MULTIPLE MYELOMA 
Disease Overview
ABOUT THE MULTIPLE MYELOMA RESEARCH FOUNDATION

Shortly after being diagnosed with multiple myeloma, Kathy Giusti and her sister Karen Andrews, a successful corporate attorney, founded the MMRF in 1998 with the hope of one day finding a cure for this fatal blood cancer. Leveraging her past experience as a leader of a major pharmaceutical company, Kathy applied her business savvy to the science of cancer research. She and the MMRF identified barriers slowing drug development, particularly for an uncommon heterogeneous disease like multiple myeloma, and developed collaborative models to overcome those obstacles.

Optimized to run like a Fortune 500 company, with a culture of speed, innovation, and results, the MMRF remains laser focused on accelerating new and better treatments for patients, leading toward a cure.

Today the MMRF works with the best scientists, pharmaceutical partners, biotech companies and academic centers in the world to facilitate developing new drugs—the treatments of which have doubled the life expectancy of our patients and are helping to transform the way cancer research is done.

As the multiple myeloma community’s most trusted source of 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 and the best treatment options, including clinical trials. All information on our website, www.themmrf.org, is tailored to patients by disease stage, so we can make sure you get the information you need at the right time.

To learn more about the MMRF, visit www.themmrf.org or call 203.229.0464.

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INTRODUCTION
This booklet is designed primarily to help patients with newly diagnosed multiple myeloma and their friends and families better understand this disease. The booklet explains what myeloma is, and how it develops within the body. Words that may be unfamiliar are bolded throughout the text at first mention and defined in the Glossary (page 26). Learning as much as possible about multiple myeloma will help you be more involved in making decisions about treatment.

Multiple myeloma is a treatable cancer and there have been dramatic improvements in survival over the last 10 years with the introduction of new treatments. Importantly, there are many promising new therapies under investigation that are bringing us closer to a cure.

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

WHAT IS MULTIPLE MYELOMA?
Multiple myeloma is a blood cancer that develops in the bone marrow (Figure 1). The bone marrow is the soft, spongy tissue found in the center of many bones where blood cells are produced. In myeloma, plasma cells, which are normal antibody-producing cells, transform into cancerous myeloma cells. Myeloma cells produce large quantities of abnormal antibodies (or immunoglobulins) called monoclonal (M) proteins as well as incomplete parts of antibodies (called light chains or Bence-Jones proteins). These cancer cells 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, resulting in weakened bones and increasing the risk of fractures (Figure 2). Although common, these lesions or other signs of bone loss do not occur in all patients with myeloma.

The MMRF booklet, *Multiple Myeloma: Treatment Overview*, and the MMRF website, www.themmrf.org, provide more information about current therapies for myeloma and emerging treatment options.
In healthy bone marrow, B-cells, a type of white blood cell, develop into antibody-producing plasma cells when foreign substances (antigens) enter the body. In multiple myeloma, DNA damage to a B-cell transforms the normal plasma cell into a multiple myeloma cell. The cancerous cell multiplies, leaving less space for normal blood cells in the bone marrow, and produces large quantities of M protein.

Myeloma cells in the bone marrow cause osteolytic lesions, which appear as "holes" on an x-ray. Weakened bones increase the risk of fractures, as shown in this x-ray of a forearm.
HOW COMMON IS MYELOMA?
More than 90,000 people are living with multiple myeloma today, and the American Cancer Society estimates that multiple myeloma will be diagnosed in 26,850 people in 2015. Multiple myeloma is the second most common blood cancer after non-Hodgkin’s lymphoma. It represents approximately 1% of all cancers and just under 2% of all cancer deaths.

Multiple myeloma is more common among men than women, occurs more frequently with increasing age, and develops twice as often among black Americans as among white Americans.

WHAT CAUSES MYELOMA?
To date, no cause for myeloma has been identified. Research suggests possible associations with a decline in the immune system, certain occupations, exposure to certain chemicals, and exposure to radiation. However, there are no strong connections, and in most cases, multiple myeloma develops in individuals who have no known risk factors. Multiple myeloma may be the result of several factors acting together. It is uncommon for myeloma to develop in more than one member of a family.

HOW DOES MYELOMA AFFECT THE BODY?
The primary effect of multiple myeloma is on the bone. The blood and the kidneys are also affected (Figure 3).

Bone
Bone loss is the most common effect of multiple myeloma, and 85% of patients diagnosed with multiple myeloma have some degree of bone loss. The most commonly affected bones are the spine, pelvis, and rib cage.

Myeloma leads to bone loss in two ways. First, the myeloma cells gather to form masses in the bone marrow that may disrupt the normal structure of the surrounding bone. Second, myeloma cells secrete substances that interfere with the normal process of bone repair and growth. Bone destruction can also cause the level of calcium in the bloodstream to go up, a condition called hypercalcemia, which can be a serious problem if appropriate treatment is not given immediately.

Blood
The growing number of myeloma cells can interfere with the production of all types of blood cells.

