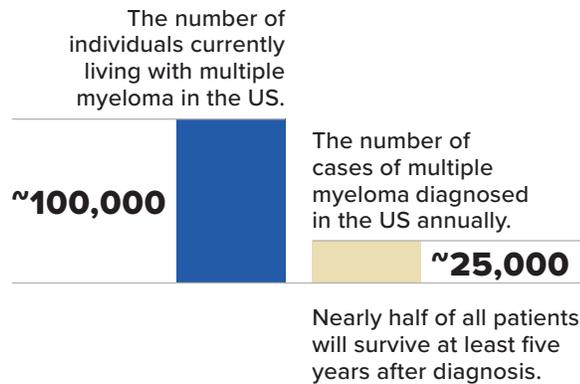


For Multiple Myeloma

Do these new drugs meet an important need?

What is Multiple Myeloma?

Multiple myeloma is a cancer of the blood in which the bone marrow produces a high number of cancerous plasma cells. The excessive growth of plasma cells can cause bone damage, anemia, hypercalcemia (high calcium levels in the blood), neutropenia (low counts of a certain type of white blood cell), and kidney failure. There is no cure for multiple myeloma, but its progression can be relatively slow. Many patients undergo multiple rounds of treatment, followed by remission and subsequent relapse.



Treating Multiple Myeloma

Over the past decade, proteasome inhibitors (PIs), such as bortezomib (Velcade®, Takeda Millennium), and immunomodulatory drugs (IMiDs), such as the second-generation IMiD lenalidomide (Revlimid®, Celgene), have been the mainstays of treatment for multiple myeloma in the US, and have resulted in significant improvements in survival. These agents are often given in combination with the synthetic corticosteroid dexamethasone, as well as other cytotoxic agents. They may be used in combination with stem cell transplant or as first-line treatment in patients ineligible for transplant.



\$75,000–\$250,000 and higher

Cost of a single course of drug therapy for patients with relapsed or refractory disease.

Regimens Under Review

Since 2012, the FDA has approved several therapies specifically for second-line or later treatment of relapsed or refractory multiple myeloma (RRMM). The majority of these drugs are used in combination with historical standard treatments, and have the potential to build on the gains in survival already seen by the introduction of PI and IMiD therapy into practice.

New Treatments	Previous Standard Treatments	Regimens Under Review
Carfilzomib (Kyprolis®, Onyx) (CFZ)	Lenalidomide (LEN)	CFZ+LEN+DEX
Daratumumab (Darzalex®, Janssen Biotech) (DARA)	Bortezomib (BOR)	DARA
Elotuzumab (Empliciti®, Bristol Meyers-Squibb) (ELO)	Dexamethasone (DEX)	ELO+LEN+DEX
Ixazomib (Ninlaro®, Takeda) (IX)		IX+LEN+DEX
Panobinostat (Farydak®, Novartis Pharmaceuticals Corp.) (PAN)		PAN+BOR+DEX
Pomalidomide (Pomalyst®, Celgene) (POM)		POM+LoDEX

How strong is the evidence that these new treatments improve patient outcomes?

Overall Survival

Data on overall survival among the newer regimens are still emerging; only two studies of POM and PAN respectively, reported results from final survival analyses.

- POM+LoDEX: 4.6 months of improved survival compared to single-agent high-dose DEX
- PAN+BOR+DEX: No statistical difference compared to BOR+DEX.

Interim analyses indicate that CFZ+LEN+DEX and ELO+LEN+DEX may also benefit overall survival. Follow-up for overall survival with IX+LEN+DEX is still ongoing. No comparative data on overall survival are currently available for DARA.

Quality of Life

Health-related quality of life data have been published for four of the six regimens reviewed:

- CFZ+LEN+DEX: greater improvements compared with LEN+DEX over 18 cycles of treatment
- POM+LoDEX: greater improvements in seven out of eight domains of health-related quality of life compared with high-dose DEX alone
- ELO+LEN+DEX and IX+LEN+DEX: no differences compared with LEN+DEX

Progression-Free Survival

Progression-free survival is defined as the length of time during or after treatment that a patient lives with cancer without evidence of worsening disease.

