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. Their mission was to ensure more access to better treatments and bring the promise of a cure for every myeloma patient.

Since its founding, the MMRF has remained steadfast in the pursuit of its mission. It is now the leading cancer research organization focused on the development and delivery of more precise therapies, and it is aggressively pursuing a world without myeloma. Working with its partners in industry, research, government, and academia, the MMRF has helped launch 15 new drugs in the past 18 years, an achievement that has almost tripled the life expectancy for myeloma patients. The MMRF is a patient-focused organization that stands with the entire myeloma community and is speeding the discovery of cures through precision medicine. Driven by data and innovative research, the MMRF is committed to empowering every patient with 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 Patient Navigator at the Patient Navigation Center, call **1-888-841-MMRF (6673)** 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 39).

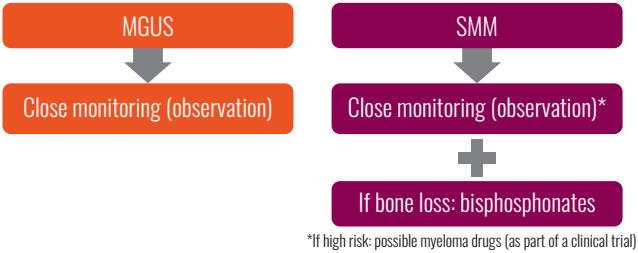
The information in this booklet is not intended to replace the services or advice of trained health professionals. Please consult with your health care professional or contact the MMRF Patient Navigation Center (1.888.841.6673) if you have specific questions relating to your health, especially questions 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.



Clinical trials are currently studying whether patients with high-risk SMM—that is, those who are at greater risk of progressing to active myeloma—do better when they receive earlier treatment and also what type of treatment is best. 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.

Furthermore, researchers are investigating ways to prevent active myeloma from developing in patients who have high-risk SMM. In particular, studies designed to identify these patients earlier in their disease course—such as the **PCROWD** and **PROMISE** studies—are under way. Data collected from these patients will help researchers identify clinical factors that may be associated with progression to active myeloma.

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 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. The Patient Navigation Center is available to answer 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

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.

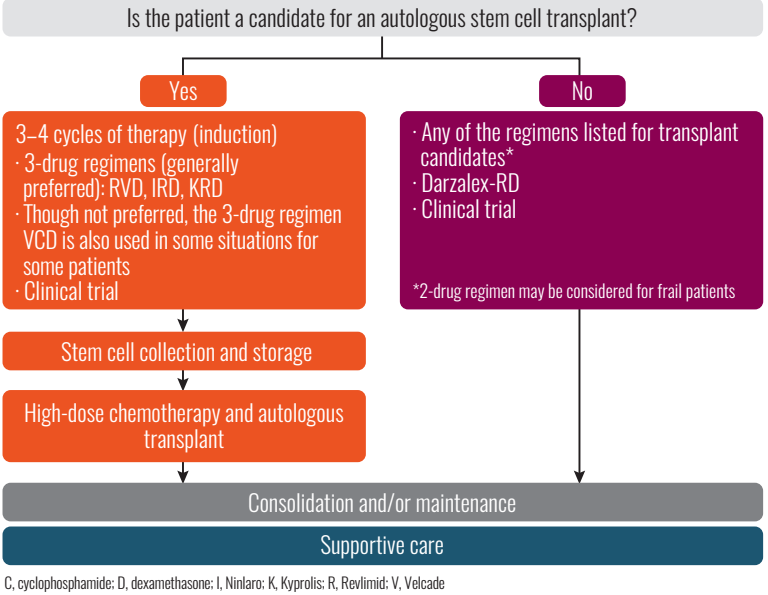
Patients should know that if one regimen stops working, another one can be used. There are many choices available today—and treatments continue to improve.

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).

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 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.