A reduction in the number of white blood cells can increase the risk of infection. Decreased red blood cell production can result in anemia, which is present in approximately 60% of patients at diagnosis. A reduction in platelets can interfere with normal blood clotting.
Approximately 85% of patients have some type of bone damage or loss. The most commonly affected areas are the spine, pelvis, and rib cage.

Blood
Low blood counts may lead to anemia and infection. Anemia is present in 60% of patients at diagnosis. Clotting problems may also occur.

Kidneys
Over half of myeloma patients have a decrease in kidney function at some point over the course of their disease.

Figure 3. Effect of myeloma on the body
Kidneys
Excess M protein and calcium in the blood overwork the kidneys as they filter blood. The amount of urine produced may decrease, and the kidneys may fail to function normally. More than half of patients will experience a decrease in their kidney (also called renal) function at some point in the course of the disease.

WHAT ARE THE SYMPTOMS OF MYELOMA?
There are often no symptoms in the early stages of myeloma. When present, symptoms may be vague and similar to those of other conditions. Some of the more common symptoms are:

■ Bone pain
■ Fatigue
■ Weakness
■ Infection
■ Loss of appetite and weight loss

In addition, symptoms related to high levels of calcium in the blood (hypercalcemia) or kidney problems may include:

■ Increased or decreased urination
■ Increased thirst
■ Restlessness, eventually followed by extreme weakness and fatigue
■ Confusion
■ Nausea and vomiting

WHAT TESTS ARE DONE TO DIAGNOSE MYELOMA?
Blood and urine tests as well as a bone marrow biopsy are part of the initial evaluation to help confirm a diagnosis of myeloma. Other tests include X-rays, MRIs, CT scans and PET scans (Table 1).

It is very important for you to have all the appropriate tests done, as the results will help your doctor better determine treatment options and prognosis. Many of these tests are also used to assess the extent of disease and to plan and monitor treatment.
## TABLE 1. COMMON TESTS AND MEDICAL PROCEDURES TO CONFIRM DIAGNOSIS OF MYELOMA

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Purpose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count (number of red blood cells,</td>
<td>Determine the degree to which myeloma is interfering with the normal</td>
<td>Low levels may signal anemia, increased risk of infection, and poor</td>
</tr>
<tr>
<td>white blood cells, and platelets; and relative</td>
<td>production of blood cells</td>
<td>clotting</td>
</tr>
<tr>
<td>proportion of white blood cells)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry profile (albumin, calcium, lactate</td>
<td>Assess function of kidney, liver, and bone status and the extent of</td>
<td>Abnormal levels may indicate changes in bone status, liver, or kidney</td>
</tr>
<tr>
<td>dehydrogenase [LDH], blood urea nitrogen [BUN], and</td>
<td>disease</td>
<td>problems. Also indicates the amount of myeloma present.</td>
</tr>
<tr>
<td>creatinine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta₂-microglobulin (β₂-M) level</td>
<td>Determine the level of a protein that indicates the presence/extent of</td>
<td>Higher levels indicate more extensive disease; aids in staging of</td>
</tr>
<tr>
<td></td>
<td>myeloma and kidney function</td>
<td>disease</td>
</tr>
<tr>
<td>Antibody (immunoglobulin, or Ig) levels and antibody</td>
<td>Determine levels of IgG or IgA antibodies that are overproduced by</td>
<td>Higher levels suggest the presence of myeloma</td>
</tr>
<tr>
<td>type (Ig type G or Ig type A)</td>
<td>myeloma cells</td>
<td></td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Detect the presence and level of various proteins, including the</td>
<td>Higher levels indicate more extensive disease; aids in classification of</td>
</tr>
<tr>
<td></td>
<td>protein made by myeloma cells—Monoclonal or M protein</td>
<td>disease</td>
</tr>
<tr>
<td>Immunofixation electrophoresis (IFE; also called</td>
<td>Identify the type of abnormal antibody proteins in the blood</td>
<td>Aids in classification of disease</td>
</tr>
<tr>
<td>immunoelectrophoresis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freelite™ serum free light chain assay</td>
<td>Measure antibody light chains made by myeloma cells called kappa or</td>
<td>Abnormal levels and/or ratio suggest the presence of myeloma or a</td>
</tr>
<tr>
<td></td>
<td>lambda</td>
<td>related disease</td>
</tr>
</tbody>
</table>

*Table 1 continued on next page*
TABLE 1. (CONTINUED) COMMON TESTS AND MEDICAL PROCEDURES TO CONFIRM DIAGNOSIS OF MYELOMA