Trial	Regimen	Median Progression-free survival (months)
ASPIRE	CFZ+LEN+DEX	26.3
	LEN+DEX	17.6
ELOQUENT-2	ELO+LEN+DEX	19.4
	LEN+DEX	14.9
SIRIUS	DARA	3.7
TOURMALINE-MM1	IX+LEN+DEX	20.6
	LEN+DEX	14.7
PANORAMA-1	PAN+BOR+DEX	12.5
	BOR+DEX	4.7
MM-003	POM+LoDEX	3.6
	HiDEX	1.8

How strong is the evidence that these new treatments improve patient outcomes? *(continued)*

Harms

Across key studies of the drugs of interest, discontinuation of study therapy due to adverse events ranged between 5% and 17% for all regimens except PAN+BOR+DEX (36%). Relative to other regimens, PAN+BOR+DEX presented a more severe toxicity profile with disproportionately higher rates of diarrhea, peripheral neuropathy, thrombocytopenia, and fatigue.

Serious adverse events of concern for the other regimens include venous and arterial thromboembolism with immunomodulatory drug therapy (i.e., POM or therapies combined with LEN), as well as cardiac toxicity with CFZ. Hematological adverse events were relatively common in all of the therapies of focus and included anemia, neutropenia, thrombocytopenia, lymphopenia, and leukopenia.

Sources of Uncertainty

- With the exception of POM+LoDEX, final overall survival data demonstrating statistically-significant improvement with newer regimens are not yet available. Progression-free survival may be problematic as a surrogate for overall survival in clinical practice, as it has not been shown to be universally predictive of survival benefit in RRMM.
- The evidence base is still emerging for newer regimens. Each regimen's performance at different points during the disease course remains unclear, and the lack of head-to-head studies makes comparison of the regimens problematic. Certainty in the evidence is further limited by the lack of Phase III comparative data for DARA.
- Doubts about whether PAN's benefits outweighed its risks led the FDA to conditionally approve PAN in only a subgroup of the Phase III PANORAMA-1 trial. An additional Phase III study of PAN+BOR+DEX in this subgroup (patients who received prior treatment with BOR and an IMiD) will not be completed until 2021.
- Despite having a higher prevalence of multiple myeloma, African American patients have been underrepresented in trials available at the time of this review. Further study of the effectiveness of newer regimens in this population is needed.

ICER Evidence Ratings

- Given the lack of head-to-head data, there is insufficient evidence to distinguish comparative net health benefit between newer regimens.
- Relative to LEN+DEX alone, we judge there to be moderate certainty that CFZ, ELO, and IX, in combination with LEN+DEX, provide an incremental or better net health benefit for both second-line and third-line or subsequent therapy.
- Evidence was insufficient to determine a net health benefit for patients receiving POM+LoDEX for second-line treatment, as the key Phase III trial only evaluated patients receiving the regimen for third-line or later use. As a third-line or subsequent therapy, we judge the evidence for POM+LoDEX to be promising but inconclusive given its comparison to a salvage option (HiDEX) not in widespread use in the U.S.
- There is insufficient evidence to determine the comparative net health benefit for DARA monotherapy as either second-line or third-line or subsequent therapy because comparative data is not yet available and the intended use of the drug is for fourth-line or later use in patients who have met specified criteria for previous treatment.
- Evidence was also insufficient to determine the net health benefit of PAN+BOR+DEX as a second-line treatment. We judge the evidence on its use as a third-line option to be promising but inconclusive given concerns about higher rates of toxicity relative to other regimens.

What is a fair price for the newer regimens based on their value to patients and the health care system?

Long-Term Cost-Effectiveness at List Price

Computer modeling of long-term clinical benefits and costs estimated a gain in quality of life from increased progression-free survival. Even considering some possible reduction in costs associated with oral administration (vs. intravenous), overall costs nevertheless increased with these newer regimens.

The incremental cost-effectiveness ratio was measured by calculating the cost per additional quality-adjusted life year (QALY).

