



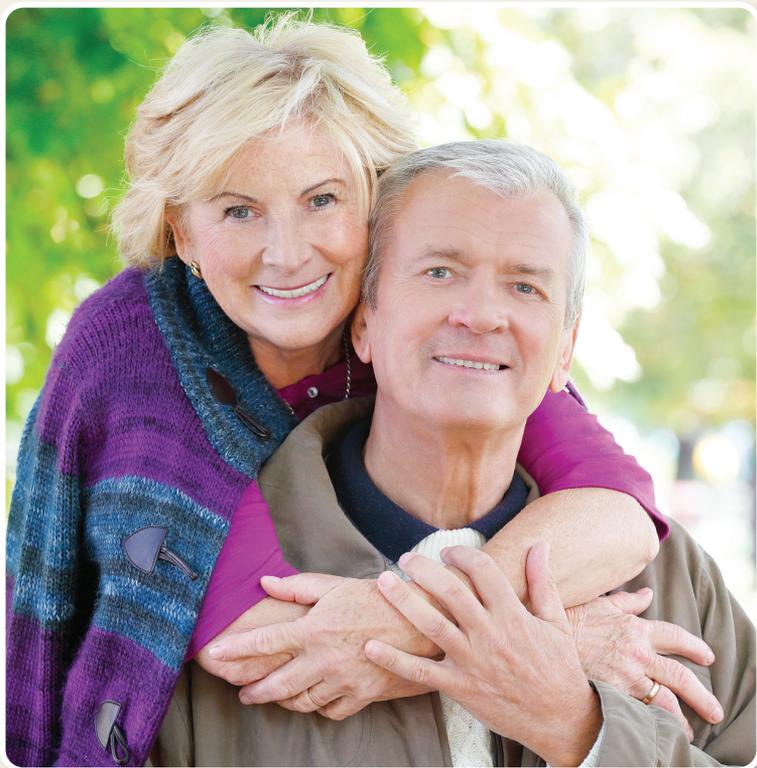
Understanding

DARZALEX[®]

(daratumumab) intravenous infusion
and

DARZALEX FASPRO[™]

(daratumumab + hyaluronidase-fihj)
subcutaneous injection



A publication of the **International Myeloma Foundation**

Improving Lives **Finding the Cure[®]**



Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.

RESEARCH The signature project of the IMF's Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF's International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF's Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

EDUCATION The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF's library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

SUPPORT The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

ADVOCACY The IMF's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.

**Contact us at 818.487.7455 or 800.452.CURE,
or visit myeloma.org.**

Improving Lives **Finding the Cure**®

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What you will learn from this booklet

The IMF's *Understanding* series of booklets is designed to acquaint you with treatments and supportive care measures for **multiple myeloma** (which we refer to simply as "myeloma"). Words in **bold+blue** type are explained in the "Terms and definitions" section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF's *Glossary of Myeloma Terms and Definitions*, located at glossary.myeloma.org.

Myeloma is a **cancer** that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful those discussions will be.

This booklet discusses Darzalex[®] (also known by its **generic drug name**, daratumumab) as well as Darzalex Faspro[™], a new formulation of daratumumab and hyaluronidase (an endoglycosidase). It will familiarize you with the way Darzalex works, how it has been tested, the indications for which it is approved, how and when it is administered, its possible **side effects**, and how to manage those side effects.

Before reading this booklet, it may be helpful to read another IMF publication, *Understanding the Immune System in Myeloma*, which will provide some background on the types and functions of **immune system** cells, how they work together to protect us, the impact of myeloma on the immune system, and the way in which Darzalex enlists immune system **cells** to help attack and kill myeloma cells.

What is Darzalex?

