

# MULTIPLE MYELOMA

## TREATMENT OVERVIEW



**MMRF**<sup>SM</sup>  
Multiple Myeloma  
Research Foundation

**POWERFUL** THINKING ADVANCES THE CURE<sup>SM</sup>



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## ABOUT THE MULTIPLE MYELOMA RESEARCH FOUNDATION



The Multiple Myeloma Research Foundation (MMRF) was founded in 1998 by identical twin sisters Kathy Giusti

and Karen Andrews soon after Kathy was diagnosed with multiple myeloma, an incurable blood cancer. The mission of the MMRF is to relentlessly pursue innovative means that accelerate the development of next-generation multiple myeloma treatments to extend the lives of patients and lead to a cure.

Thanks to the support and generosity of people like you, and by working closely with researchers, clinicians and our partners in the biotech and pharmaceutical industry, we helped bring multiple myeloma patients four new treatments that are extending lives around the globe. Today, we are on the cusp of the next breakthrough treatment, and are

supporting a pipeline of more than 50 promising compounds and combination treatments, including more than 30 clinical trials we advanced through our sister organization, the Multiple Myeloma Research Consortium (MMRC).

As the multiple myeloma community's most trusted source for information, the MMRF supports patients from the point of diagnosis throughout the course of the disease. No matter where you are in your journey with multiple myeloma, you can count on the MMRF to get you the information you need about multiple myeloma and its treatment options, including clinical trials. All information on our Web site, [www.themmr.org](http://www.themmr.org), is tailored to patients by disease stage so we can make sure you get information you need at the right time.

To learn more about the MMRF, visit [www.themmr.org](http://www.themmr.org).

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## **CONTENTS**

<b>Introduction</b>	<b>2</b>
<b>What Is Multiple Myeloma?</b>	<b>3</b>
<b>How Is Myeloma Classified and Staged?</b>	<b>4</b>
<b>How Do You Decide Which Treatment Is Appropriate?</b>	<b>8</b>
<b>What Are the Possible Goals of Treatment?</b>	<b>8</b>
<b>How Do You Know if a Treatment Is Working?</b>	<b>8</b>
<b>What Therapies Are Used in Myeloma?</b>	<b>12</b>
<b>How Is Myeloma Treated?</b>	<b>12</b>
<b>What Are My Options for Initial Therapy as a Non-transplant Candidate?</b>	<b>17</b>
<b>What Are My Options for Initial Therapy as a Transplant Candidate?</b>	<b>21</b>
<b>Choice of Initial Therapy in Myeloma</b>	<b>26</b>
<b>What Is High-dose Chemotherapy and Stem Cell Transplantation?</b>	<b>27</b>
<b>Should I Receive Maintenance Therapy?</b>	<b>28</b>
<b>What Are My Options If I Don't Respond to Therapy or Relapse?</b>	<b>30</b>
<b>What Supportive Therapies Are Used in Myeloma?</b>	<b>33</b>
<b>How Do I Find a Clinical Trial?</b>	<b>38</b>
<b>What Are Some of the Promising Therapies in Clinical Trials?</b>	<b>40</b>
<b>References</b>	<b>42</b>
<b>Glossary</b>	<b>46</b>

## INTRODUCTION

This booklet is designed primarily to help individuals with multiple myeloma, and their friends and families, better understand the treatment options for the disease. Multiple myeloma is a treatable cancer, and there are many promising new therapies under investigation that are bringing us closer to a cure. This booklet describes current therapies for myeloma and the emerging treatment options that are being tested in clinical trials. Words you may not be familiar with are **bolded** throughout the text at first mention and defined in the Glossary (page 45).

The information in this booklet is not intended to replace the services of trained health professionals (or to be a substitute for medical advice). Please consult with your healthcare professional if you have specific questions relating to your health, especially questions about diagnosis or treatment.

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The MMRF booklet, *Multiple Myeloma: Disease Overview*, discusses how myeloma develops and provides information regarding symptoms, diagnosis, and prognosis. There is additional information on the MMRF Web site: [www.themmr.org](http://www.themmr.org).

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## WHAT IS MULTIPLE MYELOMA?

Multiple myeloma is a blood cancer that develops in the **bone marrow**. In myeloma, normal **antibody**-producing **plasma cells** transform into **malignant** myeloma cells. Myeloma cells produce large quantities of one antibody (or **immunoglobulin**) called **monoclonal (M) protein**. These malignant cells also crowd out and inhibit the production of normal blood cells and antibodies in the bone marrow. In addition, groups of myeloma cells cause other cells in the bone marrow to remove the solid part of the bone and cause **osteolytic lesions**, or soft spots in the bone. Although common, these lesions or other signs of bone loss do not occur in all individuals with myeloma.

## HOW IS MYELOMA CLASSIFIED AND STAGED?

Myeloma is classified according to the results of diagnostic testing, and these results tell whether or not immediate treatment is needed. In addition, a stage is assigned to indicate the extent of disease. Both classification and staging are critical in determining treatment options.

### Classification of Myeloma

Myeloma is classified into three categories (Table 1). Individuals in the first two categories are asymptomatic and considered to have inactive disease. They do not need to receive anti-myeloma treatment. However, if such patients have evidence of osteoporosis, they should receive treatment with **bisphosphonates** to prevent or minimize damage to bone in a dosing schedule similar to that used for osteoporosis in general. Individuals with symptomatic disease have active myeloma and require treatment.

**TABLE 1. CLASSIFICATION OF MULTIPLE MYELOMA**

Classification	Characteristics	Management
<b>Monoclonal gammopathy of undetermined significance (MGUS)</b>	<ul style="list-style-type: none"> <li>• Considered a precursor to myeloma</li> <li>• Blood M protein &lt;3 g/dL <i>and</i></li> <li>• Bone marrow plasma cells &lt;10% <i>and</i></li> <li>• No evidence of other B-cell disorders</li> <li>• No related organ or tissue impairment<sup>a</sup></li> <li>• Risk of progression to malignancy: 1% per year (about 20%-25% of individuals during their lifetime)</li> </ul>	<ul style="list-style-type: none"> <li>• Close follow up (also known as “observation”)</li> </ul>
Asymptomatic, or smoldering, myeloma	<ul style="list-style-type: none"> <li>• Blood M protein ≥3 g/dL <i>and/or</i></li> <li>• Bone marrow plasma cells ≥10%</li> <li>• No related organ or tissue impairment or symptoms</li> <li>• Risk of progression to malignancy: 10% per year</li> </ul>	<ul style="list-style-type: none"> <li>• Observation, with treatment beginning at disease progression</li> <li>• Participation in a clinical trial</li> <li>• Treatment with bisphosphonates for individuals with bone loss (<b>osteoporosis</b> or <b>osteopenia</b>) similar to that used for the treatment of osteoporosis in general</li> </ul>
Symptomatic myeloma	<ul style="list-style-type: none"> <li>• M protein in blood and/or urine</li> <li>• Bone marrow plasma cells or <b>plasmacytoma</b></li> <li>• Related organ or tissue impairment</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate treatment</li> <li>• Treatment with bisphosphonates for individuals with osteolytic lesions, osteoporosis, or osteopenia</li> <li>• Participation in a clinical trial</li> </ul>

<sup>a</sup>*Myeloma-related organ or tissue impairment (end-organ damage) includes **hypercalcemia** (increased blood calcium levels), impaired kidney function, **anemia**, or bone lesions. These classifications are based on those proposed by the International Myeloma Working Group.*

**TABLE 2. THE DURIE-SALMON STAGING SYSTEM**

Stage	Criteria	Myeloma Cell Mass <sup>a</sup>
I (low cell mass)	<p><i>All of the following:</i></p> <ul style="list-style-type: none"> <li>• <b>Hemoglobin</b> value &gt;10 g/dL</li> <li>• Blood calcium value normal or &lt;12 mg/dL</li> <li>• Bone x-ray, normal bone structure, or solitary bone <b>plasmacytoma</b> only</li> <li>• Low M-protein production rate (IgG value &lt;5 g/dL; IgA value &lt;3 g/dL; <b>Bence Jones protein</b> &lt;4 g/24 hr.)</li> </ul>	<0.6
II (intermediate cell mass)	<i>Fitting neither stage I nor stage III</i>	0.6 -1.2
III (high cell mass)	<p><i>One or more of the following:</i></p> <ul style="list-style-type: none"> <li>• Hemoglobin value &lt;8.5 g/dL</li> <li>• Blood calcium value &gt;12 mg/dL</li> <li>• Advanced lytic bone lesions</li> <li>• High M-protein production rate (IgG value &gt;7 g/dL; IgA value &gt;5 g/dL; Bence Jones protein &gt;12 g/24 hr.)</li> </ul>	>1.2

<sup>a</sup>The myeloma cell mass is expressed as the number of myeloma cells per body surface area.

