MULTIPLE MYELOMA
TREATMENT
OVERVIEW

themmrf.org
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 11 new drugs in the past 15 years, 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.

To speak to a Nurse Patient Navigator at the Patient Navigation Center, call 1-888-841-MMRF (6673) or email patientnavigator@themmrf.org.

Updates to and distribution of this booklet was supported by Adaptive Biotechnologies, Celgene, CURE Magazine, and Takeda Oncology.
## CONTENTS

INTRODUCTION ................................................................. 3
WHO GETS TREATED? ......................................................... 4
WHAT FACTORS ARE CONSIDERED IN DEVELOPING A TREATMENT PLAN FOR ACTIVE MYELOMA? .................. 5
GOALS OF MYELOMA THERAPY ........................................... 6
INDUCTION THERAPY OPTIONS ........................................... 7

Revlimid ................................................................. 9
Velcade ............................................................... 10
Triplet Regimens ...................................................... 11

HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION ............................................. 12

Stem Cell Collection and Infusion ......................................... 13
Transplantation Side Effects .............................................. 14
Candidates for Stem Cell Transplantation ................................. 14
The Evolving Role of Transplantation in Myeloma ......................... 15

MAINTENANCE (OR CONTINUOUS) THERAPY ......................... 16

HOW DO I KNOW IF A TREATMENT IS WORKING? ................. 17
Is Remission the Same as Response? ..................................... 19
What Is Minimal Residual Disease (MRD)? ............................... 19

WHAT ARE MY OPTIONS IF I RELAPSE OR IF I DON’T RESPOND TO THERAPY? .................................................. 21

Revlimid and Velcade Regimens ........................................... 23

Proteasome Inhibitors ...................................................... 24

Kyprolis ............................................................... 24
Ninlaro. ............................................................. 25

Immunomodulatory Drugs (IMiDs). ....................................... 26

Pomalyst ............................................................. 26

Monoclonal Antibodies .................................................... 27
Darzalex .................................................. 27
Empliciti .................................................. 28
Novel Mechanisms of Action .......................... 29
Farydak ..................................................... 29
XPOVIO ................................................... 30
Immuno-Oncology in Multiple Myeloma ............. 31
Monoclonal Antibodies ................................ 31
CAR-T Cells and Other Immune Cell–Based Approaches .... 32
Vaccines .................................................... 32
SHOULD I PARTICIPATE IN A CLINICAL TRIAL? .... 33
Finding a Clinical Trial .................................. 35
What Are the Most Promising Agents in Clinical Trials? ....... 35
MMRF PATIENT SUPPORT AND RESOURCES ......... 37
TRANSPLANT RESOURCES .......................... 38
REIMBURSEMENT ASSISTANCE PROGRAMS .......... 38
GLOSSARY ................................................ 40
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 40).

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 booklet *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. A phase 3 clinical trial has shown that treatment with Revlimid 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.

Your overall health and characteristics of your myeloma
• Age and general health
• Other conditions
• Test results
• Symptoms

Your preferences and personal goals
• Eliminate vs control disease
• Willingness to tolerate side effects
• Symptom relief
• Personal lifestyle/situation

No one treatment plan is right for everyone.

When a diagnosis of multiple myeloma is made, it is extremely important for the patient to commit to partnering with his or her 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, or either consolidation or maintenance therapy. These principles are described later in this booklet.

Figure 3. Goals and guiding principles of myeloma therapy.

<table>
<thead>
<tr>
<th>Goals of therapy</th>
<th>Guiding principles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Induce remission (a reduction in plasma cells/M protein to a very low level)</td>
<td>1. Use three drugs for induction therapy</td>
</tr>
<tr>
<td>2. Produce a high response rate: rapid response</td>
<td>2. Aim for the deepest response</td>
</tr>
<tr>
<td>3. Improve patient’s daily functioning</td>
<td>3. Consider stem cell transplant either now or later (if eligible)</td>
</tr>
<tr>
<td>4. Lessen the impact of side effects</td>
<td></td>
</tr>
<tr>
<td>5. Prolong overall survival and preserve function and quality of life</td>
<td></td>
</tr>
</tbody>
</table>

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 (see the section below on **MAINTENANCE [OR CONTINUOUS] THERAPY**) 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?
- What resources are available for me and my family?
- What is the best way to get in touch with you for questions or emergencies?
- Can I bank my bone marrow for research?*

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

Myeloma treatments consist of three-drug combinations (triplets). Generally, triplets are preferred, though doublets (two-drug combinations) may be considered in cases where side effects are of particular concern.