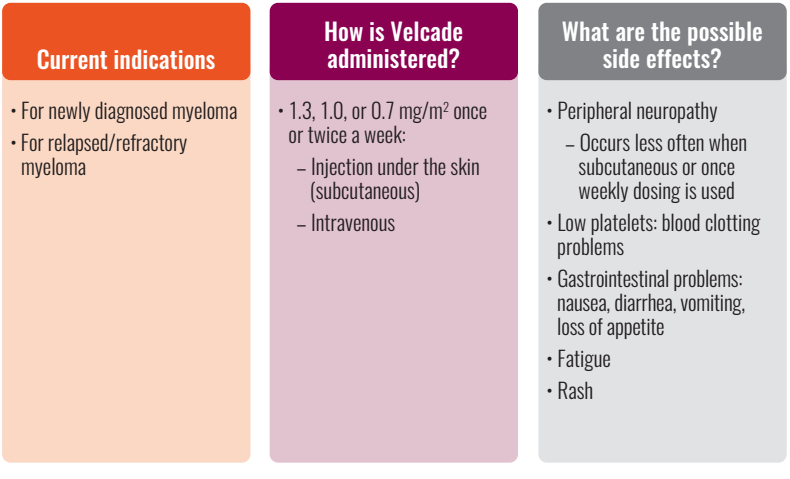
Revlimid can also decrease blood counts. When this occurs, medications like **growth factors** are sometimes given to bring the blood counts up. Some patients develop a rash when taking Revlimid, sometimes (though not frequently) to an extent where it is necessary for them to stop taking the drug.

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 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.

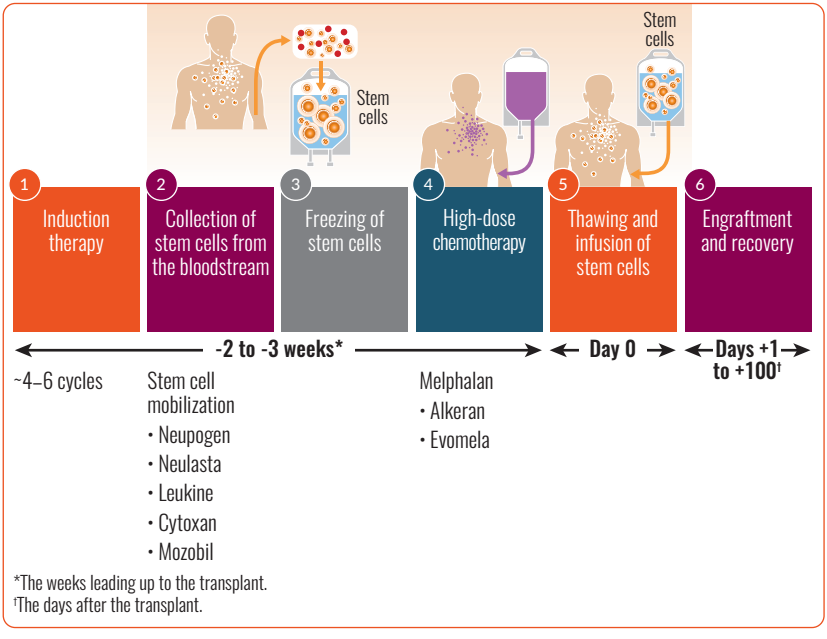
Triplets include:

- 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) and Ninlaro–Revlimid–dexamethasone (IRD) are two additional triplets used based on 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 this combination.
- 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 response. 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.



More details on the process of ASCT can be found in the companion booklet, *Autologous Stem Cell Transplantation*.

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.

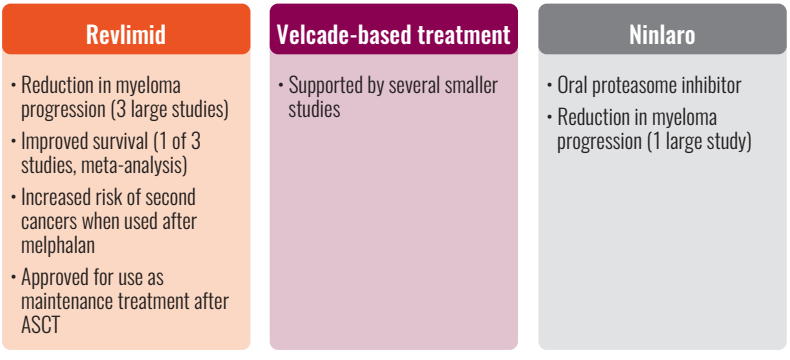
An analysis of the data from all three studies demonstrated that patients receiving Revlimid maintenance live longer than those receiving a **placebo**. Additionally, low blood counts are commonly seen with Revlimid maintenance. If blood counts get too low, it may be necessary to reduce the dose. Overall, 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 remain without relapse has prompted many doctors to discuss the option of maintenance therapy with their patients (**Figure 8**).