For second-line treatment, the cost per QALY was approximately:

- \$199,982 for CFZ+LEN+DEX
- \$427,607 for ELO+LEN+DEX
- \$433,794 for IX+LEN+DEX

For third-line treatment, the cost per QALY was approximately:

- \$238,560 for CFZ+LEN+DEX
- \$481,244 for ELO+LEN+DEX
- \$484,582 for IX+LEN+DEX

PAN+BOR+DEX was estimated to provide more QALYs at a lower cost than LEN+DEX as a third-line therapy. Cost-effectiveness vs. BOR+DEX was estimated to be \$10,230 per QALY. However, given lingering concerns over high rates of study discontinuation due to toxicity, the long-term cost-effectiveness remains uncertain.

The cost per QALY range that is generally accepted as “reasonable” value in the US is \$50,000-\$150,000 so **CFZ+LEN+DEX, ELO+LEN+DEX, and IX+LEN+DEX at list prices would not represent good value in the long-term.**

* Note that cost-effectiveness and budget impact were not estimated for DARA and POM+LoDEX. Only single-arm data are available for DARA and therefore no incremental treatment effect vs. LEN+DEX could be estimated. DARA and POM+LoDEX were studied in populations with more advanced disease (i.e., refractory to BOR and/or LEN), so their effects could not be considered comparable to those of the other regimens.

Potential Short-Term Budget Impact at List Price

Second-Line Treatment. Approximately 33,941 individuals in the US would be eligible for second-line treatment of refractory multiple myeloma. Assuming no coverage or reimbursement restrictions, we estimate that approximately 75 percent of all eligible patients, or 25,455 individuals, would be prescribed CFZ+LEN+DEX, ELO+LEN+DEX, or IX+LEN+DEX over a five-year time horizon, with 25% of patients allotted to each regimen. Over this period, the average potential budget impact per year is approximately \$226 million for CFZ+LEN+DEX, \$395 million for ELO+LEN+DEX and \$330 million for IX+LEN+DEX.

Third-line Treatment. Approximately 11,930 individuals in the US were assumed to be eligible for third-line treatment of refractory multiple myeloma. If insurers do not manage uptake, we estimate that approximately 75 percent

of all eligible patients, or 8,940 individuals, would be prescribed CFZ+LEN+DEX, ELO+LEN+DEX, IX+LEN+DEX, or PAN+BOR+DEX over a five-year time horizon, with equal shares allotted to each regimen. Over this period, the average potential budgetary impact per year is estimated to be approximately \$59 million for CFZ+LEN+DEX, \$99 million per year for ELO+LEN+DEX, \$83 million for IX+LEN+DEX, and \$12 million for PAN+BOR+DEX.”

Summary. No regimen approached ICER’s annual threshold of \$904 million for the potential budget impact at which a drug would overly strain affordability of the health care system, so **these agents do not pose a substantial threat to health system affordability in the short-term, regardless of whether they are used as second- or third-line treatments.**

**vs. BOR+DEX

What is a fair price for the newer regimens based on their value to patients and the health care system? *(continued)*

ICER's Value-Based Price Benchmark

Second-line Value-Based Price Benchmarks

Drug	VBPB	Discount from list price*
CFZ	\$673 to \$1,267 per vial	32%-64%
ELO	\$267 to \$588 per 400 mg vial	75%-89%
IX	\$181 to \$587 per capsule	80%-94%

*Discount from wholesale acquisition cost

Third-line Value-Based Price Benchmarks

Drug	VBPB	Discount from list price*
CFZ	\$432 to \$974 per vial	48%-77%
ELO	\$178 to \$466 per vial	80%-93%
IX	\$74 to \$440 per capsule	85%-97%
PAN	\$2,933 to \$3,886 per capsule	N/A

*Discount from wholesale acquisition cost

Note: The price benchmark for PAN is higher than the list price and is calculated in relation to use of this agent with BOR+DEX versus BOR+DEX alone, as this would be the more realistic comparator for pricing considerations.

ICER's value-based price benchmark incorporates two components: a range of the prices needed to achieve long-term cost-effectiveness between \$100,000-\$150,000 per QALY; and, if necessary, a lower price at which short-term potential budget impact does not threaten overall health system affordability.