### Subclassification (either A or B)

A: Relatively normal renal function (blood creatinine value <2.0 mg/dL)

B: Abnormal renal function (blood creatinine value ≥2.0 mg/dL)

## Staging of Myeloma

The myeloma staging system most widely used since 1975 has been the Durie-Salmon Staging System. With this system, the clinical stage of disease (stage I, II, or III) is based on four measurements: the hemoglobin value, the level of calcium in the blood, the number of osteolytic lesions, and the production rate of M protein (Table 2). Stages are further divided according to renal (kidney) function.

However, myeloma staging systems that are better able to predict outcome (prognosis) than the Durie-Salmon system are now being used more frequently. One such system is the International Staging System (ISS), which is based on two blood

test results: **beta<sub>2</sub>-microglobulin (β<sub>2</sub>-M)** and **albumin** (Table 3). The three stages in this system indicate different levels of estimated survival and may help in the treatment decision-making process.

The ISS, which is useful only in individuals with symptomatic myeloma, was developed based on patient responses to **front-line therapy** with conventional **chemotherapy** and/or high-dose chemotherapy and **stem cell transplantation**.

The value of the ISS in predicting outcomes with newer front-line myeloma therapies, as well as its utility following disease **relapse** (progression), is currently being studied.

**TABLE 3. INTERNATIONAL STAGING SYSTEM FOR MYELOMA**

Stage	Criteria
I	β <sub>2</sub> -M <3.5 mg/L and albumin ≥3.5 g/dL
II	β <sub>2</sub> -M <3.5mg/L and albumin <3.5 g/dL or β <sub>2</sub> -M 3.5 – 5.5 mg/L
III	β <sub>2</sub> -M ≥5.5 mg/L

*β<sub>2</sub>-M = beta<sub>2</sub>-microglobulin.*

## HOW DO YOU DECIDE WHICH TREATMENT IS APPROPRIATE?

Deciding on a particular treatment plan for myeloma is a complex process. Treatment is tailored to each individual based on a number of things, including:

- Results of the physical exam
- Results of laboratory tests
- The specific classification and stage of disease
- Age and general health
- Symptoms
- Presence of disease complications
- Prior myeloma treatment
- The individual's lifestyle, goals, and views on quality of life

## WHAT ARE THE POSSIBLE GOALS OF TREATMENT?

Depending on an individual's disease and his or her wishes, treatment plans may be designed to meet one or more different goals, which are listed in Table 4.

## HOW DO YOU KNOW IF A TREATMENT IS WORKING?

During and after treatment, your doctor will monitor your levels of M protein and your symptoms. Your doctor may also perform some of the same laboratory tests and medical procedures that were done when you were diagnosed with myeloma, such as blood tests, x-rays, or bone marrow biopsy. All of these results show how well the treatment is working and whether you are experiencing any side effects. These tests also help determine if, after an initial response to treatment, your myeloma relapses.

**TABLE 4. TREATMENT GOALS**

<b>Goal</b>	<b>Intervention/Requirement</b>
Destroy all evidence of disease	May require use of aggressive treatment that might have more severe side effects
Prevent damage to other organs of the body by controlling disease activity	Typically achieved with commonly used treatments that have side effects, but they are acceptable and tolerable
Preserve normal performance and quality of life for as long as possible	May be possible with minimal treatment
Provide lasting relief of pain and other disease symptoms, as well as manage side effects of treatment	Involves use of supportive therapies that help you feel better and manage complications
Manage myeloma that is in <b>remission</b>	May involve long-term therapy

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## **IS REMISSION THE SAME AS RESPONSE?**

When talking about cancer, being in remission typically means that there is a complete or partial disappearance of the cancer signs and symptoms, or that the cancer is under control. Response to treatment in myeloma is also sometimes referred to as remission. For example, the term “complete remission” means the same thing as complete response. Similarly, the term “partial remission” means the same thing as a partial response.

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In clinical trials, the outcome of treatment in myeloma is defined using very specific standards, or criteria. These “response criteria” allow the relative effectiveness of one treatment to be compared with other treatments.

Examples of response criteria used in myeloma clinical trials are shown in Table 5.

**TABLE 5. RESPONSE CRITERIA USED IN CLINICAL TRIALS<sup>a</sup>**

Type of Response	M Protein	% Plasma Cells in Bone Marrow	Skeletal Disease (on x-ray)
Stringent complete response (sCR) <sup>b</sup>	No longer detectable in blood and/or urine; negative <b>immunofixation</b> test; normal <b>free light chain (FLC) ratio</b>	<5%; no myeloma cells present (i.e., normal free light chain ratio)	Stable
Complete response (CR)	No longer detectable in blood and/or urine; negative immunofixation test	<5%	Stable
Near complete response (nCR) <sup>c</sup>	No longer detectable in blood and/or urine, but positive immunofixation test	<5%	Stable
Very good partial response (VGPR) <sup>b</sup>	No longer detectable in blood and/or urine, but positive immunofixation test, or 90% decrease	N/A	Stable
Partial response (PR)	≥50% decrease	N/A	Stable
Minimal response (MR) <sup>d</sup>	25%-49% decrease	N/A	Stable
Stable disease (SD)	Not meeting the definition of minimal response or progressive disease		
Progressive disease (PD)	>25% increase	>25% increase	New bone lesions or increase in size of existing lesions

<sup>a</sup> These outcomes are based on criteria developed by the EBMT (European Group for Blood and Marrow Transplant), IBMTR (International Bone Marrow Transplant Registry), and ABMTR (Autologous Blood and Marrow Transplant Registry; Bláde criteria), and the International Myeloma Working Group (IMWG Uniform Response Criteria).

<sup>b</sup> Only defined in the IMWG criteria.

<sup>c</sup> Some clinical trials modify the EBMT criteria to include the nCR category.

<sup>d</sup> Only defined in the EBMT criteria.

## WHAT THERAPIES ARE USED IN MYELOMA?

Myeloma therapy is tailored to each patient and there is no one “standard” treatment. The treatments that are often referred to as standard therapies for myeloma are those that have been traditionally used in clinical settings, and their effectiveness has been well documented within the scientific community.

Various therapies used in myeloma are briefly described in Table 6. The sections that follow will show how each of these therapies may be used in an overall approach for treating an individual with myeloma.

## HOW IS MYELOMA TREATED?

Treatment of myeloma can be complex because of the many factors that must be taken into account. In addition, many centers have developed their own guidelines for treating myeloma and these may vary from center to center. Your doctor will discuss the treatment options that are most appropriate for you.

To help doctors treat myeloma, the National Comprehensive Cancer Network (NCCN) has developed a set of general guidelines. These guidelines identify particular treatments that have been deemed appropriate based on a review of published studies and on the expertise and clinical experience of a panel of experts. (NCCN Practice Guidelines in Oncology. Multiple Myeloma. Available at [www.nccn.org](http://www.nccn.org).)