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Purpose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Assess kidney function</td>
<td>Abnormal findings may suggest kidney damage</td>
</tr>
<tr>
<td>Urine protein level (performed on a 24-hour specimen of urine)</td>
<td>Define the presence and level of Bence Jones proteins (otherwise known as a myeloma light chains)</td>
<td>Presence indicates myeloma, and higher levels indicate more extensive disease</td>
</tr>
<tr>
<td>Urine protein electrophoresis</td>
<td>Determine the presence and levels of specific proteins in the urine, including M protein and Bence Jones protein</td>
<td>Presence of M protein or Bence Jones protein indicates myeloma</td>
</tr>
<tr>
<td><strong>Bone/Bone Marrow</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging studies (bone [skeletal] survey, x-ray, magnetic resonance imaging [MRI], computerized tomography [CT], positron emission tomography [PET])</td>
<td>Assess changes in the bone structure and determine the number and size of tumors in the bone</td>
<td>Higher levels of bone changes suggest the presence of myeloma</td>
</tr>
<tr>
<td>Biopsy (on either fluid from the bone marrow or on bone tissue)</td>
<td>Determine the number and percentage of normal and cancerous plasma cells in the bone marrow</td>
<td>Presence of myeloma cells confirms the diagnosis. A higher percentage of myeloma cells indicate more extensive disease</td>
</tr>
<tr>
<td>Cytogenetic analysis (e.g., karyotyping and fluorescence in situ hybridization [FISH])</td>
<td>Assess the number and appearance of chromosomes in order to identify the presence of DNA alterations</td>
<td>Certain DNA alterations may indicate how aggressive the disease is</td>
</tr>
</tbody>
</table>
**WHAT IS THE IMPORTANCE OF GENOMICS?**

Researchers are continually working to better understand the biology of multiple myeloma, and through genomic (study of the tumor cell DNA) studies we have learned that there are many DNA alterations in myeloma cells. The ultimate goal of genomic research is to eventually develop personalized treatments based on the DNA in the myeloma cells of individual patients.

Genomic tests are conducted by analyzing the DNA from the myeloma cells taken from a small amount of bone marrow. Tests are conducted as part of the initial diagnosis and may be repeated periodically. The most common tests are karyotyping and FISH. Other more sensitive tests are used in research studies, and some cancer centers are beginning to use them as well.

To date, there is no evidence to suggest that multiple myeloma is inherited, and the changes in the DNA are most likely due to mutations in the cells that occur in patients over time.

While certain DNA alterations are indicative of how aggressive the myeloma is, patients with DNA alterations do not necessarily have a worse prognosis.

So far, there is limited information from genomic studies to guide treatment decisions, with a few notable exceptions, for example, DNA alteration t(4;14). Studies have shown that patients with t(4;14) have better outcomes when treated with a proteasome inhibitor, such as Velcade. More information about myeloma drugs, including proteasome inhibitors, is included on page 15 of this brochure.

Since researchers have not yet found any reason to believe that multiple myeloma is inherited, genomic testing is not recommended for family members.

**Should I Get a Second Opinion?**

Once your doctor has diagnosed you with multiple myeloma, it is important that you consult a specialist experienced in treating myeloma to further evaluate your disease and help develop a treatment plan. Many health insurance companies will authorize a second opinion—check with yours.

An MMRF Nurse Specialist can help you find doctors in your area.

Call **1.866.603.6628**, Monday to Friday from 9:00 a.m. to 7:00 p.m. ET or email us at **patientnavigator@themmrf.org**.
HOW IS MYELOMA CLASSIFIED AND STAGED?

Myeloma is classified according to the results of diagnostic testing, and these results indicate whether or not immediate treatment is needed. In addition, a stage is assigned to denote the extent of disease.

Classification

Myeloma is classified into three categories (Table 2).

- **Monoclonal gammopathy of undetermined significance (MGUS):** Precursor to myeloma
- **Smoldering myeloma:** asymptomatic disease
- **Active myeloma:** symptomatic disease

Patients with MGUS do not actually have the disease, but should be monitored for any signs of progression to cancer. Patients with smoldering disease are typically only monitored and may receive bone supportive drugs, called **bisphosphonates,** if they have bone lesions or bone loss. Studies are ongoing to determine whether treatment with myeloma drugs is beneficial for patients with smoldering multiple myeloma, particularly those patients who are at high risk for progression to active myeloma.

Patients with myeloma are encouraged to talk to their doctors about participating in a clinical trial.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal gammopathy of undetermined sign</td>
<td>• Blood M protein &lt; 3 g/dL and&lt;br&gt;• Bone marrow plasma cells &lt;10% and&lt;br&gt;• No evidence of other B-cell disorders&lt;br&gt;• No myeloma-defining events&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;• Considered a precursor to myeloma&lt;br&gt;• Risk of progression to malignancy: 1% per year (about 20%–25% of individuals during their lifetime)</td>
<td>• Close follow-up (also known as “observation”)</td>
</tr>
<tr>
<td>Asymptomatic, or smoldering, myeloma</td>
<td>• Blood M protein &gt; 3 g/dL or&lt;br&gt; • urine M protein ≥500 mg/24 hours and/or&lt;br&gt; • Bone marrow plasma cells 10% – 60% and&lt;br&gt; • No myeloma-defining events&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt; • Risk of progression to malignancy: 10% per year for the first 5 years following diagnosis; 5% per year thereafter</td>
<td>• Close follow-up with treatment beginning at signs of disease progression&lt;br&gt;• Option for clinical trial&lt;br&gt;• Bisphosphonates (bone-supportive drugs) for patients with bone loss</td>
</tr>
<tr>
<td>Symptomatic (active) myeloma</td>
<td>• Bone marrow plasma cells ≥10% or&lt;br&gt; plasmacytoma (mass of cancerous plasma cells) and&lt;br&gt; • One or more myeloma-defining events&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Immediate treatment with myeloma drugs&lt;br&gt;• Bisphosphonates for patients with bone loss&lt;br&gt;• Option for clinical trial</td>
</tr>
</tbody>
</table>

