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]

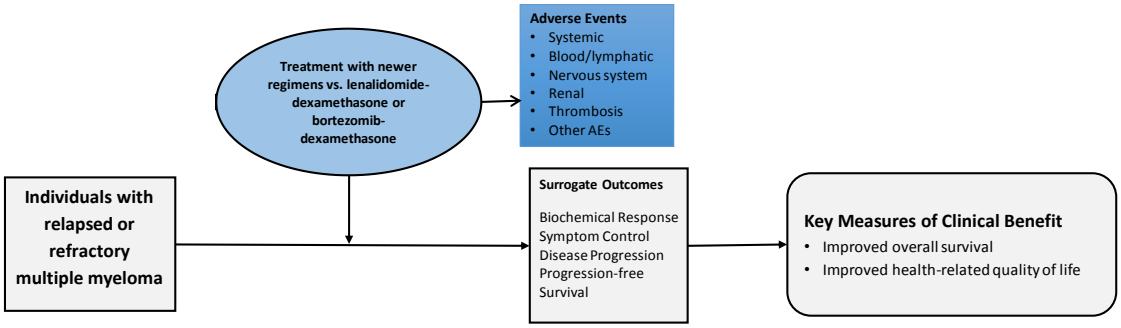
Over the past decade the treatment of MM in the U.S. has been anchored by two drugs, often given in combination with dexamethasone. The first of these drugs to enter use was the proteasome inhibitor bortezomib (Velcade®, Takeda Millennium) in 2003, followed by the immune modulator lenalidomide (Revlimid®, 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 clinical trials as well as high-quality systematic reviews where available. 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, as well as those that capture the outcomes of interest (see "Outcomes" on page 3). In addition to published studies, we will supplement our review with data from conference proceedings, regulatory documents, and other grey literature where available (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 at least one 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. Results will be presented on an overall basis 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-related measures (partial/complete response, overall response rate)
- Duration of response/time without treatment
- 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, using data from analyses stratified by number of prior treatments where available. Based on input from clinical experts as well as listed FDA indications, proposed second-line regimens include carfilzomib, elotuzumab, and ixazomib, each in combination with lenalidomide and dexamethasone. These regimens will also be analyzed as third-line treatment, along with daratumumab monotherapy, panobinostat in combination with bortezomib and dexamethasone, and pomalidomide in combination with low-dose dexamethasone.

Key model outputs will include rates of partial/complete response and progressive disease, time without treatment, requirements for subsequent therapy, treatment-related adverse events, disease-related mortality, 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.

References:

1. Multiple Myeloma Research Foundation. What is multiple myeloma? Accessed at: http://www.themmrf.org/multiple-myeloma/what-is-multiple-myeloma/, January 2016.

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3. Roy A, Kish JK, Bloudek L, et al. Estimating the costs of therapy in patients with relapsed and/or refractory multiple myeloma: a model framework. *Am Health Drug Benefits* 2015;8:204-2015.

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6. Garrison LP, Wang ST, Huang H, et al. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide treatment. *The Oncologist* 2013;18:27-36.