After being diagnosed with multiple myeloma in 1998, Kathy Giusti and her sister Karen Andrews, a successful corporate attorney, founded the MMRF 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 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 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. 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 43).

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.

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 website: www.themmrf.org.
WHAT IS MULTIPLE MYELOMA?

Multiple myeloma is a blood cancer that develops in the bone marrow. In myeloma, normal antibody-producing plasma cells (a type of white blood cell) 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 often cause soft spots in the bone (known as osteolytic lesions), which can lead to fractures and other complications. Although common, these lesions or other signs of bone loss do not occur in all individuals with myeloma.

Other problems associated with myeloma include anemia, infection, and decreased kidney function.
HOW IS MYELOMA CLASSIFIED AND STAGED?
Myeloma is classified based on the results of diagnostic testing. These results tell whether or not immediate treatment is needed. In addition, a stage is assigned to indicate the extent of disease.

CLASSIFICATION OF MYELOMA
Myeloma is classified into three categories (Table 1).

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

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 (**osteopenia** or **osteoporosis**). 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.

Generally, only patients with active myeloma require treatment with myeloma drugs.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS)</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 related organ or tissue impairment&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;• 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 ≥ 3 g/dL and/or:&lt;br&gt;  o Bone marrow plasma cells ≥ 10%&lt;br&gt;  o No related organ or tissue impairment or symptoms&lt;br&gt;• Risk of progression to malignancy: 10% per year for the first 5 years following diagnosis; 5% per year thereafter</td>
<td>Observation&lt;br&gt;• Option for clinical trial&lt;br&gt;• Bisphosphonates for bone loss, if needed&lt;br&gt;• Possible consideration of treatment with myeloma drugs for patients at very high risk of progression to symptomatic myeloma (experimental)</td>
</tr>
<tr>
<td>Symptomatic myeloma</td>
<td>• M protein in blood and/or urine&lt;br&gt;• Bone marrow plasma cells or plasmacytoma&lt;br&gt;• Organ or tissue impairment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Immediate treatment with myeloma drugs&lt;br&gt;• Bisphosphonates for bone lesions or bone loss&lt;br&gt;• Option for clinical trial</td>
</tr>
</tbody>
</table>

<sup>a</sup>Myeloma-related organ or tissue impairment includes hypercalcemia (increased blood calcium levels), impaired kidney function, anemia, or bone lesions.
STAGING OF MYELOMA

The most commonly used staging system is the International Staging System (ISS), which is based on two blood test results: \( \text{beta}_2\text{-microglobulin} (\beta_2\text{-M}) \) and \( \text{albumin} \) (Table 2).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>( \beta_2\text{-M} &lt; 3.5 \text{ mg/L} ) and albumin ( \geq ) 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>( \beta_2\text{-M} &lt; 3.5 \text{ mg/L} ) and albumin &lt; 3.5 g/dL or ( \beta_2\text{-M} 3.5 - 5.5 \text{ mg/L} )</td>
</tr>
<tr>
<td>III</td>
<td>( \beta_2\text{-M} \geq 5.5 \text{ mg/L} )</td>
</tr>
</tbody>
</table>

\( \beta_2\text{-M} = \text{beta}_2\text{-microglobulin} \).

An older staging system that is sometimes used is called the Durie–Salmon Staging System. With the Durie–Salmon Staging System, the myeloma stage is determined based on four measurements: the amount of \( \text{hemoglobin} \) and the level of \( \text{calcium} \) in the blood, the number of bone lesions, and the production rate of \( M \) protein. Stages are further divided according to kidney function.
WHAT IS THE IMPORTANCE OF GENOMICS?
Researchers are continually working to better understand the biology of multiple myeloma, and through genomic studies (studies of the tumor cell DNA), 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. Today, we know that certain DNA alterations are indicative of how aggressive the myeloma is and, in some cases, test results can help guide treatment decisions or determine eligibility for clinical trials.

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.

DNA ALTERATIONS AND TREATMENT
For most DNA alterations, there is not yet sufficient information to guide treatment decisions, with the exception of t(4:14). Studies have shown that patients with t(4:14) have better outcomes when treated with a proteasome inhibitor, such as Velcade. In fact, when patients with t(4:14) are treated with Velcade, their outcomes are better than patients with this DNA alteration who do not receive this drug (see Table 5 on page 12 for more information about Velcade).

The development of personalized treatments based on genomics is an active area of research, and clinical trials are ongoing.

Ask your doctor if a clinical trial is an option for you.
WHAT FACTORS ARE CONSIDERED IN DEVELOPMENT OF A 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 3

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 that is right for you.

---

TABLE 3. TREATMENT GOALS

<table>
<thead>
<tr>
<th>Goals</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 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>
**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.

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

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

The outcome of treatment in myeloma is defined using very specific standards or criteria as shown in Table 4.
<table>
<thead>
<tr>
<th>Type of Response</th>
<th>M Protein</th>
<th>% Plasma Cells in Bone Marrow</th>
<th>Bone Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response (sCR)(^b)</td>
<td>No longer detectable in blood and/or urine; negative immunofixation test; normal free light chain (FLC) ratio</td>
<td>&lt;5%; no myeloma cells present</td>
<td>Stable</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>No longer detectable in blood and/or urine; negative immunofixation test</td>
<td>&lt;5%</td>
<td>Stable</td>
</tr>
<tr>
<td>Near complete response (nCR)(^c)</td>
<td>No longer detectable in blood and/or urine, but positive immunofixation test</td>
<td>&lt;5%</td>
<td>Stable</td>
</tr>
<tr>
<td>Very good partial response (VGPR)(^b)</td>
<td>No longer detectable in blood and/or urine, but positive immunofixation test, or 90% decrease</td>
<td>N/A</td>
<td>Stable</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>≥50% decrease</td>
<td>N/A</td>
<td>Stable</td>
</tr>
<tr>
<td>Minimal response (MR)(^d)</td>
<td>25%-49% decrease</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Not meeting the definition of minimal response or progressive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>&gt;25% increase</td>
<td>&gt;25% increase</td>
<td>New bone lesions or increase in size of existing lesions</td>
</tr>
</tbody>
</table>

\(^a\)Based on criteria develop by the EBMT (European Group for Blood Marrow Transplant), IBMTR (International Bone Marrow Transplant Registry), and ABMTR (Autologous Blood Marrow Transplant Registry; Blade criteria), and the International Myeloma Working Group (IMWG Uniform Response Criteria).