Figure 8. Maintenance therapy options.



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.

Response type	Response criteria
Sustained **minimal (measurable) residual disease** (MRD)-negative	• MRD negativity in the bone marrow and by imaging—confirmed minimum of 1 year apart

MRD negative	• Absence of clonal plasma cells in bone marrow samples by one of two methodologies:
	  ○ **Next-generation flow (NGF)** (for example, flow MRD negative), or
	  ○ **Next-generation sequencing (NGS)** (for example, sequencing MRD negative)
	• 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)

Stringent complete response (sCR)	• A CR plus normal Freelite and absence of clonal cells in bone marrow by immunohistochemistry
Complete response (CR)	• Negative immunofixation on serum and urine • Disappearance of any soft tissue plasmacytomas • <5% plasma cells in bone marrow
Very good partial response (VGPR)	• Serum and urine M protein detectable by immunofixation (but not on electrophoresis), or • ≥90% reduction in serum M protein plus urine M protein level to <100 mg per 24 h
Partial response (PR)	• ≥50% reduction in serum M protein plus urine M protein level to <200 mg per 24 h (or reduction in 24-hour urinary M protein by ≥90%)
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%
Stable disease (SD)	• Does not meet criteria for response or progressive disease
Progressive disease (PD)	• An increase of 25% in M protein • An increase of 10% in bone marrow plasma cells

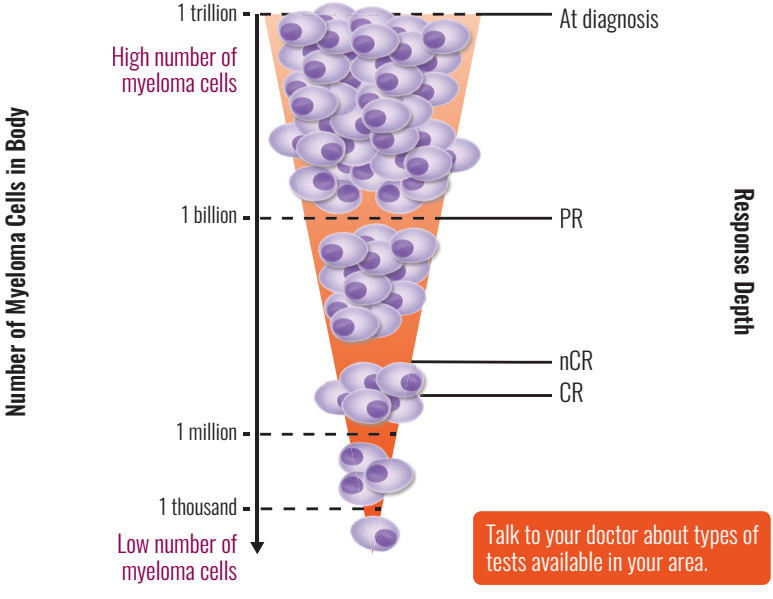
Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

For newly diagnosed myeloma patients the goal of treatment is typically a VGPR 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 CR.

WHAT IS MINIMAL (MEASURABLE) RESIDUAL DISEASE (MRD)?

Treatment advances have increased the likelihood that a patient will achieve a CR. However, achieving a CR does not eliminate all myeloma in the body. Some myeloma cells can remain in the body; this is called minimal (or measurable) residual disease (MRD), and it can cause a relapse (**Figure 9**).

Figure 9. Minimal (measurable) 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 CR 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 now being adopted in cancer centers, especially in clinical trials. Tests include:

- Flow cytometry tests such as NGF, which measure the number and characteristics of cells taken from a **bone marrow biopsy**. Flow cytometry is the most common test used in the US.

- Molecular tests such as NGS, which is a newer technology that evaluates the **DNA** of myeloma cells and can detect very low numbers of cells.

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 any myeloma cells that continue to be present 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 10**), 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.

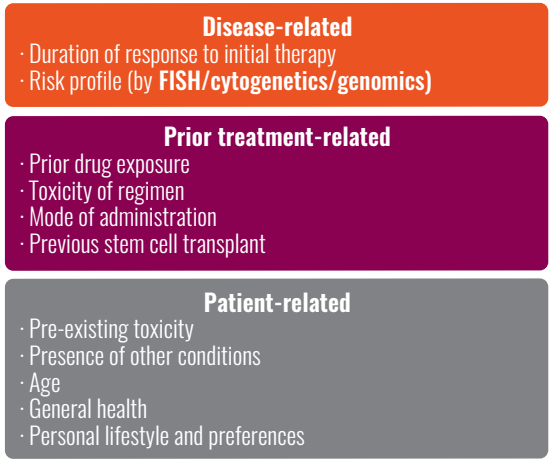
Figure 10. FDA-approved anti-myeloma agents.