Four-drug combinations have also been studied, particularly for patients with high-risk disease. 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.

Revlimid and/or Velcade plus a steroid (typically dexamethasone) is the backbone of most combination therapies.

**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).**

<table>
<thead>
<tr>
<th>Current indications*</th>
<th>How is Revlimid administered?</th>
<th>What are the possible side effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For newly diagnosed myeloma in combination with dexamethasone</td>
<td>• Oral capsule</td>
<td>• Potential for blood clots</td>
</tr>
<tr>
<td>• For relapsed/refractory myeloma in combination with dexamethasone</td>
<td>- For relapsed/refractory or newly diagnosed myeloma: 25 mg once daily for 21 days out of a 28-day cycle (3 weeks on, 1 week off)</td>
<td>• Reduced blood counts</td>
</tr>
<tr>
<td>• As maintenance therapy following ASCT</td>
<td>• For myeloma maintenance therapy: 10 mg once daily continuously for 28 days of repeated 28-day cycles</td>
<td>• Rash</td>
</tr>
</tbody>
</table>

*Black box warnings:*
• Embryo-fetal toxicity: Revlimid is available only through a restricted distribution program
• Hematologic toxicity
• Venous and arterial thromboembolism

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).

<table>
<thead>
<tr>
<th>Current indications</th>
<th>How is Velcade administered?</th>
<th>What are the possible side effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For newly diagnosed myeloma</td>
<td>• 1.3, 1.0, or 0.7 mg/m² once or twice a week:</td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td>• For relapsed/refractory myeloma</td>
<td>– Injection under the skin (subcutaneous)</td>
<td>– Occurs less often when subcutaneous or once weekly dosing is used</td>
</tr>
<tr>
<td></td>
<td>– Intravenous</td>
<td>• Low platelets: blood clotting problems</td>
</tr>
</tbody>
</table>

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 these 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 booklet Multiple Myeloma 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.

- Kyprolis–Revlimid–dexamethasone (KRD) is another triplet used based on available clinical trial data and guidelines suggesting that it is appropriate for use as induction therapy.

- 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.

- Darzalex–Revlimid–dexamethasone (Darzalex-RD)
  - For patients who are not eligible for ASCT, the Darzalex-RD triplet resulted in high response rates.
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.

1. Induction therapy
2. Collection of stem cells from the bloodstream
3. Freezing of stem cells
4. High-dose chemotherapy
5. Thawing and infusion of stem cells
6. Recovery

- Days -2 to -3 weeks*
- Days +1 to +100†

*The weeks leading up to the transplant.
†The days after the transplant.

- 4–6 cycles
- Stem cell mobilization
  - Neupogen
  - Neulasta
  - Leukine
  - Cytoxan
  - Mozobil
- Melphalan
  - Alkeran
  - Evomela
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.

In the weeks leading up to the transplant, 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.

ASCT can be performed as an inpatient (the patient stays in the hospital before, during, and immediately after the transplant) or an outpatient (the patient makes daily visits to a clinic) procedure. ASCT has a long recovery process.
**TRANSPARTION SIDE EFFECTS**

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

*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 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.

Three phase 3 trials indicate that Revlimid (at 10 mg a day) 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.

An analysis of the data from all three studies demonstrated that patients receiving Revlimid maintenance live longer than those receiving a placebo. Additionally, low blood counts are commonly seen with Revlimid maintenance. If blood counts get too low, it may be necessary to reduce the dose. Overall, more severe side effects are seen with Revlimid than with placebo. A small increase in second cancers (such as acute myeloid leukemia or various solid tumors), likely related to maintenance therapy and any subsequent doses of melphalan, was seen in all trials, but the current consensus among most 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.