<sup>a</sup>A myeloma-defining event is having:
- One or more indicators of myeloma-related organ or tissue impairment (also known as CRAB features), including hypercalcemia (increased blood calcium levels), impaired kidney function, anemia, or bone lesions.
- or
- One or more biological markers of malignancy (also known as SLiM features), including ≥60% bone marrow plasma cells, a serum free light chain ratio ≥100, or ≥1 bone lesions detectable on MRI.
Staging
The process of staging myeloma is crucial to developing an effective treatment plan. The most commonly used staging system is the International Staging System (ISS), which is based on two blood test results: **beta₂-microglobulin (ß₂-M)** and **albumin** and was recently revised to include additional factors for risk stratification (Table 3).

An older staging system that is sometimes used is called the Durie-Salmon Staging System. With the Durie-Salmon Staging System, myeloma stage is determined based on four measurements: the amount of **hemoglobin** and the level of calcium in the blood, the number of bone lesions, and the production rate of **M** protein. Stages are further divided according to kidney function.

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ß₂-M &lt;3.5 mg/L and albumin ≥3.5 g/dL and Absence of high-risk DNA abnormalities and Normal lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td>II</td>
<td>Not Stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>ß₂-M ≥5.5 mg/L and Presence of high-risk DNA abnormalities or High LDH</td>
</tr>
</tbody>
</table>

ß₂-M = beta₂-microglobulin.

*High-risk DNA abnormalities include del(17p) and/or translocation t(4;14) and/or translocation t(14;16)

HOW IS PROGNOSIS DETERMINED?
Certain test results provide important information about prognosis (Table 4). These prognostic indicators may also help decide when treatment should begin and aid in monitoring the disease. Many tests can be performed routinely in any laboratory, whereas others are performed only in specialized laboratories or a research setting.

Your age and the myeloma stage are also important factors in predicting prognosis.
### Table 4. Indicators of Prognosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Indication</th>
<th>Values Indicating Lower Risk at Diagnosis&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta&lt;sub&gt;2&lt;/sub&gt;-microglobulin (ß&lt;sub&gt;2&lt;/sub&gt;-M)</td>
<td>Higher levels reflect more extensive disease and poor kidney function</td>
<td>&lt;3.5 mg/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>Higher levels may indicate a better prognosis</td>
<td>≥3.5 g/dL</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>Higher levels indicate more extensive disease</td>
<td>Age ≤60 y: 100-190 U/L Age &gt;60 y: 110-210 U/L</td>
</tr>
<tr>
<td>Genomic analysis (cytogenetic testing: such as karyotyping or FISH)</td>
<td>Presence of specific DNA alterations may indicate how aggressive the disease is</td>
<td>Absence of high-risk DNA alterations</td>
</tr>
<tr>
<td>Freelite&lt;sup&gt;TM&lt;/sup&gt; serum free light chain assay</td>
<td>Abnormal results indicate higher risk of progression from MGUS (although risk is still low) or smoldering myeloma to active myeloma. Abnormal results also indicate poorer prognosis in myeloma.</td>
<td>MGUS: 0.26-1.65 SMM: 0.125-8.0 Myeloma: 0.03-32</td>
</tr>
</tbody>
</table>

<sup>a</sup>Note that these values are often different at other stages of the disease process, such as before or after stem cell transplantation. These values may also be defined differently at different medical laboratories.
WHAT FACTORS ARE CONSIDERED IN THE TREATMENT PLAN?

There is no one standard treatment. A patient’s individual treatment plan is based on a number of things, including:

- Age and general health
- Results of laboratory and cytogenetic (genomic) tests
- Symptoms and disease complications
- Prior myeloma treatment
- Patient’s lifestyle, goals, views on quality of life, and personal preferences
- Depending on the characteristics of a patient’s disease and his or her wishes, treatment plans may be designed to meet one or more goals, which are listed in Table 5.

In addition, many cancer centers have developed their own guidelines for treating myeloma, and these may vary between centers.

*Partner with your healthcare team to determine the treatment plan that is right for you.*

### TABLE 5. TREATMENT GOALS

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

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**WHAT THERAPIES ARE USED IN MYELOMA?**

Many therapies are available for myeloma. In addition to treatment of the disease, therapies to alleviate symptoms related to both the disease and its treatment are given (supportive therapies). Therapies that are used to control the myeloma or kill myeloma cells are listed in Table 6. Examples of supportive therapies are included in Table 7.

