

MULTIPLE MYELOMA



TREATMENT OVERVIEW



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ABOUT THE MULTIPLE MYELOMA RESEARCH FOUNDATION



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

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

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

supporting a pipeline of more than 50 promising compounds and combination treatments, including more than 40 clinical trials we advanced through our sister organization, the Multiple Myeloma Research Consortium (MMRC).

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

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

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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 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 41).

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 Web site: www.themmr.org.

WHAT IS MULTIPLE MYELOMA?

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

HOW IS MYELOMA CLASSIFIED AND STAGED?

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

Classification of Myeloma

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

TABLE 1. CLASSIFICATION OF MULTIPLE MYELOMA

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

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

TABLE 2. THE DURIE-SALMON STAGING SYSTEM

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

^aThe myeloma cell mass is expressed as the number of myeloma cells per body surface area.

Subclassification (either A or B)

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

Staging of Myeloma

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

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

test results: **beta₂-microglobulin (β₂-M)** and **albumin** (Table 3). The three stages in this system indicate different levels of estimated survival and may help in the treatment decision-making process.

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

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

TABLE 3. INTERNATIONAL STAGING SYSTEM FOR MYELOMA

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

β₂-M = beta₂-microglobulin.

HOW DO YOU DECIDE WHICH TREATMENT IS APPROPRIATE?

Deciding on a particular treatment plan for myeloma is a complex process.

Treatment is tailored to each individual based on a number of things, including:

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

WHAT ARE THE POSSIBLE GOALS OF TREATMENT?

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

HOW DO YOU KNOW IF A TREATMENT IS WORKING?

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

TABLE 4. TREATMENT GOALS

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

**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.

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

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

TABLE 5. RESPONSE CRITERIA USED IN CLINICAL TRIALS^a

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

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

^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.

TABLE 6. THERAPIES FOR MYELOMA®

Therapy	Description
Velcade® (bortezomib, Millennium: The Takeda Oncology Company) for Injection	Proteasome inhibitor approved for use across the entire spectrum of myeloma disease.
Revlimid® (lenalidomide, Celgene)	Oral agent that is an improvement over Thalomid and is effective across the spectrum of myeloma disease; approved for use in combination with dexamethasone in individuals who previously received treatment.
Kyprolis® (carfilzomib, Onyx Pharmaceuticals)	New type of proteasome inhibitor; approved use in patients who have received at least two prior therapies including Velcade and an immunomodulatory agent (such as Revlimid or Thalomid).
Pomalyst® (pomalidomide, Celgene)	Oral agent that is similar to Revlimid and Thalomid, but is more potent. It is approved for use in patients who have received at least two prior therapies including Velcade and Revlimid.
Thalomid® (thalidomide, Celgene)	Oral agent shown to be effective across the spectrum of myeloma disease; approved in combination with dexamethasone as front-line therapy. Peripheral neuropathy is a common side effect and can be irreversible.
Doxil® (doxorubicin HCl liposome injection, Ortho Biotech)	Chemotherapy agent approved for use in combination with Velcade for individuals who previously received therapy other than Velcade. Side effects include mouth sores, swelling and blisters on the hands or feet, and possible heart problems.

WHAT THERAPIES ARE USED IN MYELOMA?

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

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

HOW IS MYELOMA TREATED?

Treatment of myeloma can be complex because of the many factors that must be taken into account. In addition, many

Therapy	Description
Steroids (corticosteroids) (dexamethasone and prednisone)	Drugs used for decades to treat myeloma throughout the spectrum of disease; may be used alone or in combination with other therapies.
Conventional (standard dose) chemotherapy	The use of drug(s), administered alone or in combination, to kill cancer cells; some examples are melphalan (Alkeran®, GlaxoSmithKline) and cyclophosphamide
High-dose chemotherapy and stem cell transplantation	The use of higher doses of chemotherapy drugs followed by transplantation of hematopoietic stem cells to replace healthy cells damaged by the chemotherapy.
Radiation therapy	The use of high-energy rays to damage cancer cells and prevent them from growing
Supportive therapy	Therapies that alleviate symptoms and manage complications of the disease and its treatment, such as bisphosphonates for bone disease, low-dose radiation therapy and analgesics for pain relief, growth factors , antibiotics, intravenous immunoglobulin, orthopedic interventions, drugs (primarily anticoagulants) to prevent and reduce the severity of deep vein thrombosis (DVT) ; blood clots), antiemetics , and drugs to prevent and reduce the severity of neuropathy (nerve damage)

