maintenance Rx “eliminates” MM – it may suppress the condition.*

Disease staging:...

*You should state that ISS or m-ISS is preferred*

Velcade®, Takeda Millenimum) ...; it was approved for use in both newly-diagnosed and relapsed MM patients in 2003.

*False – the approval for newly diagnosed was in 2008*

“Unlike bortezomib, carfilzomib irreversibly binds to the proteasome, which may provide more sustained inhibition...”

*And may account for more toxicity also*

“and its analogue lenalidomide (Revlimid®, Celgene) were both FDA-approved in 2006 in combination with dexamethasone for newly-diagnosed patients...”

*Not correct*

“Also, clinical benefits are seen at successively lower daily doses (800, 25, and 4 mg for thalidomide, lenalidomide, and pomalidomide, respectively), which may correlate with reduced rates of myelosuppression, neuropathy, and asthenia for newer-generation IMiDs versus thalidomide”

*Poppycock – promotional BS*

Figure 2: ICER Evidence Rating Matrix

*Very nice work. Consider making your category “I” as insufficient – or – inconclusive and distinguish each based on the qual/quant of evidence available*

There have been no published studies of head-to-head comparisons of the treatment regimens of interest in this review.

*Agree*

*Page 22: Since death is an expected outcome, and, as you note, follow up times vary, tabulating deaths is of uncertain value*

Page 22: Data from an ASH abstract of the trial of PAN+BOR+DEX focus only on the subset of patients with  $\geq 2$  prior lines of treatment including BOR and an IMiD (i.e., the population in the FDA label), and reported only the median duration of overall survival (25.5 vs. 19.5 months, significance not reported).<sup>60</sup>

*True, but you should state here that the OS data are not yet mature and would only be tested if the PFS was significant (which it is)*

Patients in the trial of POM+LoDEX had more advanced disease, and this subgroup analysis is presented for patients with  $\leq 3$  versus  $>3$  prior lines of treatment. A statistically-significant improvement in OS was observed among patients with  $\leq 3$  prior lines of treatment (median 11.1 vs. 6.9 months; HR 0.56, 95% CI 0.33-0.96;  $p=0.02$ ).<sup>56,62</sup>

*I seem to recall that this subgroup analysis of < 3 versus > 3 was not pre-specified, thus is exploratory. If this was pre-specified, THEN the indication should have excluded use in patients with > 3 lines of Rx.*

I have additional comments, but I am stopping here since I'm out of time to work further on this.

Robert C. Kane, MD, FACP



RECEIVED FROM GARY PETERSEN

To: publiccomments@icer-review.org

I am a retired business executive with myeloma who looks at this issue as more of a monopoly created by our drug patent process which unlike utilities another government monopoly do not have a pricing review process. You want to fix this make drug companies justify their pricing to a review board which must approve price changes. Tell me anyone who has a snowballs chance in hell of getting a 700% increase in 5 years.

Major Flaws which skew the outcomes are as follow:

All drugs seem to work better in first line treatment, and that is where all of these new drugs will migrate. The study was much like reading a 5 year old newspaper. The world has moved on. Mayo's mSmart treatment guidelines do not even recommend Rd in a first line setting much less 2cd or 3rd relapse. If you put RVd as the base treatment and not RD, the economic difference between the regimens are all well below the low target of \$50,000. Nice effort, just old and incorrect assumptions.

LD would almost never be used as a 2cd or 3rd line of therapy

I see the base treatment is LD for all 2cd and 3rd lines of therapy, but this is not even a first treatment for many. First line treatment is VRd and then the difference in cost would be much less, the PFS and OS would be more than the 1 year estimate.

I guess this shows that given the current cost of drugs the incremental benefit in the 2cd and 3rd line of treatments is not really good, but not much different to the cost of VRD. This would tend to support the hit it hard up front strategy, and to find it early before it morphs into more aggressive clones.

I did costing and cost analysis during my first job, and when you are not in a monopoly mode. You set your price based on the fixed and variable costs, not based on what the traffic will bear. With a drug if  $\frac{3}{4}$  of the cost is the fixed cost of research and say \$100,000/year is the right price for an orphan disease like myeloma then \$75,000 is just getting back your R&D, but if it is a cancer like breast cancer that is 10 times larger than myeloma then the R&D recovery would be just \$7,500 or the cost per year of the drug would be \$25,000 + \$7,500 or \$32,500. If the pricing of a drug is totally inelastic, and usage is unaffected by the laws of supply and demand then it is monopolistic (made by the government patent protection) and there are laws for that.

Also if a drug's price is set correctly the first time based on a good costing model, the price should change yearly by the inflation rate, or if indexed more than once the costing professional who set the price should be looking for another job.

## **Comments to the ICER voting questions regarding the treatment options for relapsed refractory multiple myeloma**

Answer and comments to question 1.

There is adequate evidence to demonstrate net health benefit based on the specified criteria established by ICER. The published studies involving the 3 combination regimens listed in the question demonstrated 3-5 months overall survival or progression free survival when compared to the lenalidomide plus dexamethasone arm.

Answer and comment to question 2.

There is no evidence to distinguish the net health benefit of treatment between the three specified regimens. Lack of phase III clinical trials comparing these regimens against each other would limit the ability to compare the net clinical between these regimens. In addition the individual studies had differences in demographics and methodologies which also limit the ability for a direct comparison.

Answer and comment to question 3.

There is evidence to demonstrate the net clinical benefit all the regimens listed below except for Panabinostat. The median follow up which demonstrated the clinical benefit is much shorter; the rate of discontinuation of the drug due to adverse events was much higher when compared to the other combination regimens. Eventhough the regimen is comparatively most cost effective, unclear if in the long run this would translate to a net clinical benefit.

Answer and comment to question 4.

Given the lack of phase III clinical trials there is no adequate evidence to distinguish the net health benefit between regimens.

Answer and comment to question 5.

There is currently no published data to comment on the net health benefit in patients with less than three prior lines of therapy. However given the advantage of single agent with relatively

favorable toxicity profile, I won't be surprised if it will be soon considered in earlier setting, especially in patients who cannot tolerate PI or IMiDs.

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April 15, 2016; ***Submitted Electronically*** to [publiccomments@icer-review.org](mailto:publiccomments@icer-review.org). from Martin Zagari, MD, Vice President, Global Health Economics, Amgen on behalf of Amgen

Re: ICER “Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value.”

Dear Dr. Pearson:

At Amgen, a science-based company committed to developing and delivering innovative medicines, our mission is to serve patients. We appreciate the opportunity to comment on the CEPAC/ICER draft report “Treatment Options for Relapsed or Refractory Multiple Myeloma.”