\(^b\)Only defined in the IMWG criteria.

\(^c\)Some clinical trials modify the EBMT criteria to include the nCR category.

\(^d\)Only defined in the EBMT criteria.
WHAT IS MINIMAL RESIDUAL DISEASE (MRD)?

Minimal residual disease (MRD) is the presence of small amounts of tumor cells following the achievement of complete response. Currently, urine and blood tests are the standard tests used to determine the response to multiple myeloma therapy. However, even patients who achieve a complete response may relapse, suggesting that some myeloma cells may still be present.

Studies using newer more sensitive tests to detect MRD are showing that patients who achieve deeper responses with fewer remaining tumor cells may have better outcomes. With today’s therapies, more and more patients are achieving deep responses. Thus, interest in the assessment of MRD is growing.

Monitoring of MRD is relatively new and is just beginning to be adopted in cancer centers. Tests include:

- Flow cytometry: measures the number and characteristics of cells taken from a bone marrow sample. It is the most common test used in the US.

- Molecular tests (e.g., polymerase chain reaction or PCR, Sequenta ClonoSIGHT™): newer technology that evaluates the DNA of cells and can detect very low numbers of cells.

Clinical trials are ongoing incorporating MRD and are evaluating the various methods to detect it. In particular, the MMRF is collaborating with researchers to compare flow cytometry to the Sequenta ClonoSIGHT™ molecular test.
WHAT THERAPIES ARE USED IN MYELOMA?
There are two categories of myeloma therapies:

■ Therapies to control the myeloma or kill myeloma cells

■ Therapies that alleviate symptoms and manage complications of the disease and its treatment (known as supportive therapy)

This section will discuss the various therapies used to control or kill myeloma cells. Supportive therapies will be discussed on page 30 of this brochure.

The various types of therapies used to control myeloma or kill myeloma cells are briefly described in Table 5.

### TABLE 5. 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Proteasome Inhibitors</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<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 in patients with relapsed/refractory myeloma and is being studied in other types of patients.</td>
</tr>
</tbody>
</table>
### Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Doxil® <em>(doxorubicin HCl liposome injection)</em></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</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>
<tr>
<td>transplantation</td>
<td></td>
</tr>
</tbody>
</table>
INACTIVE MYELOMA (MGUS AND SMOLDERING MYELOMA)

Generally, myeloma is not treated until symptoms develop. Patients with smoldering myeloma who have bone loss (osteoporosis or osteopenia) will receive bisphosphonates, a bone supportive therapy, to reduce the risk of fractures, and other bone problems.

One study has shown that Revlimid in combination with dexamethasone prolonged the time to development of symptomatic myeloma in patients with high-risk smoldering multiple myeloma. However, this therapy is still considered experimental and there is not sufficient information on the benefits and risks of therapy at this time. A large Phase III study is underway to determine if Revlimid can delay disease progression and improve survival in this group of patients. Other therapies are also being investigated for high risk smoldering myeloma.

ACTIVE (SYMPTOMATIC) MYELOMA

Patients with symptomatic myeloma usually receive treatment aimed at reducing the amount of myeloma cells. The chart shown in Figure 1 outlines typical treatment regimens.

Patients should know that if one regimen stops working, another one can be used. There are many choices available today and treatments continue to improve.
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?**

- **Yes**
  - Proceed to autologous transplant
  - Or
  - Continue initial therapy and delay transplant

- **No**

**Response to initial therapy?**

- **Yes**
  - Continue with either:
    - Close monitoring (Observation)
    - Maintenance 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
    - If relapse occurs more than six months after initial therapy, may repeat the initial therapy
    - Revlimid- or Velcade-based regimen
    - Second transplant if stem cells available
    - Clinical trial

  - **No response or relapse**
    - **Third-line therapy**
      - Different drugs/combination than that used for initial- or second-line therapy
      - Kyprolis
      - Pomalyst-dexamethasone
      - Clinical trial

*Proteasome inhibitor-based regimens preferred for DNA alteration t(4;14)*

Figure 1. Treatment options for myeloma
WHAT ARE MY OPTIONS FOR INITIAL THERAPY?

The choice of a patient’s initial treatment 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. 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)

Four-drug combinations have also been studied. The challenge with these regimens is the potential for increased side effects, and research is ongoing to determine the balance of effectiveness and tolerability.
Melphalan (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 that includes a proteasome inhibitor (e.g., Velcade). Studies have shown patients with this DNA alteration 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.*

**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.
KEY FACTS

REVLIMID (LENALIDOMIDE)

WHAT IS REVLIMID?

Revlimid belongs to a group of medicines called immunomodulatory drugs (IMiDs™). It is chemically similar to Thalomid but is more potent and has different side effects. Revlimid is approved by the FDA for use in combination with dexamethasone (dex) to treat individuals with myeloma who have received at least one prior therapy. However, it is commonly used as a component of initial therapy in newly diagnosed myeloma and as a maintenance therapy. It is often combined with Revlimid and other myeloma drugs.

HOW IS REVLIMID TAKEN?

Revlimid capsules, are taken as an oral medication and is prescribed at various strengths and dosages. Capsules should be swallowed whole once a day at the same time each day. Please note: do not break, chew or open your capsules. 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 how patients respond and any side effects they may experience. When taken as maintenance therapy, a lower dose is usually prescribed.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF REVLIMID?

Revlimid is commonly given in combination with dexamethasone (Revlimid–dex). The most commonly reported side effects of Revlimid–dex are:

- Constipation and diarrhea
- Itching and rash
- Tiredness
- Muscle cramps

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

- Low white blood counts (neutropenia)
- Low platelets (thrombocytopenia)
- Blood clots
- Severe liver problems
- Serious skin reactions
- Tumor lysis syndrome

Studies have shown that serious blood clots may occur with Revlimid–dex. Therefore, a blood thinner, such as aspirin or low-molecular weight heparin, is prescribed to reduce the chance of development of blood clots.

There have been reports of new cancers developing in a small number of myeloma patients receiving Revlimid when used with melphalan or as maintenance therapy following a treatment including melphalan. However, the current consensus among researchers is that the benefits of Revlimid therapy likely outweigh any potential risk of second cancers. Patients should discuss potential risks versus benefits of treatment with their doctor.