^a *Approved indications listed are those for the United States.*

centers have developed their own guidelines for treating myeloma and these may vary from center to center. Your doctor will discuss the treatment options that are most appropriate for you.

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

Inactive Disease

Individuals with inactive disease, that is, those with MGUS or asymptomatic (smoldering) myeloma, are typically watched and not treated unless their disease becomes active. If such patients have evidence of osteoporosis, they should receive treatment with bisphosphonates to prevent or minimize damage to bone in a dosing schedule similar to that used for osteoporosis in general.

Recently, a clinical trial showed that one of the newer agents, Revlimid®, prolonged the time to symptomatic myeloma in patients with high-risk smoldering multiple myeloma. However, this therapy is still considered experimental and there is not sufficient data on the benefits and risks of therapy. A large national study is under-way to determine if this agent can delay disease progression and improve survival in this group of patients.

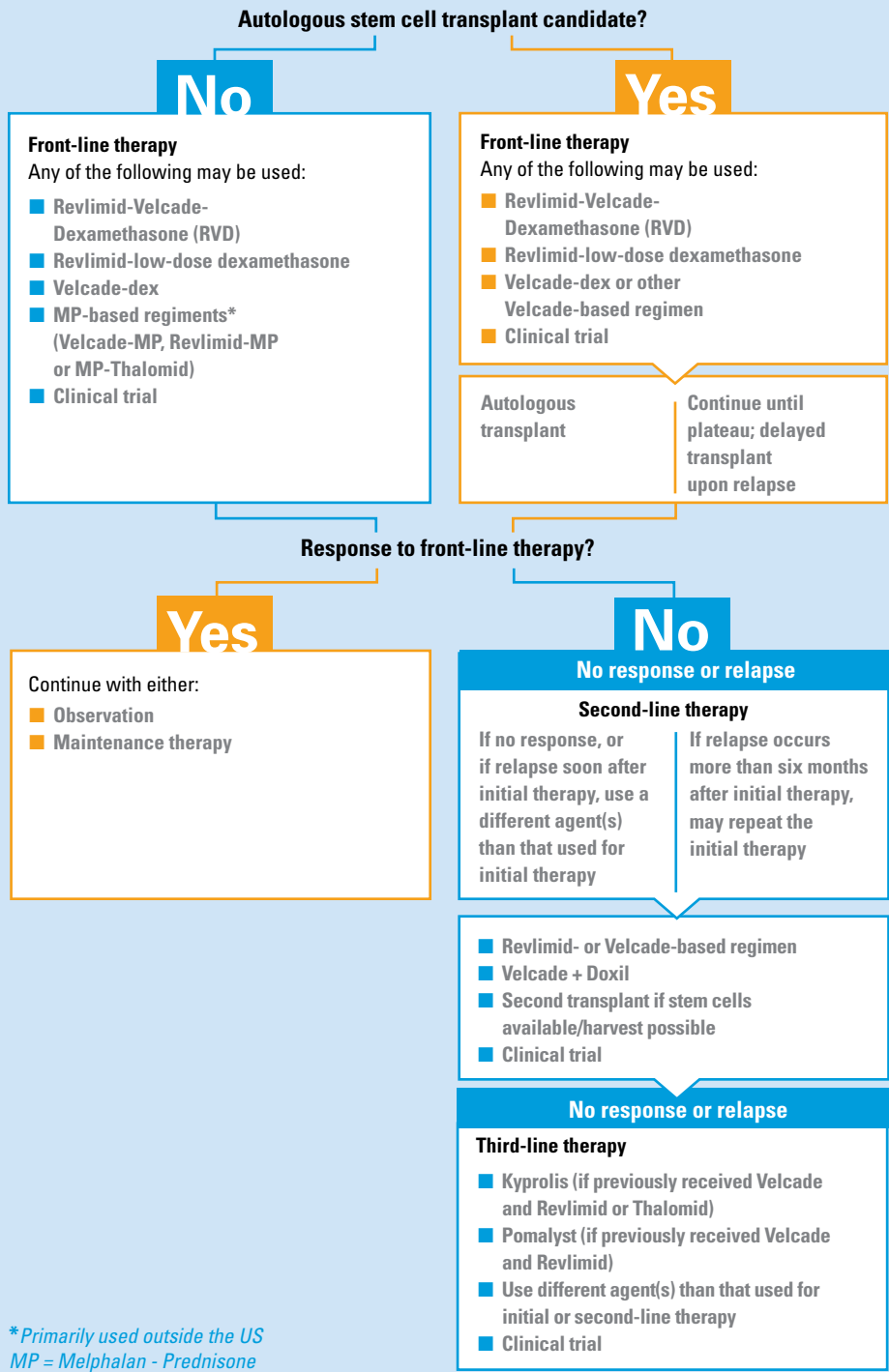
Active Disease

Individuals with symptomatic myeloma typically receive some form of treatment aimed at reducing the amount of myeloma cells. For the most part, choices for treatment are similar regardless of whether or not the individual is a candidate for, or interested in, treatment with high-dose chemotherapy and **autologous stem cell transplant**. An autologous transplant is a treatment that has been shown to offer improved response rates and survival in myeloma. Individuals in good physical condition with adequate kidney, lung and heart function are potential candidates for autologous transplant.

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

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

Figure 1. **Treatment options for myeloma**



THE EVOLVING ROLE OF TRANSPLANTATION IN MYELOMA

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

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

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

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

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

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

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