Recent Food and Drug Administration (FDA) approvals of several newer therapeutic options for relapsed and/or refractory multiple myeloma (RRMM) represent a substantial advancement for patients and symbolize the “spirit of American innovation” by “making more therapies available to more patients,” as called for by The National Cancer Moonshot Initiative.<sup>1</sup> The availability of multiple treatment options in multiple myeloma (MM), a rare and serious cancer of blood cells, enables physicians to provide patients with individualized, precision care. Physicians anticipate that the newest medicines, used in combination and sequentially, may help extend overall survival (OS) of patients with MM from about 6 years (2006-2010) to a decade or more.<sup>2,3</sup> Progress in the treatment of cancer and other serious disease contributes immensely to the improvement in patient well-being, which demands that all economic reviews on the value of medicines aim to achieve the highest level of transparency and clinical validity, strive for broad stakeholder engagement, and place scientific rigor and patient interests at the center of the analysis. At the highest level, we do not feel that ICER’s evaluation in RRMM embodies these principles, which have been generally agreed on by ISPOR, PhRMA, NPC, and many of the world’s leading technology assessment organizations.<sup>4-7</sup> Although the remainder of this response details select technical findings, we feel the overall process, including failing to adhere to such principles, contributed greatly to the issuance of a seriously flawed report that requires substantial revision.

After careful review of the ICER RRMM draft report and consistent with our previous technical comments to ICER, we found the methodology inappropriate and disagree with many of ICER’s resultant assumptions and conclusions. Specifically, ICER has:

1. Performed a cost-effectiveness evaluation using indirect comparisons when head-to-head data are available. An evaluation using head-to-head data would have achieved more clinically and economically valid results.
  - a. ICER recognized serious limitations (at least 57 mentions in the draft) due to the lack of sufficient evidence to populate key model parameters.
  - b. Lack of sufficient and appropriate data for the analysis should compel ICER to abandon infeasible indirect methods, and avoid the issuance of spurious, misleading and invalid results.
2. Used old and now irrelevant comparative data for the previous standard of care which undermines the modeled effect of new RRMM treatments.
3. Ignored direct patient-derived experience by not appropriately valuing health-related quality of life (HRQL) outcomes, thereby underestimating total quality-adjusted life years (QALYs).
4. Provided final results that not only underestimate the value of MM treatments, but also weighed these low value estimates against inappropriately low value thresholds.
5. Overestimated, in the budget impact analysis, use of newer medicines in late-stage treatment.
6. Failed to correct multiple technical errors, compromising the validity of the results and conclusions.

ICER’s arbitrary 3-page limit on comments is insufficient to allow for an adequate response to their complex analysis. We have therefore compiled more detailed data in appendices and provided these to ICER as a supplement to this 3-page “public” response.

## Detailed Discussion of Issues 1-6

1. Inappropriate use of indirect comparisons over head-to-head data: A key limitation and source of bias in any indirect comparison is missing data to account for patient and trial heterogeneity. Consistent with Amgen's comments on the Proposed Scope, ICER notes a lack of sufficient evidence in 12 key areas (57 mentions) to populate key model parameters. ICER further assumed a homogeneous population (Table 7, ICER report), even with evidence of considerable diversity in patient characteristics (Amgen Appendix 1). ICER nevertheless chose to use indirect comparison as the primary analytic method, essentially underweighting the robust head-to-head results for each medicine. An example of a seemingly spurious result from the ICER model is the inexplicably lower hazard ratio (HR) of 0.54 for progression-free survival (PFS) between PAN+BOR+DEX and LEN+DEX. This conflicts with the HR of 0.96 for PFS found in the manufacturer's own response to NICE.<sup>8</sup> Use of an indirect comparison under these circumstances effectively invalidates the results.

*Recommendation:* Use available head-to-head data (between newer agents and LEN+DEX) as primary analysis rather than indirect comparisons.

2. Irrelevant data undermine the treatment effect of newer treatments for RRMM: ICER used data for LEN+DEX that included a highly toxic, high dose DEX from the MM-009/010 trials conducted in 2007, casting doubt on the baseline median time to progression [TTP] of 11.1 and 11.3 months, respectively.<sup>9,10</sup> These data are not reflective of the LEN+DEX efficacy (median PFS, 14.7 to 17.6 months) observed in the more recent direct trials of the newer treatments (2015).<sup>11-13</sup> Using lower baseline regimen efficacy from older trials from which one extrapolates the relative treatment effect of the newer treatments will underestimate the relative efficacy of every newer intervention (Amgen, Appendix 2). Our replication of ICER's analysis using the (MM-009/010) data above revealed additional survival underestimation by ICER, likely due to an error in translating the published PFS-OS hazard ratio into their final OS curve (Amgen, Appendix 3). Taken together, these two assumptions inappropriately reduce the incremental net benefit and value of all of the newer medicines.

*Recommendation:* (1) Use LEN+DEX data from direct trials of newer medicines. (2) If indirect comparison is performed, correct the methodology error(s) referenced above.

3. Ignoring direct patient-derived data underestimates total QALYs: The systematic underestimation of treatment effect is further worsened by the failure to appropriately weight survival gains with available HRQL data. ICER assumes "consistent health state utility values across treatments evaluated in the model" during all "progression-free" (PF) states, and uses Amgen/ASPIRE as the data source for the PF state (Table 12, ICER report). However, these same patient-derived data show *higher* utilities for CFZ+LEN+DEX compared with LEN+DEX on the basis of improved HRQL for CFZ+LEN+DEX vs LEN+DEX over 18 cycles of treatment ( $P < 0.001$  [Appendix 4]).<sup>11</sup> Furthermore, the European Medicines Agency (EMA) elaborates on the relevance of this benefit.<sup>14</sup> Therefore, to assume similar utilities for CFZ+LEN+DEX and LEN+DEX ignores the importance of incorporating patient HRQL into the valuation of the newer treatments.<sup>15,16</sup>

*Recommendation:* Incorporate the impact of patient HRQL into pre-progression utilities by treatment, even if not uniformly available across comparators.

4. Compounding the systematic underestimation of QALYs by exclusively using low QALY thresholds: For reasons noted above, the QALYs gained for CFZ+LEN+DEX in ICER's analysis are considerably lower than those estimated by Amgen in the Kypolis Global Economic Model (K-GEM). The former are likely systematically lower than justified for some of the other newer treatments as well. The K-GEM was developed in collaboration with input from clinical and health-economic experts worldwide, and uses head-to-head data from the ASPIRE trial, whereas ICER's approach uses indirect comparisons and LEN+DEX data from older trials. These differences, including appropriate weighting of survival with HRQL data from ASPIRE, lead to strikingly different results. The K-GEM estimate for the incremental cost per QALY for CFZ+LEN+DEX vs LEN+DEX is \$107,520 for patients with RRMM who have received 1 to 3 prior treatments, which is more favorable (better value) than the estimates generated by ICER for second and third line use of these interventions (\$267,464 and \$312,840, respectively).