Immunomodulatory drugs	Revlimid (lenalidomide)	Pomalyst (pomalidomide)		
Proteasome inhibitors	Velcade (bortezomib)	Kyprolis (carfilzomib)	Ninlaro (ixazomib)	
Chemotherapy alkylators	Cytoxan (cyclophosphamide)	Melphalan		
Steroids	Dexamethasone	Prednisone		
Monoclonal antibodies/ADCs	Empliciti (elotuzumab)	Darzalex (daratumumab)	Sarclisa (isatuximab)	Blenrep (belantamab mafodotin)*
Novel mechanisms of action	Farydak (panobinostat)	XPOVIO (selinexor)	PEPAXTO (melflufen)	
Cellular therapy	Abecma (idecabtagene vicleucel)			

*An antibody-drug conjugate

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 11**).

Figure 11. 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 12**).

Figure 12. 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 Revlimid and dexamethasone or Darzalex and dexamethasone	• Intravenously • Once weekly or twice weekly as a 10- or 30-minute infusion	• 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.

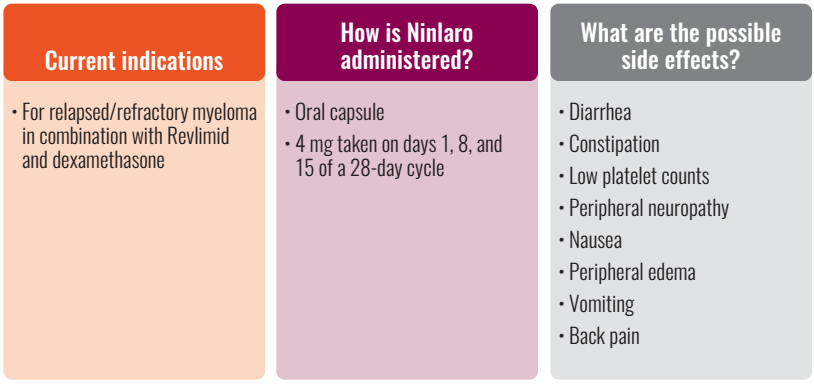
Although uncommon, there is a risk of cardiovascular side effects with Kyprolis, including congestive heart failure. Patients with heart conditions are evaluated to determine whether Kyprolis is an appropriate treatment. Patients with any heart problems taking Kyprolis are monitored closely by their 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 13**).

Figure 13. Ninlaro (ixazomib).



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 14**) and is approved for patients with relapsed/refractory myeloma.

Figure 14. Pomalyst (pomalidomide).

Current indications*	How is Pomalyst administered?	What are the possible side effects?
• For relapsed/refractory myeloma in combination with dexamethasone, or Darzalex and dexamethasone, or Empliciti and dexamethasone, or Sarclisa 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 15**).

Figure 15. Darzalex (daratumumab).

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

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.
- Darzalex plus Kyprolis and dexamethasone: In a phase 3 study, this combination reduced the risk of disease progression or death by 37%.

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.

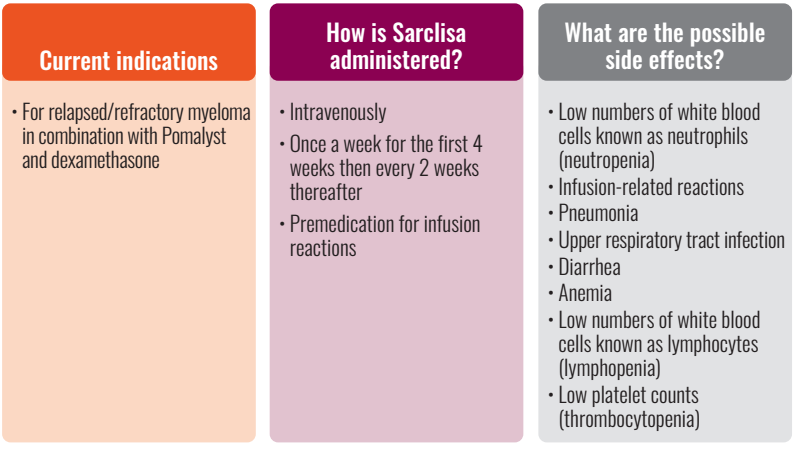
- The most common side effects included fatigue, low **red blood cell** and platelet counts, and nausea. Some patients in clinical trials experienced **infusion reactions** (chills and low-grade fever) while receiving the drug. For this reason, patients receive medications before and after administration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