Ninlaro, an oral drug in the same class as Velcade, was studied as maintenance therapy for patients following ASCT in a phase 3 trial. The results showed that more patients lived longer without disease progression on Ninlaro maintenance therapy (as compared to patients who received no maintenance therapy); additionally, Ninlaro maintenance helped to deepen the treatment response. It is possible that Ninlaro could be a suitable alternative to Revlimid, as some patients are unable to tolerate Revlimid for an extended time.
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.

**Revlimid**
- Reduction in myeloma progression (3 large studies)
- Improved survival (1 of 3 studies, meta-analysis)
- Increased risk of second cancers when used after melphalan
- Approved for use as maintenance treatment after ASCT

**Velcade-based treatment**
- Supported by several smaller studies

**Ninlaro**
- Oral proteasome inhibitor
- Reduction in myeloma progression (1 large study)

**Additional agents under investigation: Kyprolis, Darzalex, Empliciti**

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.

<table>
<thead>
<tr>
<th>Response type</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained minimal residual disease (MRD)-negative</td>
<td>• MRD negativity in the bone marrow and by imaging—confirmed minimum of 1 year apart</td>
</tr>
<tr>
<td>MRD negative</td>
<td>• Absence of clonal plasma cells in bone marrow samples by one of two methodologies:</td>
</tr>
<tr>
<td></td>
<td>○ Next-generation flow (NGF) (for example, flow MRD negative), or</td>
</tr>
<tr>
<td></td>
<td>○ Next-generation sequencing (NGS) (for example, sequencing MRD negative)</td>
</tr>
<tr>
<td></td>
<td>• MRD negativity as defined by NGF or NGS plus disappearance of every area of lesions found at baseline found by positron emission tomography (PET)/computed tomography (CT) imaging (for example, imaging plus MRD negative)</td>
</tr>
<tr>
<td>Stringent complete response (sCR)</td>
<td>• A CR plus normal Freelite and absence of clonal cells in bone marrow by immunohistochemistry</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>• Negative immunofixation on serum and urine</td>
</tr>
<tr>
<td></td>
<td>• Disappearance of any soft tissue plasmacytomas</td>
</tr>
<tr>
<td></td>
<td>• &lt;5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>• Serum and urine M protein detectable by immunofixation (but not on electrophoresis), or</td>
</tr>
<tr>
<td></td>
<td>• ≥90% reduction in serum M protein plus urine M protein level to &lt;100 mg per 24 h</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>• ≥50% reduction in serum M protein plus urine M protein level to &lt;200 mg per 24 h (or reduction in 24-hour urinary M protein by ≥90%)</td>
</tr>
<tr>
<td>Minimal response (MR)</td>
<td>• ≥25% but ≤49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>• Does not meet criteria for response or progressive disease</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>• An increase of 25% in M protein</td>
</tr>
<tr>
<td></td>
<td>• An increase of 10% in bone marrow plasma cells</td>
</tr>
</tbody>
</table>

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).**

Talk to your doctor about types of tests available in your area.
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.

With today’s therapies, more patients are achieving CR. However, achieving a CR does not always predict long-term survival, and most patients ultimately relapse. Relapse occurs as a result of the persistence of MRD after treatment. The interest in the assessment of MRD is growing, because evidence suggests that having no MRD detectable after treatment is a predictor of better clinical outcomes for patients.

An FDA-approved molecular test called the clonoSEQ assay is available to detect and monitor MRD in bone marrow samples from patients with myeloma. Results of MRD testing leads to one of two outcomes:

- MRD positive or MRD positivity (MRD+) means that myeloma cells are still detectable in the sample.
- MRD negative or MRD negativity (MRD-) means that myeloma cells are not detected in the sample. Clinical trials have shown that patients who achieve MRD negativity following treatment experience longer time without disease recurrence than those who are still MRD positive after treatment.

The extent of MRD positivity or negativity depends on the MRD test used and how sensitive it is in detecting myeloma cells in the sample (for example, one myeloma cell out of 100,000 normal cells or one myeloma cell out of 1,000,000 normal cells).
Currently, measurement of MRD depends on detecting myeloma cells in samples from the blood or bone marrow and not other areas of the body. Therefore, imaging (for example PET scan or CT scan) is also required to detect MRD outside of the blood or bone marrow. Also, it may be premature to base treatment decisions on the results of MRD testing; for example, it is unclear whether patients who are MRD positive should get more treatment or if patients who are MRD negative no longer need treatment. Also, some patients may never achieve MRD negativity and continue to survive.

