

Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks

Draft Background and Scope

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Background:

Multiple myeloma (MM) is a blood cancer in which the bone marrow produces an overabundance of malignant plasma cells that emerge into the bloodstream. Ultimately, the proliferation of plasma cells can cause bone damage, anemia, low white blood cell counts, and kidney failure.¹ Approximately 25,000 cases of MM are diagnosed in the U.S. annually, with three quarters of affected individuals over 70 years of age. There is no cure for multiple myeloma, but its progression can be relatively slow in many individuals, often involving multiple rounds of remission after treatment followed by a subsequent relapse. Recent advances in therapy have greatly improved the disease's prognosis. Nearly half of all patients will survive at least 5 years after diagnosis, and nearly 100,000 individuals are currently living with the disease in the U.S.² The costs of managing multiple myeloma are substantial, given the use of multiple therapies over the course of the disease. The cost of a single course of drug therapy has been estimated to range from \$75,000 - \$250,000 for patients with relapsed or refractory disease.³ Many patients are also treated with a hematopoietic stem cell transplant early in the disease course, the costs of which can approach \$60,000 in uncomplicated cases and double this figure in cases with infectious complications or stomatitis.^{4,5}

Over the past decade the treatment of MM in the U.S. has been anchored by two drugs, often given in combination with dexamethasone. The first of these drugs to enter use was the proteasome inhibitor bortezomib (Velcade®, Takeda Millennium) in 2003, followed by the immune modulator lenalidomide (Revlimid®, Celgene) in 2005. Other medications have more recently become available specifically for the treatment of relapsed or refractory disease, including the immune modulator pomalidomide (Pomalyst®, Celgene), proteasome inhibitors carfilzomib (Kyprolis®, Onyx) and ixazomib (Ninlaro®, Takeda), the monoclonal antibody daratumumab (Darzalex®, Janssen Biotech), the immunostimulatory antibody elotuzumab (Empliciti®, Bristol Myers-Squibb), and the histone deacetylase inhibitor panobinostat (Farydak®, Novartis Pharmaceuticals Corp.). There is uncertainty, however, regarding the comparative tradeoffs between effectiveness and toxicity of these therapies and their various combinations. Cost considerations have also increased along with the list prices and potential for multiple drug combinations in varying sequences. Thus there remains substantial uncertainty regarding how best to interpret and apply the available evidence to guide clinical practice and insurance coverage policies.

Report Aim:

This project will evaluate the health and economic outcomes of multiple treatment regimens for relapsed or refractory multiple myeloma.

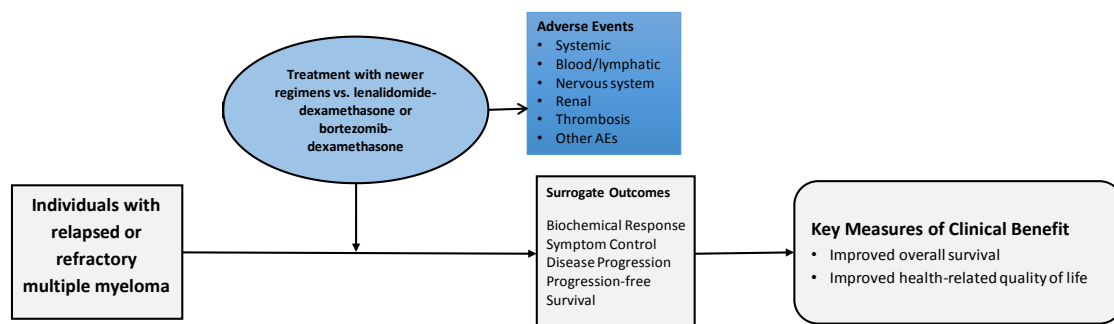
Scope of the Evidence Review Focusing on Comparative Clinical Effectiveness:

The proposed scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated as necessary. We will not restrict studies according to clinical development phase, comparators, or study setting; however, we will limit our review to those studies that match FDA-approved indications for use and dosing for the regimens of interest, as well as those that capture the key outcomes (see “Outcomes” on page 3). Studies comparing one of the listed regimens for this assessment to an investigational regimen without a current FDA indication will be excluded. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <http://www.icer-review.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/>).

Analytic Framework:

The analytic framework for this assessment is depicted in Figure 1 below.