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

Revlimid may cause birth defects and should not be taken by pregnant women. Therefore, it is only available under a special restricted access program called Revlimid REMS™ (formerly known as RevAssist®).
VELCADE (BORTEZOMIB)

WHAT IS VELCADE?
Velcade is a proteasome inhibitor used for both newly diagnosed and relapsed/refractory patients. It is usually given with dexamethasone and is often combined with Revlimid as well as myeloma drugs.

HOW IS VELCADE GIVEN?
Velcade is given either as an injection under the skin subcutaneously (SubQ) or intravenously (IV), typically on a weekly basis. Alternatively, it may be given intravenously twice a week.

There is no difference in the effectiveness of Velcade based on the method or frequency of dosing. However, there are fewer side effects, particularly peripheral neuropathy (a nerve disorder affecting the hands and feet which is often painful), with subcutaneous dosing. Similarly, weekly intravenous dosing has fewer side effects as compared to twice-weekly dosing.

Doctors may have different preferences for which route of administration is used and often tailor the choice based on the characteristics of the patient’s myeloma and his or her preferences.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF VELCADE?
The most commonly reported side effects of Velcade include:

- Gastrointestinal effects: nausea, diarrhea, vomiting, and loss of appetite
- Low blood counts (thrombocytopenia, neutropenia, and anemia)
- Peripheral neuropathy
- Fatigue
- Rash
- Fever

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

Velcade is typically given in combination with other anti-myeloma drugs, such as dexamethasone, Revlimid, and others. Different combinations of drugs may result in different side effects.
TRIPLET TREATMENT REGIMENS

REVLMID-VELCADE-DEXAMETHASONE (RVD)
Revlimid plus Velcade and dex (RVD) is one of the most commonly used regimens today. Studies have shown that this combination produces a very high response rate among patients with newly diagnosed symptomatic myeloma.

VELCADE-CYCLOPHOSPHAMIDE-DEX
High response rates and rapid responses have been seen in Phase II trials with the combination of Velcade, cyclophosphamide, and dexamethasone (VCD or CyBorD). Overall response rates (total of all responses) in these trials ranged from 84% to 100%. In two of these trials, complete and near complete response rates of 39% to 47% were seen.

VELCADE-THALOMID-DEX (VTD)
The combination of Velcade, Thalomid and, dexamethasone has been demonstrated to be highly effective in a Phase III study including 480 patients. Patients who received VTD achieved significantly better responses both before and after transplantation than those taking Thalomid–dex. Survival without any evidence of disease progression (progression–free survival) after transplantation was also better. This regimen is more commonly used outside the US.

DOUBLET TREATMENT REGIMENS

REVLMID-LOW-DOSE DEX (Rd)
The effectiveness of Revlimid–low–dose dex is well established. In a Phase III trial with 445 patients 96% of patients, taking Revlimid–low–dose dexamethasone were alive one year after the beginning of treatment and 87% were alive two years later. Outcomes were similar regardless of age.

Further, data from another large Phase III study involving 1,623 patients showed that those who received Revlimid–dex continuously (until progression of their myeloma) had better outcomes as compared to those who stopped therapy after 18 cycles (72 weeks). For example, the period of time prior to progression of myeloma was prolonged (progression–free survival). Patients should discuss the appropriate length of treatment in their case with their doctors.

VELCADE-DEX
The effectiveness of Velcade in combination with dexamethasone as initial therapy was demonstrated in two large Phase III trials. Importantly, Velcade–dex was shown to be as effective in patients with whose myeloma has characteristics indicative of more aggressive disease as it was in patients without these characteristics.
WHAT IS HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION?

High-dose chemotherapy (usually melphalan) with stem cell transplantation is a treatment that, for many eligible patients, offers a chance for durable remission of the disease. 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 2).

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.

Stem cells are collected after approximately four cycles of initial (induction) myeloma therapy in order to reduce the amount of myeloma cells. Medications that stimulate the production of stem cells are often given to ensure collection of sufficient stem cells for several transplants. These include colony stimulating factors (e.g., Neupogen, Neulasta, and Leukine), chemotherapy, and a drug called Mozobil® (plerixafor). This process of stimulating the growth of stem cells is known as mobilization.

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

- **Autologous transplants**: stem cells collected from the patient. Autologous transplants are the most common type of transplants for myeloma, as there are fewer complications than transplants that require a donor.

**TABLE 6. TRANSPLANTS PERFORMED IN MYELOMA**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Autologous                    | - Most common type performed in myeloma  
- Uses stem cells collected from the patient                                                                                               |
| Tandem (double) autologous    | - Two autologous transplants typically performed within six months of each other  
- Generally, a second transplant is of benefit only if a complete response or very good partial response is not achieved with the first transplant  
- Increased side effects over a single transplant  
- Used less frequently due to the high response rates achieved with current therapies                                                          |
| Allogeneic                    | - Uses stem cells from a matched donor  
- Performed infrequently because of high risk of complications, including infections and graft–versus–host disease (GVHD)                    |
| Mini (nonmyeloablative) allogenic | - Have largely replaced standard allogeneic transplants  
- Utilizes moderately high–dose chemotherapy, which does not completely destroy the bone marrow  
- Can be performed alone or following an autologous transplant  
- Best performed in the setting of a clinical trial until more long–term results are available                                                    |
Allogeneic transplants involve collecting stem cells from a matched donor (usually a relative). This type of transplant is infrequently performed today because of the high risk of complications, although it does offer beneficial effects against the myeloma. A mini (non–myeloablative) allogeneic transplant is a modified form of allogeneic transplant that uses somewhat lower doses of chemotherapy to make the transplant safer.

Information regarding these transplants, as well as others being investigated in clinical trials, is summarized in Table 6.

Some patients choose to have a transplant as part of their initial treatment, while others may prefer to delay transplantation until later in the disease course. Studies are ongoing to determine the best approach.

Common side effects of high–dose chemotherapy and transplantation include nausea, vomiting, diarrhea, mucositis (inflammation of the lining of the mouth and digestive tract), and fatigue. In addition, because the high–dose chemotherapy attacks healthy, disease–fighting cells as well as cancerous cells, there is an increased risk of infection. Other possible, but infrequent side effects may include organ damage, particularly to the lungs, liver, and kidneys.

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.

Several Phase III trials indicate that Revlimid provides significant benefits. Benefits following transplant were seen in two large trials—one conducted in the United States and one conducted in France.