Public Deliberation and Evidence Votes

Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) Panel Votes

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) deliberated on key questions raised by ICER’s report on treatments for multiple myeloma at a public meeting on May 26, 2016. The results of the vote are presented below.

For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following one line of therapy:

1. Is the evidence adequate to demonstrate that the net health benefit of treatment of each regimen listed below is greater than that of treatment with lenalidomide and dexamethasone?

a. carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)

Yes: 11 votes	No: 0 votes
---------------	-------------

b. elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)

Yes: 10 votes	No: 1 votes
---------------	-------------

c. ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Yes: 9 votes	No: 2 votes
--------------	-------------

Comments: Members of the Midwest CEPAC voting yes commented that, while they felt there to be adequate evidence of improved net health benefit with each of these newer regimens, more evidence would be helpful to guide clinical practice. In particular, further study should confirm improvements in overall survival, identify patient subpopulations that may benefit from specific treatments, and provide head-to-head comparisons of different treatment sequences of available agents.

2. Is the evidence adequate to distinguish the net health benefit of treatment among these three regimens?

- carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Yes: 2 votes	No: 9 votes
--------------	-------------

Comments: The primary justification given for the “no” votes was that there were no head-to-head studies and that the indirect comparison performed by ICER staff through a network meta-analysis found that the relative benefits of these treatment regimens were very similar across the study populations.

Public Deliberation and Evidence Votes *(continued)*

For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to or has relapsed following two or more lines of therapy:

3. Is the evidence adequate to demonstrate that the net health benefit of treatment with the regimens listed below is greater than that of comparator treatment listed?

a. carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX) vs. LEN+DEX

Yes: 10 votes	No: 1 votes
----------------------	--------------------

b. elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX) vs. LEN+DEX

Yes: 11 votes	No: 0 votes
----------------------	--------------------

c. ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX) vs. LEN+DEX

Yes: 11 votes	No: 0 votes
----------------------	--------------------

d. panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX) vs. BOR+DEX

Yes: 5 votes	No: 6 votes
---------------------	--------------------

Comments: As illustrated by the votes, members of the Midwest CEPAC were most concerned with the evidence on PAN+BOR+DEX, largely due to concerns about toxicity. Members voting yes believed that the levels of toxicity seen in the Phase III trial might be mitigated by the use of subcutaneous BOR rather than the intravenous administration used for most patients in the trial. A member voting no shared that while he was tempted to vote yes as a result of this possibility, the weight of the evidence remained equivocal.

4. Is the evidence adequate to distinguish the net health benefit of treatment among these regimens:

- carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Yes: 3 votes	No: 8 votes
---------------------	--------------------

Comments: As with the similar voting results for this question regarding net health benefit in second-line use, the primary justification given for the “no” votes was that there were no head-to-head studies and that the indirect comparison performed by ICER staff through a network meta-analysis found that the relative benefits of these treatment regimens were very similar across the study populations.

Public Deliberation and Evidence Votes *(continued)*

5. For adults with relapsed and/or refractory multiple myeloma who are not currently on maintenance treatment and are not being considered for stem cell transplant, is the evidence adequate to determine the net health benefit of treatment with daratumumab in patients with **less than three** prior lines of therapy?

Yes: 4 votes	No: 6 votes
---------------------	--------------------

* 1 member abstained

Comments: At the time of this vote, clinical experts shared that there was new evidence, soon to be publicly released, that may change opinion on the usage of daratumumab in earlier lines of therapy. Members were counseled to consider only the currently-available evidence as they did for the other regimens of interest. One member abstained from voting as a result. Members wanted to highlight that this is a “point in time vote” and that they would like to revisit this question as more evidence emerges.