Figure 1. Analytic Framework: Management of Relapsed/Refractory Multiple Myeloma



Populations

The population of focus for the review will be adults with multiple myeloma whose disease has not responded to the most recent previous line of treatment (i.e., refractory) or has relapsed following such treatment, are not currently on maintenance treatment, and are not being considered for stem cell transplant.

Interventions

The interventions of interest are listed below and on the following page. Regimens listed are based on FDA-labeled indications for treatment of relapsed/refractory disease as well as expert input regarding the treatment approaches that are currently of greatest clinical interest.

- Carfilzomib with lenalidomide and dexamethasone
- Daratumumab monotherapy

- Elotuzumab with lenalidomide and dexamethasone
- Ixazomib with lenalidomide and dexamethasone
- Panobinostat with bortezomib and dexamethasone
- Pomalidomide with low-dose dexamethasone

Comparators

The primary comparators of interest will be the historical standard treatments for this population, either lenalidomide or bortezomib in combination with dexamethasone. We recognize, however, that several recent trials have involved comparisons to dexamethasone alone and/or placebo, or have utilized single-arm designs. Results for each treatment will be presented across all comparators as well as stratified by type of comparator for agents whose effects have been compared to multiple regimens.

Outcomes

This review will examine key clinical outcomes associated with multiple myeloma, including surrogate outcomes common to cancer trials. In order to inform considerations regarding possible treatment sequencing, results will be summarized on an overall basis as well as stratified by number of prior treatments where such data are available. Outcomes of interest will include:

- Overall survival
- Disease progression-related measures (progression-free survival, time to progression)
- Biochemical response (overall response rate)
- Duration of response
- Symptom control
- Health-related quality of life
- Treatment-related adverse events:
 - Rates of key adverse events by type (e.g., systemic, nervous system, blood/lymphatic, etc.)
 - Rates of Grade 3 or 4 key adverse events
 - Discontinuation due to adverse events

Evidence tables will be developed for each selected study, and results will be summarized in qualitative fashion. In addition, quantitative indirect comparisons of certain outcomes using Bayesian network meta-analysis will be considered where feasible.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Simulation Models Focusing on Comparative Value:

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the regimens of interest relative to standard treatment with bortezomib+dexamethasone and lenalidomide+dexamethasone. Model structure will be based in part on a previously-published lifetime model of multiple myeloma from a health-system perspective.⁶ The model will focus attention on regimens most likely to be used for second- and third-line treatment respectively; key model estimates will differ to reflect differences in disease severity and quality of life for patients receiving second- vs. third-line treatment. Effectiveness will be estimated based on network meta-analyses of progression-free

and/or overall survival. Data will be stratified according to number of prior treatments where available, subject to examinations of and adjustment for between-study heterogeneity.

Based on input from clinical experts as well as listed FDA indications, the second-line regimens to be modeled include carfilzomib, elotuzumab, and ixazomib, each in combination with lenalidomide and dexamethasone. These regimens will also be analyzed as third-line treatment, along with panobinostat in combination with bortezomib and dexamethasone. Note that, while considered in scope for the evidence review, neither daratumumab nor pomalidomide will be included in the model. There are no currently-available clinical trial data comparing daratumumab to an alternative treatment regimen, and methods to incorporate single-arm data in network meta-analyses are considered immature and unvalidated.^{7,8} In addition, pomalidomide has only been studied in patients refractory to bortezomib and lenalidomide, rendering any explicit cost-effectiveness comparisons to these regimens problematic.

Key model outputs will include rates of progression-free and progressive disease as well as time spent in these health states, treatment-related adverse events, disease-related survival, and the impact of these measures on health-related quality-of life. Costs will include those of current and subsequent treatment, management of adverse events, and ongoing myeloma-related care. Results will be expressed primarily in terms of the cost per quality-adjusted life year (QALY) gained.

We will also assess the potential budgetary impact of each regimen over a 5-year time horizon, utilizing information on treatment costs and cost offsets from extended response and/or time off treatment. Potential budgetary impact analyses will assume a product “uptake” rate over the 5-year period based on ICER criteria. Finally, we will develop a “value-based price benchmark” for each regimen reflecting prices aligned with long-term cost-effectiveness thresholds and below a threshold for potential budgetary impact that would exceed growth targets for national health care costs.

More information on ICER’s methods for estimating product uptake and calculating value-based price benchmarks can be found at: <http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf>.

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