- In the US trial (568 patients), survival was longer in patients who received Revlimid. This is the first study to show a survival benefit with Revlimid maintenance therapy.

- In the French trial (614 patients), the risk of a patient’s disease progressing after transplantation was reduced by half in patients receiving Revlimid compared to those receiving a placebo.

In both studies, low blood counts were commonly seen with Revlimid maintenance, and overall, more severe side effects were seen with Revlimid compared with placebo.
Another study has shown the benefit of maintenance therapy with Revlimid after initial therapy (front-line) in patients who were not eligible for transplant. 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, but so far, no survival benefit has been seen.

A small increase in second cancers, likely related to the maintenance therapy, was seen in all of these studies, but the current consensus among researchers is that the benefits likely outweigh the risks.

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

Additionally, several smaller (Phase II) trials show that maintenance therapy with Velcade can also improve outcomes. Some doctors recommend maintenance therapy with Velcade for patients with high risk myeloma, such as DNA alteration t(4;14).

Ask your doctor if maintenance therapy is an option for you. Discuss the potential benefits versus risks.
WHAT ARE MY OPTIONS IF I DON’T RESPOND TO THERAPY OR RELAPSE?

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 are 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

To accelerate development of new therapies for myeloma, all eligible patients should consider participating in a clinical trial.
KEY FACTS

KYPROLIS (CARFILZOMIB)

WHAT IS KYPROLIS?

Kyprolis is a next-generation proteasome inhibitor in the same drug class as Velcade. It is approved by the FDA for patients with multiple myeloma who have received at least two prior therapies, including Velcade and an IMiD (such as Revlimid or Thalomid) and have demonstrated disease progression on or within 60 days of completion of their last therapy.

Clinical trials are underway to evaluate Kyprolis in combination with other therapies and in other types of patients.

HOW IS KYPROLIS GIVEN?

Kyprolis is administered intravenously (IV) at a dose of 20 mg/m² for the first cycle, given on two consecutive days each week for three weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (28-day cycle). For all subsequent cycles, a higher dose of 27 mg/m² is given on the same days of the 28-day cycle. Dexamethasone is given along with Kyprolis for the first two cycles.

Fluids are given intravenously both before and after the Kyprolis infusion to reduce the risk of certain side effects.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF KYPROLIS?

In clinical trials, side effects varied by patient and were considered manageable. Common side effects include:

- Blood count drops
- Nausea
- Diarrhea
- Shortness of breath
- Fever, mostly associated with reactions to the infusion
- Headache
- Infections, mostly upper respiratory

The incidence of peripheral neuropathy was notably low (14%) and generally mild when it occurred. The most commonly reported serious side effects are:

- Anemia
- Low platelet count
- Low white cell count
- Pneumonia

Although uncommon, there is a risk of cardiovascular side effects with Kyprolis, including congestive heart failure. Based on the severity of a patient’s heart condition, doctors will evaluate whether or not Kyprolis is an appropriate treatment. Patients with any heart problems taking Kyprolis will be monitored closely by their doctors.
POMALYST (POMALIDOMIDE)

WHAT IS POMALYST?
Pomalyst is an oral immunomodulatory agent (IMiD™) that is similar to Revlimid and Thalomid but is more potent. It is approved for use in combination with dexamethasone in patients with multiple myeloma who have received at least two prior therapies that included Velcade (bortezomib) and Revlimid (lenalidomide) and who have demonstrated disease progression on or within 60 days of completion of their last therapy.

HOW IS POMALYST GIVEN?
Pomalyst is taken orally, typically at a dose of 4mg daily for three out of four weeks (days 1–21 of each 28-day cycle). Each Pomalyst capsule should be taken with water. Pomalyst should not be taken with food and should be taken at least two hours before or two hours after a meal. Dexamethasone is taken at a dose of 40mg weekly. The dose of dexamethasone is reduced to 20mg weekly for patients older than 75 years old.

Aspirin or another blood thinner is usually taken along with Pomalyst and low dose–dex in order to reduce the risk of developing a blood clot.

Pomalyst and dexamethasone are taken for as long as they continue to work to against the myeloma.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF POMALYST?
The most common side effects include:
- Fatigue
- Loss of strength/weakness
- Low white cell blood counts
- Anemia
- Constipation
- Nausea
- Diarrhea
- Shortness of breath
- Upper-respiratory tract infections
- Back pain
- Fever

The most common serious side effects are:
- Low white blood cell counts and associated fevers
- Anemia
- Low platelets
- Blood clots

The dose of Pomalyst may be adjusted in patients who experience low white blood cell or platelet counts or other serious side effects while receiving Pomalyst.

Women who are pregnant or who plan to become pregnant must not take Pomalyst. This precaution is due to its similarity to thalidomide and some signs of birth defects in animals. A program called Pomalyst REMS™ has been created to prevent exposure to Pomalyst during pregnancy.
**REVLIMID-BASED REGIMENS**

Revlimid–Velcade–dex or Revlimid–dex may be options depending on whether patients received them previously and how they responded.

Revlimid is also being combined with new drugs in clinical trials and, depending on the trial, even patients who previously received Revlimid may be eligible.

**Revlimid–Velcade–dex (RVD)**

Revlimid–Velcade–dex may be an option if not used for initial therapy. Good responses have been seen including complete responses.

**Revlimid–Dex**

The FDA approval of Revlimid–dex was based on two Phase III trials in 705 relapsed or refractory patients who had received at least one prior treatment. Revlimid–dex was compared to dex alone. Sixty percent of patients treated with Revlimid–dex responded, and the time without progression of myeloma (time to progression) was significantly longer than those treated with dex alone (10.9 months vs 4.6 months). Patients taking Revlimid–dex lived longer as well.

**VELCADE-BASED REGIMENS**

Velcade-based regimens may be an option for patients with relapsed or refractory myeloma, depending on what combination they received previously and how they responded to treatment.

Velcade continues to be evaluated in clinical trials in combination with other drugs, including new agents in development. Depending on the study, even patients who previously received Velcade may be eligible.

**Velcade alone**

While Velcade is infrequently used alone today, it was originally approved by the FDA based on a Phase III study in which Velcade alone was compared to high-dose dex. Results of this study showed that patients with relapsed/refractory myeloma who were treated with Velcade had significantly higher response rates, longer time-to-disease progression, and longer survival as compared with high-dose dex. In addition, patients whose disease had characteristics indicating poor prognosis benefited from Velcade.