A **subcutaneous formulation** of Darzalex—called Darzalex Faspro—has also been approved; its safety and efficacy are no different than the intravenous formulation. Darzalex Faspro is approved for use—in combination with Revlimid and dexamethasone or Velcade, melphalan, and prednisone—in newly diagnosed myeloma patients who are ineligible for ASCT. It is also approved for use—alone or in combination dexamethasone and either Revlimid or Velcade—in relapsed/refractory myeloma patients.

Sarclisa

Sarclisa (isatuximab) is approved for use—in combination with Pomalyst and dexamethasone—in multiple myeloma patients with relapsed/refractory disease who have received at least two previous lines of treatment including Revlimid and a proteasome inhibitor (**Figure 16**).

Figure 16 . Sarclisa (isatuximab).



A regimen of Sarclisa, Pomalyst, and dexamethasone was compared to Pomalyst and dexamethasone in a phase 3 trial. On average, patients receiving Sarclisa in combination with Pomalyst and dexamethasone lived significantly longer without their disease worsening than did patients receiving Pomalyst and dexamethasone.

The most common side effects included infusion-related reactions, pneumonia, diarrhea, and low blood counts.

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 or Pomalyst 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 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.

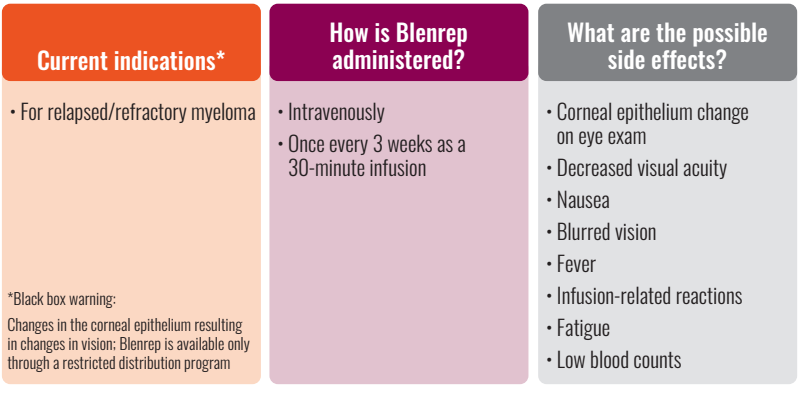
The most common side effects included fatigue, diarrhea, fever, constipation, cough, infection of the nose and throat (nasopharyngitis), upper respiratory tract infection, pneumonia, peripheral neuropathy, and decreased appetite.

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

Blenrep

Blenrep (belantamab mafodotin) is the first agent in a category called **antibody–drug conjugates (ADCs)** to be approved for multiple myeloma (**Figure 18**). ADCs use a monoclonal antibody that is coupled to a cancer drug or a **toxin** to fight cancer. Blenrep is the first monoclonal antibody to target the **B-cell maturation antigen (BCMA)** on myeloma cells.

Figure 18. Blenrep (belantamab mafadotin).



Blenrep is used for the treatment of patients with relapsed/refractory myeloma who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. In a phase 2 clinical trial, Blenrep used as therapy on its own was shown to be effective in patients who received at least four prior therapies. The most common side effects seen in the study included **keratopathy** (reversible changes to a part of the eye that resulted in vision changes), decreased **visual acuity**, nausea, blurred vision, fever, infusion-related reactions, and fatigue.

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 19**). HDAC inhibitors work at the DNA level to help slow the growth of multiple myeloma cells.

Figure 19. Farydak (panobinostat).

Current indications*	How is Farydak administered?	What are the possible side effects?
• 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 20**).

Figure 20. XPOVIO (selinexor).