For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

6. Given the available evidence, what is the **care value** of treatment with each of the following three regimens listed below versus treatment with lenalidomide and dexamethasone:

a. carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX):

Low: 2 votes	Intermediate: 9 votes	High: 0 votes
---------------------	------------------------------	----------------------

b. elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX):

Low: 4 votes	Intermediate: 7 votes	High: 0 votes
---------------------	------------------------------	----------------------

c. ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX):

Low: 4 votes	Intermediate: 7 votes	High: 0 votes
---------------------	------------------------------	----------------------

Comments: A majority of the Council found each of the second-line regimens to be of intermediate value. While no members voted that the regimens were high value, those voting for intermediate value cited the significant clinical benefit provided by these regimens in spite of cost-effectiveness results that exceeded commonly-cited thresholds. Members also mentioned the challenge of achieving cost-effectiveness thresholds when new treatments are added to regimens already containing very expensive medications. However, one clinical expert cautioned that some of the cost estimates may be systematically understated because the regimens with indications for treatment of fixed duration are in practice given on a “treat to progression” basis, thereby increasing their costs in clinical practice.

Public Deliberation and Evidence Votes *(continued)*

For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to or has relapsed following two or more lines of therapy:

7. Given the available evidence, what is the *care value* of treatment with any of the regimens listed below versus that of comparator treatment (either lenalidomide and dexamethasone OR bortezomib and dexamethasone):

a. carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX):

Low : 2 votes	Intermediate: 9 votes	High: 0 votes
----------------------	------------------------------	----------------------

b. elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX):

Low : 6 votes	Intermediate: 5 votes	High: 0 votes
----------------------	------------------------------	----------------------

c. ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX):

Low : 5 votes	Intermediate: 6 votes	High: 0 votes
----------------------	------------------------------	----------------------

d. panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX):

Low: 4 votes	Intermediate: 4 votes	High: 3 votes
---------------------	------------------------------	----------------------

Comments: The voting splits for the first three regimens were similar to those for second-line use, although more Council members voted low value given that the ICERs were even higher for third-line use. For PAN-BOR-DEX, while the regimen has the lowest cost and most favorable cost-effectiveness ratio, voting was influenced by the view of one of the clinical experts that no myeloma expert would consider panibinostat clinically superior to carfilzomib, elotuzumab or ixazomib.

Key Policy Implications and Recommendations

Clinical Research Community

- Researchers, funding agencies, manufacturers, and patients should work together to design and conduct clinical research to address critical evidence gaps, including the lack of information on the comparative effectiveness and value of different sequences of available drugs.

Patients

- Patient organizations should be given a leadership role in efforts to change the way clinical trials are designed and to advocate for ongoing and rigorous study in real-world populations. Through this effort patient organizations should seek to reduce barriers that impede high participation in clinical research that will guide future clinical practice.

Manufacturers

- Drug manufacturers should improve the quality of evidence available around the time of drug approval and adoption to better inform treatment decisions.
- Manufacturers should consider extensions to both survival and time on treatment in their pricing strategies for new therapies.
- Manufacturers should take the lead in designing mechanisms to discount all components of a treatment regimen, as advances in multiple myeloma therapy often involve increasing the number of drugs provided to patients during a given treatment course.

Insurers

- Multiple myeloma is a condition in which many patients will cycle through most or all available treatments, and there is substantial variation in drug mechanisms of action and in the personal patient values that guide consideration of the trade-offs between extended survival and different side effect profiles. Given this background, and in the absence of better evidence, payers should not consider step therapy or “fail first” coverage policies for myeloma treatments.

Clinicians

- Clinicians should consider costs and cost-effectiveness in discussing the sequencing of treatment options for multiple myeloma.
- Provider groups that bear financial risk for costs of care should seek mechanisms to manage costs across the health system and avoid too narrow a focus on drug costs within individual classes or patient populations.

Note the above are summary statements from the policy roundtable discussions. For additional detail and context, please see the write-up in the final report.

Conclusion

In Summary

The introduction of most newer regimens for second- and third-line use in multiple myeloma appears to confer clinical benefits in terms of lengthening progression-free and possibly overall survival as well as improved quality of life. However, at current wholesale acquisition costs, the estimated cost-effectiveness of these regimens

exceeds the range of \$100,000-\$150,000 per QALY that is used as a benchmark for reasonable long-term value. The potential budget impact of newer regimens for refractory multiple myeloma is not estimated to exceed ICER's short-term (five-year) threshold linked to national health care cost growth targets.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).