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**TABLE 6. THERAPIES FOR MYELOMA**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMiDs™ (Immunomodulatory Drugs)</strong></td>
<td></td>
</tr>
<tr>
<td>Revlimid® (lenalidomide)</td>
<td>Oral medication that is effective across the spectrum of myeloma disease.</td>
</tr>
<tr>
<td>Pomalyst® (pomalidomide)</td>
<td>Newer IMiD that is similar to Revlimid but is more potent. It is FDA approved for use in patients with relapsed/refractory myeloma and is being studied in other types of patients.</td>
</tr>
<tr>
<td>Thalomid® (thalidomide)</td>
<td>Older drug shown to be effective across the spectrum of myeloma disease. Peripheral neuropathy (nerve problems) is a common side effect and can be irreversible. It is less infrequently used in the US.</td>
</tr>
<tr>
<td><strong>Proteasome Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Velcade® (bortezomib)</td>
<td>Medication used across the entire spectrum of myeloma disease. Given as an injection under the skin (subcutaneously) or intravenously.</td>
</tr>
<tr>
<td>Kyprolis® (carfilzomib)</td>
<td>Newer proteasome inhibitor given intravenously. It is FDA approved for use alone and in combination with Revlimid and dexamethasone in patients with relapsed/refractory myeloma and is being studied in other types of patients.</td>
</tr>
<tr>
<td>Ninlaro® (ixazomib)</td>
<td>Oral medication approved for use in combination with Revlimid and dexamethasone in patients who have received at least one prior therapy.</td>
</tr>
</tbody>
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*Table 6 continued on next page*
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histone Deacetylase (HDAC) Inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>Farydak® (panobinostat)</td>
<td>Oral medication approved for use in combination with Velcade and dexamethasone in patients with relapsed/refractory myeloma.</td>
</tr>
<tr>
<td><strong>Monoclonal Antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>Darzalex™ (daratumumab)</td>
<td>Intravenous therapeutic antibody approved for use in patients with relapsed/refractory myeloma.</td>
</tr>
<tr>
<td>Empliciti™ (elotuzumab)</td>
<td>Intravenous therapeutic antibody approved for use in combination with Revlimid and dexamethasone in patients who have received one to three prior therapies.</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Doxil® (doxorubicin HCl liposome injection)</td>
<td>Drug given intravenously in patients with relapsed/refractory myeloma, usually in combination with Velcade. Side effects include mouth sores, swelling, blisters on the hands or feet, and possible heart problems. It is less frequently used.</td>
</tr>
<tr>
<td>Alkylator chemotherapy</td>
<td>Other types of chemotherapy drugs that have been used for many years to treat myeloma. They may be used in combination with other types of myeloma drugs. Examples are melphalan and cyclophosphamide.</td>
</tr>
<tr>
<td><strong>Steroids (corticosteroids)</strong></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (dex) and prednisone</td>
<td>Drugs used for decades to treat myeloma throughout the spectrum of disease; used in combination with other myeloma drugs.</td>
</tr>
<tr>
<td><strong>Stem Cell Transplantation</strong></td>
<td></td>
</tr>
<tr>
<td>High-dose chemotherapy and stem cell transplantation</td>
<td>The use of higher doses of chemotherapy, usually melphalan, followed by transplantation of blood–producing stem cells to replace healthy cells damaged by the chemotherapy.</td>
</tr>
</tbody>
</table>
### TABLE 7. KEY SUPPORTIVE THERAPIES FOR MYELOMA

<table>
<thead>
<tr>
<th>Myeloma Symptom/Complication</th>
<th>Therapies</th>
</tr>
</thead>
</table>
| Bone disease                 | • Calcium and Vitamin D  
                              | • Exercise  
                              | • Bisphosphonates and other medications  
                              | • Orthopedic interventions  
                              | • Low dose radiation therapy                                              |
| Anemia                       | • Iron, folate, or vitamin B12 supplements (if deficient)  
                              | • Red blood cell *growth factors* (Procrit, Epogen, Aranesp)  
                              | • Blood transfusions for severe anemia                                      |
| Infection                    | Prevention  
                              | • Flu and pneumonia vaccines  
                              | • Antibody treatment (immunoglobulin IgG)\(^a\)  
                              | • Antifungal and preventive shingles medications\(^a\)  
                              | • Preventive antibiotics (controversial)  
                              | Treatment  
                              | • White blood cell growth factors (colony stimulating growth factors, Neupogen, Neulasta, and Leukine)  
                              | • Antibiotics or antifungal medications as needed                          |
| Kidney impairment            | • Stay hydrated  
                              | • Avoid anti-inflammatory drugs (e.g., Advil, Motrin, and Aleve)  
                              | • Procedure to reduce blood thickness (plasmapheresis)  
                              | • Dialysis if severe                                                       |
| Pain                         | • Pain medications (e.g., over-the-counter medications,  
                              | • narcotic medications as needed                                           |

\(^a\) *In certain cases*
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 these results show how well the treatment is working and may also help to detect any side effects. These tests also help determine if, after an initial response to treatment, your myeloma relapses.