Darzalex is the first **monoclonal antibody** that targets the CD38 **protein** on the surface of myeloma cells that has been approved by the US Food and Drug Administration (FDA). Although antibodies are a naturally-occurring part of the immune system, Darzalex and other antibodies used to treat cancer are made in a laboratory. A laboratory-made **antibody** (also called **immunoglobulin**) is designed to function like a naturally occurring antibody and to target a specific single protein on the surface of cancer cells. It is therefore also called a "targeted therapy." Of the four therapies for myeloma approved by the FDA in 2015, only Darzalex has single-agent activity and was approved based on its superiority to existing treatments for myeloma.

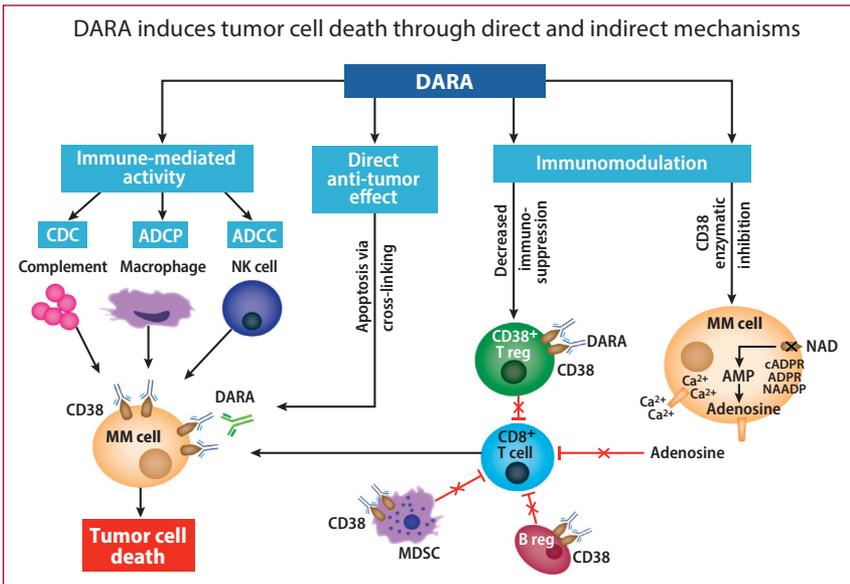
How does Darzalex work?

Darzalex targets CD38, a **glycoprotein**. “CD” in CD38 stands for “cluster of differentiation,” a system for identifying the various **molecules** that serve as binding sites, or **antigens**, to which antibodies bind on the surface of cells. CD38 is widely expressed on the surface of myeloma cells, but is only expressed at low levels on other cells in the **bone marrow**, making it easier for them to recover after therapy.

When Darzalex binds to CD38, it causes myeloma cell death in multiple ways:

- It kills myeloma cells directly.
- It recruits immune system cells called **macrophages**, which bind to the Darzalex-CD38 complex and then engulf and destroy myeloma cells.
- It attracts **natural killer (NK) cells**, which target and kill myeloma cells.
- It recruits **complement proteins** that boost the killing power of antibodies and punch holes in the targeted myeloma cells.
- It modulates the immune response by decreasing immune system suppression.
- It inhibits CD38 from functioning as an **enzyme** that regulates **calcium** flux in the cell. Blocking the transfer of calcium ions is toxic to cancer cells but spares normal cells.

Figure 1. Daratumumab (DARA) mechanisms of action



Usmani SZ et al. Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma. Abstract #29. Oral presentation at American Society of Hematology (ASH) 2015.

Who is a candidate for Darzalex?

In the US, Darzalex is FDA-approved for the treatment of adult patients with myeloma as part of the following treatments:

- In newly diagnosed patients who are eligible for autologous stem cell transplant (ASCT), in combination with Velcade® (bortezomib) + thalidomide + dexamethasone (VTd).
- In newly diagnosed patients who are ineligible for ASCT, in combination with Revlimid® (lenalidomide) + dexamethasone (Rd), or Velcade + melphalan + prednisone (VMP).
- In patients who have received at least 1 prior therapy, in combination with Velcade + dexamethasone (Vd).
- In patients with **relapsed** or **refractory** myeloma who have received 1 to 3 previous lines of therapy, in combination with Kyprolis® (carfilzomib) + dexamethasone (Kd).
- In patients who have received at least 2 prior therapies including Revlimid + a **proteasome inhibitor** (Kyprolis, Ninlaro® [ixazomib], or Velcade), in combination with Pomalyst® (pomalidomide) + dexamethasone (Pd).
- As monotherapy in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor + an **immunomodulatory drug** (Pomalyst, Revlimid, or thalidomide), or who are double-refractory to a proteasome inhibitor and an immunomodulatory drug.

