Revlimid (Lenalidomide) Now FDA Approved as First-Line Therapy for Patients with Multiple Myeloma

By Lisa A. Raedler, PhD, RPh, Medical Writer

Multiple myeloma is a cancer of plasma cells in the bone marrow that often leads to bone destruction and bone marrow failure.1,2 According to the American Cancer Society, more than 26,800 new cases of multiple myeloma were diagnosed in 2015, and 11,240 deaths were attributed to multiple myeloma in the same year.3

Representing approximately 1% of all cancers, multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma.4 The incidence of multiple myeloma is higher among men than it is among women.1 Individuals aged ≥65 years, those with a family history of multiple myeloma, and those with a history of monoclonal gammopathy of undetermined significance have a higher risk for multiple myeloma compared with individuals without these features.1 Several common complications of multiple myeloma include bone pain, kidney dysfunction, bone loss, impaired immunity, and anemia.5

Although the overall incidence of multiple myeloma continues to increase, the mortality rates associated with this malignancy have declined during the past 20 years.1,6 Specifically, the advent of novel therapy options for multiple myeloma, as well as improvements in high-dose therapy and supportive care have contributed to extended survival for patients with multiple myeloma.6

New anticancer drugs and novel combinations have emerged in part as a result of improved understanding of the bone marrow microenvironment and the biology of multiple myeloma.7 Immune modulators and proteasome inhibitors now represent the cornerstones of initial treatment for multiple myeloma based on their proven ability to enhance the overall response rates and survival.2,7

Because novel agents for multiple myeloma have had a considerable impact on the healthcare budget, understanding their relative cost-effectiveness is important for ensuring efficient use.8,9

Overall, 2 recent evaluations of the economics of these new agents in multiple myeloma resulted in similar conclusions.5,9 One of the studies used claims data from more than 2600 US-based patients with multiple myeloma, and found that the 1-year costs of bortezomib-based therapy were similar to those of non-novel combinations (approximately $112,000 each), whereas the costs of thalidomide- and lenalidomide-based regimens were significantly higher (approximately $130,500 and $159,200, respectively) than non-novel combinations. This study also showed that patients taking thalidomide and lenalidomide had higher out-of-pocket costs in light of Medicare Part D's coverage gap for outpatient drugs.8

The second study modeled the cost-effectiveness of novel agents combined with melphalan and prednisone in patients with newly diagnosed multiple myeloma who were ineligible for a transplantation. The researchers concluded that adding bortezomib to melphalan and prednisone was more cost-effective than adding thalidomide or lenalidomide to melphalan and prednisone.9

Despite significant strides in drug therapy and autologous stem-cell transplant (ASCT) procedures, the majority of patients with multiple myeloma are not cured.2 Approved drug regimens for the initial treatment of multiple myeloma include parenteral therapies (eg, intravenous infusions or subcutaneous injections) that may require multiple office visits and/or placement of a peripheral or central catheter.9 None of the currently approved regimens for newly diagnosed multiple myeloma is an all-oral combination.

Lenalidomide Approved as First-Line Therapy in Multiple Myeloma

On February 18, 2015, the US Food and Drug Administration (FDA) approved a new indication for lenalidomide (Revlimid; Celgene), expanding its use, in combination with low-dose dexamethasone, for the first-line treatment of patients with newly diagnosed multiple myeloma.10 This expanded indication was based on the safety and efficacy results from phase 3 studies, including the FIRST (also known as MM-020 and IFM 07-01) clinical trial, a 3-arm study that compared the continuous use of the combination of lenalidomide plus dexamethasone with the 3-drug regimen of melphalan, prednisone, and thalidomide (MPT) for 18 months. In a secondary analysis, lenalidomide plus low-dose dexamethasone was also compared with lenalidomide given for 18 cycles. All patients had newly diagnosed multiple
myeloma and were not candidates for ASCT.10–12 Lenalidomide, an oral agent, was first approved by the FDA in 2006 for the treatment of patients with multiple myeloma who had received 1 previous therapy based on the results from 2 clinical trials.12–15 In both studies, the median time to progression was significantly longer for patients taking lenalidomide plus dexamethasone compared with patients taking dexamethasone alone.12–15

In addition to multiple myeloma, lenalidomide is FDA approved for the treatment of patients with transfusion-dependent anemia as a result of low- or intermediate-1–risk myelodysplastic syndromes associated with a deletion 5q abnormality, with or without additional cytogenetic abnormalities.12

Lenalidomide is also approved for the treatment of patients with mantle-cell lymphoma that has relapsed or progressed after 2 therapies, one of which included bortezomib.12

**Mechanism of Action**

Lenalidomide, an analog of thalidomide, is an immunomodulatory agent with multiple actions. It inhibits the proliferation and induces the apoptosis of hematopoietic tumor cells based on in vitro cellular assays. Lenalidomide also enhances T-cell–mediated and natural killer cell–mediated immunity, and blocks proinflammatory cytokines, such as tumor necrosis factor–α and interleukin-6. The combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis in multiple myeloma cells.12

**Dosing and Administration**

Lenalidomide is supplied in 6 capsule strengths—2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg. The recommended dose for patients with multiple myeloma is 25 mg daily taken orally on the first 21 days of each 28-day cycle. Treatment should continue until disease progression.12

Lenalidomide can be taken with or without food. Patients should not break, chew, or open the capsules.12

**Clinical Trial: FIRST**

The new indication for lenalidomide as first-line treatment for multiple myeloma was based on the FIRST study, a phase 3, multicenter, randomized, open-label, 3-arm clinical trial that compared the efficacy and safety of lenalidomide plus dexamethasone versus MPT and versus lenalidomide given for 18 cycles in patients with newly diagnosed multiple myeloma who were not candidates for ASCT.