Current indications	How is XPOVIO administered?	What are the possible side effects?
• 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 • In combination with Velcade and dexamethasone for patients who have received at least 1 prior therapy	• Oral tablet • 80 mg taken twice a week or 100 mg taken once a week	• Low platelet count • Low white blood cell counts • Fatigue • Anemia • Decreased appetite • Decreased weight • Diarrhea • Vomiting • Low sodium levels • Constipation • Shortness of breath • Upper respiratory infection

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.

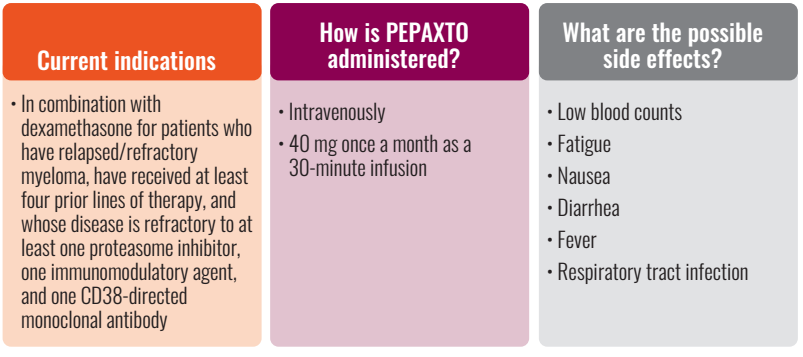
XPOVIO plus Velcade and dexamethasone was compared to Velcade and dexamethasone in a phase 3 trial. The three-drug regimen reduced the risk of disease progression or death by 30% compared to Velcade and dexamethasone.

The most common side effects included diarrhea, nausea and vomiting, fatigue, and reductions in platelets, white blood cells, and red blood cells.

PEPAXTO

PEPAXTO (melflufen) is the first in a new drug class, the peptide conjugates. PEPAXTO is taken in by the myeloma cell. Once inside, PEPAXTO releases a cytotoxic agent (melphalan), leading to myeloma cell death (**Figure 21**).

Figure 21. PEPAXTO (melflufen).



The efficacy of PEPAXTO was studied in a multicenter, single-arm trial in 157 patients with relapsed/refractory myeloma, 97 of whom were considered triple-class refractory (that is, patients who received treatment with—and did not respond satisfactorily to or progressed while on treatment with—the three main classes of drugs currently used to treat myeloma: proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies). Response to PEPAXTO treatment was seen in 24% of the triple-class–refractory patients.

The most common side effects included low blood counts, fatigue, nausea, diarrhea, fever, and respiratory tract infection.

CELLULAR THERAPY

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

Abecma

Abecma (idecabtagene vicleucel) is a first-in-class BCMA-directed personalized immunotherapy called **chimeric antigen receptor (CAR) T-cell therapy**. Abecma is manufactured using a patient's T cells that have been collected from his or her blood. The T cells are modified in a laboratory to recognize BCMA, a protein expressed on multiple myeloma cells. CAR T cells are then infused back into the patient and able to find and kill myeloma cells (**Figure 22**).

Figure 22. Abecma (idecabtagene vicleucel).

Current indications*	How is Abecma administered?	What are the possible side effects?
• For patients who have relapsed/refractory myeloma and have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent *Black box warnings: • Cytokine release syndrome • Neurologic toxicities • Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome • Prolonged cytopenia • Abecma is available only through a restricted distribution program	• Intravenously • One-time infusion of 300 to 460 × 10^6 CAR T-cells 2 days after completing lymphodepleting chemotherapy (cyclophosphamide 300 mg/m^2 IV and fludarabine 30 mg/m^2 IV for 3 days)	• Low blood counts • Cytokine release syndrome • Neurotoxicity • Infection • Fatigue • Musculoskeletal pain • Hypogammaglobulinemia • Diarrhea

The efficacy of Abecma was studied in a multicenter, single-arm trial in 100 patients with relapsed/refractory myeloma. Patients received a range of 300 to 460 × 10^6 CAR-positive T cells. The overall response rate was 72%, and 28% of patients achieved a stringent complete response (sCR). The median time to response was 30 days, and median duration of response was 11 months. In patients who achieved sCR, the median duration of response was 19 months.

The most common side effects included low blood counts, **cytokine release syndrome**, neurotoxicity, infection, 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, Darzalex, Sarclisa, and Blenrep) 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, Darzalex, and Sarclisa are three 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.