WHAT ARE THE OPTIONS FOR INITIAL THERAPY?
The selection of initial treatment of symptomatic myeloma in newly diagnosed patients depends on many factors, including the features of the myeloma itself, anticipated risk of side effects, convenience, and the familiarity of the treating physician with the given regimen. Options are similar regardless of whether patients are candidates for, or are interested in, undergoing transplantation.

Patients who are candidates for transplant may choose to have a transplant after three to four cycles of initial therapy (also known as induction therapy) or may decide to continue their initial therapy and potentially consider transplant later in the disease course. In an effort to further improve outcomes, ongoing treatment (maintenance therapy) may be considered following transplantation.

The length of therapy varies for patients who are not candidates for transplant or who choose not to undergo transplant. While some doctors recommend continuous treatment until there is evidence of myeloma progression, others recommend treatment for a fixed period of time, generally until the response of the disease to the treatment reaches a plateau.

The specific characteristics of your myeloma, your preferences, and your doctor’s perspective are considerations in determining the length of therapy. Studies are ongoing to determine the best approach.

For those patients who receive therapy for a fixed period, either maintenance therapy with a myeloma drug or close monitoring with no therapy (referred to as observation) are options.

Myeloma treatments consist of either triplets (three drugs) or doublets (two drugs). Generally, triplets are preferred. Doublets may also be considered, particularly in cases where the side effects of triplets are a concern. Clinical trials are an option that patients may want to discuss with their doctors.
**Triplets include:**
- Revlimid-Velcade-dex (RVD): most commonly used
- Velcade-cyclophosphamide-dex (VCD or CyBorD)
- Velcade-Thalomid-dex (VTD)

**Doublets include:**
- Revlimid-dex (Rd)
- Velcade-dex (Vd)

Melpahalan (MP) based regimens are also options for patients who are not candidates for transplant. These regimens are infrequently used in the US, as there are effective options available with fewer side effects. MP-based regimens include: Velcade-MP (VMP), Revlimid-MP (MPR) or Thalomid (MPT).

MP-based regimens should not be used in patients who are candidates for transplant, as melphalan is known to interfere with the ability to collect the stem cells necessary for transplantation.

Patients who have the DNA alteration t(4;14), as determined by cytogenetic testing, should receive a treatment regimen including a proteasome inhibitor (e.g., Velcade). Studies have shown that patients with t(4;14) who received treatment with Velcade do better. So far, there are not enough studies to recommend specific treatment approaches for other DNA alterations, but this is an active area of research.

You and your doctor will discuss the treatment regimen that is right for you.
Initial treatment

**Triplets:** Revlimid-Velcade-dexamethasone (RVD),
Velcade-cyclophosphamide-dexamethasone (VCD/CyBorD),
Velcade-Thalomid-dexamethasone (VTD)

**Doublets:** Revlimid-low-dose dexamethasone (Rd), Velcade-dexamethasone (Vd)

**MP-based regimens** *(non-transplant only, mostly outside the U.S.):* Velcade-MP, Revlimid-MP or MP-Thalomid

**Clinical trial**

Autologous stem cell transplant candidate?

**No**

Response to initial therapy?

**No**

- **Second-line therapy**
  - If no response, or if relapse soon after initial therapy, add an additional therapy or use different agent(s) than that used for initial therapy
  - Revlimid- or Velcade-based regimen
  - Kyprolis + Revlimid-low-dose dexamethasone
  - Ninlaro + Revlimid-dexamethasone

**Yes**

- **Third-line therapy**
  - Empliciti + Revlimid-dexamethasone
  - Second transplant if stem cells available
  - Clinical trial

No response or relapse

**Proteasome inhibitor-based regimens preferred for DNA alteration t(4;14)**
High-dose chemotherapy and stem cell transplantation is a treatment that, for many patients, offers a chance for durable remission of myeloma.

High-dose chemotherapy, though effective in killing myeloma cells, also destroys normal blood-forming cells, called stem cells, in the bone marrow. Stem cell transplantation replaces these important cells (Figure 5).

More patients are considered to be candidates for transplant today than in the past. Whether a patient is considered a candidate for transplant is based on their age and overall health. Guidelines for patient eligibility vary between cancer centers.

Ask your doctor if you are eligible for transplantation.

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 blood and are referred to as peripheral blood stem cell (PBSC) transplants. Bone marrow transplants are no longer done in multiple myeloma cases.

Stem cell transplantation is done after completion of initial (induction) therapy. The most common type of transplant in myeloma is an autologous transplant. With an autologous transplant, the patient’s stem cells are collected (also called “harvested”) and are reintroduced following high-dose chemotherapy.