A total of 1623 patients (median age, 73 years) enrolled in the FIRST clinical trial.11,12 The majority of patients had an Eastern Cooperative Oncology Group performance status of grade 0 or 1 (78%), stage I or II disease (59%), and mild or moderate renal impairment, defined as creatinine clearance between 30 mL/min and 80 mL/min (67%).12

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**Table**

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Lenalidomide + low-dose dexamethasone (N = 535)</th>
<th>Lenalidomide used for 18 cycles (N = 541)</th>
<th>Melphalan, prednisone, and thalidomide (N = 547)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression-free survival, mo</td>
<td>25.5 (95% CI, 20.7-29.4)</td>
<td>20.7 (95% CI, 19.4-22.0)</td>
<td>21.2 (95% CI, 19.3-23.2)</td>
</tr>
<tr>
<td>HR: lenalidomide + low-dose dexamethasone vs melphalan, prednisone, and thalidomide</td>
<td>0.72 (95% CI, 0.61-0.85)</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>Median overall survival, mo</td>
<td>58.9 (95% CI, 56.0-NE)</td>
<td>56.7 (95% CI, 50.1-NE)</td>
<td>48.5 (95% CI, 44.2-52.0)</td>
</tr>
<tr>
<td>HR: lenalidomide + low-dose dexamethasone vs melphalan, prednisone, and thalidomide</td>
<td>0.75 (95% CI, 0.62-0.90)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>75.1</td>
<td>73.4</td>
<td>62.3</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>15.1</td>
<td>14.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Very good partial response, %</td>
<td>28.4</td>
<td>28.5</td>
<td>18.8</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>31.6</td>
<td>30.7</td>
<td>34.2</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; NE, not estimable.

The Table describes the efficacy end points in the FIRST trial. The median progression-free survival for patients receiving lenalidomide plus dexamethasone was significantly higher than for patients receiving the MPT regimen (25.5 vs 21.2 months, respectively; hazard ratio [HR], 0.72; \( P < .001 \)). The final analysis of overall survival also showed a benefit for the lenalidomide-based combination compared with the MPT regimen (58.9 vs 48.5 months; HR, 0.75).

The researchers concluded that lenalidomide plus dexamethasone significantly improved progression-free survival and overall survival compared with the MPT regimen and with lenalidomide alone for 18 cycles in patients with newly diagnosed multiple myeloma who were not candidates for ASCT.

### Adverse Events

The safety data were evaluated from 1613 patients in the FIRST study. The median treatment duration in the lenalidomide plus dexamethasone arm was 18.4 months (range, 0.16-56.7). The most frequently reported grade 3 or 4 adverse reactions were neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cutaneous, lymphopenia, dyspnea, deep vein thrombosis, hyperglycemia, and leukopenia. The overall rate of infections was higher in the lenalidomide-based combination arm compared with the MPT arm (75% vs 56%, respectively), as was the rate of grade 3 or 4 adverse reactions.

The most common adverse reactions (all grades) reported with the combination of lenalidomide plus dexamethasone in the FIRST study at a rate of >20% overall and at least 5% higher than in the MPT regimen included diarrhea (46% vs 17%, respectively), back pain (32% vs 21%), asthenia (28% vs 23%), insomnia (28% vs 10%), rash (26% vs 19%), cough (23% vs 13%), decreased appetite (23% vs 13%), pyrexia (21% vs 14%), muscle spasms (21% vs 11%), and abdominal pain (21% vs 11%).

### Contraindications

Lenalidomide is contraindicated in pregnant women, because of the risk for severe birth defects and embryofetal death. Lenalidomide is also contraindicated in patients who have demonstrated hypersensitivity (eg, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to the drug.

### Drug Interactions

Digoxin concentrations increase when lenalidomide is used concurrently. Periodic monitoring of digoxin plasma levels is recommended for such patients.

### Warnings and Precautions

**Boxed warning.** Lenalidomide is approved with a boxed warning regarding the risk for embryofetal toxicity if the drug is used in pregnancy, the risk for hematologic toxicity, the need for antithrombotic prophylaxis to mitigate the risk for venous and arterial thromboembolism, and its availability only through a REMS (Risk Evaluation and Mitigation Strategy) program.

**Embryofetal toxicity.** Lenalidomide is an analog of thalidomide, a known human teratogen that causes severe birth defects and embryofetal death.