Increasingly, patients who are not candidates for transplant are being treated with the same drug regimens as transplant candidates. Treatment options include:

- Revlimid-Velcade-dex (RVD)
- Revlimid-low-dose dexamethasone
- Velcade-based regimens, such as Velcade-dex
- MP-based regimens (Velcade-MP, MP-Revlimid, MP-Thalomid)
- Investigational regimen in a clinical trial

Notably, MP-based regimens are primarily used outside of the US.

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

Revlimid-Velcade-Dex (RVD)

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

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

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

In most cases, the neuropathy was mild. A large national Phase III study is being done to evaluate the efficacy and safety of RVD compared with Revlimid-dex for patients eligible for high-dose chemotherapy and transplantation.

Revlimid-Low-Dose Dex

The combination of Revlimid-low-dose dexamethasone is a commonly used treatment for patients who are not transplant candidates. This treatment was studied in Phase III trial of 445 patients. One year after the beginning of treatment, 96 percent of patients taking Revlimid-low-dose dex were alive and 87 percent were alive two years later. Outcomes were similar regardless of age.

KEY FACTS

REVLIMID (LENALIDOMIDE)

WHAT IS REVLIMID?

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

HOW IS REVLIMID TAKEN?

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

WHAT ARE THE POSSIBLE SIDE EFFECTS OF REVLIMID?

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

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

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

- Low blood counts (neutropenia, thrombocytopenia, anemia)

- High blood sugar
- Blood clots
- Fatigue
- Pneumonia

Studies have shown that serious blood clots occur more frequently after treatment with Revlimid-dex than placebo-dex, so use of aspirin or a blood thinner is recommended for individuals receiving this combination.

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

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

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

Velcade-Dex

The combination of Velcade and dexamethasone is another option for patients who are ineligible for transplantation. The effectiveness of this treatment has been established in two large Phase III trials.