Amgen therefore strongly believes that CFZ+LEN+DEX is a cost-effective regimen even under one of the value thresholds applied by ICER. However, Amgen contends that thresholds proposed by ICER still do not reflect patient and clinician perspectives for RRMM. In oncology in the U.S., a broad range of value thresholds have been proposed (around \$150,000 to \$300,000 per QALY). Specifically, patients with metastatic cancer and other serious illnesses were found to have a threshold closer to \$300,000.<sup>17</sup> Multiple preference studies have suggested higher values for end of life interventions, such as late-stage cancer treatments.<sup>17-21</sup>

***Recommendation:** Use a range of cost-effectiveness thresholds from \$150,000-\$300,000 for assessing value, in addition to using head-to-head data for each newer treatment.*

5. **Overestimating late-stage treatment use:** For the analysis of budget impact, ICER assumptions regarding the percentage of patients with MM treated for their disease do not align with the cited source (see Amgen Appendix 5).<sup>22</sup> ICER also does not provide a rationale or justification for the high uptake pattern of newer medicines cited for second and third lines (Amgen Appendix 6).

***Recommendation:** Use realistic and justifiable estimates of the patient pool eligible for treatment and for medicine use rates.*

6. **Failure to correct multiple errors:** A detailed description of factual errors identified in the ICER report is provided in Appendix 7. Important flaws potentially affecting value calculations include those related to the overall survival (OS) HRs for ELO-LEN-DEX (0.77 instead of 0.71, Table 3, ICER report); efficacy estimates from the TOURMALINE-MM1 and PANORAMA-1 studies (Table 3, ICER report); inaccurate reference of PFS data from MM-009/MM-010 (actual data reported was TTP); and inaccurate calculation of dose intensities for LEN as part of the ELO-LEN-DEX regimen ( 51% instead of 80% [Appendix 8], Table 8, ICER report), which dramatically influences the cost-effectiveness results.

***Recommendation:** Rectify errors, and prioritize head-to-head comparative models over indirect analysis when rerunning models.*

**Analytical recommendations summary and implications for voting questions:** ICER has recognized the serious flaws with its own methodological approach, and despite this has chosen to move forward with an inappropriate analysis resulting in spurious conclusions that are highly discrepant with more valid evidence. Using separate models, ICER should re-conduct analyses of the newer treatments using the head-to-head data available for each newer agent, assign an incremental cost/QALY value for each agent, and compare that value with a reasonable range of value thresholds for cancer in the U.S. (eg, \$150,000 through \$300,000 per QALY). The resulting valuations should then serve as the primary value benchmark for each newer treatment within its respective labeled indication. Because of the trial heterogeneity noted above, ICER should largely abandon the use of indirect comparisons and newer treatments should not be “stack ranked.” Amgen believes this revised approach to assessing product cost effectiveness and value will provide more constructive results to the community by highlighting the realistic value of treatments that add years to peoples’ lives. Voting questions should be modified accordingly to focus on the head-to-head model/results for each new medicine individually.

**Conclusions:** Making the best evidence-based treatment decisions starts by using high-quality evidence in the right ways. Given the methodological flaws and factual errors present in the ICER draft report, Amgen strongly recommends that ICER re-evaluates the effectiveness and value of newer treatment options for MM using a series of simple and transparent models that take into account direct comparisons wherever possible. ICER should also apply appropriate value to improved survival by comparing model results with a range of potential incremental cost/QALY thresholds of up to about \$300,000.

## Response References

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April 21, 2016

Bristol-Myers Squibb (BMS) would like to thank ICER and Midwest CEPAC for allowing public comments on the Midwest CEPAC draft report, *Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value*, and draft voting questions.

Our comments are outlined below.

**1. Cost-effectiveness thresholds:**

**Cost-effectiveness thresholds that define whether an intervention is worth paying for are arbitrary and the ones mentioned in the report do not reflect the value of health outcomes in cancer care.** For example, one study of patients with metastatic cancer found that patients were willing to pay substantially larger amounts for a one-year life extension than thresholds reported by ICER.<sup>1</sup> If cost-effectiveness thresholds consider the social value of treatment, then they would likely be higher than those referred to in the report. The wide range of cost-effectiveness thresholds mentioned in the literature perfectly illustrates the extreme uncertainty in labeling a drug as cost-effective based on its estimated incremental cost-effectiveness ratio.

***Recommendation:** Rather than risking labeling a drug incorrectly as not cost-effective based on picking an inappropriate cost-effectiveness threshold and thereby withholding potential gains in health outcomes with these newer treatments, it is more appropriate to limit presentation to the actual cost-effectiveness ratios.*

**2. Budget impact framework:**

**The budget impact framework establishes arbitrary budget caps for societal expenditures on medical innovations and fundamentally ignores the value of innovation in healthcare.** The framework is inappropriate for measuring value, because it focuses on drug costs, while ignoring benefits to patients, caregivers, and society. Moreover, the focus on a 'budget cap' subjects innovative therapies to restrictions based on arbitrary budget thresholds, thus creating disincentives for innovation and healthcare investment. Under the current budget impact framework, an expensive cure for cancer that applies to a large population would likely exceed the budget cap despite having high value to society.

***Recommendation:** Do not utilize the budget impact framework to assess the value of innovative treatments. However, if ICER continues to use the budget impact framework against our recommendation, the report should be transparent about which stakeholder interests are represented.*

**3. Presentation of evidence:**

- a. Presenting cost-effectiveness results for third line setting without referencing differences in quality of evidence is misleading.** The clinical effectiveness portion of the report assigns differing evidence ratings across the various treatment regimens. However, the presentation of cost effectiveness results in Tables 13 and 14 does not mention the evidence rating. Given that the level of evidence for clinical benefit differs across therapies, it is misleading to present ICERs for the various regimens in the same set of results without referencing the discrepancy in evidence levels. Readers who view Tables 13 and 14 without reading the full report may assume

that the ICER assigned evidence ratings are the same for all regimens without having an accurate representation of the body of evidence.

**Recommendation:** *Include a row in Tables 13 and 14 with the evidence rating for the therapies and provide readers with the full context of the evidence base.*

- b. **Presenting a non-generalizable single payer's coverage policy is inappropriate.** Given *ExpressScripts* is the only formulary information provided in the report, readers are provided with a narrow depiction of coverage. Moreover, *ExpressScripts* being a Pharmacy Benefit Management organization is not representative of coverage for the treatments studied in this review since they are typically covered through medical benefit policies in most healthcare plans.