Clinical trials continue to study MRD and various methods for detecting it. The MMRF is working with the myeloma community and the FDA to use MRD as an end point in clinical trials. If approved, MRD assessment will enable the health care team to determine—earlier than is possible with currently available tests—when a patient relapses. It could also shorten the amount of time a patient is on a clinical trial if a patient’s response can be determined earlier and more accurately using MRD assessment.

**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.
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.**

**Disease-related**
- Duration of response to initial therapy
- Risk profile (by FISH/cytogenetics/genomics)

**Prior treatment-related**
- Prior drug exposure
- Toxicity of regimen
- Mode of administration
- Previous stem cell transplant

**Patient-related**
- Pre-existing toxicity
- Presence of other conditions
- Age
- General health
- Personal lifestyle and preferences

FISH, fluorescence in situ hybridization

Republished with permission of American Society of Hematology, from Relapsed multiple myeloma, Lonial S, *Hematology Am Soc Hematol Educ Program* 2010;2010; permission conveyed through Copyright Clearance Center, Inc.
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**
  - For relapsed/refractory myeloma alone or in combination with dexamethasone or with Revlimid plus dexamethasone

- **How is Kyprolis administered?**
  - Intravenously
  - Once weekly or twice weekly as a 10- or 30-minute infusion

- **What are the possible side effects?**
  - 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).**

- **Current indications**
  - For relapsed/refractory myeloma in combination with Revlimid and dexamethasone

- **How is Ninlaro administered?**
  - Oral capsule
  - 4 mg taken on days 1, 8, and 15 of a 28-day cycle

- **What are the possible side effects?**
  - Diarrhea
  - Constipation
  - Low platelet counts
  - Peripheral neuropathy
  - Nausea
  - Peripheral edema
  - Vomiting
  - Back pain

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).

<table>
<thead>
<tr>
<th>Current indications*</th>
<th>How is Pomalyst administered?</th>
<th>What are the possible side effects?</th>
</tr>
</thead>
</table>
| • For relapsed/refractory myeloma in combination with dexamethasone, or Darzalex and dexamethasone, or Empliciti and dexamethasone | • Oral capsule  
• 4 mg taken once daily for 3 weeks on, 1 week off | • Fatigue and weakness  
• Low white blood cell counts  
• Anemia  
• Gastrointestinal effects (constipation, nausea, or diarrhea)  
• Shortness of breath  
• Upper respiratory infection  
• Back pain  
• Fever  
• Blood clots |

*Black box warnings:

• Embryo-fetal toxicity; Pomalyst is available only through a restricted distribution program

• Venous and arterial thromboembolism

Phase 2 and 3 studies showed that patients responded to the combination of Pomalyst and low-dose dexamethasone 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, 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.

Pomalyst has been approved for use in combination with dexamethasone and certain monoclonal antibodies as a treatment for some myeloma patients.

Numerous clinical trials are continuing to evaluate the use of 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 newly diagnosed myeloma who are not eligible for ASCT and those with relapsed/refractory myeloma (**Figure 16**).

**Figure 16. Darzalex (daratumumab).**

<table>
<thead>
<tr>
<th><strong>Current indications</strong></th>
<th><strong>How is Darzalex administered?</strong></th>
<th><strong>What are the possible side effects?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• For newly diagnosed myeloma patients who are ineligible for ASCT, in combination with Revlimid and dexamethasone or Velcade, melphalan, and prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For relapsed/refractory myeloma alone or in combination with Revlimid and dexamethasone, or Velcade and dexamethasone, or Pomalyst and dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intravenous injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Once a week for the first 8 weeks then every 2 weeks for 4 months, then monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– The first prescribed dose may be split over 2 consecutive days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Infusion reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Back pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In relapsed/refractory myeloma patients:

- **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:** 59% of patients responded to the combination of Darzalex with Pomalyst.