MP-Based Regimens

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

- The overall response rate was significantly higher among patients receiving Velcade-MP compared with MP (71 percent vs. 35 percent).
- Thirty percent of patients receiving Velcade-MP achieved a complete response (a rate that is similar to that achieved with an autologous transplant), compared with four percent of patients receiving MP.

- After five years, patients receiving Velcade-MP had a 44 percent improvement in survival over those receiving MP.

In an effort to further improve the outcomes achieved with Velcade-MP, researchers added Thalomid to create a four-drug regimen. This combination, also known as VMPT, significantly improved the amount of time patients remained free of disease (known as **progression-free survival**) and the overall response rates compared with Velcade-MP. However, the potential increase in side effects natural with additional drugs must be considered. This combination is infrequently used in the US.

The combination of MP and Revlimid has also led to good response rates compared with MP. Results of a Phase III trial involving 459 patients in which MP-Revlimid was compared to MP alone has shown:

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

More research is needed to determine the effect of MP-Revlimid on the time without progression of myeloma (progression-free and survival). The time-to-myeloma progression was longer for patients treated with MP-Revlimid *with* Revlimid maintenance compared with MP. However, without maintenance Revlimid, the time-to-myeloma progression was similar to MP. (*See page 25 for more information about maintenance therapy.*)

MP-Thalomid (MPT) is another combination sometimes used to treat myeloma. The results of Phase III studies have shown that MP-Thalomid leads to better responses and survival than MP alone.

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

For the most part, options for transplant candidates are similar to those for non-transplant candidates and include:

- Revlimid-Velcade-dexamethasone (RVD)
- Revlimid-low-dose dexamethasone
- Velcade-dex and other Velcade-based regimens
- Investigational agent in a clinical trial

Melphalan and prolonged use of Revlimid before stem cell mobilization are not recommended for transplant candidates because these agents may impair the ability to collect stem cells for use in an autologous transplant.

Revlimid-Velcade-Dex (RVD)

Revlimid-Velcade-dex is a commonly used treatment. It has shown promising results in a Phase II trial. Eighty-four percent of patients responded to the therapy and 25 percent achieved a near complete or complete response.

Revlimid-Low-Dose-Dex

The combination of Revlimid-low-dose dexamethasone is an option for patients who are transplant candidates. This treatment was studied in a Phase III trial of 445 patients. One year after the beginning of treatment, 96 percent of patients taking Revlimid-low-dose dex were alive and 87 percent were alive two years later.

Velcade-Based Regimens

Several Velcade-based regimens have been shown to produce good outcomes as initial therapy.

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 poor prognostic features (e.g., DNA abnormalities) as it was in patients without these features.

Velcade-Thal-Dex

Velcade has been added to Thal-dex. In a large Phase III study (480 patients), Velcade-Thal-dex achieved significantly better responses both before and after transplantation. Progression-free survival after transplantation was also better. This regimen is more commonly used outside the US.

Velcade-Cyclophosphamide-Dex

The combination of Velcade, cyclophosphamide and dex (VCD or CyBorD) is another option based on high response rates and rapid responses seen in Phase II trials. Overall response rates in these trials ranged from 84 percent to 100 percent. In two of these trials complete/near-complete response rates of 39 percent to 47 percent were seen.

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

Four-Drug Combinations

The challenge with four-drug regimens is the potential for increased side effects, and research is ongoing to determine the balance of effectiveness and tolerability.

KEY FACTS

VELCADE (BORTEZOMIB)

WHAT IS VELCADE?

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

HOW IS VELCADE GIVEN?

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

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

An alternate way to give Velcade, as an injection under the skin (subcutaneously), has been shown to reduce serious side effects, including peripheral neuropathy, without compromising efficacy. This method of administration has been approved by the FDA.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF VELCADE?