What is Darzalex Faspro?

Darzalex Faspro is a combination of Darzalex and hyaluronidase (an endoglycosidase). This new formulation of Darzalex is given as an abdominal injection under the skin (subcutaneously, SQ). Darzalex Faspro has been determined to be equally effective when compared to the original formulation of Darzalex.

Who is a candidate for Darzalex Faspro?

In the US, Darzalex Faspro is FDA-approved in myeloma as part of the following treatments:

- In newly diagnosed patients who are ineligible for ASCT, in combination with Rd or VMP.
- In patients who have received at least 1 prior therapy, in combination with Vd.
- As monotherapy in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor + an immunomodulatory drug, or who are double-refractory to a proteasome inhibitor and an immunomodulatory drug.

How is Darzalex given?

Darzalex is administered in two ways:

1. The original formulation of Darzalex is administered intravenously (infused into the vein, IV) at a doctor's office or a hospital clinic.
2. Darzalex Faspro is given as an abdominal SQ injection that takes only a few minutes. The injection is administered by a healthcare professional.

Please note that switching from IV to SQ administration must first be discussed with your doctor.

What are the dose and schedule of Darzalex?

For the IV formulation of Darzalex

The first dose of Darzalex is usually given over a period of up to 8 hours. Especially with the first dose, the slower the rate of infusion, the less likely it is that a severe **administration-related reaction** will occur. If the first dose is well tolerated, subsequent doses may be given more rapidly at your doctor's discretion. Medications are given before and after each Darzalex infusion to help prevent a reaction.

A split-dosing regimen, the option to split the first infusion of Darzalex over two consecutive days is approved in both the United States and Europe. The concentration of Darzalex in the body was found to be comparable regardless of whether the first dose was administered as a single infusion or a split-dosing infusion. Please note that split-dosing cannot be done with the subcutaneous administration of Darzalex Faspro.

- The dose of Darzalex, whether alone or in combination with Revlimid + dexamethasone, is 16 mg/kg of body weight. It is given weekly for weeks 1–8, every 2 weeks for weeks 9–24, and every 4 weeks for weeks 25 onward until disease progression.
- In combination with Velcade + dexamethasone, Darzalex is given at the standard dose, but is given weekly for weeks 1–9, every 3 weeks for weeks 10–24, and every 4 weeks for weeks 25 onward until disease progression.

For the SQ formulation of Darzalex Faspro

Darzalex Faspro is given on the same schedule as the intravenous administration of Darzalex. Darzalex Faspro is administered by a healthcare professional as an abdominal SQ injection that takes only a few minutes. Although the risk of injection-related reactions with Darzalex Faspro is

much lower, patients are monitored for a few hours after the first one or two doses.

- The recommended dosage of Darzalex Faspro is 1,800 mg Darzalex + 30,000 units hyaluronidase per 15 mL (120 mg and 2,000 units/mL) solution in a single-dose vial.
- Patients are pre-medicated with a corticosteroid, acetaminophen, and a histamine-1 receptor antagonist. Post-injection medications may also be recommended.

Ongoing clinical trials

There are many **clinical trials** of Darzalex that are ongoing. These studies are investigating the use of Darzalex for newly diagnosed myeloma, in high-risk **smoldering multiple myeloma (SMM)**, as post-ASCT maintenance therapy in minimal residual disease (MRD) positive patients, and for relapsed/refractory myeloma.