In newly diagnosed myeloma patients who are ineligible for ASCT:

- **Darzalex plus Revlimid and dexamethasone:** A phase 3 trial showed that more patients responded to the combination with Darzalex and that this combination also reduced the risk of disease progression.
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.

A subcutaneous formulation of Darzalex is currently being investigated to ensure that its safety and efficacy are no different than the intravenous formulation.

Empliciti

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

Figure 17. Empliciti (elotuzumab).

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

Empliciti plus Revlimid and dexamethasone 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.

Empliciti, Pomalyst, and low-dose dexamethasone was compared to Pomalyst and low-dose dexamethasone, also in a phase 3 trial. The addition of Empliciti resulted in a 46% reduction in risk of disease progression or death compared to Pomalyst and low-dose dexamethasone alone.
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 patients with newly diagnosed myeloma.

**NOVEL MECHANISMS OF ACTION**

Drugs with a novel *mechanism of action* work in different ways than drugs in the other classes. Myeloma drugs with novel mechanisms of action target certain proteins involved in cell growth and division. These drugs may target proteins that are specific to myeloma cells or all cells.

**Farydak**

Farydak (panobinostat) is the first approved myeloma therapy from the histone deacetylase (HDAC) inhibitor class of drugs (Figure 18). HDAC inhibitors work at the DNA level to help slow the growth of multiple myeloma cells.

**Figure 18. Farydak (panobinostat).**

<table>
<thead>
<tr>
<th>Current indications*</th>
<th>How is Farydak administered?</th>
<th>What are the possible side effects?</th>
</tr>
</thead>
</table>
| • For relapsed/refractory myeloma in combination with Velcade and dexamethasone | • Oral capsule  
• 20 mg taken once every other day | • Diarrhea  
• Peripheral neuropathy  
• Asthenia/fatigue  
• Nausea  
• Peripheral edema  
• Decreased appetite  
• Vomiting  
• Low blood counts  
• Electrolyte abnormalities |

*Black box warnings:  
• Severe diarrhea  
• Cardiac toxicities

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 4-month delay in the return of their disease.

The most common side effects included gastrointestinal toxicities (nausea/vomiting, diarrhea, weight loss), low sodium levels, infections, and reductions in platelets, white blood cells, and red blood cells.

### XPOVIO

XPOVIO (selinexor) is the first in a new drug class called nuclear export inhibitors. XPOVIO targets—and disrupts the function of—a protein called XPO1, which ultimately leads to myeloma cell death. (Figure 19).

#### Figure 19. XPOVIO (selinexor).

<table>
<thead>
<tr>
<th>Current indications</th>
<th>How is Selinexor administered?</th>
<th>What are the possible side effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In combination with dexamethasone for relapsed/refractory myeloma patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody</td>
<td>• Oral tablet</td>
<td>• Low platelet count</td>
</tr>
<tr>
<td></td>
<td>• 80 mg taken twice a week</td>
<td>• Low white blood cell counts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreased appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreased weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low sodium levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Shortness of breath</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Upper respiratory infection</td>
</tr>
</tbody>
</table>

In a phase 2 trial of the combination of XPOVIO and dexamethasone, 25% of patients responded. These patients had received at least four prior antimyeloma treatment regimens and were refractory to at least two proteasome inhibitors, at least two immunomodulatory drugs, and an anti-CD38 monoclonal antibody.
In this study, the most common side effects with this combination included diarrhea, peripheral neuropathy, fatigue, and reductions in platelets, white blood cells, and red blood cells.

XPOVIO combined with Velcade and dexamethasone is being investigated in a phase 3 clinical trial in patients with relapsed/refractory myeloma.

**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.

Another type of antibody-based treatment uses a monoclonal antibody that is coupled to a cancer drug or a *toxin*; this type of agent is called an *antibody-drug conjugate*. The antibody part of the conjugate binds to a myeloma cell, and the attached cancer drug kills the myeloma cell.

Another antibody-based therapy is the *bispecific T-cell engager* (also known as a *BiTE*). BiTEs are made from two antibody fragments that have been fused together: one that targets myeloma cells (making them easier for the immune system to find) and another that helps immune cells (by boosting their ability to find myeloma cells).
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.