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

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

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

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

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

CHOICE OF INITIAL THERAPY IN MYELOMA

The choice of a patient's initial regimen depends on many factors, including the features of the myeloma itself, as well as drug availability, convenience, anticipated risk of side effects and the familiarity of the treating physician with the given regimen. In general, all of the regimens discussed above represent excellent advances in the treatment of myeloma and patients should know that if one regimen stops working another one can be used. There are many choices available today and treatments continue to improve.

WHAT IS HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION?

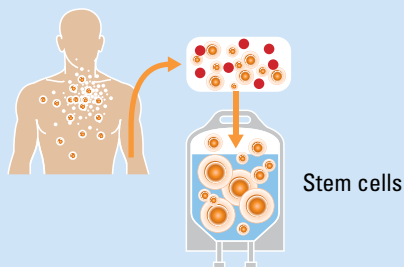
High-dose chemotherapy (usually melphalan) with stem cell transplantation is a therapeutic strategy that, for many patients, offers a chance for durable remission of the disease. High-dose chemotherapy, though more effective in killing myeloma cells than conventional chemotherapy, also destroys normal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

Stem cells are normally found in the bone marrow and in the peripheral blood (blood found in the arteries or veins). Virtually all transplants in myeloma are

Figure 2. **Stem cell transplantation**

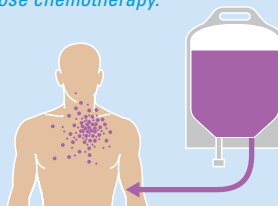
1. Collection

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



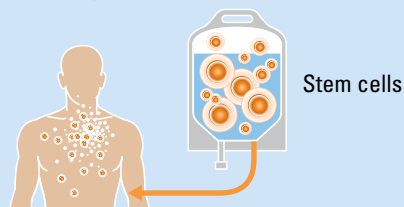
2. High-dose chemo

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



3. Infusion

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



Transplanted stem cells begin to produce new blood cells.

now obtained from the peripheral blood and are referred to as **peripheral blood stem cell (PBSC)** transplants.

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

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

- Autologous transplants involve collecting stem cells from the individual with myeloma after three to four cycles of initial therapy are administered to reduce the amount of myeloma cells. Autologous transplants are the most common transplant procedures in myeloma.

TABLE 7. TRANSPLANTS PERFORMED IN MYELOMA

Type	Description
Autologous	<ul style="list-style-type: none">• Most common type performed in myeloma
Tandem (double) autologous	<ul style="list-style-type: none">• Two autologous transplants typically performed within six months of each other• In general, a second transplant is of benefit only if a complete response or very good partial response is not achieved with the first transplant• Increased side effects over a single transplant• Being used less frequently with the increased use of newer agents in the induction setting and resultant improved response rates
Allogeneic	<ul style="list-style-type: none">• Performed infrequently because of high risk of complications, including infections and graft-versus-host disease (GVHD)
Mini (nonmyeloablative) allogeneic	<ul style="list-style-type: none">• Have largely replaced allogeneic transplants• Utilize 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 donor (usually a relative) that are infused into the individual with myeloma after high-dose therapy. This type of transplant is infrequently performed today because of the high risk of complications, although it does offer beneficial effects. A **mini (non-myeloablative) allogeneic transplant** is a modified form of allogeneic transplant that attempts to preserve the beneficial effects of allogeneic transplants while making them safer.

Information regarding these transplants, as well as others being investigated in clinical trials, is summarized in table 7.

Possible side effects of high-dose chemotherapy and transplantation include nausea, vomiting, diarrhea, **mucositis** (inflammation of the lining of the digestive tract), fatigue and organ damage, particularly to the heart, lungs, liver and kidneys. In addition, because the high-dose chemotherapy attacks healthy, disease-fighting cells as well as cancerous cells, stem cell transplants are associated with an increased risk of infection.

SHOULD I RECEIVE MAINTENANCE THERAPY?

There is increasing evidence supporting the role of maintenance therapy after the completion of front-line therapy alone or after front-line therapy and transplantation. Because myeloma is not curable, it will recur even in individuals who have a complete response after treatment. The overall goal of maintenance therapy is to maintain the response for as long as possible, thus improving survival.