*<sup>a</sup>Approved indications listed are those for the United States.*

**TABLE 6. THERAPIES FOR MYELOMA<sup>a</sup>**

Therapy	Description
Velcade® (bortezomib, Millennium: The Takeda Oncology Company) for Injection	<b>Proteasome</b> inhibitor approved for use across the entire spectrum of myeloma disease
Revlimid® (lenalidomide, Celgene)	Oral agent that is an improvement over Thalomid® and is effective across the spectrum of myeloma disease; approved for use in combination with dexamethasone in individuals who previously received treatment
Thalomid (thalidomide, Celgene)	Oral agent shown to be effective across the spectrum of myeloma disease; approved in combination with dexamethasone as front-line therapy
Doxil® (doxorubicin HCl liposome injection, Ortho Biotech)	Chemotherapy agent approved for use in combination with Velcade for individuals who previously received therapy other than Velcade
<b>Steroids (corticosteroids)</b> (dexamethasone and prednisone)	Drugs used for decades to treat myeloma throughout the spectrum of disease; may be used alone or in combination with other therapies
Conventional (standard dose) chemotherapy	The use of drug(s), administered alone or in combination, to kill cancer cells; some examples are melphalan (Alkeran®, GlaxoSmithKline) and cyclophosphamide
High-dose chemotherapy and stem cell transplantation	The use of higher doses of chemotherapy drugs followed by transplantation of <b>hematopoietic stem cells</b> to replace healthy cells damaged by the chemotherapy.
<b>Radiation therapy</b>	The use of high-energy rays to damage cancer cells and prevent them from growing
Supportive therapy	Therapies that alleviate symptoms and manage complications of the disease and its treatment, such as bisphosphonates for bone disease, low-dose radiation therapy and analgesics for pain relief, <b>growth factors</b> , antibiotics, intravenous immunoglobulin, orthopedic interventions, drugs (primarily <b>anticoagulants</b> ) to prevent and reduce the severity of <b>deep vein thrombosis (DVT)</b> ; blood clots), <b>antiemetics</b> , and drugs to prevent and reduce the severity of <b>neuropathy</b> (nerve damage)

The choice of initial treatment for myeloma depends on whether an individual has symptoms (active disease) or not (inactive disease).

### Inactive Disease

Individuals with inactive disease, that is, those with MGUS or asymptomatic (smoldering) myeloma, are typically watched and not treated unless their disease becomes active. If such patients have evidence of osteoporosis, they should receive treatment with bisphosphonates to prevent or minimize damage to bone in a dosing schedule similar to that used for osteoporosis in general. Recently, a clinical trial showed that one of the newer agents, Revlimid®, prolonged the time to symptomatic myeloma in patients with high-risk smoldering multiple myeloma. However this therapy is still considered experimental and there is not sufficient data on the benefits and risks of therapy. A large national study is underway to determine if this agent can delay disease progression and improve survival in this group of patients.

### Active Disease

Individuals with symptomatic myeloma typically receive some form of treatment aimed at reducing the amount of myeloma cells. The choices for treatment depend

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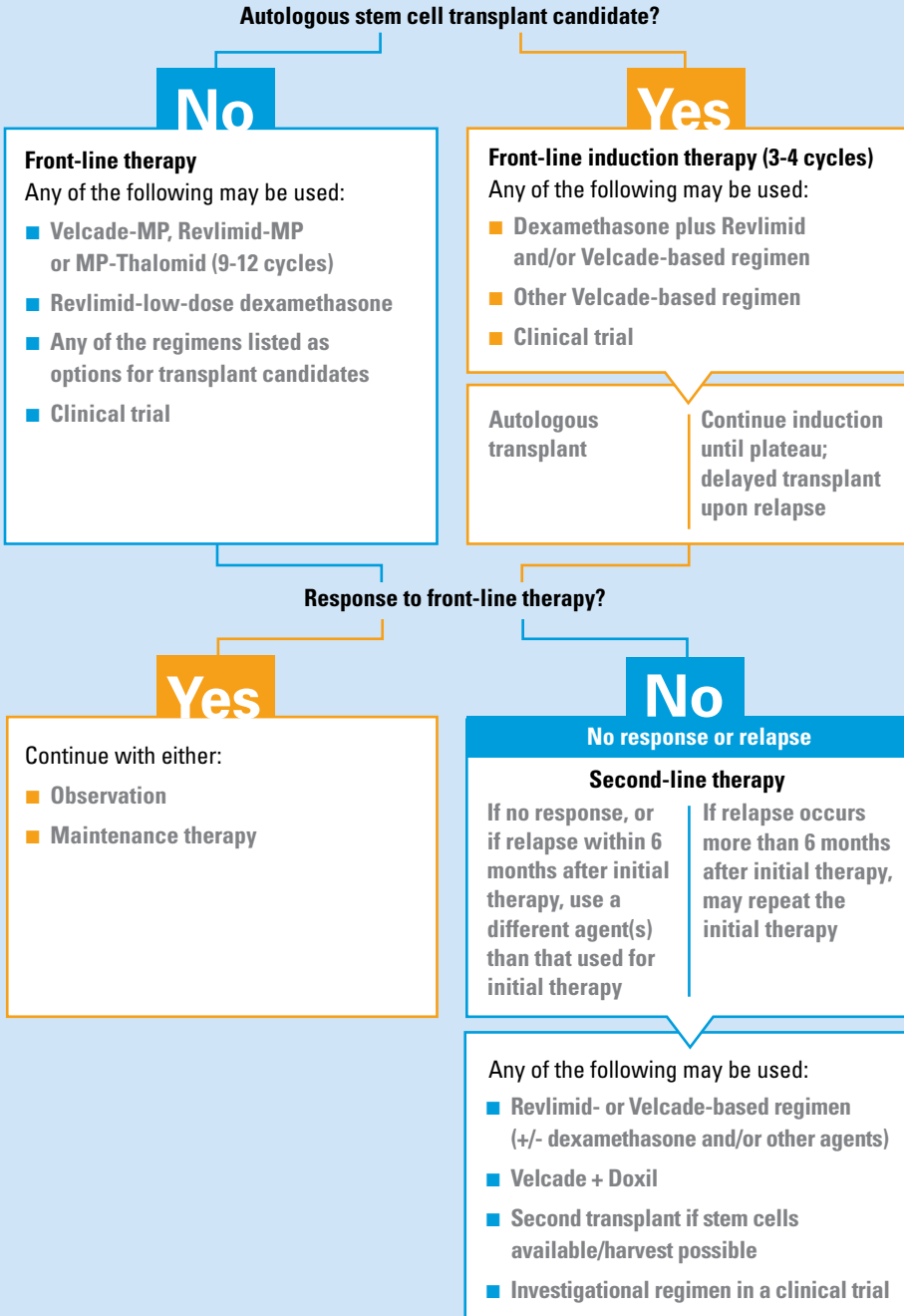
To further advance new therapies for myeloma, it is highly recommended that all eligible patients consider participating in a clinical trial.

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on whether or not the individual is a candidate for, or interested in, treatment with high-dose chemotherapy and **autologous stem cell transplant**. An autologous transplant is a treatment that has been shown to offer improved response rates and survival in myeloma. Individuals in good physical condition with adequate kidney, lung, and heart function are potential candidates for autologous transplant.

The chart shown in Figure 1 outlines typical options appropriate for an individual with active myeloma. Both transplant candidates and individuals not eligible for transplant receive some form of initial (front-line) therapy. (These options are discussed in further detail in the next section.)

Figure 1. Treatment options for myeloma



## THE EVOLVING ROLE OF TRANSPLANTATION IN MYELOMA

The improved response rates that have been found with use of newer agents as initial therapy have raised questions about the role of transplantation in the treatment of myeloma. Preliminary results from several studies appear to indicate that transplantation remains a standard therapy and may improve outcomes when compared to standard therapy with newer agents. However, longer follow-up is needed in order to compare survival, and the potential toxicities associated with transplantation must be balanced with the benefits.

Therefore, people with myeloma should carefully discuss the benefits and risks of all treatment options with their doctors.

All individuals who are eligible for transplantation are encouraged to have stem cells obtained (also known as “harvested”) so that the cells are available if the individual later chooses to undergo transplantation.

- For non-transplant candidates, initial therapy is continued for about a year or until the response of the disease to the treatment reaches a plateau and levels off. At that time, the individual may be monitored closely with no therapy (often referred to as “observation”) or the individual may consider maintenance therapy, which may also be done as part of a clinical trial.
- Transplant candidates achieving a response or stable disease with their initial therapy (also known as **induction therapy**) may have a transplant right away or may decide to continue their initial therapy and delay the transplant until relapse.

Subsequent treatment options are often selected based on the treatments already received and the outcome. Individuals may also receive supportive care as required to treat complications of the disease and its treatment. Participation in a clinical trial is an option at virtually every stage of the disease.

Note that the order of the treatment options listed does not imply their degree of effectiveness.

## WHAT ARE MY OPTIONS FOR INITIAL THERAPY AS A NON-TRANSPLANT CANDIDATE?

In the past, the most common initial therapy for individuals who were not candidates for transplant had been the combination of the chemotherapy drug melphalan and the corticosteroid prednisone (MP). However, clinical studies, with Velcade (bortezomib), Thalomid® (thalidomide), and Revlimid (lenalidomide) have shown that adding one of these agents to MP improves response rates. The combinations of Velcade plus MP and Thalomid plus MP have also been shown to offer improved survival compared with MP alone. Thus, the use of MP in combination with any one of the newer agents is a recommended option for initial therapy in patients who are not eligible for transplant.