**Velcade–Doxil**

Doxil, a chemotherapy drug, is FDA approved for use in combination with Velcade in previously treated patients who have not received a therapy other than Velcade. Results of a Phase III trial showed that this combination reduced the chance of disease progression, prolonged the length of the response, and led to longer survival in patients with relapsed and refractory disease compared with Velcade alone. However, it is associated with many side effects that can be serious. These include low blood counts, anemia, fatigue, weakness, diarrhea, peripheral neuropathy, and hand–foot
syndrome (swelling and blistering of the hands and feet). Due to its side effects, this therapy is not frequently used.

KYPROLIS
Kyprolis (carfilzomib) is a next-generation proteasome inhibitor in the same drug class as Velcade. In 2012 it was approved by the FDA for patients with multiple myeloma who have received at least two prior therapies, including Velcade and an IMiD (such as Revlimid or Thalomid) and have demonstrated disease progression on or within 60 days of completion of their last therapy.

The benefit of Kyprolis in patients with relapsed/refractory disease was shown in a large Phase II study conducted in collaboration with the Multiple Myeloma Research Consortium (MMRC), an affiliate organization of the MMRF. A total of 266 patients were treated with Kyprolis after receiving an average of five prior myeloma therapies. Twenty-three percent of these patients achieved a partial response or better, and, on average, responses lasted 7.8 months. Notably, 20.6% of patients who did not respond to or could not tolerate Velcade and one or more IMiDs responded to Kyprolis. The average patient in this study lived 15.4 months following initiation of treatment with Kyprolis.

For the most part, side effects were considered manageable. Common side effects include blood count drops, nausea, diarrhea, shortness of breath, fevers (mostly associated with reactions to the infusion), headache, and infections (mostly upper respiratory). The incidence of peripheral neuropathy was notably low (14% of patients); when it occurred, it tended to be mild.

Although uncommon, there is a risk of cardiovascular side effects with Kyprolis, including congestive heart failure. If a patient has a heart condition, doctors will evaluate whether or not Kyprolis is an appropriate treatment depending on its severity. Patients with any heart problems taking Kyprolis will be monitored closely by their doctors.

Studies are evaluating Kyprolis in combination with other myeloma drugs as well as the potential for use in additional types of patients.

POMALYST
Pomalyst (pomalidomide) is an IMiD that is similar to Revlimid (lenalidomide) and Thalomid (thalidomide) but is more potent.

The combination of Pomalyst and dex was approved in 2013 by the FDA for patients with multiple myeloma who have received at least two prior therapies that included both Velcade and Revlimid and who have demonstrated disease progression on or within 60 days of completion of their last therapy.

A large Phase II trial involving 221 patients with relapsed myeloma who were refractory to their last myeloma therapy showed that 29.2% of patients receiving Pomalyst–low-dose dex
achieved a partial response or better, with responses lasting an average of 7.4 months. Notably, all patients had previously received both Velcade and Revlimid.

Pomalyst–low–dose dex was compared to high–dose dex in a Phase III trial with 455 patients with refractory myeloma who had failed therapy with both Velcade and Revlimid, given either alone or in combination. Overall responses rates were 29% with Pomalyst–low–dose dex versus 10% with high–dose dex alone. Patients taking Pomalyst–low–dose dex lived longer than those who received high–dose dex alone.

Side effects vary by patient and are considered manageable. The most common side effects include fatigue and loss of strength/weakness, low white cell blood counts, anemia, constipation, nausea, diarrhea, shortness of breath, upper–respiratory tract infections, back pain, and fever. Similar to other IMiDs, some patients who received Pomalyst in clinical trials developed blood clots. For this reason, aspirin or another blood thinner is given along with Pomalyst.

Numerous clinical trials are underway evaluating Pomalyst in other types of patients and in combination with other myeloma drugs.

OTHER TREATMENTS

Various chemotherapy agents and combinations are also used in the treatment of relapsed/refractory disease. Many new regimens, including combinations with experimental drugs, are being studied in clinical trials.

One promising new treatment is Panobinostat in combination with Velcade–dex. A Phase III study has evaluated this combination. Although the full results are not yet released, Panobinostat–Velcade–dex is known to extend the time without evidence of myeloma (progression–free survival) when compared to Velcade–dex alone.

Further, there are some drugs that are approved by the FDA for other blood cancers that have been shown to be beneficial to patients with multiple myeloma in clinical trials (e.g., bendamustine and vorinostat).

HOW ARE SYMPTOMS AND SIDE EFFECTS MANAGED?

Myeloma often weakens bones, affects blood counts resulting in anemia and infection, and causes reduced kidney function. Medications used to treat myeloma also have side effects. For example, some medications have the potential to lower blood counts and cause peripheral neuropathy or blood clots. There are various therapies available to address the symptoms and complications of the myeloma as well as side effects of therapy. These are called supportive therapies or supportive care.

The following table provides a brief overview of some of the types of supportive therapies that may be used to manage symptoms and complications of myeloma.
Bone disease

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

BONE DISEASE
Bisphosphonates and other medications
Bone damage (osteolytic lesions and osteoporosis) is very common in multiple myeloma, occurring in approximately 85% of patients. Weakened bones can result in fractures and compression of the spinal cord, and there is the potential for spinal cord collapse.

Bisphosphonates are drugs that help prevent myeloma bone disease from getting worse, decrease bone pain, and reduce the likelihood of fracture. They are prescribed in the majority of patients. Two types of bisphosphonates, zoledronic acid (Zometa) and pamidronate (Aredia), are used in the treatment of bone complications in patients with myeloma. They
are more potent than other bisphosphonates that are used to treat osteoporosis in people who do not have cancer. Both drugs are equally effective in reducing the complications of myeloma bone disease. These medications are also used to treat hypercalcemia (elevated calcium levels in the blood), another common problem in myeloma.

Bisphosphonates are given intravenously every three to four weeks. Zoledronic acid is most often recommended due to its shorter infusion time (as little as 15 minutes versus two hours with pamidronate).

Potentially serious side effects with bisphosphonates include reduced kidney function (renal impairment) and osteonecrosis of the jaw (ONJ), a painful condition in which the jawbone is exposed.