**Recommendation:** *Remove isolated examples of private insurance coverage to avoid misrepresentation of the coverage on a broader scale.*

- c. **The NCCN classification for elotuzumab is inaccurate.** The NCCN guidelines section of the report states that elotuzumab is indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent. However, NCCN guidelines (v3.2016 MYEL-D) state that elotuzumab is “indicated in combination with lenalidomine and dexamethasone for the treatment of patients who have received *one to three* prior therapies”.<sup>2</sup>

**Recommendation:** *Correct the NCCN guidelines section of the ICER report for elotuzumab by replacing the currently incorrect information with: “The NCCN guideline update in January 2016, reflected in version 3.2016, added elotuzumab with lenalidomide and dexamethasone to the list of preferred regimens for patients with relapsed/refractory myeloma and designated the regimen as category 1. NCCN included a footnote specifying an indication for the treatment of patients who have received one to three prior therapies.”*

#### 4. Voting questions

- a. **The voting questions pertaining to health benefits that were evaluated during the regulatory process are not relevant to the ICER review.** The efficacy and safety of medical treatments are evaluated in the rigorous FDA drug review and approval process.

**Recommendation:** *Replace voting questions that focus on net health benefit with those that focus on value to patients, caregivers, and society.*

- b. **ICER's process of incorporating voting results into the final report and recommendations lacks transparency.** An important component of voting is the possibility of dissenting votes within voters. The process by which ICER arbitrates dissenting votes in its recommendations and more generally the extent to which dissent even occurs in the first place is unknown.

**Recommendation:** *Be transparent regarding the way the voting results are incorporated into the final report.*

#### References

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**RE: Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value (Draft Report)**

Dear Sonya,

We appreciate your organization's interest in making the health care system more effective and efficient. We agree it is imperative to support the achievement of the best patient outcomes in the most efficient way. As we mentioned in our previous letters, we still believe the Institute for Clinical and Economic Review (ICER) is utilizing an approach and methodology which are not designed to achieve this purpose.

After reviewing the draft report, we do commend ICER for recognizing the difference in trial populations between those included in the cost-effectiveness analysis, and those in the Pomalyst (POM) registration trial (MM-003)<sup>i</sup>. However, we noticed some inconsistencies as follows:

- As mentioned in the report, ICER could not include POM in the network meta-analysis because the MM-003 "trial population had more advanced disease" than the other regimens assessed. Yet POM received an evidence rating of P/I (promising but inconclusive) in 3rd- and subsequent lines.
- If the double-refractory nature of the trial population makes comparisons across the network inappropriate, it should follow that any rating of the evidence in the context of this particular assessment should also be inappropriate.
- In our view, including POM in the summary evidence ratings (Table 6) is misleading because:
  - Unlike the regimens included in the analysis, POM was studied in a double refractory population, where a majority of patients failed both an immunomodulatory agent and a proteasome inhibitor.
  - In this patient population, POM in combination with low-dose dexamethasone (LoDex) is the only regimen studied in a multi-centered, randomized Phase 3 trial (MM-003) that has demonstrated a significant advantage in both PFS (HR: 0.45; 95% CI 0.35, 0.59; p<0.001) and OS (12.7 vs. 8.1 months; HR 0.74; 95% CI 0.56-0.97; p=0.03)<sup>i</sup>
  - In contrast to the benefit found in the MM-003 trial, the P/I rating in 3<sup>rd</sup>L+ is derived from ICER's belief that the evidence on POM+Lodex provides "moderate certainty of a net health benefit that is likely at least comparative to other salvage options."
    - However, as mentioned elsewhere in the report, of all the regimens reviewed, POM was the only one associated with a statistically significant survival advantage versus the comparator.

- No references are provided to support ICER's comparative claim that the advantage is "likely at least comparative" to other options.
  - Hence, any statements about the comparative effectiveness of "other salvage options" are out of context and not evidence-based, as the report did not assess evidence in the treatment of double refractory MM.
- In addition, the report states that that POM's "true level of net health benefit is unclear. This is because observed PFS benefits were modest"(p34). In our view, the assessment of whether the benefit is modest or not is arbitrary and not evidence-based for the following reasons:
  - No explanation or frame of reference is given for why the benefit would be considered modest.
  - To our knowledge, no other Phase 3, multicenter, global, randomized trial of rMM patients who are refractory to both lenalidomide and a proteasome inhibitor have been published. Hence the assessment of whether the benefit is modest or not is without scientific basis.
  - The evidence that is available does show statistically significant improvement in outcomes. The ICER report itself acknowledges that "data for OS among the regimens of interest are relatively limited." Of all the regimens reviewed, POM was the only one associated with a statistically significant survival advantage versus the comparator.

To address any confusion that the issues above might create, **we recommend that ICER remove POM from the evidence rating table.** We believe the latter does not appropriately address the reasons for the received rating, and may result in confusion regarding the available data on the product. At the least, adding footnotes to the table may provide some more context around why the P/I rating was received. In addition, we recommend revising the language regarding POM's benefit in rMM to include more reference to the available evidence from the MM-003 (p34). We also recommend minimizing value judgments on POM's benefit and how it may compare to other agents in rMM as none of these are based on empirical evidence.

Other areas in the report where we would like to provide feedback on are below:

1. We noticed the NICE guidelines for each regimen are included alongside the NCCN guidelines (p18)
  - However, no reason is provided as to why the NICE guidelines have been chosen for inclusion in the report, and others, such as those by the Canadian Agency for Drugs and Technologies in Health (CADTH) have been limited to inclusion in the appendix.
  - There is a large difference in standards of practice for the treatment of multiple myeloma in the UK compared to the US. This makes the type of evidence required for an HTA review in the UK different from that in the US. In addition, CEA thresholds in every country may differ, and therefore could lead to different conclusions.
  - While it is reasonable to review previously published HTA reviews for the purposes of the report, we believe the body of the report should focus on well-

accepted guidelines of the most relevance to a US audience, including NCCN and IMWG.

2. We noticed the report recognizes that all results relating to PAN+BOR+DEX should be interpreted with caution, and “the relative treatment effect of PAN+BOR+DEX versus LEN+DEX ... has much greater uncertainty than the other comparisons.”
  - However, Table 14 contains comparative information for PAN+BOR+DEX without any mention of the caveats in proximity to the table.
  - We believe presenting comparative data for PAN+BOR+DEX in summary tables can be misleading if not enough context is provided. We recommend that Table 14 and any table summarizing comparative results for PAN+BOR+DEX should be accompanied by a footnote summarizing the following caveats:
    - Issues with censoring and high rates of toxicity leading to discontinuation in the trial.
    - No direct comparative evidence to Rd.
    - Reliance on the network meta-analysis for comparison with no adjustment for heterogeneity in patient populations.

In closing, we’d like to reaffirm that multiple myeloma is an example of a disease where innovation has had a tremendous effect in moving the disease from a deadly cancer to a near-chronic manageable condition. In multiple myeloma we have seen a dramatic improvement in patient outcomes as a result of novel therapies over the last 20 years, (with almost a doubling of 5-year relative survival rates from 2003- 2014).<sup>ii</sup>

Ensuring patients who need Celgene medicines can receive them is central to our purpose. We are committed to continuing our efforts, in collaboration with payers and other stakeholders, to ensure an optimal outcome for patients.