Further, Revlimid-low dose-dex and Velcade-dex are also recommended options for initial therapy in these patients.

### Velcade-MP

Velcade is FDA-approved for use in individuals with previously untreated myeloma. The approval was based on data from a Phase III trial known as VISTA, which enrolled 682 patients. The combination of Velcade and MP (Velcade-MP or VMP) was found to be significantly better than MP in individuals who were not eligible for transplant in several ways:

- The overall response rate was significantly higher among patients receiving Velcade-MP compared with MP (71% vs. 35%).
- Thirty percent of patients receiving Velcade-MP achieved a complete response (a rate that is similar to that achieved with an autologous transplant), compared with 4 percent of patients receiving MP.
- After five years, patients receiving Velcade-MP had a 44% improvement in survival over those receiving MP.

## KEY FACTS

# VELCADE (BORTEZOMIB)

## WHAT IS VELCADE?

Velcade is a proteasome inhibitor approved for use in the US to treat myeloma.

## HOW IS VELCADE GIVEN?

Velcade is given intravenously (injection into a vein). When used with MP as front-line therapy, Velcade is typically given for approximately 9 to 12 months. Velcade is usually given twice a week for two weeks and then 10 days off. However, two studies show a lower risk of serious neuropathy without loss of efficacy with the use of Velcade at a once-weekly dosing schedule. Thus many physicians are using the once-a-week schedule.

When used as **second-line therapy** and beyond, Velcade is given on specific days of a 21-day cycle (days 1, 4, 8, and 11). Up to eight cycles may be given. As in the frontline setting, many physicians are using the once-a-week schedule to reduce the risk of neuropathy. The dose/schedule of Velcade may be changed further if an individual has serious side effects.

An alternate way to give Velcade, as an injection under the skin (subcutaneously), has been shown to reduce serious side effects, including peripheral neuropathy, without comprising efficacy. This method of administration is being reviewed for approval by the FDA. However, subcutaneous administration of Velcade is currently being used off-label and in the clinical trial setting.

## WHAT ARE THE POSSIBLE SIDE EFFECTS OF VELCADE?

The most commonly reported side effects of Velcade plus MP are:

- Low blood counts (**thrombocytopenia, neutropenia**, anemia)
- Gastrointestinal effects (nausea, diarrhea, constipation, vomiting, appetite loss)
- Peripheral neuropathy or nerve pain
- Loss/lack of strength
- Cough
- Insomnia
- Fluid buildup

The most commonly reported severe side effects of Velcade plus MP are:

- Low platelet and blood cell counts
- Peripheral neuropathy or nerve pain
- Fatigue or loss/lack of strength
- Pneumonia
- Diarrhea
- Low potassium levels.

Neuropathy, which is a particularly bothersome side effect, typically improves or resolves after therapy is stopped.

This evidence led to Velcade-MP being strongly recommended as a treatment option in the NCCN guidelines. The drawback to the combination, however, is an increased risk for peripheral neuropathy and gastrointestinal side effects. Some researchers have begun to address this issue by reducing the dose of Velcade as well as evaluating alternate means of administration. Two recent studies have shown that giving Velcade just once weekly during the first four cycles of treatment can significantly decrease the rate of peripheral neuropathy. In addition, an alternate way to give Velcade, as an injection under the skin (subcutaneous), has been shown to reduce serious side effects, including peripheral neuropathy, without compromising efficacy. This method of administration is being reviewed for approval by the FDA.

In an effort to further improve the outcomes achieved with Velcade-MP, researchers added Thalomid to create a four-drug regimen. This combination, also known as VMPT, significantly improved the amount of time patients remained free of disease (known as **progression-free survival**) and the overall response rates compared with Velcade-MP. In particular, the rates of complete response were significantly higher with VMPT than with Velcade-MP (38% vs. 24%). As with other studies of Velcade-based combinations, the dosing of Velcade was changed to a once-a-week schedule midway through the study, significantly reducing the number of people who had peripheral neuropathy without affecting the number of people with a good outcome. However, the potential increase in side effects natural with additional drugs must be considered.

Neutropenia, infections, and DVT have been the most common side effects associated with Revlimid-dex. To prevent DVT, drugs such as aspirin or anticoagulants are recommended for individuals receiving Revlimid-dex.

### MP-Thalomid

MP-Thalomid (MPT) is another combination sometimes used to treat myeloma. The results of phase III studies have shown that MP-Thalomid leads to better responses and survival than MP alone. However, side effects occurred more often after treatment with MP-Thalomid, including low **white blood cell** counts (neutropenia), DVT, neurologic effects, and infections. Anticoagulants are recommended for individuals receiving this regimen because of the increased risk of DVT.

### MP-Revlimid

The combination of MP and Revlimid has also led to good response rates compared with MP among individuals who are not eligible for transplantation.

Results of a Phase III trial involving 459 patients in which MP-Revlimid was compared to MP alone has shown:

- A response rate of 77% for MP-Revlimid compared with 50% for MP alone
- A complete response rate of 18% for MP-Revlimid compared with 5% for MP alone

More research is needed to determine the effect of MP-Revlimid on progression-free and overall survival. The time to progression was longer for patients treated with MP-Revlimid *with* Revlimid maintenance compared with MP. However, without maintenance Revlimid, the time to progression was similar to MP. (*See page 28 for more information about maintenance therapy.*) In this study, there were a small number of second primary cancers reported. Many doctors believe that the improved outcomes with this regimen outweigh the risk of a secondary cancer. However, longer-term follow-up is needed. Patients should discuss the potential benefits and risks of this regimen with their doctor. A trial comparing MP-Revlimid to MP-Thalomid is ongoing.

### **Revlimid-Low-dose Dex**

The combination of Revlimid and a low dose of the corticosteroid dexamethasone (dex) offers an advantage of fewer side effects while improving survival compared with Revlimid and high-dose dexamethasone (a dose traditionally used for the treatment of myeloma). The results of a large phase III study showed that the one-year survival rate was better for Revlimid plus low-dose dex (96%) compared with Revlimid plus high-dose dex (87%). The low-dose dex combination also led to a lower rate of side effects (35%) than the high-dose regimen (52%). Revlimid plus low-dose dex is now a recommended treatment option for individuals with untreated myeloma who are not eligible for transplantation and is increasingly being used in this setting since it is well tolerated and has a three-year survival rate in the elderly population comparable to Velcade-MP.

### **Velcade-dex**

The combination of Velcade and dexamethasone is another option for patients who are ineligible for transplantation. A study of 300 patients showed that response rates with this treatment were similar to other Velcade-based combinations, including Velcade-MP.

### **WHAT ARE MY OPTIONS FOR INITIAL THERAPY AS A TRANSPLANT CANDIDATE?**

Certain chemotherapy agents, such as high-dose melphalan, may impair the ability to collect stem cells for use in an autologous transplant. For this reason, candidates for high-dose chemotherapy and autologous transplant typically receive other agents as initial (induction) therapy. Dexamethasone, once a common induction therapy, is now used more frequently, especially at lower doses, in combination with newer agents.

### **Velcade-based Regimens**

Several Velcade-based regimens have been shown to produce good outcomes as induction therapy before high-dose chemotherapy and transplantation.

#### ***Velcade-Dex***

The effectiveness of Velcade in combination with dexamethasone as induction therapy was demonstrated in two large phase III trials. Response rates with Velcade-dex were improved over that seen with an older regimen known as VAD. Importantly, Velcade-dex was shown to be as effective in patients with poor prognostic features as it was in patients without these features. As a result of these findings, Velcade-dex is considered a standard of care in the induction setting and is a recommended option in NCCN guidelines.

### ***Velcade-Thal-Dex***

Velcade has been added to Thal-dex, a treatment that has yielded good outcomes. For example, in a large phase III study (480 patients), Velcade-Thal-dex achieved significantly better responses both before and after transplantation. Progression-free survival after transplantation was also better. This combination is also recommended in the NCCN guidelines.

Because both Velcade and Thalomid increase the risk of peripheral neuropathy, the French IFM study group reduced the dose of Velcade. The response rates were better for this combination (referred to as v-Thal-dex) than for Velcade-dex alone in a study of 205 patients.