The companion booklet *Multiple Myeloma Immunotherapy* and the MMRF website (www.themmrf.org) provide more information about the different types of immunotherapy.
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.

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2*</th>
<th>Phase 3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>Optimal dose</td>
<td>Preliminary effectiveness</td>
</tr>
<tr>
<td></td>
<td>Side effects</td>
<td>Additional safety</td>
</tr>
<tr>
<td></td>
<td>Metabolism</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Single arm (all patients receive experimental therapy)</td>
<td>Single arm Two arms of different treatments or doses: patients randomly assigned to an arm</td>
</tr>
<tr>
<td>Study size</td>
<td>Small (&lt;50)</td>
<td>Varies</td>
</tr>
</tbody>
</table>

*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. 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 Navigation 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 888.841.MMRF (6673) to speak with a MMRF Nurse Patient Navigator, 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 888.841.MMRF (6673).

The MMRF would like to thank Jesus G. Berdeja, MD, Director of Multiple Myeloma Research and Senior Investigator, Hematologic Malignancies at the Sarah Cannon Research Institute in Nashville, Tennessee, and Faith E. Davies, MBBCh, MRCP, MD, FRCPath, Director of the Clinical Myeloma Program at the Perlmutter Cancer Center at New York University Langone Health in New York, New York, and our patient advocates Allan and Deb Osborne of Millis, Massachusetts, and Cindy Chmielewski of Lawrenceville, New Jersey, for their contributions to this booklet.
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 Navigation Center for answers to your questions about disease management, treatments, clinical trials, and assistance with finding financial and other available resources.

Telephone: 1.888.841.6673  
Monday—Friday, 9:00 AM to 7:00 PM 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 and Cancer 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: info@panfoundation.org

Amgen Inc
Product: Neupogen/Neulasta/Kyprolis/Xgeva
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

**Karyopharm**
*Product:* XPOVIO  
*Website:* www.karyforward.com  
*Phone:* 1-877-KARY4WD (1-877-527-9493)

**Janssen**
*Product:* Darzalex  
*Website:* https://www.janssencarepath.com  
*Phone:* 844-55DARZA

**Novartis**
*Products:* Zometa/Farydak  
*Website:* www.patientassistanceonnow.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-T1POINT (1-844-817-6468), 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)

**antibody-drug conjugate** A monoclonal antibody that is coupled to an anti-tumor drug (such as a toxin, a radioactive isotope, or a chemotherapy)

**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

**bispecific T-cell engager (BiTE)** An engineered anti-myeloma agent created by fusing two antibody fragments together; one antibody fragment binds to surface proteins on myeloma cells and the other binds to a protein found on the surface of immune cells

**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

colonies-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

end point The specific result that is being measured by a clinical trial

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

formulation The preparation of a drug

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.

**mechanism of action** The specific biochemical process through which a drug produces an effect on the body.

**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.
**next-generation flow** A highly sensitive test that uses bone marrow samples to detect minimal residual disease

**next-generation sequencing** A highly sensitive test that uses genomic assessment of bone marrow samples to detect minimal residual disease

**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 a clinical trial, conducted with a small number of participants to assess a drug’s safety and dosage levels

**phase 2** The second stage of a clinical trial, conducted with a larger number of participants to assess a 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 a 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 (sCR)  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

subcutaneous (SC)  Drug or treatment that is given under the skin

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

toxin  A poisonous substance

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
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 or to 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/patient

Find a Clinical Trial Near You

Clinical trials are critically important to developing new myeloma treatments and better understanding 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
Don’t miss out on the latest myeloma updates! Sign up today to receive all of our educational programming and myeloma news!

Name: 

Address: 

City: State: ZIP: 

Telephone: Mobile: 

Email: 

Or sign up at themmrf.org/connect

I AM A: (CHECK BOX)

☐ Patient  ☐ Patient Friend  
☐ Patient Spouse  ☐ Healthcare Professional  
☐ Patient Family  ☐ MMRF Supporter 

*Please tear off reply card and tape all three sides before mailing.
Contact one of our Patient Nurse Navigators at the Patient Navigation Center

1-888-841-MMRF (6673)

Hours: Mon–Fri, 9 AM–7 PM ET
Email: patientnavigator@themmrf.org