MULTIPLE MYELOMA

TREATMENT OVERVIEW






MULTIPLE MYELOMA Research Foundation

themmrf.org

MULTIPLE MYELOMA
Research Foundation

ABOUT THE
MULTIPLE MYELOMA RESEARCH FOUNDATION

The Multiple Myeloma Research Foundation (MMRF) was established in 1998 by identical twin sisters Kathy Giusti and Karen Andrews shortly after Kathy's diagnosis with multiple myeloma. Kathy and Karen soon learned that little progress against this disease had been made in decades, and that myeloma patients had few treatment options. They decided that it was time to accelerate change.

Working with its partners in industry, research, government agencies, and academia, the MMRF has helped launch ten new treatments in the past decade, an achievement that has almost tripled the life expectancy for myeloma patients. As a patient-founded organization, the MMRF stands with those who are battling multiple myeloma—patients, families, caregivers, doctors, and researchers—and is focused squarely on speeding the discovery of a cure. We see a world where every person has precisely what he or she needs to prevent or defeat multiple myeloma.

As the multiple myeloma community's most trusted source of information, the MMRF supports patients from the time of diagnosis throughout the course of the disease. All information on the MMRF website (**www.themmrf.org**) is organized by disease stage, so patients can get the information they need, when they need it.

To learn more about the MMRF, visit **www.themmrf.org** or call **(203) 229-0464**.

To speak to a Nurse Patient Navigator at the Patient Support Center, call **1-866-603-MMCT (6628)** or email **patientnavigator@themmrf.org**.

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INTRODUCTION

The treatment landscape for patients with multiple myeloma has more options than ever before. This booklet is designed to help patients with myeloma—and their friends, families, and caregivers—better understand the treatment options for the disease. This booklet describes current therapies for myeloma as well as emerging treatment options that are being tested in **clinical trials**. Words that may be unfamiliar are **bolded** and defined in the **Glossary** (page 36).

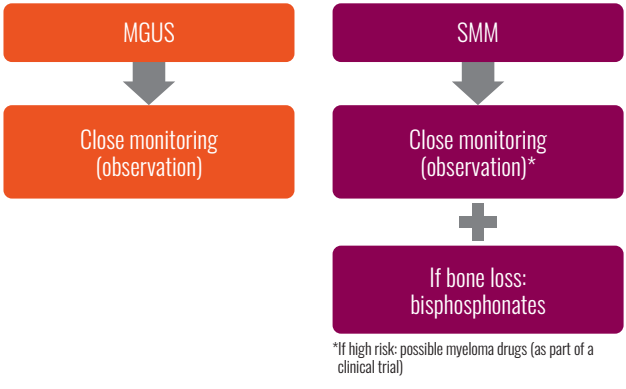
The information in this booklet is not intended to replace the services or advice of trained health professionals. Please consult with your health care professional if you have specific questions relating to your health, especially questions about myeloma diagnosis or treatment.

The companion brochure (***Multiple Myeloma Disease Overview***) and the MMRF website (**www.themmrf.org**) provide more information about how myeloma develops, as well as its symptoms, diagnosis, and **prognosis**.

WHO GETS TREATED?

Generally, myeloma is not treated until symptoms develop. There are two asymptomatic precursors to **active myeloma, monoclonal gammopathy of undetermined significance (MGUS)** and **smoldering multiple myeloma (SMM)**. These are conditions in which there is detectable monoclonal protein (M protein) in the blood and clonal **plasma cells** in the **bone marrow** but no symptoms or organ damage. Patients with MGUS are monitored approximately every 3 months for signs of progression to active myeloma. Patients with SMM who also have bone loss (**osteoporosis** or **osteopenia**) receive **bisphosphonates** to reduce the risk of fractures and other bone problems (**Figure 1**).

Figure 1. Treatment approach to asymptomatic myeloma.



Studies are ongoing to determine whether treatment with myeloma drugs helps patients with SMM, particularly those at high risk for progression to active myeloma. One study has shown that treatment with Revlimid and dexamethasone delayed progression to active myeloma in patients with high-risk SMM. However, information on the benefits and risks of this therapy is not yet complete, so this therapy is still considered experimental. There are many ongoing clinical studies looking at the effectiveness of several different treatments for patients with high-risk SMM and MGUS.

Generally, only patients with **active** myeloma require treatment with myeloma drugs.

WHAT FACTORS ARE CONSIDERED IN DEVELOPING A TREATMENT PLAN FOR ACTIVE MYELOMA?

There is no one standard treatment for myeloma. Each patient's treatment plan is based on a number of factors specific to him or her (**Figure 2**).

Figure 2. Your personal treatment plan: partnering with your health care team.

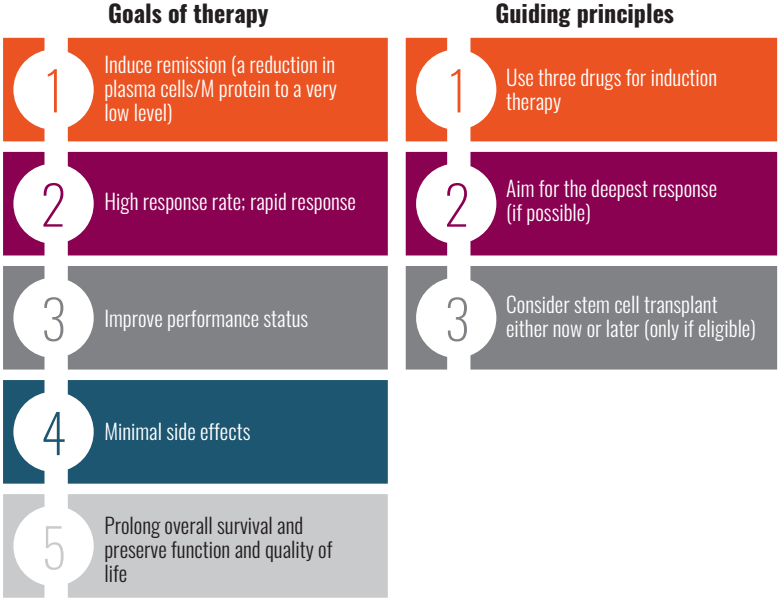
When a diagnosis of multiple myeloma is made, it is extremely important for the patient to commit to partnering with the doctor and the health care team to review all the patient-specific factors of the disease and determine what treatment will work best. The patient should also share his or her treatment goals. Depending on the characteristics of the disease and the patient's wishes, treatment plans may be designed to meet one or more goals.

And remember: in the **MMRF**, you have an advocate by your side—one who is an expert on all things myeloma, who is committed to helping you get the care and support you need, and who understands what you're going through.

GOALS OF MYELOMA THERAPY

Patients with active myeloma usually receive treatment aimed at reducing—or at least providing relief from—symptoms and reducing the number of myeloma cells in the bone marrow, which is determined by measuring the level of M protein in the blood. Achieving a response as quickly as possible—keeping safety in mind—is also a priority (**Figure 3**). The guiding principles for treatment include using a three-drug combination regimen as initial therapy (also called **induction** or **frontline therapy**), aiming for as deep a treatment response as possible (reducing plasma cells and M protein to a very low level), and considering a **stem cell** transplant, consolidation, or **maintenance therapy**. These principles are described later in this booklet.