### ***Velcade-Revlimid-dex***

Velcade plus Revlimid and dex (RVD) has also shown promise. Data from a small early study showed that this combination produced one of the highest response rates found among individuals with newly diagnosed myeloma.

- 100% of the 66 patients had a response to this treatment, with a complete response achieved in 39%
- 97% of patients were alive 18 months after initiation of treatment

Notably, there appears to be no difference in outcomes regardless of whether or not patients proceeded to receive a transplant.

The side effects of RVD were manageable, but peripheral neuropathy developed in many patients. In most cases, the neuropathy was mild. A large national phase III study is being done to evaluate the efficacy and safety of RVD compared with Revlimid-dex for patients eligible for high-dose chemotherapy and transplantation.

***Velcade-Cyclophosphamide-Dex***

The combination of Velcade, cyclophosphamide, and dex (VCD or CyBorD) is a recommended option based on high response rates and rapid responses seen in three phase II trials that together enrolled almost 500 patients. Overall response rates in these trials ranged from 84% to 100%. In two of these trials complete/near-complete responses rates of 39% to 47% were seen.

A number of other Velcade-based combinations are being evaluated in early studies.

***Four-drug combinations***

Other combinations with good outcomes in early studies with small numbers of patients are two four-drug combinations: Velcade plus Revlimid, Doxil, and dex and Velcade plus cyclophosphamide, Revlimid, and dex. The challenge with four-drug regimens is the potential for increased side effects, and further research is needed to determine the balance of effectiveness and tolerability.

### Revlimid-Low-Dose-Dex

Revlimid-dex is another recommended option for induction therapy. Because a lower dose of dex would make the treatment option more tolerable, especially for individuals older than 65 years of age, researchers explored whether the dose of dex could be lowered without compromising the outcome.

A phase III trial of 445 patients who were eligible for transplantation showed that Revlimid plus high-dose dex led to better response rates, but these response rates did not lead to better overall survival. In fact, the one-year and two-year overall survival was better for Revlimid plus low-dose dex (96% vs. 87% for one-year survival and 87% vs. 75% for two-year

survival). There were fewer side effects with low-dose dex as well. As a result, Revlimid plus low-dose dex has increasingly become a standard approach.

Revlimid-dex was also found to be superior to Thal-dex in an analysis of 411 patients treated at the Mayo Clinic. In that study, Rev-dex was found to lead to better response rates, time to tumor progression, and overall survival (Table 7). A randomized trial is needed to confirm these results.

Neutropenia, infections, and DVT have been the most common side effects associated with Revlimid-dex. To prevent DVT, drugs such as aspirin or anticoagulants are recommended for individuals receiving Revlimid-dex.

**TABLE 7. COMPARISON OF REVLIMID-DEX AND THAL-DEX AS INDUCTION THERAPY IN AN ANALYSIS OF 411 PATIENTS TREATED AT THE MAYO CLINIC**

Outcome	Revlimid-Dex	Thal-Dex
Very good partial response or better	34%	12%
Partial response or better	80%	61%
Time to tumor progression	27 mos.	17 mos.

## KEY FACTS

# REVLIMID (LENALIDOMIDE)

## WHAT IS REVLIMID?

Revlimid belongs to a group of medicines called immunomodulatory drugs. It is chemically similar to Thalomid, but is more potent and has different side effects. Revlimid is approved for use in combination with dexamethasone (dex) to treat individuals with myeloma who have received at least one prior therapy.

## HOW IS REVLIMID TAKEN?

Revlimid comes as capsules in several strengths. The recommended starting dose of Revlimid is 25 mg/day given on days one to 21 of repeated 28-day cycles. Dosing is continued or may be modified based upon clinical and laboratory findings.

## WHAT ARE THE POSSIBLE SIDE EFFECTS OF REVLIMID?

The most commonly reported side effects of Revlimid-dex are:

- Gastrointestinal effects (constipation, diarrhea, nausea)
- Fatigue, loss/lack of strength
- Insomnia
- Muscle cramps
- Low blood counts (neutropenia, anemia)
- Fever, headache, dizziness
- Fluid buildup
- Shortness of breath
- Shaking

The most commonly reported serious side effects with Revlimid-dex are:

- Low blood counts (neutropenia, thrombocytopenia, anemia)

- High blood sugar
- DVT
- Fatigue
- Pneumonia

Studies have shown that blood clotting events, such as DVT and pulmonary embolism, occur more frequently after treatment with Revlimid-dex than placebo-dex, so use of aspirin or an anticoagulant is recommended for individuals receiving this combination.

There have been reports of new primary cancers developing in a small number of myeloma patients receiving Revlimid when used with melphalan either as part of high-dose chemotherapy or the MP-Revlimid regimen. Many doctors believe that the benefits of Revlimid therapy likely outweigh any potential risk of second cancers. Nevertheless, as is the case with any potential side effects, patients should discuss potential risks versus benefits of treatment with their doctor.

Because Revlimid may affect the ability to obtain stem cells for transplantation, it is suggested that stem cells be collected prior to prolonged administration of Revlimid.

Revlimid may cause birth defects and should not be taken by pregnant women. It is only available under a special restricted access program called RevAssist®.

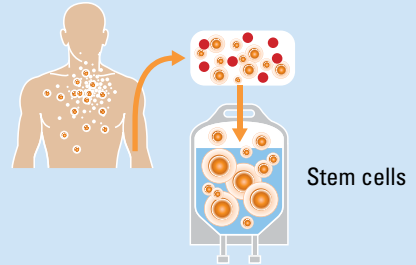
## CHOICE OF INITIAL THERAPY IN MYELOMA

As discussed above, many new regimens are available for transplant candidates and non-transplant candidates. Most of the new regimens have not yet been compared with each other to make clear-cut recommendations on which regimen a patient should get. The choice of the regimen depends on many factors, including the baseline features of the myeloma itself, as well as drug availability, convenience, anticipated risk of side effects, and the familiarity of the treating physician with the given regimen. In general, all of the regimens discussed above represent excellent advances in the treatment of myeloma and patients should know that if one regimen stops working another one can be used. There are many choices available today and the treatments continue to improve.

Figure 2. **Stem cell transplantation**

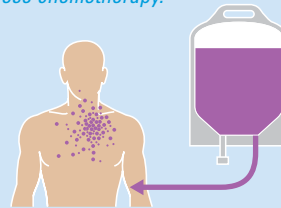
### 1. Collection

*In stem cell transplantation, peripheral blood stem cells (PBSCs) are collected (also called “harvested”) from the individual with myeloma following administration of growth factors with or without chemotherapy, or from a donor.*



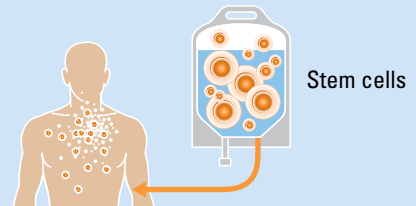
### 2. High-dose chemo

*The cells are processed in the laboratory, frozen, and stored until needed. The person receives high-dose chemotherapy.*



### 3. Infusion

*The stem cells are then thawed and infused into the individual with myeloma.*



*Transplanted stem cells begin to produce new blood cells.*

## WHAT IS HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION?

High-dose chemotherapy (usually melphalan) with stem cell transplantation is a therapeutic strategy that, for many patients, offers a chance for durable remission of the disease. High-dose chemotherapy, though more effective in killing myeloma cells than conventional chemotherapy, also destroys normal blood-forming cells in the bone marrow. Stem cell transplantation replaces these important cells (Figure 2).

Stem cells are normally found in the bone marrow and in the peripheral blood (blood found in the arteries or veins). Virtually all transplants in myeloma are now obtained from the peripheral blood and are referred to as **peripheral blood stem cell (PBSC)** transplants.

Growth factors are often given to help stimulate the growth of stem cells so that a sufficient number can be obtained. This process of stimulating the growth of stem cells is known as **mobilization**. A drug called Mozobil® (plerixafor injection, Genzyme Corp., a Sanofi company)

may be used in combination with growth factors in order to further enhance stem cell mobilization.

Stem cell transplants are categorized by the source of stem cells:

- Autologous transplants involve collecting stem cells from the individual with myeloma after three to four cycles of initial therapy are administered to reduce the amount of myeloma cells. Autologous transplants are the most common transplant procedures in myeloma.
- **Allogeneic transplants** involve collecting stem cells from a donor (usually a relative) that are infused into the individual with myeloma after high-dose therapy. This type of transplant is infrequently performed today because of the high risk of complications, although it does offer beneficial effects. A **mini (non-myeloablative) allogeneic transplant** is a modified form of allogeneic transplant that attempts to preserve the beneficial effects of allogeneic transplants while making them safer.