Thank you,

Claudio Faria, Pharm.D., MPH  
Sr. Director – Health Economics & Outcomes Research  
Celgene Corporation

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<sup>i</sup> San Miguel J et al. *Lancet Oncol.* 2013;14:1055-1066.

<sup>ii</sup> National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER Cancer Statistics Review, 1975-2010. Table 18.8: Myeloma, 5-Year Relative and Period Survival (Percent) by Race, Sex, Diagnosis Year and Age. Available at [http://seer.cancer.gov/archive/csr/1975\\_2010/results\\_merged/sect\\_18\\_myeloma.pdf](http://seer.cancer.gov/archive/csr/1975_2010/results_merged/sect_18_myeloma.pdf). Accessed August, 2015. Bergsagel P. Where We Were, Where We Are, Where We Are Going: Progress in Multiple Myeloma. *ASCO 2014 Educational Book*. Available at <http://meetinglibrary.asco.org/content/114000199-144>. Accessed August, 2015.

April 21, 2016

Institute for Clinical and Economic Review

Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC)

Dear ICER and Council Members,

On behalf of Janssen Scientific Affairs, LLC, we appreciate the opportunity to comment on the draft report “Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value.”

We understand ICER’s interest in pursuing this analysis, given the significant changes and evolving landscape in relapsed/refractory multiple myeloma. However, we believe the report’s accuracy and clarity can be improved, and our detailed comments for your consideration are provided below:

1. On page 7, Table 1, under “Class”, we suggest including “CD38-directed” to distinguish the specific mechanism of action of daratumumab from that of other monoclonal antibodies.<sup>1</sup>
2. In addition, in the same table, please specify the drug concentration and vial size (20 mg/ml; 100 mg/5 ml vial and 400 mg/20 ml vial)<sup>1</sup> for calculation of drug cost for a given patient.
3. Also on pages 7 and 43, Table 1 and Table 10 respectively, please cite the source and date accessed for “Unit Price” and clarify the cost are WAC.
4. On page 7, Table 1, the “Dosage Strength” column should be titled simply “Dosage,” as the mg/kg values are not dosage strengths of the intravenous formulations.
5. The full indication for daratumumab should be consistently stated throughout the report. On pages 9, 11, 35, and 52, daratumumab is mentioned as indicated for patients with at least three prior therapies, or for fourth line or later use. However, daratumumab is currently indicated for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double refractory to a PI and an immunomodulatory agent.<sup>1</sup> This indication was approved under the FDA accelerated approval program based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials, which are ongoing.
6. Daratumumab is inaccurately listed as “Category 1” therapy in NCCN guidelines on page 11. However, the NCCN guideline update in January 2016, reflected in version 3.2016, indicated that daratumumab has “Category 2A” evidence.<sup>2</sup> We recommend updating this information in the report.

7. On page 21, the absolute death rate is inaccurate. In Lonial et al, no patients discontinued due to drug-related treatment-emergent adverse events, infusion-related reactions, or death. 29% died after treatment with daratumumab, 27% because of progressive disease and 2% because of adverse events (cardiopulmonary failure secondary to H1N1 influenza complications, and general health deterioration secondary to complication of aspiration pneumonia).<sup>3</sup> We recommend revising this information in the report.
8. On page 21, the report inaccurately indicates that overall survival results for daratumumab are not available. However, the median overall survival of 17.5 months (95% CI 13.7-NE) are described on page 7 in Lonial et al already referenced in the draft report.<sup>3</sup> We recommend including the overall survival results for daratumumab.
9. The report's rationale for excluding daratumumab from the meta-analysis is incomplete. The report explains on page 27 that daratumumab was not included in the network meta-analysis because methods to incorporate single arm trial data are immature. In addition, daratumumab would have been excluded even if a comparator arm was present in the key clinical trials because the trial population had more advanced disease than the patients included in other multiple myeloma treatments. In the key clinical trial (Lonial et al), patients were heavily pretreated with a median of 5 prior lines of therapies, 95% of patients were refractory to both proteasome inhibitor and immunomodulatory agent, 97% were refractory to their last line of therapy, 90% were refractory to bortezomib, 88% were refractory to lenalidomide, 63% were refractory to pomalidomide, 48% were refractory to carfilzomib.<sup>3</sup> For balance, we recommend clarifying the reasons why daratumumab could not be included in the network meta-analysis.
10. Reference 71 does not support the statement on page 27 regarding single-arm data methodology. Consider replacing this reference with Ip S et al.<sup>4</sup>
11. On page 28, Figure 5 is misleading and implies that all interventions were studied in a similar fashion. The figure should be updated with footnotes, to reflect the differences across studies. This applies to all charts and figures (e.g. C1, C5).
12. On page 31, Table 5, the same sources of information should be used consistently for all multiple myeloma treatments. It is not appropriate to utilize different sources of information for different multiple myeloma treatments as the patient population may differ and could lead to misrepresenting treatment profiles as different populations and methodologies may have been utilized.
13. The two single-arm studies mentioned on page 32 are inaccurately described as phase II. In fact, one study (GEN501)<sup>5</sup> is a phase I/II dose-escalation/dose-expansion study and MMY2002 (SIRIUS)<sup>3</sup> is a phase II study.
14. On page 34, Table 6, and page 35, it is more accurate to describe the data needed for calculating the comparative net health benefit as "not available" when only single-arm data exists. We recommend indicating that daratumumab evidence is "not available" at the time of this assessment, rather than "insufficient," for estimating comparative net health benefit.

15. We recognize the methodology of this assessment focuses on trials for which there is an aligned indication and no comparative study data results for the current indication for daratumumab were available at the time of this report. However, relevant to the content on page 35, results of a pivotal, randomized, comparative phase III study of daratumumab + bortezomib/dexamethasone versus bortezomib/dexamethasone in patients with relapsed multiple myeloma will be presented at the ASCO Annual Meeting on June 5, 2016.<sup>6</sup>
16. On page 78, regarding Lonial et al (SIRIUS)<sup>3</sup>, for enhanced accuracy, the following updates are recommended:
- Under “Study Design and Duration of F/u”: Change “Phase III” to “Phase II” study and remove “crossover permitted” as SIRIUS is a single-arm study, so crossover is irrelevant.
  - Under “Patient Characteristics”: Update median age to 63.5 years.
  - Under “Outcomes”: Update to include the median overall survival is 17.5 months (95% CI 13.7-NE).
17. On page 79, regarding Lokhorst et al (GEN501)<sup>5</sup>, for enhanced accuracy, the following updates are recommended:
- Under “Study Design and Duration of F/u”: Change “Phase II-II” to “Phase I/II.”
  - Under “Outcomes”: For PFS: specify PFS reflects the “median PFS.”
18. On page 109, Table C6 on risk definitions: In the SIRIUS line, the listed IMWG risk stratification criteria are not “Standard,” but rather are the low-risk stratification criteria. Standard IMWG risk criteria are defined as per Chng Wj et al.<sup>7</sup>

The information provided is because of your specific unsolicited request and is not intended as an endorsement of any usage not contained in the DARZALEX™ (daratumumab) Prescribing Information. For complete information, please refer to the full Prescribing Information, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, available at [https://www.janssenmd.com/pdf/darzalex/DARZALEX\\_PI.pdf](https://www.janssenmd.com/pdf/darzalex/DARZALEX_PI.pdf).