An allogeneic transplant is another type of transplant. For this type of transplant, stem cells are obtained from a donor (usually a relative of the myeloma patient) and infused into the patient after high-dose chemotherapy. Allogeneic transplants are infrequently performed today because of the high risk of complications. A mini (nonmyeloablative) allogeneic transplant is a modified form of allogeneic transplant in which a lower dose of chemotherapy is used.

Patients may choose to undergo high-dose chemotherapy and transplantation as part of their initial treatment or delay it until later in the disease course. Studies are ongoing to determine the best approach.

THE EVOLVING ROLE OF TRANSPLANTATION IN MYELOMA

The improved response rates seen in initial therapy with today’s myeloma regimens 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 offer the best chance for a long-lasting remission for those who are candidates. Clinical trials are ongoing to more definitively determine its advantages, and the potential toxicities associated with transplantation must be balanced with the benefits.

Patients should carefully discuss the benefits and risks of transplantation with their doctors.

All patients who are eligible for transplantation are encouraged to have stem cells obtained (also known as “harvested”) so that the cells are available if the patient chooses to undergo transplantation at some point during the course of their disease.
SHOULD I RECEIVE MAINTENANCE THERAPY?
Since myeloma is not yet curable, it may recur even in patients who obtain a complete response. The goal of maintenance therapy is to maintain the response for as long as possible and hopefully improve survival. There is increasing evidence supporting the role of maintenance therapy after the completion of initial therapy or after transplantation.

Studies are showing that maintenance therapy may improve survival and help keep myeloma in remission after transplantation. They also suggest that maintenance therapy provides benefit for patients who have not received a transplant. Two large trials showed that Revlimid provided significant benefit as maintenance therapy after transplantation, with one study demonstrating improved survival. Another study has shown that maintenance therapy with Revlimid is also beneficial for patients who do not undergo transplantation after their initial therapy. A small increase in second cancers likely related to the maintenance therapy was seen in all these studies, but the current consensus among researchers is that the benefits likely outweigh the risks.

Additionally, several smaller studies (Phase II) trials show that maintenance therapy with Velcade can also improve outcome.

While more data will be needed to determine if there is a consistent survival benefit with maintenance therapy, these results have prompted many doctors to discuss the option of maintenance therapy with their patients.

Ask your doctor if maintenance therapy is an option for you.

WHAT ARE THE OPTIONS FOR RELAPSED OR REFRACTORY MYELOMA?
If myeloma does not respond to initial therapy or if relapse occurs soon 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 by itself. An additional drug may be added to the treatment regimen, or a different combination of drugs may be used as second-line therapy. If relapse occurs after a period of response to initial therapy, the initial therapy may be repeated, or another regimen may be given.
There are many treatments available for relapsed or refractory myeloma, and many new drugs are being studied as well. Even if patients were refractory to a particular therapy, they may respond if it is used in a different combination with other myeloma drugs. Treatment options include:

- Any myeloma drug that has not been previously used or a different combination of myeloma medications
- Stem cell transplant (if possible)
- Participation in a clinical trial

Participating in a clinical trial offers access to the very latest advances in treatment. Ask your doctor if a clinical trial is right for you.

**WHAT DOES THE FUTURE LOOK LIKE FOR MYELOMA TREATMENTS?**

Many new drugs are in development, and researchers continue to study the best combination of available drugs, the best approaches to treatment, and the biology of the disease. As research in myeloma evolves, new treatments have the potential to substantially improve survival and patients’ quality of life.
QUESTIONS TO ASK YOUR DOCTOR

1. Should I be treated now, or should therapy be delayed?

2. What is the expected outcome of the treatment? What are the goals of this therapy (is it given primarily to treat the disease or to relieve symptoms)?

3. What is the recommended treatment? Is it a single drug or a combination of drugs? How is the drug administered: orally or intravenously (by IV)? How long is treatment given? How will I be monitored?

4. Am I a candidate for stem cell transplantation? If so, what kind—autologous or allogeneic?

5. How likely is a complete or partial remission? What factors contribute to better or worse odds?

6. How will I feel during and after treatment? What kinds of side effects might I expect? What should I do if I experience side effects? What kind of impact will treatment have on my daily life?

7. How long is the typical recovery time? Is there any follow-up or maintenance therapy?

8. What is the cost of therapy? What costs will my insurance cover, and what costs will I have to pay?

9. What are the alternatives to this treatment? How do the different therapies (standard and alternative) compare with respect to effectiveness and side effects?

10. Are there any clinical trials that are appropriate for me? If so, what is involved? What are the potential risks and benefits? What are the costs?

11. If one or more types of treatment fail, what are my options?
GLOSSARY

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

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

**Anemia** A 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 (Ig).

**Autologous transplant** Stem cell transplant in which cells are collected from the individual being treated. The most common type of transplant performed in myeloma.