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

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

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

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

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

While more data are needed to *definitively* determine the survival benefit of maintenance therapy, the results have led investigators to include maintenance

therapy in many recent studies of front-line therapy. The results are also likely to prompt more doctors to discuss risks (e.g., second cancers) versus benefits (improved progression-free and possibly overall survival) of maintenance therapy with their patients.

Results of several Phase III trials show that use of Velcade as maintenance therapy can also improve outcome. Importantly, each of these studies shows that administration of Velcade as maintenance therapy on a weekly schedule, rather than the conventional twice-weekly schedule, was effective and offered an improved safety profile.

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

If myeloma does not respond to initial (front-line) therapy or if relapse occurs 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, and another treatment option 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/**refractory disease** and many promising new agents are under investigation. Options for treating relapsed or refractory disease include:

- A variety of approved agents, including Revlimid-dex, Velcade (with or without dex), Velcade-Doxil, Thal-dex, Kyprolis (if previously received both Velcade and Revlimid or Thalomid), and conventional chemotherapy agents such as melphalan and cyclophosphamide
- Various published multi-drug combination regimens based on novel therapies with or without steroids and/or chemotherapy
- Stem cell transplant (if possible)
- Participation in a clinical trial

Revlimid-Dex

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

individuals with relapsed or refractory myeloma. The overall response rate with Revlimid-dex was over 60 percent, more than double that seen with placebo-dex.

Time without progression of myeloma (progression-free survival) was 10.9 months with Revlimid-dex and 4.6 months with dexamethasone alone. Eighty-two percent of patients taking Revlimid-dex were alive one year after the initiation of therapy.

Velcade

Velcade is another option for patients with relapsed or refractory myeloma. Results of a Phase III trial in patients with relapsed or refractory myeloma showed significantly longer time-to-disease progression, higher response rate and improved survival with Velcade compared with high-dose dexamethasone. In addition, patients with poor prognostic factors also benefitted from Velcade. Although Velcade can be used alone in treating relapsed or refractory disease, it is more commonly used in combination with dex, as well as with other agents.

Velcade-Doxil

Doxil is approved for use in combination with Velcade to treat individuals who have previously received a therapy other than Velcade. Approval was based on interim results of a Phase III trial that showed that adding Doxil to Velcade reduced the risk of disease progression and prolonged the length of the response in individuals with relapsed and refractory disease compared with Velcade alone. The combination also led to longer survival, but is associated with many side effects which can be serious. Serious side effects include low blood counts, anemia, fatigue, weakness, diarrhea, peripheral neuropathy hand-foot syndrome (swelling and blistering of the hands and feet).

There have been manufacturing problems with Doxil that have lead to drug shortages.

Other Velcade-Based Regimens

Velcade continues to be evaluated in clinical trials in combination with other drugs, including emerging therapies.

Kyprolis

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

Results of a large Phase II study involving 266 patients who had received an average of five myeloma therapies prior to entering this trial showed that 23 percent of patients achieved a partial response or better. On average, responses lasted 7.8 months and average survival was 15.4 months. Notably, 20.6 percent of patients who did not respond to or could not tolerate Velcade and one or more IMiDs (such as Revlimid or Thalomid) responded to Kyprolis alone.

In clinical trials, side effects varied by patient and were considered manageable. Side effects occurring in 25 percent or more of patients included: 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 incidence was notably low (14 percent).

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 immunomodulatory agent (such as Revlimid or Thalomid) and have demonstrated disease progression on or within 60 days of completion of their last therapy.

HOW IS KYPROLIS GIVEN?

Kyprolis is administered intravenously 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.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF KYPROLIS?