Figure 3. Goals and guiding principles of myeloma therapy.



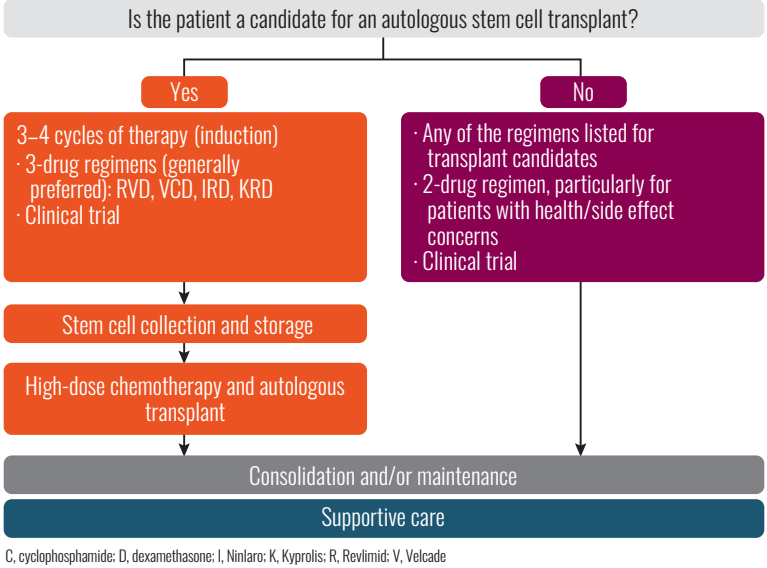
Patients should know that if one regimen stops working, another one can be used. There are many choices available today—and treatments continue to improve.

INDUCTION THERAPY OPTIONS

The choice of a patient's initial treatment depends on many factors. These include the features of the myeloma itself, the anticipated risk of **adverse events**, convenience for the patient, and the familiarity of the doctor with the given regimen. One of the first questions that must be answered, by both the patient and the doctor, is whether the patient is a candidate for **autologous stem cell transplantation** (ASCT).

Determining whether ASCT is an option is an important factor in selecting induction therapy (**Figure 4**).

Figure 4. Treatment approach for newly diagnosed myeloma.



C, cyclophosphamide; D, dexamethasone; I, Ninlaro; K, Kyprolis; R, Revlimid; V, Velcade

Patients who are candidates for ASCT may choose to have a transplant after three or four cycles of induction therapy, or they may decide to complete their induction therapy and consider transplant later. Depending on the response to induction therapy and/or the cell transplant, maintenance therapy—a stage of treatment designed to preserve a patient's response to a previous therapy—may be an option.

The length of therapy varies for patients who do not undergo ASCT. Clinical trials that address the most appropriate duration of therapy are still ongoing. In the meantime, some doctors recommend continuous treatment until there is evidence of myeloma progression, whereas others recommend treatment for a fixed period of time, generally until the treatment response reaches a plateau (a stabilization of the M protein levels). The specific characteristics of a patient's myeloma, as well as his or her preferences and the doctor's perspective, are other considerations that influence how long a therapy is given.

For 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.

Key questions to ask your health care team when preparing for induction therapy.

- What treatment options should I consider? What are the treatment choices? What are the risks and benefits of each?
- What can I do to prepare for treatment?
- How will treatment affect my normal routine?
- What lab values and test results are important to track for a response or to monitor for side effects?
- Is there a clinical trial that might be better suited for my type of myeloma or prognosis?
- Can I bank my bone marrow for clinical research?*
- What resources are available for me and my family?
- What is the best way to get in touch with you for questions or emergencies?

*Tissue banking may not be an option at some oncology offices

Myeloma treatments consist of combinations of two drugs (doublets) or three drugs (triplets). Generally, triplets are preferred, though doublets are of value in cases where side effects are of particular concern.

Four-drug combinations have also been studied. The challenge with these regimens is their greater potential for side effects. Research is ongoing to determine the best balance of effectiveness and tolerability.

Clinical trials are another option that patients should discuss with their doctors.

The two drugs that make up the backbone of most doublets and triplets are Revlimid and Velcade.

REVLIMID

Revlimid (lenalidomide) is an **immunomodulatory drug (IMiD)**. It is approved by the FDA for multiple myeloma patients with newly diagnosed or **relapsed/refractory disease** (patients who have recurrence of myeloma after a response to therapy or who have progressed during therapy). Also, it is approved for use as maintenance therapy following ASCT (**Figure 5**).

Figure 5. Revlimid (lenalidomide).

Current indications*	How is Revlimid administered?	What are the possible side effects?
• For newly diagnosed myeloma in combination with dexamethasone • For relapsed/refractory myeloma in combination with dexamethasone • As maintenance therapy following ASCT *Black box warnings: • Embryo-fetal toxicity; Revlimid is available only through a restricted distribution program. • Hematologic toxicity • Venous and arterial thromboembolism	• Oral capsule • For relapsed/refractory or newly diagnosed myeloma: 25 mg once taken once daily for 21 days out of a 28-day cycle (3 weeks on, 1 week off) • For myeloma maintenance therapy: 10 mg once daily continuously for 28 days of repeated 28-day cycles	• Potential for blood clots • Reduced blood counts • Rash • Fatigue • Muscle pain or muscle cramping • Diarrhea • Small chance of second new cancers when given with melphalan

Revlimid is given orally and is usually taken once a day.

Fatigue is a common side effect of Revlimid that can sometimes be managed by adjusting the dose.

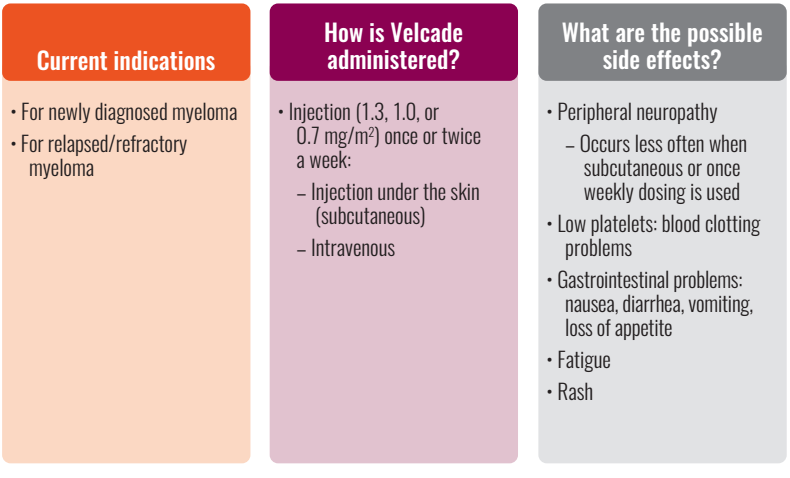
Revlimid can also decrease blood counts. When this occurs, medications like **growth factors** are sometimes given to bring the blood counts up. Some patients develop a rash when taking Revlimid, sometimes (though not frequently) to an extent where it is necessary for them to stop taking the drug.