Information regarding these transplants, as well as others being investigated in clinical trials, is summarized in the table below.

Possible side effects of high-dose chemotherapy and transplantation include nausea, vomiting, diarrhea, **mucositis** (inflammation of the lining of the digestive tract), fatigue, and organ damage, particularly to the heart, lungs, liver,

and kidneys. In addition, because the high-dose chemotherapy attacks healthy, disease-fighting cells as well as cancerous cells, stem cell transplants are associated with an increased risk of infection.

### SHOULD I RECEIVE MAINTENANCE THERAPY?

There is increasing evidence supporting the role of maintenance therapy after the completion of front-line therapy alone or after front-line therapy and transplantation.

**TABLE 8. TRANSPLANTS PERFORMED IN MYELOMA**

Type	Description
Autologous	<ul style="list-style-type: none"> <li>• Most common type performed in myeloma</li> </ul>
<b>Tandem (double) autologous</b>	<ul style="list-style-type: none"> <li>• Two autologous transplants typically performed within six months of each other</li> <li>• In general, a second transplant is of benefit only if a complete response or very good partial response is not achieved with the first transplant</li> <li>• Increased side effects over a single transplant</li> <li>• Being used less frequently with the increased use of newer agents in the induction setting and resultant improved response rates</li> </ul>
Allogeneic	<ul style="list-style-type: none"> <li>• Performed infrequently because of high risk of complications, including infections and <b>graft-versus-host disease (GVHD)</b></li> </ul>
Mini (nonmyeloablative) allogeneic	<ul style="list-style-type: none"> <li>• Have largely replaced allogeneic transplants</li> <li>• Utilize moderately high-dose chemotherapy, which does not completely destroy the bone marrow</li> <li>• Can be performed alone or following an autologous transplant</li> <li>• Best performed in the setting of a clinical trial until more long-term results are available</li> </ul>

Because myeloma is not curable, it will recur even in individuals who have a complete response after treatment. The overall goal of maintenance therapy is to maintain the response for as long as possible, thus improving survival.

The results of studies are now showing that maintenance therapy may help to improve survival and keep myeloma in remission after transplantation. Two large trials—one conducted in the United States (568 patients) and one conducted in France (614 patients)—showed that Revlimid provides significant benefit as maintenance therapy after transplantation.

- In the US study, the overall survival rate was higher for patients who received Revlimid. This is the first study to show a survival benefit with Revlimid maintenance therapy.
- In the French trial, the risk of a patient's disease progressing after transplantation was reduced by half in patients receiving Revlimid compared to those receiving placebo.

In both studies, low blood counts were commonly seen with Revlimid maintenance, and more severe side effects were seen with Revlimid compared with placebo.

Another study has shown the benefit of maintenance therapy with Revlimid after front-line therapy alone. This study was conducted in 459 patients over 65 years of age who were not eligible for transplantation. Patients received MP-Revlimid followed by maintenance with Revlimid or MP alone. Both response rates and time to disease progression were longer for patients treated with MP-Revlimid *with* Revlimid maintenance compared with MP. However, it is not yet known whether maintenance therapy with Revlimid following MP-Revlimid has an impact on survival.

A small increase in second cancers was seen in these three studies, but the consensus among the researchers was that the benefits likely outweigh the risks. As is the case with any potential side effects, patients should discuss their risk of second cancers with their doctor.

While more data are needed to *definitively* determine the survival benefit of maintenance therapy the results have led investigators to include maintenance therapy in many recent studies of front-line therapy. The results are also likely to prompt more doctors to discuss risks (eg, second cancers) versus benefits (improved progression-free and possibly overall survival) of maintenance therapy with their patients.

Researchers are also evaluating other regimens for maintenance therapy, including Thalomid (alone or in combination with dex or prednisone) or Velcade (alone or with Thalomid). In particular, one large trial in Sweden showed that giving Velcade after transplant improved the response rate and time without disease progression.

## WHAT ARE MY OPTIONS IF I DON'T RESPOND TO THERAPY OR RELAPSE?

If myeloma does not respond to initial (front-line) therapy or if relapse occurs within six months after the completion of initial therapy, the myeloma is considered to be refractory, or resistant to the treatment. Therefore, the disease is not likely to respond to the same treatment, and another treatment option may be used as second-line therapy. If relapse occurs more than six months after the completion of initial therapy, the initial therapy may be repeated or another regimen commonly used as initial therapy may be given.

There are many treatments available for relapsed/**refractory disease** and many promising new agents are under investigation. Options for treating relapsed or refractory disease include:

- A variety of approved agents, including Revlimid-dex, Velcade (with or without dex), Velcade-Doxil, Thal-dex, and conventional chemotherapy agents such as melphalan and cyclophosphamide
- Various published multi-drug combination regimens based on novel therapies with or without steroids and/or chemotherapy, such as Velcade-Revlimid-dex

- Stem cell transplant (if possible)
- Participation in a clinical trial

### Revlimid-Dex

The FDA approval of Revlimid in combination with dex for relapsed or refractory myeloma was based on the results of two phase III trials in which Revlimid-dex was compared with placebo-dex in a total of 705 individuals with myeloma who had received at least one prior treatment. Revlimid significantly increased the length of time patients remained disease free and delayed time-to-progression in individuals with relapsed or refractory myeloma

(Table 9). The overall response rate with Revlimid-dex was over 60 percent, more than double that seen with placebo-dex.

The most common side effects seen with Revlimid-dex compared with placebo-dex included constipation, muscle cramp, diarrhea, neutropenia, and anemia. Serious side effects were primarily **hematologic** in nature and individuals receiving Revlimid-dex were at increased risk for thrombotic events (DVT and pulmonary embolism) compared with those receiving placebo-dex. The risk of DVT was also increased in individuals receiving Revlimid-dex who also received **erythropoietin**.

**TABLE 9. PHASE III REVLIMID TRIALS: POOLED FOLLOW-UP ANALYSIS**

Endpoint	Revlimid-dex (N=353)	Placebo-dex (N=351)
Median time-to-progression (TTP)	11.1 months	4.6 months
Overall response rate (ORR)	61%	22%
Complete response (CR)	15%	2%
Median progression-free survival (PFS)	10.9 months	4.6 months
One-year overall survival (OS)	82%	75%

## Velcade

Velcade is an FDA-approved treatment option for myeloma. Results of a Phase III trial in patients with relapsed or refractory myeloma showed significantly longer time-to-disease progression, higher response rate, and improved survival with Velcade compared with high-dose dexamethasone. In addition, patients with poor prognostic factors also benefitted from Velcade. Patients receiving Velcade experienced increased gastrointestinal effects, neuropathy, low blood counts, and temporary reversible decreases in platelet count. Although Velcade can be used alone in treating relapsed or refractory disease, it is more commonly used in combination with dex, as well as with other agents.

## Velcade-Doxil

Doxil is approved for use in combination with Velcade to treat individuals who have previously received a therapy other than Velcade. Approval was based on interim results of a Phase III trial that showed that adding Doxil to the standard Velcade regimen reduced the risk of disease progression and prolonged the length of the response in individuals with relapsed and refractory disease compared with Velcade alone. The combination also led to longer survival. The patterns of side effects in the study were consistent with the side effects typically seen with the individual agents. The most common serious side effects seen with the combination were low platelet and white blood cell counts.

### Other Velcade-based Regimens

Velcade continues to be evaluated in clinical trials in combination with other drugs, such as Thalomid, dex, Revlimid, and Doxil; conventional chemotherapy drugs, such as melphalan, cyclophosphamide, and doxorubicin; and emerging therapies in relapsed/refractory disease. For example, the combination of Velcade-Revlimid-dex was shown to be very effective in a Phase II trial. Eighty-four percent of patients responded to the therapy and 25 percent achieved a near complete or complete response.

### Other Chemotherapy Regimens for Second-line Therapy

Various chemotherapy agents and combinations are also used in the treatment of relapsed/refractory disease. A variety of combination therapies, many including newer and novel agents, are under investigation in clinical trials for use in this setting.