ADCs are another type of antibody-based treatment which uses a monoclonal antibody that is coupled to a cancer drug or a toxin. The antibody part of the conjugate binds to a myeloma cell, and the attached cancer drug kills the myeloma cell. Blenrep is the first ADC to be approved in myeloma.

Another antibody-based therapy is the bispecific antibody and the **bispecific T-cell engager** (also known as a **BiTE**). Bispecific antibodies and BiTEs are made from two antibodies (or fragments of antibodies) 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

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. The first CAR T-cell therapy (Abecma; idecabtagene vicleucel) was approved in 2021. Some CAR T-cell therapies are being studied in larger, phase 3 clinical trials.

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.

	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. The Multiple Myeloma Research Consortium (MMRC)—a sister organization to the MMRF—actually does research. The MMRC is a unique collaboration of 23 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 **themmrf.org/resources/clinical-trial-finder**. Or you can call 888.841.MMRF (6673) to speak with an MMRF 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 Patient Navigator help guide you through the process at themmrf.org/resources/clinical-trial-finder

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).

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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 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

Connect with an MMRF Myeloma Mentor™:
themmrf.org/resources/myeloma-mentors

This is a phone-based program offering the opportunity for patients and/or caregivers to connect one-on-one with a trained patient and/or caregiver mentor to share their patient journeys and experiences.

FIND AND PARTICIPATE IN A CLINICAL TRIAL

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

Clinical Trial Search: themmrf.org/resources/clinical-trial-finder

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 themmrf.org/get-involved

REIMBURSEMENT ASSISTANCE PROGRAMS

Patient Access Network
Website: 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)
Contact: www.panfoundation.org/contact

Amgen Inc
Products: Neupogen/Neulasta/Kyprolis/Xgeva
Website: www.amgenassist360.com
Phone: 1-888-4ASSIST (1-888-427-7478)

Bristol-Myers Squibb
Products: Empliciti/Pomalyst/Revlimid/Thalomid/Abecma
Website: www.bmsaccesssupport.bmscustomerconnect.com/patient
Phone: 1-800-861-0048

GlaxoSmithKline
Product: Blenrep
Website: www.gskforyou.com/reimbursement-resource-center
Services: Access, Copay and Patient Assistance Programs for Specialty and Oncology Products
Phone: 1-800-745-2967

Janssen
Product: Darzalex
Website: www.janssencarepath.com/patient/darzalex/patient-support
Phone: 1-844-55DARZA (1-844-553-2792)

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

Novartis
Product: Zometa
Website: www.patientassistancenow.com
Phone: 1-800-245-5356

Oncopeptides
Product: PEPAXTO
Website: www.oncoursesupport.com
Phone: 1-844-300-ONCO (1-844-300-6626)

Sanofi
Product: Sarclisa
Website: www.sanoficareassist.com
Phone: 1-833-WE+CARE (1-833-930-2273)

Secura Bio
Product: Farydak
Website: www.securabio.com/patient-support-programs
Phone: 1-844-9SECURA (1-844-973-2872)

Takeda Oncology Company
Product: Velcade/Ninlaro
Website: www.here2assist.com/patient/home
Phone: 1-844-817-6486, 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

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); example includes Blenrep

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

B-cell maturation antigen (BCMA) A protein found on the surface of myeloma cells

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

chimeric antigen receptor T (CAR-T) cell therapy A form of immunotherapy in which a patient's immune cells (mostly T cells) are collected, engineered in a lab to be better able to identify and attack myeloma cells, and then returned to the patient

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

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)

computed tomography (CT) Imaging technique that uses a computer to generate three-dimensional x-ray pictures (also referred to as *computerized axial tomography [CAT]*)

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

cytokine release syndrome (CRS) A common, infection-like side effect following infusion of CAR T cells in which a patient experiences fevers, chills, and low blood pressure

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

keratopathy Changes to a part of the eye that result in vision change

maintenance therapy Treatment that is given to patients following a response to induction therapy 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

minimal (measurable) 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

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

PCROWD study A clinical trial conducted to identify changes in cells of patients with myeloma precursor conditions (MGUS or SMM) (visit www.enroll.pcrowd.org)

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

PROMISE study A clinical trial conducted to identify new ways to prevent multiple myeloma in individuals with its precursor conditions (MGUS or SMM) (visit www.enroll.promisestudy.org)

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 increased 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

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

visual acuity Sharpness of vision

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 or to view the complete calendar, visit:
themmrf.org/resources/education-programs

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