In clinical trials, side effects varied by patient and were considered manageable. Side effects occurring in 25 percent or more of patients included:

- 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 incidence was notably low (14 percent). The most commonly reported serious side effects are:

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

Pomalyst

Pomalyst, otherwise known as pomalidomide, was approved in February 2013 by the FDA for patients with multiple myeloma who have received at least two prior therapies of established benefit which included both Velcade® (bortezomib) and Revlimid® (lenalidomide) and who have demonstrated disease progression on or within 60 days of completion of their last therapy. Pomalyst® is an oral immunomodulatory agent (IMiD™) that is similar to Revlimid® (lenalidomide) and Thalomid® (thalidomide) but is more potent.

Results of a large Phase II trial involving 221 patients with relapsed myeloma who were refractory to their last myeloma therapy and had received both Velcade and Revlimid evaluated Pomalyst alone and in combination with low-dose dexamethasone. This study showed that 29.2 percent of patients receiving the combination achieved a partial response or better, with responses lasting an average of 7.4 months. In addition, 7.4 percent of patients receiving Pomalyst alone achieved a partial response or better.

The combination of Pomalyst and low-dose dexamethasone was compared to high-dose dexamethasone 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. This study showed that patients receiving the combination of Pomalyst plus low-dose dexamethasone lived longer than those receiving high dose dexamethasone. On average, time without progression of myeloma was 3.6 months with Pomalyst and low-dose dexamethasone versus 1.8 months with high-dose dexamethasone alone. Overall responses rates were 24 percent with Pomalyst and low-dose dexamethasone versus 3 percent with high-dose dexamethasone alone.

Side effects vary by patient and are considered manageable. The most common side effects, occurring in 30 percent or more of patients, include fatigue and low of strength/weakness, low white cell blood counts, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain and fever. Some patients who received Pomalyst in clinical trials developed blood clots. For this reason, aspirin or another blood thinner is given along with Pomalyst.

Other Chemotherapy Regimens

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

KEY FACTS

POMALYST (POMALIDOMIDE)

WHAT IS POMALYST?

Pomalyst® is an oral immunomodulatory agent (IMiD™) that is similar to Revlimid® (lenalidomide) and Thalomid® (thalidomide) but is more potent. It is approved for patients with multiple myeloma who have received at least two prior therapies of established benefit which included both 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 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.

Typically, aspirin or another blood thinner is taken along with Pomalyst and low dose dexamethasone 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 KYPROLIS?

The most common side effects include:

- Fatigue

- Low of strength/weakness
- Low white cell blood counts
- Anemia
- Constipation
- Nausea
- Diarrhea
- Dyspnea
- Upper-respiratory tract infections
- Back pain
- Fever

The most common serious side effects seen in clinical studies were:

- Low white blood cell counts and fever associated with low white blood counts
- 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 has been created (Pomalyst REMS™) to prevent exposure to Pomalyst during pregnancy.

- Doctors and pharmacists must register with the program in order to prescribe and dispense Pomalyst.
- Patients must register and meet all the conditions of the program in order to take Pomalyst.

WHAT SUPPORTIVE THERAPIES ARE USED IN MYELOMA?

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

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

Bisphosphonates and Other Drugs to Treat Bone Disease

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

HOW CAN I KEEP MY MOUTH HEALTHY WHILE RECEIVING BISPSPHONATES?

- 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
-

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

Because kidney function may be affected by bisphosphonates, it is recommended that individuals with mild or moderate kidney impairment receive reduced doses of Zometa when starting treatment. Under certain circumstances, pamidronate can be successfully substituted for Zometa if kidney failure develops while taking Zometa.

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

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

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

Growth Factors

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

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

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

Another growth factor approved for use in myeloma is Kepivance® (palifermin, Biovitrum). Palifermin is indicated to decrease the occurrence and duration of severe oral mucositis in individuals with hematologic cancers undergoing high-dose chemotherapy followed by a stem cell transplant. Oral mucositis, which occurs because the cells lining the mouth and throat are damaged by chemotherapy and/or radiation, is a painful condition that can interfere with eating and drinking and can result in infection.