There is somewhat greater risk of kidney impairment with zoledronic acid. Therefore, patients who have mild or moderate kidney impairment prior to therapy usually receive reduced doses of zoledronic acid when starting treatment. To reduce the risk of developing kidney impairment during therapy, creatinine levels (a protein that is an indicator of potential concerns) are monitored by blood tests. Blood tests are done before each dose of bisphosphonate therapy, and the dose will be reduced if there are significant increases in creatinine levels. Under certain circumstances, pamidronate can be successfully substituted for zoledronic acid if kidney failure develops while taking zoledronic acid.

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**HOW CAN I KEEP MY MOUTH HEALTHY WHILE RECEIVING BISPHOSPHONATES?**

- 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
Some studies indicate that long-term use of bisphosphonates may be associated with a small risk of damage to the jawbone known as osteonecrosis, and that this risk may be higher with zoledronic acid.

To reduce the chance of developing osteonecrosis of the jaw, patients receiving bisphosphonates should maintain their oral health (see sidebar). Interrupting or stopping bisphosphonates may be considered in severe cases of osteonecrosis.

Some myeloma experts recommend stopping bisphosphonates after two years in patients with very good partial responses or complete responses. However, there are some studies that suggest that staying on zoledronic acid longer may be better.

Talk to your doctor about how long you should stay on bisphosphonate therapy.

In addition, there is evidence that zoledronic acid may have an anti-myeloma effect. A large Phase III trial in the United Kingdom showed that zoledronic acid significantly improved survival in patients with bone disease by an average of 5.5 months compared with another oral bisphosphonate used outside the United States. Researchers could not attribute the beneficial effect of zoledronic acid to bone effects alone, raising the possibility that the drug may have other favorable anti-myeloma effects.

Experts recommend consideration of bisphosphonate therapy in all patients receiving initial myeloma treatment, even if bone damage is not seen on x-rays. However, the benefit of bisphosphonate therapy in patients in whom bone disease is not detected by other tests, such as MRI, PET, or CT scans, is unknown.

Another bone supportive therapy that is not a bisphosphonate, Xgeva (denosumab), is being studied in a Phase III trial in patients with multiple myeloma. Xgeva is a novel agent that is currently approved by the FDA to prevent bone complications in patients with other types of cancers.

**Orthopedic Interventions**

Orthopedic interventions may be required to help control pain or maintain function or mobility. These may include physical therapy, splinting of bones, or surgical intervention to prevent or treat fractures or procedures to repair compression fractures of the spine. Two minimally invasive surgical procedures—**vertebroplasty** and **balloon kyphoplasty**—are used to reinforce the vertebra of the spine and usually can be done without hospitalization.

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
Figure 3. Balloon kyphoplasty

1. During balloon kyphoplasty, a balloon is inserted into the compressed bone through a tiny tube. The incision is approximately 1 cm in length.

2. The balloon is inflated in an attempt to both raise the collapsed vertebra and return it to its normal position.

3. The balloon is 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.
relieve pain and improve function and quality of life in patients with myeloma. Kyphoplasty has the potential to provide relatively rapid relief (approximately one month following the procedure).

**Radiation Therapy**
Low-dose radiation may sometimes be used to reduce bone pain as well. It is directed to specific bone lesions that are causing problems. However, it can affect the bone marrow and result in reduced blood counts, which may cause anemia, a weakened immune system, and blood clotting problems.

**ANEMIA**
Sixty percent of patients have anemia when initially diagnosed with multiple myeloma. Further, some of the medications used to treat myeloma can also result in lower red blood cell counts, resulting in anemia.

There are many symptoms that may be indicative of anemia, including fatigue, depression/mood changes, difficulty breathing, weight loss, rapid heart, nausea, dizziness, and difficulty sleeping. Let your doctor know if you experience any of these symptoms, so your blood counts can be checked for anemia.

In addition to myeloma and myeloma medications, iron, folate, and vitamin B-12 deficiencies can cause anemia.

The first step in treatment of anemia is to identify and treat any causes of anemia other than myeloma or myeloma medications. Your doctor will prescribe iron or vitamin supplements if needed.

If your anemia is moderate or severe, your doctor may prescribe medications to stimulate the bone marrow to produce more red blood cells (Procrit, Epogen Aranesp). Use of these medications with certain myeloma therapies, such as IMiDs (Revlimid, Pomalyst, or Thalomid), may not be appropriate due to an increased risk of blood clots. Some patients with severe anemia may require blood transfusions.

**INFECTION AND LOW WHITE BLOOD CELL COUNTS**
Myeloma patients may be more susceptible to infections. They may have reduced levels of infection-fighting white blood cells either due to their disease or myeloma therapy (for example, Revlimid, Pomalyst, or chemotherapy). In addition, the abnormal antibodies produced by myeloma cells may crowd out normal antibodies, resulting in a weakened immune system.

Preventative steps can be taken to reduce the risk of infections. Patients should be sure to receive flu and pneumonia vaccinations. Patients who have experienced serious recurrent infections may receive an intravenous antibody treatment.
(immunoglobulin IgG). Patients who are taking high-dose dexamethasone may be prescribed antifungal medications. Patients who are taking Velcade may be prescribed preventative herpes medications as Velcade may increase patient’s susceptibility to herpes.

Patients who have low numbers of white blood cells, as a result of their disease or treatment (e.g., high dose chemotherapy or IMiDs), may receive medications called colony stimulating factors (Neupogen, Neulasta, or Leukine) to stimulate the production of infection-fighting white blood cells. Antibiotics or antifungal medications may be used to treat infections as needed.

**KIDNEY IMPAIRMENT**

More than half of patients with myeloma experience kidney problems at some point in the course of their disease. Kidney impairment can also be caused by other conditions, such as hypertension and diabetes, and some medications can affect the kidney as well.

Blood tests can detect certain proteins (such as creatinine) that are indicative of reduced kidney function. A decrease in the amount of urine is one sign of kidney problems, and patients should let their doctors know if they experience any changes in their urination.

Patients who develop kidney problems should make sure to drink plenty of fluids and avoid taking non-steroidal anti-inflammatory drugs (NSAIDs), such as Aleve (naproxen) and Advil/Motrin (ibuprofen).

In some cases, a procedure called plasmapheresis may be helpful in order to slow or prevent kidney failure. The abnormal antibodies produced by myeloma can cause the blood to become thick, which can affect the kidney. With plasmapheresis, blood is withdrawn and the excess M-protein is separated out. Fluid is then infused back into the patient.