We welcome the opportunity to discuss any of the material contained within this reply and thank you, in advance, for your consideration.

Thank you,

Pulkita Patel, Pharm. D., BCOP

Associate Director, Medical Information

Janssen Scientific Affairs, LLC

Inquiry #: 00565533



## References:

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2. National Comprehensive Cancer Network. Multiple myeloma (Version 3.2016). [http://www.nccn.org/professionals/physician\\_gls/pdf/myeloma.pdf](http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf). Accessed April 8, 2016.
3. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. 2016;Epub ahead of print. DOI:10.1016/S0140-6736(15)01120-4.
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5. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373(13):1207-1219.
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7. Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014; 28: 269–77.

April 21, 2016

Dear Ms. Khan,

We thank you for your thorough review of our data as part of the evaluation of treatment options for relapsed or refractory multiple myeloma and the opportunity to review the ICER draft report. We are pleased to see that the report confirms the cost-effectiveness of panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX), in reference to the comparator, lenalidomide and dexamethasone (LEN+DEX). We also appreciate your objective and thorough evaluation of the clinical effectiveness of the treatments included in the review.

In this response letter, we address 6 specific aspects of the ICER draft report:

**FDA Approval Post-ODAC:** The ICER report cited the Food and Drug Administration's (FDA's) Oncologic Drugs Advisory Committee (ODAC) report multiple times as a source of uncertainty around the benefit of PAN+BOR+DEX. Some of the statements raised concerns that evidence assessing the true risk-benefit of PAN+BOR+DEX was confounded by the complicated review process including the involvement of ODAC. We would like to clarify that the ODAC was called upon to provide recommendations regarding the benefits and risks of PAN in the full trial population, which included patients with 1 to 3 prior lines of therapy. This evaluation did not specifically address the prespecified subgroup for which PAN+BOR+DEX is now approved. In fact, the approval of PAN was obtained post-ODAC with convincing evidence of clinical efficacy in a population with a high unmet need. The FDA approval was based on the statistically significant progression-free survival (PFS) benefit (hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.36–0.76) and favorable assessment of the risk-benefit profile in the pre-specified 193-patient subgroup (patients who received prior BOR and IMiDs) of the full PANORAMA-1 trial population ([Table 1](#)). In addition, the PFS benefit was even greater (7.8-month PFS benefit in the PAN+BOR+DEX arm compared to the placebo+BOR+DEX arm: 12.5 vs. 4.7 months; HR: 0.47) in a more difficult-to-treat subset of patients with higher unmet need, ie, patients who received 2 or more prior regimens including BOR and IMiDs (N=147) ([Table 2](#)). This group is in fact the approved population by the FDA. Data from this group of 147 patients was the basis for approval by the European Medicines Agency (EMA) and Swissmedic and was also used by the National Institute of Health and Care Excellence (NICE) as the basis for their positive coverage decision from the PAN health technology assessment (HTA).<sup>1</sup>

For the purposes of the ICER appraisal, Novartis recommends using the subset of 147 patients for the clinical effectiveness assessment. These data represent the FDA-approved indication for use and dosing and would be consistent with the methods stated in the report.

**Post-Marketing Requirement and Safety Concerns:** We acknowledge the safety concerns raised by ICER. One of the factors that may have contributed to the safety profile (specifically the rate of diarrhea) was the route of BOR administration. At the time that the PANORAMA-1 study was conducted, BOR was administered intravenously (IV). The combination of PAN and IV BOR potentially contributed to some early discontinuations in the trial (due to diarrhea in particular). Subsequently, clinical practice has evolved to include subcutaneous (SC) BOR. More recent data suggest that PAN in combination with SC BOR is associated with a lower incidence of diarrhea. Notably, in the PANEX Extended Treatment Protocol,<sup>2</sup> where the majority of the patients received SC BOR (34 of 39 patients), the rate of grade 3/4 diarrhea was lower than in the PANORAMA-1 trial (11.8% vs 25%).

To further address dosing and route of administration, we have agreed with the FDA to conduct a post-marketing trial to generate further data with this mode of administration.

**Robustness of Evidence:** PAN was approved based on the subset analysis of the PANORAMA-1 trial, a phase 3, double-blind randomized controlled trial (RCT), thus supporting the strength of evidence in this population. Furthermore, the 2 publications of PANORAMA-1 were the only studies included in the ICER analysis to have been rated as good quality based on US Preventive Services Task Force (USPSTF) criteria. The PANORAMA-1 trial has been used by independent practice guideline organizations to assess PAN. The National Comprehensive Cancer Network's (NCCN's) guidelines for multiple myeloma, version 3.2016, include PAN+BOR+DEX on the list of preferred regimens for patients with relapsed/refractory myeloma and designate the regimen as category 1 option for patients who have received at least 2 prior therapies, including an IMiD and BOR. NICE recommends PAN+BOR+DEX for relapsed and/or refractory myeloma patients who have received at least 2 prior regimens including BOR and IMiD.

**General Methodological Considerations:** There are a few methodological considerations that may need to be revisited as ICER moves forward in finalizing the evaluation process:

- In the ICER comparison of PFS outcomes, it was noted that the gain in median PFS was generally lower for PAN+BOR+DEX (3.9 months based on the full trial population) compared to other regimens. The more appropriate comparison would be to utilize the data for 147-patient population described previously. The gain in median PFS was 7.8 months (HR: 0.47; 95% CI: 0.31–0.72) in the BOR and IMiD group that received  $\geq 2$  prior regimens, which are comparable to the outcomes reported for elotuzumab, carfilzomib, and ixazomib (range: 5–9 months).
- PAN+BOR+DEX PFS data were questioned due to the shorter median duration of follow-up (6.4 months vs 23 to 32 months in the other trials) (page 23). A closer look shows that the median duration for PAN (as reported in San Miguel 2014) was for PFS, while the median duration of follow-up reported in the other trials was for overall survival (OS). The duration of follow-up for OS in the PANORAMA-1 study was 31.3 months,<sup>3</sup> which is comparable to the 23 to 32 months reported in other studies.
- In the ICER report on page 49, PAN+BOR+DEX was mentioned as the only regimen where the 95% credible interval for PFS crosses 1. The CI including 1 might be the consequence of the lack of a direct link between these 2 therapies in the network meta-analysis (NMA), rather than evidence of uncertainties in the efficacy of PAN+BOR+DEX. Also note that assessing the proportional hazards (PH) assumption for PFS (PAN+BOR+DEX vs LEN+DEX in matched populations) indicated that the

PH assumption was violated; therefore, time-dependent (ie, 3-weekly) HRs were estimated (HRs were <1 for the first 15 cycles).<sup>4</sup> This approach was previously accepted by both NICE and the Scottish Medicines Consortium. We would appreciate if ICER could include this in the interpretation of the sensitivity analysis results discussed on Page 49.