### WHAT SUPPORTIVE THERAPIES ARE USED IN MYELOMA?

Supportive therapies address the symptoms and complications of the disease and are used along with other treatments as necessary. Supportive therapies commonly used in myeloma include:

- Bisphosphonates and other drugs to treat bone disease
- Growth factors
- Antibiotics
- Intravenous immunoglobulin
- Orthopedic interventions
- **Plasmapheresis**
- Pain control measures

## **Bisphosphonates and Other Drugs to Treat Bone Disease**

Bisphosphonates are drugs that help prevent myeloma bone disease from getting worse, decrease bone pain, and reduce the likelihood of fracture. Two drugs in this class, pamidronate (Aredia®) and zoledronic acid (Zometa®, Novartis), are approved for the treatment of bone complications in individuals with myeloma, as well as bone metastases and hypercalcemia of malignancy. Zometa and pamidronate are equally effective in reducing the skeletal complications of myeloma bone disease. However, Zometa is more convenient due to its shorter infusion time.

A large Phase III trial in the United Kingdom recently reported that after 4 years of follow-up both patients with and without bone disease benefitted from Zometa. Both groups had a reduced incidence of skeletal complications. This study also showed that Zometa may have an anti-myeloma effect. Zometa significantly improved overall survival in patients with bone disease by an average of 5.5 months compared with another bisphosphonate not available in the United States. The beneficial effect of Zometa on overall survival could not be explained by bone effects alone, raising the possibility that the drug may have other favorable anti-myeloma effects.

Because kidney function may be affected by bisphosphonates, it is recommended that individuals with mild or moderate kidney impairment receive reduced doses of Zometa when starting treatment. Pamidronate is recommended for individuals with severe kidney impairment.

Some studies indicate that long-term use of bisphosphonates may be associated with damage to the jawbone known as osteonecrosis, and that this risk may be higher with Zometa. Thus, it is recommended that only myeloma patients with bone disease receive Zometa due to the small risk of osteonecrosis of the jaw.

It is recommended that individuals with myeloma receiving bisphosphonates take steps to maintain their oral health (see sidebar). Interrupting or stopping bisphosphonates may be considered in severe cases of osteonecrosis. A recent clinical practice guideline suggests considering stopping bisphosphonates after a period of two years in individuals with responsive or stable disease. In addition, clinical trials are evaluating less-frequent dosing of bisphosphonates.

Another drug showing promise for the treatment of myeloma bone disease is Xgeva® (denosumab, Amgen). Xgeva, which is not a bisphosphonate, is a novel agent currently approved by the FDA to prevent bone complications in patients with other types of cancers. Although Xgeva is not currently approved for use in myeloma, a large phase III trial is being conducted to compare Xgeva and Zometa specifically in patients with multiple myeloma.

### Growth Factors

A variety of growth factors are used in myeloma. For example, certain individuals experiencing moderate to severe treatment-related anemia (hemoglobin <10 g/dL) may receive erythropoietin (such as Procrit® [epoetin alfa, Ortho Biotech]) or a related product Aranesp® (darbepoetin alfa, Amgen®) to help their bone marrow produce more red blood cells. Use of these agents with certain myeloma therapies, such as Thalomid or Revlimid, may not be appropriate due to an increased risk of blood clots.

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### HOW CAN I KEEP MY MOUTH HEALTHY WHILE RECEIVING BIPHOSPHONATES?

- Complete major dental work before beginning bisphosphonate therapy
  - Practice good oral hygiene
  - Schedule regular dental visits
  - Let your dentist know you are receiving bisphosphonates
  - Manage dental problems conservatively (least invasive strategy)
  - Keep your doctor informed of dental issues/need for dental work
-

Individuals who have low numbers of white blood cells (as a result of their disease, chemotherapy, or therapies such as Revlimid-dex) and those who have a delayed recovery from high-dose chemotherapy with stem cell transplantation may receive growth factors known as **colony-stimulating factors (CSFs)**. CSFs stimulate production of infection-fighting white blood cells. Examples of CSFs include Neupogen® (filgrastim, Amgen®), Neulasta® (pegfilgrastim, Amgen®) and Leukine® (sargramostim, Genzyme Corp., a Sanofi company).

Keeping white blood cell counts up and preventing infection can help keep individuals with myeloma on track with their chemotherapy dose and schedule, which helps ensure that they receive the maximum benefit from their therapy. After high-dose chemotherapy and stem cell transplant, CSFs help increase numbers of white blood cells, reduce infection and the need for antibiotics, and shorten hospital stays.

Another growth factor approved for use in myeloma is Kepivance® (palifermin, Biovitrum). Palifermin is indicated to decrease the occurrence and duration of severe oral mucositis in individuals with

hematologic cancers undergoing high-dose chemotherapy followed by a stem cell transplant. Oral mucositis, which occurs because the cells lining the mouth and throat are damaged by chemotherapy and/or radiation, is a painful condition that can interfere with eating and drinking and can result in infection.

### Orthopedic Interventions

Orthopedic interventions may be required to help control pain or maintain function or mobility. These may include physical therapy, splinting of bones to prevent or treat fractures, or surgical procedures to repair compression fractures of the spine. Two minimally invasive surgical procedures—**vertebroplasty** and **balloon kyphoplasty**—are used to reinforce the vertebra. Vertebroplasty involves the injection of a cement-like substance to reinforce the vertebra. Balloon kyphoplasty involves the insertion of an inflatable balloon to restore the height of the compressed vertebra, followed by injection of bone cement to maintain the re-established height (Figure 3). By stabilizing the affected vertebrae, these procedures help relieve pain and improve function and quality of life in individuals with myeloma.

### Figure 3. Balloon kyphoplasty

1.

*During balloon kyphoplasty, two balloons are inserted into the compressed bone through a tiny tube (only one balloon is shown here). The incision is approximately 1cm in length.*



2.

*The balloons are inflated in an attempt to both raise the collapsed vertebra and return it to its normal position.*



3.

*The balloons are deflated and removed. The cavity is filled with bone cement in an attempt to both support the surrounding bone and prevent further collapse.*



4.

*The bone cement forms an internal cast that holds the vertebra in place.*



## HOW DO I FIND A CLINICAL TRIAL?

Clinical trials help identify new treatments for diseases. Participation in clinical trials is very important. All participants receive the therapy being tested for multiple myeloma or the best available standard treatment. Individuals enrolled in clinical trials receive close monitoring, as well as the opportunity to benefit from the newest treatments available. However, it is important to understand that new treatments may be equivalent to, more effective than, or not as effective as standard treatment options. They may also have unexpected side effects.

Clinical trials take place at cancer centers, hospitals, clinics, or doctors' offices. Before you enroll, all details of the treatment will be explained and you must consent to participate. Remember, you can withdraw from a clinical trial at any time.

Clinical trials are defined according to their phase, with each phase serving a distinct purpose (Table 10). Based on the results of clinical trials, the FDA approves treatments that are safe, effective, and shown to be better than the standard treatments available.

**TABLE 10. PHASES OF CLINICAL TRIALS**

Phase	Size (no. of participants)	Purpose	Approximate Duration <sup>a</sup>
I	Small (15-30)	Determines safety and dosage, as well as how the drug is absorbed and acts in the body	1 year
II	Moderate (30-100)	Evaluates effectiveness and safety	1-2 years
III	Large (100-1000+)	Compares effectiveness and safety with standard treatment	2-4 years

<sup>a</sup>*Trials may occasionally close earlier than or exceed approximate duration.*

The MMRF Patient Navigator Program is designed to match individuals with appropriate clinical trials. To take advantage of this program, you (or your caregiver or family member) can complete a simple questionnaire online at [www.themmr.org](http://www.themmr.org). Or, you can call 866.603.MMCT (6628) to speak with a Clinical Trials Specialist who will ask you questions and talk to you about clinical trials that will be appropriate for you. The Specialist can also help you enroll in a trial, if you choose. Speak with your doctor regarding questions about specific trials and treatment options.

**Weblinks: Clinical Trial Information**

MMRF Patient Navigator Program

<https://myeloma.trialx.com/>

National Cancer Institute

[www.cancer.gov](http://www.cancer.gov)

CenterWatch Clinical Trial Listing Service

[www.centerwatch.com](http://www.centerwatch.com)

## WHAT ARE SOME OF THE PROMISING THERAPIES IN CLINICAL TRIALS?

There are a variety of new treatments with novel mechanisms of action in various stages of preclinical and clinical development for myeloma. These agents act in different ways against myeloma and many lack some of the common side effects seen with conventional cancer drugs. However, the availability of some of these drugs may be limited to individuals at particular stages of disease and they are not without side effects of their own.