Figure 3. **Balloon kyphoplasty**

1.

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



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. Vertebroplasty involves the injection of a cement-like substance to reinforce the vertebra. Balloon kyphoplasty involves the insertion of an inflatable balloon to restore the height of the compressed vertebra, followed by injection of bone cement to maintain the re-established height (Figure 3). By stabilizing the affected vertebrae, these procedures help relieve pain and improve function and quality of life in individuals with myeloma.

HOW DO I FIND A CLINICAL TRIAL?

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

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

Clinical trials are defined according to their Phase, with each Phase serving a distinct purpose (Table 8). Based on the results of clinical trials, the FDA approves treatments that are safe, effective, and shown to be better than the standard treatments available.

TABLE 8. PHASES OF CLINICAL TRIALS

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

^aTrials may occasionally close earlier than or exceed approximate duration.

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

Weblinks: Clinical Trial Information

MMRF Patient Navigator Program

www.myelomatrials.org

National Cancer Institute

www.cancer.gov

CenterWatch Clinical Trial Listing Service

www.centerwatch.com

WHAT ARE SOME OF THE PROMISING THERAPIES IN CLINICAL TRIALS?

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

Table 9(see page 38) lists therapies in Phase III clinical trials.

Weblink: Emerging Therapies

For more detailed information about these and other therapies, see the MMRF's website (www.themmr.org) or www.myelomatrials.org or call 866.603.MMCT(6628).

YOUR TREATMENT OPTIONS

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

TABLE 9. EMERGING THERAPIES FOR MYELOMA IN PHASE III CLINICAL TRIALS

Name	Company
Aplidin (plitidepsin)	PharmaMar
Elotuzumab (HuLuc63)	Facet Biotech/Bristol-Myers Squibb
Ixazomib cirate (MLN9078)	Millennium: The Takeda Oncology Company
Masitinib (AB1010)	AB Science
Panobinostat (LBH589)	Novartis

Would like to thank Ravi Vij, M.D. 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 by plasma cells that helps protect the body from infection and disease. Also called immunoglobulin.

Anticoagulant Drug that prevents blood from clotting.

Antiemetic Drug that prevents or alleviates nausea and vomiting.

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

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

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

Beta₂-microglobulin (β₂-microglobulin or β₂-M) A protein normally found on the surface of various cells in the body. Increased blood levels occur in inflammatory conditions and certain lymphocyte disorders, such as myeloma.

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

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

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

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

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

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

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

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

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

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

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

Growth factor Substance that stimulates cells to multiply.

Hematologic Pertaining to the blood.

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

Hemoglobin Oxygen-carrying substance in red blood cells.

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

Immunofixation A sensitive test for trace amounts of M protein.

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

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

Malignant Cancerous, continuing to divide.

Median A type of average, determined by selecting the middle value from among all the values (there are an equal number of values higher and lower than the median value). For example, a median survival of five years does not mean that patients

will live for five years. Rather, it means that 50 percent of patients will live longer than five years and 50 percent less than five years.

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

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

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

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

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

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

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

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

Osteopenia Condition of decreased bone density.

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

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

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

Plasmacytoma Single tumor composed of malignant plasma cells that occurs in bone or soft tissue. Myeloma may develop in individuals with a plasmacytoma.

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

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

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

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

Refractory disease Disease that is not responsive to therapy.

Relapse Return of disease or disease progression.

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

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

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

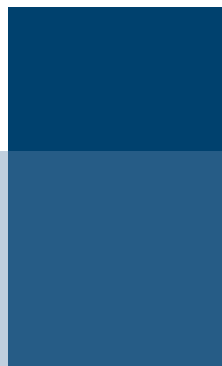
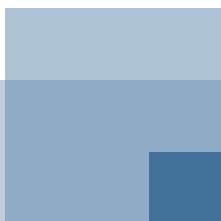
Tandem autologous transplant Stem cell transplant in which an individual undergoes two planned autologous transplants within six months.

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

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

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

NOTES



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