- As noted, PAN is 1 of only 2 key product trials considered by ICER that was double-blinded. Comparing open-label and double-blind in the same NMA introduces further heterogeneity. Therefore, we request this limitation be acknowledged in this final report.

**Preferred Listing by Eminent Health Plans:** The report lists PAN as a non-plan-preferred alternative in third-line therapy for Express Scripts. The current payer market assessment confirms broad coverage for PAN in 93% of affected commercial lives and 88% of affected Medicare lives. We suggest removing the sentence related to Express scripts on page 10 from the report.

**Concluding Remarks:**

Numerous approvals and listings by key HTA bodies and eminent health plans clearly delineate the clinically significant benefit of the PAN regimen in the approved population.

Rating panobinostat as “inconclusive” as a second-line therapy is not relevant to the approved population since the drug is indicated for third or later lines of therapy. We recommend it be removed from the second-line therapy rating.

Additionally, we request that the ICER committee consider reassessing the clinical efficacy rating of PAN+BOR+DEX regimen in the third or subsequent line of therapy.

The evidence provided above highlights the clinical efficacy of the PAN+BOR+DEX regimen under its approved indication and supports the conclusiveness of its net benefit.

Sincerely,

William Hinshaw  
Executive Vice President  
US Oncology

Richard C. Woodman, MD  
Senior Vice President  
US Oncology, CDMA

## Appendix

**Table 1: Prior BOR & IMiD (n=193)**

Key Trials	Patient Characteristics	Treatment	Comparator	Harms (Treatment Arm)
PANORAMA-1 Double-blind RCT Phase 3 Panobinostat (PAN): <b>Label population</b>	<ul style="list-style-type: none"> <li>• Median age: 60</li> <li>• ISS Stage III: 20%</li> <li>• Previous SCT: 72%</li> <li>• 1 prior regimen: n/a</li> <li>• Prior BOR+DEX: 95%</li> <li>• Prior LEN: 36%</li> </ul>	<b>PAN+BOR+DEX</b> (n=94) • Median f/u: 45.1 m	<b>Placebo+BOR+DEX</b> (n=99) • Median f/u: 40.2m	<ul style="list-style-type: none"> <li>• D/C due to AEs: 31.5%</li> <li>• SAEs: 56.5%</li> <li>• Tx-related deaths: 6.5%</li> </ul>
		<ul style="list-style-type: none"> <li>• OS HR: 1.03 (95% CI: 0.72, 1.47)*</li> <li>• PFS HR: 0.52 (95% CI: 0.36-0.76)</li> </ul>		
		<ul style="list-style-type: none"> <li>• Median PFS: 10.6 m</li> <li>• ORR: 58.5%</li> </ul>	<ul style="list-style-type: none"> <li>• Median PFS: 5.8 m</li> <li>• ORR: 41.4%; p value=0.0189</li> </ul>	

\*OS was derived from population treated for 12 months.

**Table 2: ≥2 Prior Lines of Therapy (including BOR & IMiD) (n=147)**

Key Trials	Patient Characteristics	Treatment	Comparator	Harms (Treatment Arm)
PANORAMA-1 Double-blind RCT Phase 3 Panobinostat (PAN): <b>Indicated population</b>	<ul style="list-style-type: none"> <li>• Median age: 61</li> <li>• ISS Stage III: 21%</li> <li>• Previous SCT: 74%</li> <li>• 1 prior regimen: n/a</li> <li>• Prior BOR+DEX: 95%</li> <li>• Prior LEN: 38%</li> </ul>	<b>PAN+BOR+DEX</b> (n=73) • Median f/u: 52.9 m	<b>Placebo+BOR+DEX</b> (n=74) • Median f/u: 46.3m	<ul style="list-style-type: none"> <li>• D/C due to AEs: 31.9%</li> <li>• SAEs: 59.7%</li> <li>• Tx-related deaths: 6.9%</li> </ul>
		<ul style="list-style-type: none"> <li>• OS HR: 1.01 (95% CI: 0.68, 1.50)*</li> <li>• PFS HR: 0.47 (95% CI: 0.31-0.72)</li> </ul>		
		<ul style="list-style-type: none"> <li>• Median PFS: 12.5 m</li> <li>• ORR: 58.9%</li> </ul>	<ul style="list-style-type: none"> <li>• Median PFS: 4.6 m</li> <li>• ORR: 39.2%; p-value=0.02296</li> </ul>	

\*OS was derived from population treated for 12 months.

**References:**

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3. Novartis. PANORAMA 1 clinical study report.
4. Company Evidence Submission. Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (ID663). National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA). May 2015.

We appreciate the opportunity to provide feedback to the Institute for Clinical and Economic Review (ICER) on its draft assessment of *Treatment Options for Relapsed or Refractory Multiple Myeloma*. Takeda Oncology supports the robust and transparent evaluation of evidence related to treatment regimens for multiple myeloma (MM), a rare and incurable disease, and understands the challenges of the disease, as well as the difficulties of conducting such a review. The impact of innovative medicines on the outlook of MM patients is an epitome of progress in the war against cancer<sup>i</sup>. Since developing VELCADE nearly 20 years ago, Takeda Oncology is proud to continue addressing unmet needs in efficacy, safety and treatment burden by delivering therapies like NINLARO, the first and only oral proteasome inhibitor that may help patients overcome real-world barriers to receiving effective therapy.

We agree with ICER's draft assessment that the recently approved innovative therapies:

- Have greatly improved the lives of patients living with MM.<sup>ii</sup>
- Provide a similar and meaningful progression-free survival (PFS) benefit over currently available therapies, including lenalidomide and dexamethasone (Rd).<sup>iii</sup>
- Have a limited budget impact that does not approach thresholds for payer management.<sup>iv</sup>

Furthermore, ICER has stated that there are not sufficient data to draw sound, evidence-based conclusions on the comparative value of these innovative therapies.<sup>v</sup> Takeda Oncology agrees with this conclusion.