Also, Revlimid can increase the risk of blood clots, which is why every patient prescribed Revlimid has to also take, at the very least, a baby aspirin daily to prevent blood clots. Patients who have other blood clotting risk factors (for example, having previously developed a blood clot or being sedentary) might need to take something stronger than aspirin, such as Lovenox or an oral or injectable blood thinner.

VELCADE

Velcade (bortezomib) was the first **proteasome inhibitor** to be approved by the FDA for multiple myeloma patients with newly diagnosed and relapsed/refractory disease (**Figure 6**).

Figure 6. Velcade (bortezomib).



Velcade can be given either **intravenously** or as an injection under the skin. Its most common side effects are gastrointestinal symptoms (for example, nausea or diarrhea) but are usually mild. Velcade can lower the platelet count, but the effect does not usually last long. Rash and fatigue also sometime occur in patients taking Velcade, but these symptoms are less common.

The most significant side effect of Velcade is peripheral **neuropathy**, which is damage to the peripheral nerves that can produce numbness, tingling, and in some cases pain in the arms, legs, and feet that can become disabling. Patients experiencing these symptoms must notify their doctors, as adjusting the dose can prevent the neuropathy from getting worse.

More details on the adverse events of therapy can be found in the companion brochure *Disease Overview*.

TRIPLET REGIMENS

Because they involve combinations of three myeloma drugs, triplet regimens offer the promise of greater effectiveness—though at the potential cost of an increased risk of side effects.

Triplets include:

- Revlimid–Velcade–dexamethasone (RVD): most commonly used
  - Revlimid combined with Velcade and a drug called dexamethasone 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 myeloma.
- Velcade–cyclophosphamide–dexamethasone (VCD or CyBorD)
  - High response rates and rapid responses have been seen in clinical trials with the combination of Velcade, cyclophosphamide, and dexamethasone.

DOUBLET REGIMENS

Two-drug combinations are often used in cases where minimizing the risk of side effects is a particularly important consideration.

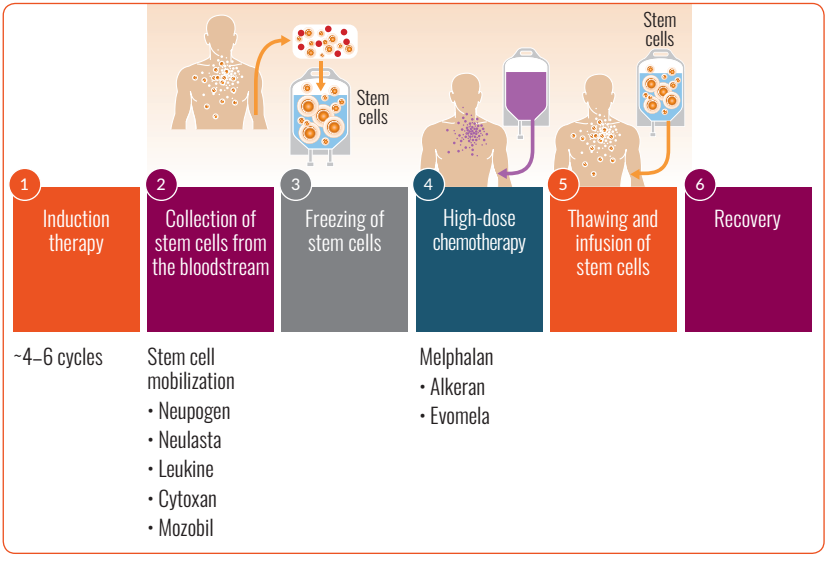
Doublets include:

- Revlimid–dexamethasone (Rd)
  - The effectiveness of Revlimid and low-dose dexamethasone is well established in a late-stage (**Phase 3**) clinical trial.
- Velcade–dexamethasone (Vd)
  - The effectiveness of Velcade combined with dexamethasone as initial therapy was demonstrated in two large Phase 3 trials. Importantly, this combination was shown to be effective in patients with both normal-risk and high-risk disease.

HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION

High-dose chemotherapy (usually melphalan) with ASCT is a treatment that, for many eligible myeloma patients, offers the best chance for long-lasting remission. High-dose chemotherapy, though effective in killing myeloma cells, also destroys normal blood-forming cells (called hematopoietic stem cells) in the bone marrow. Stem cell transplantation replaces these important cells (**Figure 7**). Results of this approach to myeloma therapy have improved with the release of several newer drugs.

Figure 7. ASCT.



STEM CELL COLLECTION AND INFUSION

Stem cells are normally found in the bone marrow and in the peripheral blood (blood in the arteries or veins). Virtually all transplants in myeloma are now obtained from the patient's own peripheral blood and are referred to as autologous **peripheral blood stem cell (PBSC)** transplants. Bone marrow transplants are rarely done in multiple myeloma.

Stem cells are collected after approximately four cycles of induction therapy to ensure that the number of myeloma cells in the body is reduced. Drugs 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** (for example, Neupogen, Neulasta, and Leukine) 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. This is the most common type of transplant for myeloma, as there are fewer complications than with transplants from a donor.
- **Allogeneic transplants**: stem cells collected from a matched donor (usually a relative). This type of transplant is unusual today because of the high risk of complications, though it does offer beneficial effects against the myeloma. This procedure is experimental and thus should only be performed in a clinical trial. A **mini (non-myeloablative) allogeneic transplant** uses somewhat lower doses of chemotherapy to make the transplant safer.

TRANSPLANTATION SIDE EFFECTS

There are several common side effects associated with high-dose chemotherapy and transplantation (**Figure 8**).

Figure 8. Side effects of high-dose chemotherapy.

Fatigue	• Expected • May last 1–3 months
Nausea & vomiting	• Symptoms much more manageable with newer antiemetics • Try to prevent nausea
Diarrhea	• May include stomach cramping • Encourage small amounts of food, more often • Avoid milk, milk products, high-fiber foods
Mucositis	• Pain, sores in mouth; sore throat • Pain meds, mouth swishes • Avoid tart, acidic, salty, spicy foods • Soft food better tolerated
Low blood counts	• White blood cells drop to zero, raising infection risk • **Prophylactic antimicrobials** • Hemoglobin and platelets will drop • Transfusion with blood/platelets • Counts begin to recover 10–12 days after chemotherapy

Also, because 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 damage to the lungs, liver, and kidneys.

CANDIDATES FOR STEM CELL TRANSPLANTATION

More patients are considered to be candidates for transplant today than in the past. A patient's suitability for transplant is based on his or her age and overall health. Guidelines for patient eligibility may vary between cancer centers.

Ask your doctor if you are eligible for transplantation. Patients who are eligible should carefully discuss the benefits and risks of transplantation with their doctors.

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. A European study compared early transplant (right after induction) to late transplant (after relapse) and showed that patients who got an early transplant tended to have a longer time in remission than did those who got a late transplant. This result does not mean that all patients necessarily live longer after receiving an early transplant; however, those who did receive an early transplant were able to maintain their low disease status or remission without progressing for a longer time than the patients who received a late transplant. For now, early transplantation (for suitable candidates) remains a standard therapy and may offer the best chance for a long-lasting remission.

Clinical trials in the US are ongoing to more accurately determine the advantages of early transplant. For any individual patient, the potential toxicities associated with transplantation must be balanced with the potential benefits.