Table 11 lists therapies in Phase III clinical trials.

### **Weblink: Emerging Therapies**

For more detailed information about these and other therapies, see the MMRF's website ([www.themmr.org](http://www.themmr.org)) or [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## YOUR TREATMENT OPTIONS

This booklet has presented many treatment options in multiple myeloma. Your doctor can provide more information about treatments that are most appropriate for you. Enrollment in a clinical trial may present additional options; your doctor can determine which trials are appropriate and available in your area.

Research continues in the field of myeloma and there are many promising new therapies under investigation that are bringing us closer to a cure. Your doctor and the MMRF can help you get more information.

**TABLE 11. EMERGING THERAPIES FOR MYELOMA IN PHASE III CLINICAL TRIALS**

Name	Company
Aplidin (plitidepsin)	PharmaMar
Carfilzomib (PR-171)	Onyx Pharmaceuticals
Elotuzumab (HuLuc63)	Facet Biotech/Bristol-Myers Squibb
Panobinostat (LBH589)	Novartis
Perifosine (KRX-0401)	Keryx
Pomalidomide (CC-4047)	Celgene Corporation
Siltuximab (CNTO 328)	Janssen Biotech, Inc.
Zolinza® (vorinostat)	Merck

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## GLOSSARY

**Albumin** Major protein found in the blood. A person's albumin level can provide some indication of overall health and nutritional status.

**Allogeneic transplant** Stem cell transplant in which cells are collected from another person.

**Anemia** Decrease in the number of red blood cells in the blood.

**Antibody** Protein produced by plasma cells that helps protect the body from infection and disease. Also called immunoglobulin.

**Anticoagulant** Drug that prevents blood from clotting.

**Antiemetic** Drug that prevents or alleviates nausea and vomiting.

**Autologous transplant** Stem cell transplant in which cells are collected from the individual being treated.

**Balloon kyphoplasty** Procedure used to treat spinal compression fractures whereby a balloon is inserted into the compressed vertebra and inflated to elevate the collapsed section. The cavity is filled with bone cement, stabilizing and preserving the re-established height.

**Bence Jones protein** A short (light chain) protein that is produced by myeloma cells.

**Beta<sub>2</sub>-microglobulin (β<sub>2</sub>-microglobulin or β<sub>2</sub>-M)** A protein normally found on the surface of various cells in the body. Increased blood levels occur in inflammatory conditions and certain lymphocyte disorders, such as myeloma.

**Bisphosphonate** Type of drug used to treat osteoporosis and bone disease in individuals with cancer. Bisphosphonates work by inhibiting the activity of bone-destroying cells called osteoclasts.

**Bone marrow** Soft, spongy tissue found in the center of many bones where blood cells are produced.

**Calcium** Mineral important in bone formation. Elevated blood levels occur when there is bone destruction.

**Chemotherapy** The use of drugs to kill rapidly dividing cancer cells.

**Colony-stimulating factor (CSF)** Growth factor that stimulates the bone marrow to produce white blood cells.

**Corticosteroid** A potent class of drugs that has anti-inflammatory, immunosuppressive, and antitumor effects. Dexamethasone and prednisone are examples of corticosteroids.

**Deep vein thrombosis (DVT)** Condition where a blood clot forms in one of the deep veins in the body, usually in the legs or lower abdomen.

**Erythropoietin** Growth factor that stimulates the bone marrow to produce red blood cells.

**Free light chain (FLC) ratio** Ratio of the levels of the two types of immunoglobulin light chains (kappa and lambda) normally present in serum. An abnormal ratio suggests the presence of myeloma cells.

**Front-line therapy** The initial treatment given (also known as first-line therapy).

**Graft-versus-host disease (GVHD)** Complication of allogeneic transplants resulting from donor immune cells recognizing the recipient's cells as foreign and mounting an attack against them.

**Growth factor** Substance that stimulates cells to multiply.

**Hematologic** Pertaining to the blood.

**Hematopoietic stem cell** Parent cell that grows and divides to produce red blood cells, white blood cells, and platelets. Found primarily in the bone marrow but also in the peripheral blood. (Hematopoietic stem cells are different from embryonic stem cells.) See also stem cell transplantation.

**Hemoglobin** Oxygen-carrying substance in red blood cells.

**Hypercalcemia** High levels of calcium in the blood due to increased bone destruction.

**Immunofixation** A sensitive test for trace amounts of M protein.

**Immunoglobulin (Ig)** Protein produced by plasma cells that helps protect the body from infection and disease. Also called antibody.

**Induction therapy** Treatment prior to a stem cell transplant in order to reduce the tumor burden.

**Malignant** Cancerous, continuing to divide.

**Median** A type of average, determined by selecting the middle value from among all the values (there are an equal number of values higher and lower than the median value). For example, a median survival of five years does not mean that patients will live for five years. Rather, it means that 50 percent of patients will live longer than five years, and 50 percent less than five years.

**Mini (non-myeloablative) allogeneic transplant** Modified form of allogeneic transplant that involves moderately high-dose chemotherapy; attempts to preserve the beneficial effects of allogeneic transplants while making them safer.

**Mobilization** The process of stimulating the growth of stem cells in order to ensure that a sufficient number of stem cells can be obtained for transplantation.

**Monoclonal gammopathy of undetermined significance (MGUS)** A precancerous and asymptomatic condition noted by the presence of M protein in the blood or urine. MGUS may eventually progress to myeloma.

**Monoclonal (M) protein** Identical immunoglobulin protein produced by myeloma cells. M protein is found in the blood or urine and is used as a marker for the amount of myeloma disease present in the body.

**Mucositis** Inflammation of mucous membranes lining the digestive tract; a common and painful side effect of chemotherapy or radiotherapy that can result in sores and infection.

**Neuropathy** Disorder of the nerves that can result in abnormal or decreased sensation, or burning/tingling. When the hands and feet are affected, it is referred to as peripheral neuropathy.

**Neutropenia** Below-normal number of neutrophils (type of white blood cell that functions to destroy bacteria.)

**Osteolytic lesion** Soft spot in the bone where bone tissue has been destroyed. The lesion appears as a hole on a standard bone x-ray.

**Osteopenia** Condition of decreased bone density.

**Osteoporosis** Generalized bone loss typically associated with old age, but which can also occur in myeloma.

**Peripheral blood stem cell (PBSC)** Stem cell found in the bloodstream.

**Plasma cell** Antibody-secreting immune cell that develops from a B cell.

**Plasmacytoma** Single tumor composed of malignant plasma cells that occurs in

bone or soft tissue. Myeloma may develop in individuals with a plasmacytoma.

**Plasmapheresis** Procedure whereby blood is withdrawn from the individual with myeloma, the plasma containing the excess M protein is separated out, and the cells and replacement fluid are infused back into the individual. Plasmapheresis may slow down or prevent kidney failure in individuals with myeloma.

**Progression-free survival (PFS)** Length of time during or after treatment that an individual remains disease-free.

**Proteasome** Complex of enzymes that plays a role in the regulation of cell function and growth by breaking down proteins in a cell after they have performed their functions, allowing various cellular processes to continue in an orderly fashion.

**Radiation therapy** Use of high-energy rays to damage cancer cells and prevent them from growing; sometimes used to relieve uncontrolled pain and in cases of imminent risk of bone fracture or spinal-cord compression.

**Refractory disease** Disease that is not responsive to therapy.

**Relapse** Return of disease or disease progression.

**Remission** Complete or partial disappearance of cancer signs and symptoms, or when a cancer is under control; may be used interchangeably with response.

**Second-line therapy** Treatment that is given after failure of front-line therapy (disease is refractory) or after disease relapses.

**Stem cell transplantation** Therapeutic procedure in which bone marrow or peripheral blood stem cells are collected, stored, and infused into an individual following high-dose chemotherapy to restore blood cell production.

**Tandem autologous transplant** Stem cell transplant in which an individual undergoes two planned autologous transplants within six months.

**Thrombocytopenia** Decrease in the number of platelets (small cell fragments in the blood that help it to clot).

**Vertebroplasty** Procedure used to treat spinal compression fractures whereby cement is injected into the affected vertebrae to stabilize them.

**White blood cell** Also called a leukocyte. One of the major cell types in the blood. Responsible for immune defenses.



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