Nevertheless, we are surprised that given the clinical and economic value of NINLARO - the proven efficacy, manageable safety profile and improved convenience at a lower price - the assessment did not reflect these benefits. This leads to some questions regarding the methodology:

- Why is the cost of managing adverse events (AEs) in ICER's model lower with a three- drug regimen than with the two-drug regimen for each of the three Rd-based trials analyzed?<sup>vi</sup> This contradicts the results of each of the trials where frequency of all AEs is higher with the triplet regimen, as expected biologically.
- Why does the drug combination that offers the least benefit, with the most AEs and highest data uncertainty, become the preferred option in ICER's model? Although the authors recognize this internal contradiction and provide caution on the interpretation, the internal contradiction remains unresolved.<sup>iv</sup>
- Why does the least expensive drug (NINLARO), when given for a similar duration, yield the most expensive total drug cost?<sup>vii</sup>
- Rd was used as the control arm in multiple trials and resulted in vastly different PFS, demonstrating that patient characteristics were different across trials. How is it that these differences in study populations are not recognized in ICER's model?
- Finally, and most importantly, why has the multiple myeloma patient experience not been incorporated?

**Why is the cost of managing AEs in ICER's model lower with a three-drug regimen than with the two-drug regimen for each of the three Rd-based trials analyzed?**

According to the draft assessment, the cost to manage AEs of a triplet regimen is lower than for a doublet regimen.<sup>vi</sup> This is in spite of the increased incidence of AEs demonstrated in all four trials with the addition of a third drug. We're not clear how that is possible.

Additionally, the model excludes AEs of less than 5% incidence, and does not take into account the impact of more rare events like Grade 3/4 ischemic heart disease and heart failure. These AEs are significantly more costly and more severe with large impact on healthcare resources and patient lives. In addition, Grade 1/2 AEs, which may be differentiated across therapies and affect real-world outcomes and quality of life, are not even considered.

Further, in computing the impact of AEs on quality-of-life, the same values are used across all adverse events when we believe they should be differentiated by severity and impact on patients. In this assessment, avoiding AEs that have a negative impact on patients but have a small, associated healthcare cost will have almost no impact, in spite of the obvious added value of such drugs.

**Why does the drug combination that offers the least benefit, with the most AEs and highest data uncertainty, become the preferred option in ICER's model?**

ICER acknowledges the following about one of the combinations assessed:<sup>viii</sup>

"[...] these results should be interpreted with caution as our estimate of treatment effect for this regimen was far more uncertain than that for the other regimens, and that overall efficacy findings [...] were questioned by regulators and HTA agencies [...]."

Nevertheless, this very regimen is the model's preferred regimen.

**Why does the least expensive drug (NINLARO), when given for a similar duration, yield the most expensive total drug cost?**

ICER concludes that the three newly approved Rd-based triplets have similar efficacy, yet it is not logical that the least expensive drug (NINLARO) yields the highest total drug cost when given for the same duration in the trials. We do not know what the methodological origins of this contradiction are. We hypothesize that given that ICER did not have an understanding of the dose intensity in each of the trials, the model may overestimate the amount of drug used. Dose intensity may be defined differently across trials for different products; as a result, cost may be over or underestimated for different regimens. For example, we know that if a patient uses a full-dose of NINLARO for one cycle and no dose for subsequent cycles, the patient's reported dose intensity in NINLARO's trial will be 100%, while the actual drug used would be much less. What number did ICER use when computing the total drug cost? This could have accounted for an artificially higher cost in ICER's model.

**How is it that these differences in study populations are not recognized in ICER's model?**

ICER's assessment is that there is no significant difference in characteristics between the patients in the Rd-based trials.<sup>ix</sup> Nevertheless, outcome differences across trials in the use of the same regimen (Rd) would suggest otherwise (11 months PFS in MM-09; 17.6 months PFS in ASPIRE).

The network meta-analysis methodology has limitations when evaluating study populations with significant differences among patients. Such limitations are evident in a +/-60% difference in the median progression-free survival of the Rd regimen across studies conducted more than a decade apart. No formal



testing for heterogeneity appears to have been conducted. Therefore, results should be presented with sufficient caveats regarding the difficulties in comparing efficacy across the varying trial designs and study populations. We're concerned that ICER's methodology does not take into account the heterogeneity of the disease. There are multiple factors that determine the best course of treatment and possible outcomes for each individual patient, many of which are not included in this assessment.

#### **Why has the multiple myeloma patient experience not been fully incorporated?**

Health Technology Assessments (HTAs) regularly take into account patients' perspectives and recognize the value that these perspectives can bring. Patients and their advocates should play a role in all stages of the process from scoping to decision making to dissemination of results.<sup>x</sup>

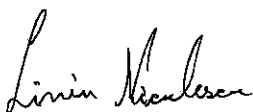
After nearly two decades of partnering with patients and caregivers, we've learned about the journey that patients take to receive therapy. We know that current therapies requiring frequent infusions or injections at a hospital, clinic or physician's office create barriers to treatment. For example, patients and caregivers may need to take time off work or struggle with transportation. We've seen the difficulties that elderly or immobile patients sometimes have in coming to the clinic. We've seen the stress and impact of a MM diagnosis on patients and caregivers. These are costs that impact caregivers, patients and society.<sup>xi</sup> Despite the obvious advantages of regimens that would reduce these costs, such as an all oral therapy like NINLARO+Rd, ICER's model does not capture the associated costs like travel expenses, lost wages and caregiver time in its calculations nor the benefits of such improvements.

#### **Conclusion**

Takeda Oncology appreciates ICER's efforts, however, we are concerned that the current model could mislead patients, physicians, payers and policymakers and may result in practice decisions that limit access for patients living with MM. We are unsure how the assumptions and methodologies used in conducting the economic evaluation can overcome differences in patient populations and lack of data.

Due to the lack of comparative and real-world data available for newly approved therapies and the complexity of treating patients with multiple myeloma, we hope that ICER will take the time to better understand the heterogeneity of the disease, meet with the various stakeholders (including patients, physicians, advocacy groups and manufacturers) and conduct a final assessment when sufficient data are available for a sound conclusion.

We are proud to have launched NINLARO, providing patients with a combination of efficacy, a manageable safety profile and the convenience of oral delivery at a price per cycle that is approximately 5% to 50% less expensive than the recently introduced new agents.<sup>xii</sup> In the war on cancer, MM is one successful example where drug therapies have significantly improved the outlook for patients. But more remains to be done.



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- <sup>ii</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. pg. 1
- <sup>iii</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. pg. 33
- <sup>iv</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. Pg. 55
- <sup>v</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. pg. 27
- <sup>vi</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. Table 13, pg. 47
- <sup>vii</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. Table 1, pg. 7
- <sup>viii</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report. pp 55-56
- <sup>ix</sup> Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value. Draft report, table 7 pg 39
- <sup>x</sup> Facey K, Boivin A, Gracia J, et al. *Int J Technol Assess Health Care*. 2010;26:334-40.
- <sup>xi</sup> Duh MS, Hackshaw MD, Ivanova I, et al. *Sarcoma*. 2013;2013:947413.
- <sup>xii</sup> Wolters Kluwer Medi-Span Price Rx Web site. Accessed April 20, 2016.