All patients who are eligible for transplantation are encouraged to have stem cells obtained (harvested) so that the cells are available if the patient chooses to undergo transplantation at some point during the course of their disease.

Questions to ask your doctor about stem cell transplantation.

- Am I a candidate for high-dose chemotherapy and stem cell transplantation?
- When is the best time for me to undergo transplantation?
- Does your center do stem cell transplants? How many transplants has your center performed in multiple myeloma in the last year? Is procedure performed as an inpatient or outpatient?
- How long will I be in the hospital?
- What kind of changes in my lifestyle will I need to make?
- When do I go back to you for follow-up?

MAINTENANCE (OR CONTINUOUS) THERAPY

Myeloma is not yet curable, so it can 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 induction therapy or after transplantation.

Several Phase 3 trials indicate that Revlimid provides significant benefits following transplant. This finding is the basis for the FDA's approval of Revlimid as maintenance therapy in patients following ASCT. Revlimid is given until disease progresses or the patient experiences unacceptable toxicity.

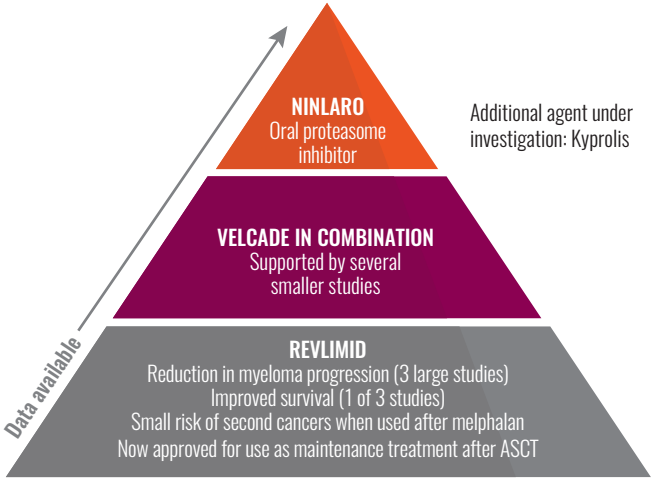
- In a US study, survival was longer in patients who received Revlimid. This is the first study to show a survival benefit with Revlimid maintenance therapy.
- In a French trial, the risk of a patient's disease progressing after transplantation was reduced by half in patients receiving Revlimid compared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

In both studies, low blood counts were commonly seen with Revlimid maintenance. If blood counts get too low, it may be necessary to reduce the dose. Overall, more severe side effects were seen with Revlimid than with placebo. A small increase in second cancers, likely related to maintenance therapy and any subsequent doses of melphalan, was seen in all of these studies, but the current consensus among researchers is that the benefits likely outweigh the risks for most patients.

Additionally, several smaller (**Phase 2**) trials show that maintenance therapy with Velcade can also improve outcomes. Some doctors recommend maintenance therapy with Velcade for patients with high-risk myeloma or those who cannot tolerate Revlimid.

Although more data are needed to determine if there is a consistent survival benefit of maintenance therapy, the improvement seen in the length of time patients stay in remission has prompted many doctors to discuss the option of maintenance therapy with their patients (**Figure 9**).

Figure 9. Maintenance therapy options.



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

HOW DO I KNOW IF A TREATMENT IS WORKING?

During and after treatment, doctors monitor symptoms and may also perform some of the same tests that were done when the patient was initially diagnosed with myeloma. The results of these tests show how well the treatment is working and may detect side effects. These tests also help determine if, after an initial response to treatment, the myeloma relapses.

The outcome of treatment in myeloma is defined using very specific standards or criteria (**Table 1**).

Table 1. Measuring response to myeloma therapy.

		Tests					
		M protein reduction		Bone marrow			
Response type	Abbreviation	Blood	Urine	Immuno-fixation	Plasma cells	Immuno-fluorescence	Freelite ratio
Stringent complete response	sCR	0	0	Negative	0	Negative	Normal
Complete response	CR	0	0	Negative	<5%	—	—
Very good partial response	VGPR	≥90%	<100 mg/ 24 hrs	—	—	—	—
Partial response	PR	≥50%	≥90%	—	—	—	—
Minimal response	MR	≥25–49%	50–89%	—	—	—	—
Stable disease	SD	Does not meet criteria for response or progressive disease					
Progressive disease	PD	An increase of 25% (and 0.5 g/dL) in M protein; an increase of 10% in bone marrow plasma cells					

Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

For newly diagnosed myeloma patients the goal of treatment is typically a **very good partial response** or better. That is, there is no (or only a very small amount of) M protein detectable in the blood or urine. Luckily, with the treatments that are available today, more and more patients are achieving a complete response.

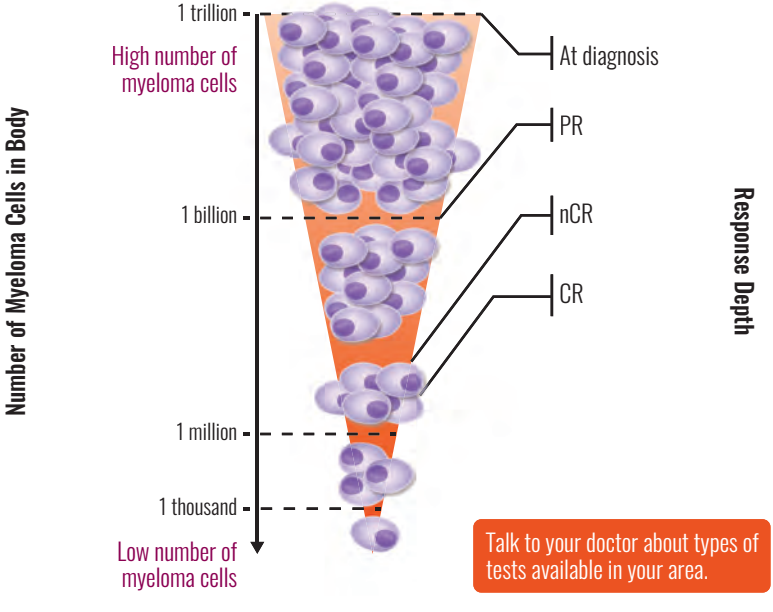
IS REMISSION THE SAME AS RESPONSE?

When talking about cancer, remission typically means that there is a complete or partial disappearance of 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**.

WHAT IS MINIMAL RESIDUAL DISEASE (MRD)?

Treatment advances have increased the likelihood that a patient will achieve a complete response. However, achieving a complete response does not eliminate all myeloma in the body. Some myeloma cells can remain in the body; this is called **minimal residual disease** (MRD), and it can cause a relapse (**Figure 10**).

Figure 10. Minimal residual disease (MRD).



Conventional blood tests are not sensitive enough to detect these remaining cells, but this is changing. MRD measurement aims to detect any myeloma cells that remain in the body after a complete response is achieved.

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. MRD monitoring is only just beginning to be adopted in cancer centers. Tests include:

- Flow cytometry, which measures the number and characteristics of cells taken from a **bone marrow biopsy**. It is the most common test used in the US.
- Molecular tests, which are newer technologies that evaluate the **DNA** of myeloma cells and can detect very low numbers of cells.