**B-cells** White blood cell that gives rise to a plasma cell. Plasma cells produce antibodies which fight infections.

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

**Beta_2-microglobulin (β_2-microglobulin or β_2-M)** A protein normally found on the surface of various cells in the body. Increased blood levels occur in inflammatory conditions and certain blood cell 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 (osteoclasts).

**Blood urea nitrogen (BUN)** A byproduct of protein metabolism that is normally filtered out of the blood and found in the urine. Elevated levels in the blood can indicate decreased kidney function.

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

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

**Chromosome** A thread-like structure in a living cell that contains genetic information.

**Complete blood count (CBC)** Blood test that measures the number of red blood cells, white blood cells, and platelets in the blood and the relative proportions of the various types of white blood cells.

**Computerized tomography (CT)** Imaging technique that uses a computer to generate three-dimensional x-ray pictures. Also referred to as computerized axial tomography (CAT).
Corticosteroids A potent class of drugs that have anti-inflammatory, immunosuppressive, and antitumor effects. Dexamethasone and prednisone are examples of corticosteroids.

Creatinine A product of energy metabolism of muscle that is normally filtered out of the blood and found in the urine. Elevated levels in the blood can indicate decreased kidney function.

DNA Genetic material of the cell located in the chromosomes.

Electrophoresis Laboratory test used to measure the levels of various proteins in the blood or urine.

Fluorescence in situ hybridization (FISH) A laboratory technique used to determine how many copies of a specific segment of DNA are present or absent in a cell.

Growth factor Substance that stimulates cells to multiply.

Hemoglobin Oxygen-carrying substance in red blood cells.

Hypercalcemia Condition noted by elevated levels of calcium in the blood due to increased bone destruction.

Immunofixation electrophoresis (IFE) Type of electrophoresis that uses a special technique to identify specific types of antibodies (immunoglobulins); also called immunoelectrophoresis.

Immunoglobulin (Ig) See antibody.

Induction therapy Treatment used as a first step in shrinking the cancer.

Karyotyping A test to examine chromosomes in a sample of cells, which can help identify genetic problems as the cause of a disorder or disease. This test can count the number of chromosomes and look for structural changes in chromosomes.

Lactate dehydrogenase (LDH) An enzyme found in body tissues. Elevated blood levels occur when there is tissue damage and may occur in myeloma, where they reflect tumor-cell burden.

Light chains Short protein chains on antibodies.

Magnetic resonance imaging (MRI) Imaging technique that uses magnetic energy to provide detailed images of bone and soft tissue.
**Maintenance therapy** Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time.

**Monoclonal antibody** Type of man-made antibody that is used in the diagnosis and treatment of various diseases. All monoclonal antibodies of a specific type are identical to each other.

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

**Monoclonal (M) protein** Abnormal antibody (immunoglobulin) found in large quantities in the blood and urine of individuals with myeloma.

**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.

**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.

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

**Plasmacytoma** Single tumor comprised of cancerous plasma cells that occurs in bone or soft tissue. Myeloma may develop in patients with a plasmacytoma.

**Platelets** Small cell fragments in the blood that help it to clot.

**Positron emission tomography (PET)** Imaging technique in which radioactive glucose (sugar) is used to highlight cancer cells.

**Prognosis** The predicted course of a disease and the outcome after treatment.

**Proteasome inhibitor** A type of drug that slows myeloma cell growth and kills myeloma cells by interfering with processes that play a role in cell function.

**Red blood cell** Oxygen-transporting blood cell. Anemia occurs when there are low levels of red blood cells.
Refractory disease Disease that is not responsive to therapy.

Relapse Return of disease or disease progression.

Second-line therapy Treatment that is given after failure of initial therapy (disease is refractory or resistant to treatment) or after disease relapses.

Stem cell Parent cell that grows and divides to produce red blood cells, white blood cells, and platelets. Found in the bone marrow and blood.

Stem cell transplantation Therapeutic procedure in which blood-forming stem cells are collected, stored, and infused into patient following high-dose chemotherapy to restore blood cell production.

White blood cell One of the major cell types in the blood. Attacks infection and cancer cells as part of the immune system.
MMRF PATIENT SUPPORT AND RESOURCES

The MMRF is dedicated to supporting the myeloma community by providing a broad range of resources for those living with myeloma and their family members. We are here to help guide you through your multiple myeloma journey every step of the way.

Your Questions Answered
Speak to a myeloma nurse specialist for answers to your questions about disease management, treatments, clinical trials, and assistance with finding financial and other available resources.

Telephone: 1.866.603.6628, Monday—Friday, 9:00 a.m. to 7:00 p.m. ET
Email: patientnavigator@themmrf.org

Find and Participate in Clinical Trial
Search for a clinical trial in your area, or let our myeloma nurse specialist help guide you through the process.

Clinical Trial Search: www.myelomatrials.org

Connect With Patients Like You
Join the MMRF Community Gateway to connect with others who are living with multiple myeloma.

Register today:
www.mmrfcommunitygateway.org

Support the MMRF
Help support our efforts to accelerate research and find a cure! Participate in an event or donate today.

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