**MANAGEMENT OF TREATMENT-RELATED SIDE EFFECTS**

Myeloma medications, like all medications have the potential to cause side effects. This section reviews some of the side effects that may occur, but is not comprehensive, as the side effects can vary with the different medications and combinations in your treatment regimen.

Side effects can often be managed, and it is important to let your healthcare team know if you are experiencing any side effects.
### TABLE 8. MANAGEMENT OF SELECTED TREATMENT-RELATED SIDE EFFECTS

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Related Treatment</th>
<th>Management</th>
</tr>
</thead>
</table>
| Blood clots            | • IMiDs (Revlimid, Pomalyst, and Thalomid) in combination with other myeloma medications  
                          • Dexamethasone  
                          • Chemotherapy  
                          • Red blood cell growth factors (Procrit, Epogen, and Aranesp) | • Preventative blood thinners: aspirin or low-molecular weight heparin (e.g., Lovenox and Fragmin) most common.  
                          • In certain cases, Coumadin may be prescribed  
                          • Avoid long periods without moving, if possible |
| Peripheral neuropathy  | • Proteasome inhibitors, especially Velcade, when given intravenously on a twice-weekly schedule  
                          • Thalomid | • Changes in myeloma medication dose  
                          • Some medications, such as Neurontin (gabapentin), may be helpful  
                          • Some types of vitamins or other supplements (less proven) |
| Gastrointestinal problems | • Revlimid  
                          • Pomalyst  
                          • Thalomid  
                          • Velcade  
                          • Kyprolis  
                          • Dexamethasone  
                          • Chemotherapy | **Constipation**  
                          • Stool softener plus laxatives (preventative medications in some cases)  
                          • Fluids and high-fiber foods  
                          • Physical activity, as possible |
|                        |                                                                                  | **Nausea/Vomiting**  
                          • Antiemetic medications (e.g., Zofran, Kytril, Emend, Anzemet, and Aloxi)  
                          • Fluids and small meals |
|                        |                                                                                  | **Diarrhea**  
                          • Antidiarrheal medication  
                          • Fiber supplement  
                          • Fluids and a bland, low-fiber diet |
BLOOD CLOTS
Patients with myeloma are at an increased risk of developing blood clots, particularly those who are newly diagnosed and those who have had blood clots in the past. There are other factors that put patients at greater risk of developing blood clots, such as older age, family history, some other medical conditions, obesity, and long periods of immobilization (e.g., hospitalization and long airplane rides).

In addition, several myeloma medications are associated with an increased risk of developing serious blood clots known as deep vein thrombosis. These include IMiDs (Revlimid, Pomalyst, and Thalomid) when taken in combination with other myeloma drugs, dexamethasone, chemotherapy, and red blood cell growth factors (erythropoietin). In particular, patients taking IMiDs should receive blood thinners to reduce the chance of developing blood clots. Aspirin is recommended to most patients, while molecular weight heparin is prescribed to those at greater risk. In some cases, additional medications may be recommended as well.

PERIPHERAL NEUROPATHY
Peripheral neuropathy is a condition affecting the nerves that causes pain, tingling, burning sensations, and numbness in the hands and feet. Proteasome inhibitors (particularly Velcade) and an older IMiD, Thalomid, have been associated with the development of peripheral neuropathy. Other conditions, such as diabetes, can also cause neuropathy. The presence of existing neuropathy is a consideration in the selection of which myeloma therapy is given, and depending upon its severity, myeloma medications that do not have this side effect may be selected.

The way Velcade is given affects the risk of development of neuropathy as well as its severity. Today, Velcade is most often given as an injection under the skin (subcutaneous), which reduces the chance of developing neuropathy. If given intravenously, once-weekly is less likely to result in neuropathy as compared to twice-weekly. Patients taking Kyprolis, a newer proteasome inhibitor, are significantly less likely to develop neuropathy, and if it occurs, it is typically mild.

In contrast to Thalomid, peripheral neuropathy is uncommon with the newer IMiDs (Revlimid and Pomalyst) that are more commonly used. However, the newer IMiDs can exacerbate neuropathy that existed prior to myeloma treatment.

Changes in dose are the main way peripheral neuropathy is managed in patients taking Velcade. If peripheral neuropathy is severe, doctors will tell patients to stop taking Velcade, and another medication will be prescribed. Peripheral neuropathy usually improves or resolves after the treatment dose is reduced or treatment is stopped.
In addition, some medications, such as gabapentin (Neurontin), may be helpful as well as certain vitamins or other supplements, but these are less proven. Always speak with your doctor about any vitamins or supplements before taking them.

GASTROINTESTINAL PROBLEMS
Commonly used myeloma medications may cause a variety of gastrointestinal problems, such as constipation, diarrhea and nausea/vomiting. Medications as well as changes in diet may be helpful. It is important to drink plenty of fluids.

Constipation
Depending on your situation, your doctor may recommend that you take a stool softener and/or laxatives as prevention. Drinking plenty of fluids, eating a high fiber diet, and physical activity may be helpful. Be sure to let your healthcare team know if you have not had a normal bowel movement after three days.

Diarrhea
If you experience diarrhea, your doctor will recommend either an over-the-counter or prescription antidiarrheal medication and may advise you to take a fiber supplement. Drinking plenty of fluids and eating a bland, low-fiber diet is usually recommended.

In some cases, diarrhea can be serious. Call your doctor immediately if you:
- Have six or more loose bowel movements per day for more than two days in a row
- Notice blood in the stool
- Cannot urinate for at least 12 hours
- Have a fever
- Lose five pounds or more after the diarrhea starts
- Have a swollen and/or painful abdomen
- Feel dizzy or lightheaded when moving to a standing position

Nausea and Vomiting
If you experience nausea or vomiting, your doctor will prescribe an antiemetic medication (e.g., Zofran, Kytril, Emend, Anzemet, and Aloxi). Antiemetics work best when taken regularly as advised by your doctor, not only when you feel nauseated or after you have vomited. Eating small meals throughout the day as well as drinking at least eight glasses of fluids in small amounts may be helpful as well.
SHOULD I PARTICIPATE IN A CLINICAL TRIAL?
Clinical trials are critically important in order to develop new myeloma treatments and better understand the biology of the disease. The more people who enroll in clinical trials, the faster we can develop new drugs and obtain the answers to important questions about myeloma.

Patients who enroll in clinical trials have the opportunity to be amongst the first to receive the newest drugs or drug combinations in development and receive close monitoring.