Clinical trials continue to study MRD and various methods for detecting it.

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

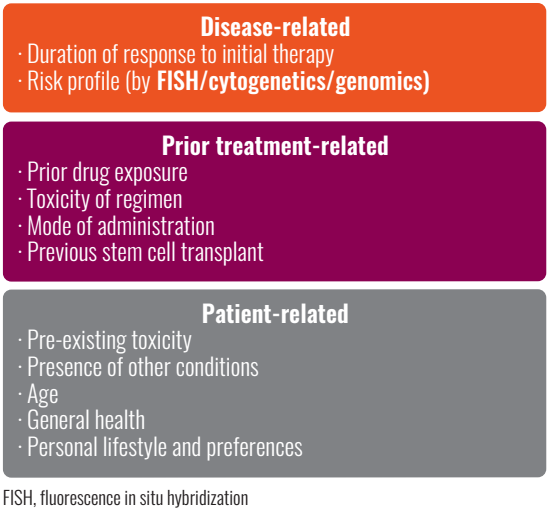
As with newly diagnosed patients, patients who relapse and/or become refractory to therapy have benefited from the availability of novel agents. There are a number of treatments available (**Figure 11**), which include molecularly targeted and immunotherapeutic agents. In some cases, older treatments (such as Thalomid, Doxil, and older chemotherapies) may be appropriate, particularly for patients not responding to other agents.

Figure 11. FDA-approved anti-myeloma agents.

Immunomodulatory drugs	Revlimid (lenalidomide)	Pomalyst (pomalidomide)	
Proteasome inhibitors	Velcade (bortezomib)	Kyprolis (carfilzomib)	Ninlaro (ixazomib)
Chemotherapy alkylators	Cytoxan (cyclophosphamide)	Melphalan	
Steroids	Dexamenthasone	Prednisone	
HDAC inhibitors	Farydak (panobinostat)		
Monoclonal antibodies	Empliciti (elotuzumab)	Darzalex (daratumumab)	

In patients with myeloma that has relapsed or is refractory to treatment, several factors need to be taken into account to select a regimen that balances effectiveness and the risk of toxicity (**Figure 12**).

Figure 12. Factors to consider in choosing therapy for relapsed/refractory myeloma.



FISH, fluorescence in situ hybridization

Many treatments are available for relapsed or refractory myeloma, and many potential new drugs are currently being studied. If myeloma does not respond to induction therapy, or if relapse occurs soon after induction therapy is completed, the myeloma is considered to be refractory. However, patients who are refractory to a particular drug may respond if the drug is used in combination with other myeloma medications.

Treatment options include:

- Any myeloma drug that has not been previously used
- A different combination of myeloma medications (which can include a previously used drug)
- Stem cell transplant (if appropriate)
- Participation in a clinical trial

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

REVLIMID AND VELCADE REGIMENS

Treatment regimens in which Revlimid is combined with Velcade and dexamethasone (RVD) may be options depending on whether patients received them previously and how they responded.

Combining current and new drugs in development with the treatment regimens based around Revlimid or Velcade is continually being evaluated in clinical trials.

PROTEASOME INHIBITORS

Proteasome inhibitors slow myeloma cell growth and kill myeloma cells by interfering with processes that play a role in cell function.

Kyprolis

Kyprolis (carfilzomib) is approved for patients with relapsed/refractory myeloma (**Figure 13**).

Figure 13. Kyprolis (carfilzomib).

Current indications	How is Kyprolis administered?	What are the possible side effects?
• For relapsed/refractory myeloma alone or in combination with dexamethasone or with Revlimid plus dexamethasone	• Intravenous injection • Given on two consecutive days each week for three weeks followed by a 12-day rest period	• Fatigue • Anemia • Nausea • Low platelet count • Shortness of breath • Diarrhea • Fever • Hypertension • Cardiac symptoms

The benefit of Kyprolis alone in patients with relapsed or refractory disease was shown in a Phase 2 study. Although patient responses to Kyprolis given alone were good, myeloma specialists often prefer to use Kyprolis in combination (with Revlimid or dexamethasone) to improve effectiveness.

Common side effects of Kyprolis include reductions in some blood cell counts, nausea, diarrhea, shortness of breath, fever, headache, and infections. The incidence of peripheral neuropathy was notably low (14% of patients) in the Phase 2 study; when it occurred, it tended to be mild.

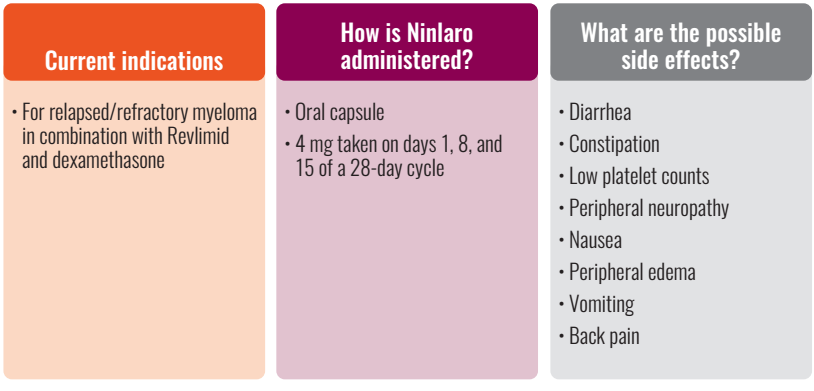
Although uncommon, there is a risk of cardiovascular side effects with Kyprolis, including congestive heart failure. Patients with heart conditions are evaluated to determine whether Kyprolis is an appropriate treatment. Patients with any heart problems taking Kyprolis are monitored closely by their doctors.

Studies are ongoing to evaluate Kyprolis in combination with other myeloma drugs and to assess its potential for use in additional types of patients.

Ninlaro

Ninlaro (ixazomib) is the first oral proteasome inhibitor approved for patients with relapsed/refractory myeloma (**Figure 14**).

Figure 14. Ninlaro (ixazomib).



Ninlaro plus Revlimid: A regimen of Ninlaro, Revlimid, and dexamethasone was compared to Revlimid and dexamethasone in a Phase 3 trial. On average, patients receiving Ninlaro in combination with Revlimid and dexamethasone lived significantly longer without their disease worsening compared to patients receiving Revlimid and dexamethasone. Responses also lasted longer in the group receiving Ninlaro.

The most common side effects include gastrointestinal effects (diarrhea, constipation, nausea, or vomiting), **thrombocytopenia**, peripheral neuropathy, **peripheral edema**, and back pain. The most common serious side effects were thrombocytopenia and diarrhea.

Ninlaro is being evaluated in Phase 3 trials in newly diagnosed myeloma in combination with Revlimid and dexamethasone and as maintenance therapy.