**Females of reproductive potential.** Women must avoid pregnancy while taking lenalidomide and for at least 4 weeks before taking lenalidomide and after completing lenalidomide therapy. Negative pregnancy tests must be obtained before starting and during lenalidomide treatment.

**Males.** Because lenalidomide is present in the semen of patients receiving the drug, males must always use a condom during sexual contact with females of reproductive potential while taking lenalidomide and for up to 28 days after discontinuing lenalidomide, even if a successful vasectomy has been performed. Males taking lenalidomide must not donate sperm.

**Blood donation.** Because donated blood may be given to a pregnant woman, patients must not donate blood during treatment with lenalidomide, and for 1 month after discontinuing lenalidomide.

**Hematologic toxicity.** Patients taking lenalidomide should be monitored for hematologic toxicities, particularly neutropenia. Complete blood counts should be performed weekly for the first 2 cycles, every 2 weeks during the third cycle, and every 4 weeks thereafter. Lenalidomide dose interruption and/or modification may be necessary.

**Venous and arterial thromboembolism.** Venous and arterial thromboembolic events have occurred in patients who received lenalidomide. Thromboprophylaxis is recommended.

**Chronic lymphocytic leukemia (CLL)-related mortality.** In a clinical trial, the use of single-agent lenalidomide increased mortality risk in patients with CLL compared with chlorambucil. Lenalidomide should not be used in patients with CLL outside of clinical trials.

**Second primary malignancies.** Second primary malignancies have been reported with lenalidomide. Patients should be monitored for the development of second primary malignancy.

**Hepatotoxicity.** Liver failure, including fatal cases, has been reported in patients receiving lenalidomide and low-dose dexamethasone. Liver function tests should be assessed periodically. Lenalidomide should be stopped if liver enzymes are elevated. Treatment at a lower dose may
be considered after enzyme levels return to baseline.\textsuperscript{12}

\textbf{Hypersensitivity reactions.} Angioedema and severe dermatologic reactions have been reported with lenalidomide. The interruption or the discontinuation of lenalidomide should be considered for grade 2 or 3 skin rash. The discontinuation of lenalidomide is recommended for angioedema, grade 4 rash, exfoliative or bullous rash, and other serious dermatologic reactions. Lenalidomide capsules contain lactose.\textsuperscript{12}

\textbf{Tumor lysis syndrome (TLS).} TLS can occur in patients receiving lenalidomide. Patients who are at risk for TLS should be monitored closely.\textsuperscript{12}

\textbf{Tumor flare reaction (TFR).} TFR has occurred during the investigational use of lenalidomide for CLL and lymphoma. Lenalidomide should be withheld if grade 3 or 4 TFR occurs.\textsuperscript{12}

\textbf{Impaired stem-cell mobilization.} A decrease in the number of CD34+ cells collected after >4 cycles of lenalidomide has been reported. ASCT candidates should consult with a transplant center early in treatment to optimize the timing of stem-cell collection.\textsuperscript{12}

\section*{Use in Specific Populations}

\textbf{Pregnancy.} Lenalidomide is contraindicated during pregnancy.\textsuperscript{12}

\textbf{Lactation.} There are no data regarding the presence of lenalidomide in human milk.\textsuperscript{13}

\textbf{Females and males of reproductive potential.} Females of reproductive potential must avoid pregnancy 4 weeks before taking lenalidomide, while taking lenalidomide, and for at least 4 weeks after completing therapy.\textsuperscript{12} Males must always use a condom during any sexual contact with females of reproductive potential while taking lenalidomide, and for up to 28 days after discontinuing lenalidomide.\textsuperscript{12}

\textbf{Pediatric use.} There are no data to establish the safety and effectiveness of lenalidomide in patients aged <18 years.\textsuperscript{12}

\textbf{Geriatric use.} In clinical trials with lenalidomide, patients aged >75 years were more likely to have adverse events, including grade 3 or 4 events, compared with patients aged ≤75 years.\textsuperscript{12}

\textbf{Renal impairment.} Adjustments to the starting dose of lenalidomide are recommended in patients with moderate-to-severe renal impairment, and in patients on dialysis.\textsuperscript{12}

\textbf{Hepatic impairment.} Lenalidomide has not been studied in patients with liver impairment.\textsuperscript{12}

\section*{Conclusion}

The new indication for lenalidomide for use in patients with newly diagnosed multiple myeloma means that this oral immunomodulator can now be used in all patients with this malignancy. The new FDA indication provides a convenient oral treatment option for patients with multiple myeloma based on data demonstrating superior efficacy compared with combination chemotherapy in patients with newly diagnosed disease. The final results of the FIRST study demonstrated extended progression-free survival and overall survival with the continuous use of lenalidomide and low-dose dexamethasone compared with the MPT regimen in patients who are not candidates for ASCT.

Researchers continue to evaluate the clinical activity of lenalidomide-based combinations in patients with multiple myeloma, as well as in other hematologic malignancies and advanced-stage solid tumors.\textsuperscript{16}