*Placebos are not given. All clinical trial participants receive the experimental therapy being tested for multiple myeloma or the best available standard treatment.*

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.

Before any drug is considered for testing in humans, there must be evidence of activity against the disease as shown by laboratory and animal studies (preclinical studies).

Clinical trials are defined according to their phase, with each phase serving a distinct purpose (Table 9). 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.

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.

**TABLE 9. PHASES OF CLINICAL TRIALS**

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

\(^a\)Trials may occasionally close earlier than or exceed approximate duration.
OTHER TYPES OF CLINICAL TRIALS
Other types of clinical trials are longitudinal, registry, and expanded access studies. These studies are not intended to develop new drugs. Rather, they provide important information about existing treatments or a better understanding of the disease.

- Longitudinal studies: long-term studies with a large number of patients
- Registry studies: provide additional information about available drugs in a large number of patients
- Expanded access studies: allow early access to experimental therapies when no alternatives are available

THE MMRF CoMMpass℠ STUDY - A GROUNDBREAKING STUDY
The MMRF CoMMpass℠ Study is a landmark study focused on learning more about the biology of myeloma throughout the course of the disease, particularly the genetics of myeloma. Approximately 1,000 newly diagnosed patients will be followed for at least five years.

To learn more about The MMRF CoMMpass℠ Study and how to enroll, call 866.603.6628, or email patientnavigator@themmrf.org.

FINDING A CLINICAL TRIAL
The MMRF Patient Navigator Program is designed to match patients 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.myelomatrials.org. Or, you can call 866.603.MMCT (6628) to speak with a Patient Support Nurse who will ask you questions and talk to you about clinical trials that could be appropriate for you. The Patient Support Nurse can also help you enroll in a trial, if you choose.

Speak with your doctor regarding questions about specific trials and treatment options.
WHAT ARE SOME OF THE MOST PROMISING AGENTS IN CLINICAL TRIALS?

There are a variety of new agents in various stages of development for myeloma. Agents in development may act in different ways against myeloma than currently available drugs, may have fewer side effects, or may have more convenient dosing. However, the availability of some of these drugs may be limited to individuals at particular stages of disease, and the drugs are not without side effects of their own. Table 10 lists some newer agents that are currently in Phase III, the most advanced stage of drug development. Numerous other agents are in Phase II studies.

YOUR TREATMENT OPTIONS

This booklet has presented many treatment options for multiple myeloma. Your doctor can provide more information about treatments that are most appropriate for you.

Enrollment in a clinical trial may provide additional options. Your doctor can determine which trials are appropriate and available in your area.

TABLE 10. EMERGING THERAPIES FOR MYELOMA IN PHASE III CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Name</th>
<th>Drug Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplidin (plitidepsin)</td>
<td>Anti-cancer drug derived from a marine organism</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Ixazomib (MLN9708)</td>
<td>Oral proteasome inhibitor</td>
</tr>
<tr>
<td>Panobinostat (LBH589)</td>
<td>HDAC inhibitor</td>
</tr>
</tbody>
</table>

For more detailed information about these emerging agents and other advances in myeloma, visit the MMRF’s website [www.themmrf.org](http://www.themmrf.org) or call 866.603.MMCT (6628).

The MMRF would like to thank Keith Stewart, M.B., Ch.B. for his contributions to this brochure.
**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 that helps protect the body from infection and disease. Also called an immunoglobulin.

**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 fractures in the spine (spinal compression fractures).

**B-cells** White blood cells that are responsible for producing infection-fighting antibodies.

**Bence Jones protein** A protein that is produced by myeloma cells. It is also known as a light chain.

**Beta$_2$-microglobulin (β or β$_2$-M)** A protein normally found on the surface of various cells in the body. Increased blood levels occur in myeloma.

**Bisphosphonate** Type of drug used to treat osteoporosis and bone disease in individuals with cancer.

**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.

**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.

**DNA** Genetic material of the cell located in the chromosomes.

**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 antibody components, light chains, normally present in the blood. 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.

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 that helps protect the body from infection and disease. Also called an antibody.

Induction therapy Treatment prior to a stem cell transplant in order to reduce the amount of myeloma cells.

Maintenance therapy Additional treatment given after initial myeloma therapy with the goal of improving long term outcomes.

Malignant Cancerous, continuing to divide.

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 Gammapathy 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 antibody (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 the lining the mouth and digestive tract; painful side effect of chemotherapy, particularly when given in high doses, which can result in mouth 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.

**Overall response rate** The total of all types of responses seen in a clinical study (complete response + very good partial response + partial response + minor response).

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

**Phase I** The initial small study of a drug in humans. It is used to determine a drug’s safety and dosage levels.

**Phase II** The second stage of drug studies. The purpose is to obtain a preliminary determination of a drug’s effectiveness and gain additional information about its safety.

**Phase III** The most advanced stage of drug development involving large numbers of patients. Usually required for FDA approval of drugs.

**Plasma cell** Antibody-secreting immune cell that develops from a type of white blood cell (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 that may slow down or prevent kidney failure.

**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.

**Radiation therapy** Use of high-energy rays. Sometimes used to relieve uncontrolled bone pain.
**Refractory disease** Disease that is not responsive to therapy.

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

**Remission** A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

**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 blood-producing stem cells are collected, stored, and infused into a patient following high-dose chemotherapy in order to restore blood cell production.

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

**Tumor lysis syndrome** Serious metabolic complication that is caused when cancer cells die.

**Vertebroplasty** Procedure used to treat fractures of the spine (spinal compression fractures).

**White blood cell** One of the major cell types in the blood. Responsible for immune defenses.
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

Recently Diagnosed with Multiple Myeloma?
If you are newly diagnosed, learn about the MMRF CoMMpass℠ Study to help advance our understanding of myeloma. Contact us before starting any cancer treatment.

www.themmrf.org/CoMMpass
Telephone: 1.866.603.6628

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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MMRF nurse specialists can guide you through your multiple myeloma journey every step of the way.

Phone: 1.866.603.6628
Email: patientnavigator@themmrf.org

Monday–Friday
9:00 a.m. to 7:00 p.m. ET

www.MMRFCoMMunityGateway.org

The MMRF CoMMunity Gateway connects you to people and myeloma clinical trials tailored to you!
Speak to a patient support nurse
PH: 1.866.603.6628
Email: patientnavigator@themmrf.org