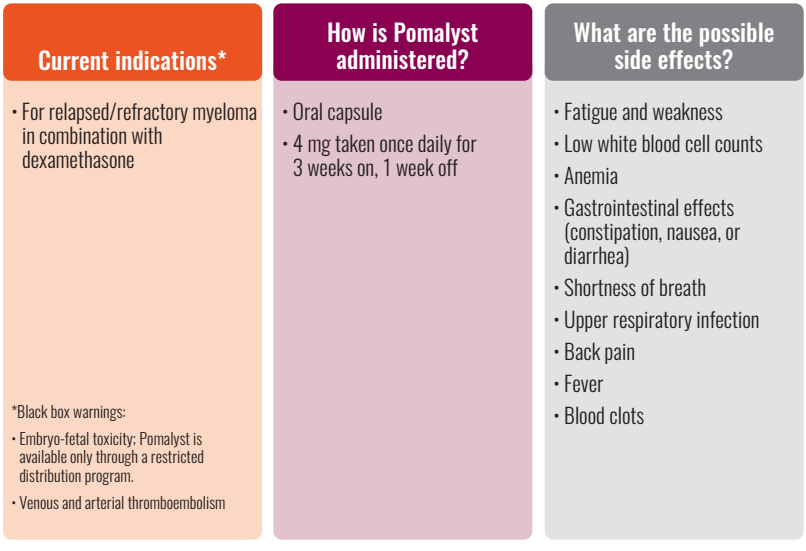
IMMUNOMODULATORY DRUGS (IMiDs)

The drug listed below is in the same class as Revlimid.

Pomalyst

Pomalyst (pomalidomide) is more potent than Revlimid (**Figure 15**) and is approved for patients with relapsed/refractory myeloma.

Figure 15. Pomalyst (pomalidomide).



Pomalyst plus low-dose dexamethasone: Phase 2 and 3 studies showed that patients responded to Pomalyst even when they had previously received both Velcade and Revlimid.

Side effects vary by patient and are considered manageable. The most common 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 with Pomalyst.

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

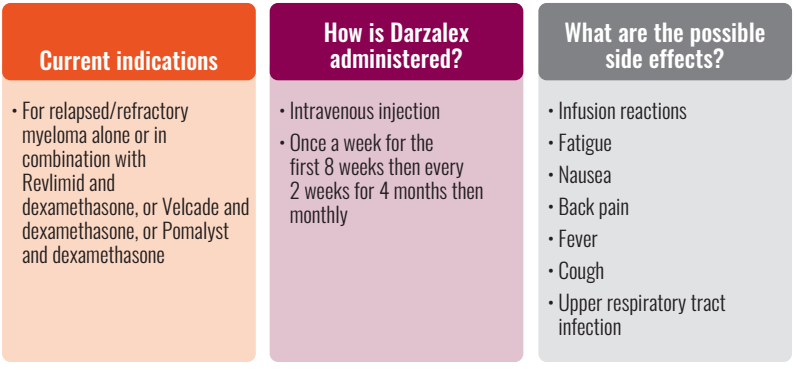
MONOCLONAL ANTIBODIES

Monoclonal antibodies can kill myeloma cells by targeting myeloma cell surface proteins.

Darzalex

Darzalex (daratumumab) is the first monoclonal antibody approved for use in patients with relapsed/refractory myeloma (**Figure 16**).

Figure 16. Darzalex (daratumumab).



Darzalex alone: Darzalex was evaluated in a Phase 2 trial with relapsed or refractory myeloma patients who had received an average of five prior therapies. Approximately one third of the patients responded and the responses lasted an average of 7 months.

Darzalex plus Revlimid and dexamethasone or Velcade and dexamethasone: In two Phase 3 studies, these combinations reduced the risk of disease progression or death in over 60% of patients compared to the combinations without Darzalex.

Darzalex plus Pomalyst and dexamethasone: Fifty-nine percent of patients responded to the combination of Darzalex with Pomalyst.

The most common side effects included fatigue, low **red blood cell** and platelet counts, and nausea. Some patients in clinical trials experienced **infusion reactions** (shakes and shivers while receiving the drug). For this reason, patients receive medications before and after administration of Darzalex to reduce the risk of these reactions.

Darzalex is being evaluated in combination with other agents in newly diagnosed disease and earlier-stage disease.

Empliciti

Empliciti (elotuzumab) is approved for multiple myeloma patients with relapsed/refractory disease (**Figure 17**).

Figure 17. Empliciti (elotuzumab).

Current indications	How is Empliciti administered?	What are the possible side effects?
• For relapsed/refractory myeloma in combination with Revlimid and dexamethasone	• Intravenous injection • Once a week for the first 8 weeks then every 2 weeks	• Fatigue • Diarrhea • Fever • Constipation • Cough • Peripheral neuropathy • Infusion reactions • Nasopharyngitis • Upper respiratory tract infection • Decreased appetite • Pneumonia • Small chance of second new cancer

Empliciti plus Revlimid and dexamethasone: This combination was compared to Revlimid and dexamethasone in a Phase 3 trial. The three-drug regimen reduced the risk of disease progression or death by 30% compared to Revlimid and dexamethasone.

The most common side effects included fatigue, diarrhea, fever, constipation, cough, infection of the nose and throat (nasopharyngitis), upper respiratory tract infection, pneumonia, peripheral neuropathy, and decreased appetite.

A combination of Empliciti, Revlimid, and dexamethasone is being evaluated in a Phase 3 trial in newly diagnosed myeloma.

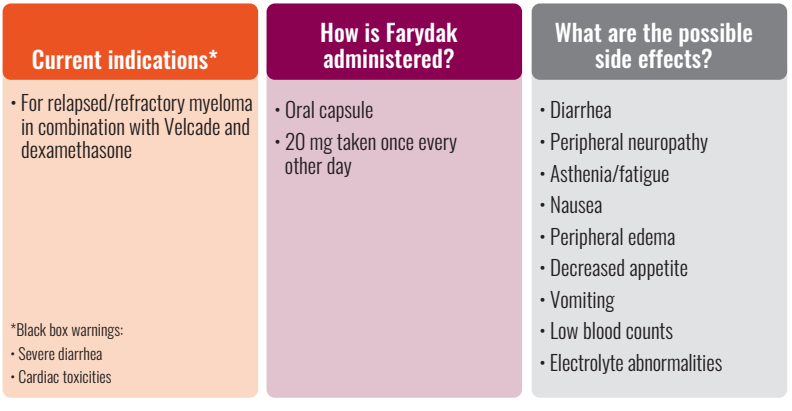
HISTONE DEACETYLASE INHIBITORS

Histone deacetylase (HDAC) inhibitors work at the DNA level to help slow the growth of multiple myeloma cells.

Farydak

Farydak (panobinostat) is the first approved myeloma therapy from this class of drugs (**Figure 18**).

Figure 18. Farydak (panobinostat).



EKG, electrocardiogram

Farydak plus Velcade and dexamethasone: This combination was compared to Velcade and dexamethasone in a Phase 3 trial. Of the patients in the trial who had previously received at least two prior therapies that included both Velcade and an IMiD, those who received Farydak saw a four month-delay in the return of their disease.

The most common side effects included reductions in **platelets**, **white blood cell**, and red blood cell counts, as well as diarrhea, peripheral neuropathy, and fatigue.

IMMUNO-ONCOLOGY IN MULTIPLE MYELOMA

Cancer **immunotherapy** is a rapidly evolving field in multiple myeloma. There has been growing recognition of the role played by the suppression of the immune system that occurs in myeloma—indeed, the most common cause of death among myeloma patients is infection. Restoring the immune protection lost to myeloma is believed to be an important potential pathway to new levels of treatment success, and the addition of monoclonal antibodies (Empliciti and Darzalex) to the myeloma drug list has been an important step in that direction. Several other immunotherapeutic agents and approaches are in clinical development.

Monoclonal Antibodies

Antibody therapy is the use of injected antibodies to attack the myeloma cells in the body. Empliciti and Darzalex are two monoclonal antibodies that are currently in common use as myeloma drugs, and others that are currently approved for other cancers are actively being studied as potential myeloma treatments. Several different types of antibodies are used in antibody therapy, and each type uses a different approach to attack myeloma

CAR-T Cells and Other Immune Cell–Based Approaches

Immune cell therapy is the process of extracting a patient's own immune cells, engineering them in a lab to be better able to identify and attack myeloma cells, and then returning them to the patient.

Several immune cell therapies are being investigated as possible myeloma treatments. They are experimental, however, and thus far have only been studied in a small number of patients. Early (**Phase 1**) clinical trials have shown promising efficacy, with many patients achieving a complete response.

Vaccines

Vaccine therapy is a new myeloma management strategy that has recently received greater attention for patients undergoing ASCT. During the recovery period after the transplant, the patient receives vaccines that prime his or her immune system to more quickly and more powerfully attack myeloma cells if the disease recurs. Studies of this treatment are ongoing.

SHOULD I PARTICIPATE IN A CLINICAL TRIAL?

Clinical trials are essential to the development of new myeloma treatments, providing new therapeutic options for myeloma patients at all stages of the disease. The greater the number of people there are enrolling in clinical trials, the faster new treatments can be made available to patients. It is only through patient participation in clinical trials that we have achieved the high number and various types of myeloma treatments available today.

Patients who enroll in clinical trials have the opportunity to be amongst the first to receive the newest drugs and therapies in development—before they are available commercially.

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 people, evidence of activity against the disease must have been demonstrated in laboratory and animal studies—these are called ***preclinical studies***.

In all myeloma clinical trials, participants receive the experimental therapy being tested or the best available standard treatment.

Clinical trials take place in different stages, with each phase serving a distinct purpose (**Table 2**).

Table 2. Clinical trial stages.

	Phase 1	Phase 2*	Phase 3†
Objectives	Optimal dose Side effects Metabolism	Preliminary effectiveness Additional safety	Definitive effectiveness and safety
Treatment	Single arm (all patients receive experimental therapy)	Single arm Two arms of different treatments or doses: patients randomly assigned to an arm	Two arms: patients randomly assigned to receive experimental therapy or standard therapy
Study size	Small (<50)	Varies	>200

*When no standard treatment is available, FDA may approve drugs based on trial results

†Conducted to receive FDA approval of new drugs, in most cases

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 a patient enrolls, all details of the treatment are explained and the patient must consent to participate. Patients who agree to participate in a clinical trial are free to withdraw at any time.

Most research foundations fund research but don't actually conduct research. But the Multiple Myeloma Research Consortium (MMRC)—a sister organization to the MMRF—actually does research. The MMRC is a unique collaboration of 25 centers in the United States and Canada. The MMRC evaluates new agents and drug combinations for their safety, efficacy, and feasibility in Phase 1 and 2 clinical trials.

FINDING A CLINICAL TRIAL

The MMRF Patient Support Center 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 MMRF Nurse Patient Navigator at our Patient Support Center, who will ask you questions and talk to you about clinical trials in your area or ones that may be appropriate for you.

How do I find a clinical trial?

1. Ask your treating hematologist or oncologist about any available trials
2. Check with any academic medical centers close to your home
3. Search for a clinical trial in your area, or let an MMRF Nurse Patient Navigator help guide you through the process at themmrf.org/trialfinder

WHAT ARE 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.

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

For more detailed information about emerging agents and other advances in myeloma, visit the MMRF's website www.themmrf.org or call 866.603.MMCT (6628).

The MMRF would like to thank Faith E. Davies, MBBCh, MRCP, MD, FRCPath, Professor of Medicine and Medical Director of the Myeloma Institute Little Rock at the University of Arkansas for Medical Sciences in Little Rock, Arkansas, and our patient advocates Allan and Deb Osborne of Millis, Massachusetts and Cindy Chmielewski of Lawrenceville, New Jersey, for their contributions to this brochure.

MMRF PATIENT SUPPORT AND RESOURCES

The MMRF is dedicated to supporting the myeloma community by providing a broad range of resources for myeloma patients and their family members and caregivers. The MMRF is available to help guide you through your multiple myeloma journey every step of the way.

YOUR QUESTIONS ANSWERED

Speak to an MMRF Nurse Patient Navigator at the Patient Support Center 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 A CLINICAL TRIAL

Search for a clinical trial in your area or let MMRF Nurse Patient Navigators help guide you through the process.

Clinical Trial Search: themmrf.org/trialfinder

SUPPORT THE MMRF

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

Telephone: 1.203.229.0464
Donate now/Take action:
Visit www.themmrf.org

TRANSPLANT RESOURCES

Blood & Marrow Transplant Information Network
Visit www.bmtinfonet.org

National Bone Marrow Transplant
Visit www.nbmtlink.org/

BMT Support Online
Visit www.bmtsupport.org

Bone Marrow Foundation
Visit www.bonemarrow.org

REIMBURSEMENT ASSISTANCE PROGRAMS

Patient Access Network

www.panfoundation.org
Services: Help and hope to people with chronic or life-threatening illnesses for whom cost limits access to critical medical treatments
Phone: 1-866-316-PANF (1-866-316-7263)
Email: contact@panfoundation.org

Amgen Inc

Product: Neupogen/Neulasta/Kyprolis
Website: www.amgenassist360.com
Services: Insurance verification, co-pay and reimbursement assistance
Phone: 1-888-427-7478

Bristol-Myers Squibb

Product: Empliciti
Website: http://www.bmsaccesssupport.bmscustomerconnect.com/
Services: Financial help
Phone: 1-800-861-0048

Celgene

Products: Pomalyst/Revlimid/Thalomid
Website: www.celgenepatientsupport.com
Services: Financial help, understanding your insurance, starting your medication, forms and resources
Phone: 1-800-931-8691

Janssen

Product: Darzalex
Website: https://www.janssencarepath.com
Phone: 1-877-227-3728

Novartis

Products: Zometa/Farydak
Website: www.patientassistancenow.com
Phone: 1-800-245-5356

Takeda Oncology Company

Product: Velcade
Website:www.velcade.com/Paying-for-treatment
Phone: 1-866-835-2233, Option 2

Product: Ninlaro
Website: www.ninlaro.com/1point
Phone: Ninlaro 1Point: 1-844-N1POINT (1-844-617-6468), Option 2

GLOSSARY

active myeloma Multiple myeloma in which the percentage of plasma cells in the bone marrow is greater than 10% and in which the patient shows one or more CRAB symptoms (see definition at *CRAB*)

adverse event (AE) Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs after a medical treatment or procedure; AEs may or may not be related to the treatment or procedure

allogeneic transplant Procedure in which stem cells collected from another person are transplanted into a patient

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*; see also *monoclonal antibody*)

antiemetic Drug that prevents or relieves nausea and vomiting

antimicrobial Drug that kills or slows the growth of bacteria

autologous stem cell transplant (ASCT) Procedure in which stem cells collected from a patient are transplanted back into that patient; the most common type of transplant performed in myeloma.

bisphosphonate Type of drug used to treat osteoporosis and bone disease

bone marrow Soft, spongy tissue found in the center of many bones and site of blood cell production

bone marrow biopsy Removal of a sample of bone marrow for examination; performed using a needle

chromosome Thread-like structure in a living cell that contains DNA (genetic information)

clinical trial A study of the safety and effectiveness of a therapeutic agent using consenting human subjects

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

complete response (CR) A treatment outcome in which the level of plasma cells in the bone marrow is no more than 5%, there is no evidence of myeloma proteins in the serum or urine as measured by standard laboratory techniques, and all signs and symptoms of cancer have disappeared (though cancer still may be in the body); also called *complete remission*

CRAB Acronym for the following group of clinical indicators of organ damage: increased calcium level, renal (kidney) failure, anemia, bone lesions; the presence of one or more of these indicators can help establish a diagnosis of multiple myeloma

cytogenetics The number and structure of chromosomes in cells

DNA Genetic material of the cell located in the chromosomes

fluorescence in situ hybridization (FISH) Laboratory technique used to measure the number of copies of a specific DNA segment in a cell and the structure of chromosomes

frontline therapy Initial treatment given to a newly diagnosed patient (also known as *induction therapy, first-line therapy*, or *frontline treatment*)

growth factor Substance that stimulates cells to multiply

genomics Study of DNA sequences of myeloma cells to detect mutations and to see how DNA changes over time

histone deacetylase (HDAC) inhibitors Drugs that work at the DNA level to help slow the growth of multiple myeloma cells; example includes Farydak

immunoglobulin (Ig) Protein that helps protect the body from infection (also called antibody)

immunomodulatory drugs (IMiDs) Drugs that fight cancer by altering the function of the immune system; examples include Thalomid, Revlimid, and Pomalyst

immunotherapy Prevention or treatment of disease with drugs that stimulate the immune system

induction therapy The first treatment a patient receives for myeloma; also refers to the use of anti-myeloma drugs prior to high-dose chemotherapy and stem cell transplant (see also *frontline therapy*)

infusion reaction Symptoms that sometimes develop after a patient receives intravenous drugs; commonly include chills, fever, nausea, weakness, headache, skin rash, and/or itching; although rare, severe reactions such as difficulty breathing or low blood pressure can occur

intravenous (IV) Administration of a drug directly into a vein

maintenance therapy Treatment that is given to patients in remission over a long period of time to reduce the risk of relapse

mini (non-myeloablative) allogeneic transplant Allogeneic (cells from a donor [either a sibling or a non-family member]) transplant combined with high-dose chemotherapy

minimal residual disease (MRD) Presence of small numbers of myeloma cells in the bone marrow during or after treatment, even when the patient shows no symptoms or signs of disease

mobilization The process of stimulating stem cell growth to ensure that enough stem cells can be collected for transplantation

monoclonal antibody Antibody produced in a laboratory that is used to diagnose and treat some diseases

monoclonal gammopathy of undetermined significance (MGUS) A condition that can occur before a patient develops or shows any symptoms of cancer; indicated by the presence of M protein in the serum or urine, MGUS may eventually progress to myeloma

monoclonal (M) protein Abnormal antibody found in large quantities in the blood and urine of individuals with myeloma

neuropathy Disorder of the nerves that can disrupt sensation or cause burning/tingling; when the hands and feet are affected, it is referred to as *peripheral neuropathy*

osteopenia Decreased bone density

osteoporosis Bone loss typically associated with old age; can occur in myeloma

partial response (PR) Treatment outcome where there is a greater than 50% decrease in M protein and disappearance of some (but not all) signs and symptoms of cancer; also referred to as *partial remission*

peripheral blood stem cell (PBSC) Stem cells collected from the blood

peripheral edema Abnormally large amount of fluid in the circulatory system or in tissues

Phase 1 The first round of clinical trial, conducted with a small number of participants to assess the drug's safety and dosage levels

Phase 2 The second stage of a clinical trial, conducted with a larger number of participants to assess the drug's effectiveness and further evaluate its safety

Phase 3 The most advanced stage of drug development, conducted with a large number of participants to confirm the drug's effectiveness, identify and monitor its side effects, compare it to commonly used treatments, and collect information that will allow the drug to be used safely; usually required for FDA approval of drugs

placebo Drug or treatment that is designed to look like the medicine being tested but that does not have the active ingredient; rarely used in cancer treatment trials

plasma cell Antibody-secreting immune cell that develops from a B cell; in myeloma, it is this cell that has become cancerous or abnormal

platelets Small cell fragments in the blood that help it to clot

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

preclinical studies Experiments conducted in the laboratory and in animals to identify a target for therapy and to confirm its anticancer activity

prognosis Prediction of the course and outcome of a disease

prophylactic Preventing the spread or occurrence of infection

proteasome inhibitors Drugs that slow myeloma cell growth and kill myeloma cells by interfering with processes that play a role in cell function; examples include Velcade, Ninlaro, and Kyprolis

red blood cell Blood cell that carries oxygen

refractory disease Myeloma that progresses during therapy

relapsed disease Myeloma that progresses after initially responding to therapy

smoldering multiple myeloma (SMM) Myeloma characterized by M protein and slightly increased numbers of plasma cells in the bone marrow and an absence of symptoms; patients with SMM are monitored and only treated if their disease progresses; about 5% of myeloma patients have SMM

stem cell Cell that grows and divides to produce red blood cells, white blood cells, and platelets; found in bone marrow and blood

stringent complete response A treatment outcome in which there are no detectable abnormal plasma cells in the bone marrow or M protein in the serum or urine and in which free light chain ratio test is normal

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

very good partial response (VGPR) Treatment outcome in which there is a greater than 90% decrease in M protein; also known as *very good partial remission*

white blood cell One of the major cell types in the blood; attacks infection and cancer cells as part of the immune system



MMRF RESOURCES
IN PERSON OR ONLINE

Attend a Multiple Myeloma Patient Summit

Learn about standard and emerging therapies including stem cell transplants, promising clinical trials, and more for optimal disease management. Attend a complimentary symposium for all the information you need to make well-informed decisions about your treatment and care.

To register, view past summits and the complete calendar, visit:
themmrf.org/patient

View Past Programs on Demand

Access our archive of recorded Patient Summit symposia and webcasts. Hear expert perspectives on key clinical research and the rapidly evolving myeloma treatment landscape.

All available online, and free, at:
themmrf.org/education

Find a Clinical Trial Near You

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, the faster we can find answers. Patients who enroll in clinical trials have the opportunity to be among the first to receive the newest drugs or drug combinations in development and receive close monitoring.

To find a clinical trial near you, visit:
themmrf.org/trialfinder

Contact one of our
Patient Nurse Navigators at
the Patient Support Center

866-603-MMCT (6628)

Hours: **Mon-Fri, 9am-7pm ET**

Email: **patientnavigator@themmrf.org**

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