Warnings and precautions with Darzalex

Interference with blood tests

- Darzalex binds to the CD38 cell surface antigen on red blood cells and interferes with blood compatibility testing, including antibody screening and cross-matching done prior to blood transfusions. Your doctor should type and screen your blood before you start treatment with Darzalex in case you need a blood transfusion subsequently.
- Darzalex has been known to interfere with the results of serum protein **electrophoresis (SPEP)** and **immunofixation electrophoresis (IFE)** tests used to monitor myeloma. This led to false positive test results for patients with IgG kappa myeloma protein, leading to inaccuracies in detecting complete response and disease progression. In January 2018, the FDA approved a new assay for evaluating monoclonal protein in serum by IFE for myeloma patients treated with Darzalex.

Risk of hepatitis B virus reactivation

Darzalex can cause hepatitis B virus (HBV) to become active again. In clinical trials with Darzalex, HBV reactivation has been reported in less than 1% of patients, but there were fatal cases. HBV reactivation can occur at any treatment phase, so regular monitoring is required on a long-term basis. More studies are needed to identify HBV reactivation risk factors and to establish prevention strategies in myeloma patients.

Risk of herpes zoster infection

A small percentage of patients in clinical trials with Darzalex developed reactivation of the herpes zoster virus. All patients should receive preventive treatment with an antiviral medication, such as acyclovir or valacyclovir, within one week after starting Darzalex and continuing for three months following treatment. Please discuss preventive antiviral treatment with your doctor before starting treatment with Darzalex.

Pregnancy

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after stopping Darzalex treatment.

Special precautions with Darzalex Faspro

Hypersensitivity

Your doctor will permanently discontinue Darzalex Faspro for life-threatening reactions.

Neutropenia

Due to the possibility of low white blood cell counts (**neutropenia** and **lymphopenia**), your doctor will monitor your complete blood cell counts during treatment, and monitor for signs of infection.

Thrombocytopenia

Due to the possibility of low platelet counts (**thrombocytopenia**), your doctor will monitor your complete blood cell counts during treatment with Darzalex Faspro.

Embryo-fetal toxicity

Darzalex Faspro can cause fetal harm. Females of reproductive potential should use effective contraception.

Interference with cross-matching and red blood cell antibody screening

Your doctor will screen you prior to starting treatment with Darzalex Faspro. Blood banks should be informed that you have received Darzalex Faspro.

What are the possible side effects of Darzalex, and how are they managed?

In the Darzalex registration trials evaluated by the FDA before approval, side effects that occurred in >20% or more of the patients were: infusion reactions, fatigue, nausea, back pain, fever, cough, and upper respiratory tract infection (URI). In addition, Darzalex may cause blood cell counts to drop, with significant numbers of patients experiencing low red blood cell counts (**anemia**), thrombocytopenia, and neutropenia and lymphopenia.

Blood counts are carefully monitored during treatment with Darzalex. If they are too low, your doctor will either hold your dose of Darzalex until your counts improve or will provide you with supportive care in the form of transfusions or medications that stimulate the formation of new blood cells.

Infusion reactions for the intravenous formulation

Infusion reactions to monoclonal antibodies are caused by the release of **cytokines** and are sometimes referred to as “cytokine-release syndrome.” Reactions are often flu-like, and include nasal congestion, fever, chills, cough, throat irritation, difficulty breathing, low blood pressure, nausea, and rash.

Infusion reactions occurred in 46% of the patients in the registration trials for Darzalex, most of them mild to moderate, and most occurring during or within four hours after the first infusion. Infusion reactions occurred in 5% of the patients with the second infusion and in 4% with subsequent infusions. Infusion reactions that were severe enough to require hospitalization occurred in 3% of patients. There were no life-threatening infusion reactions.

Prevention and treatment of infusion reactions

Medications are given both before and after Darzalex infusions to minimize the risk of infusion reactions.

Approximately one hour before every infusion of Darzalex, all patients receive:

- An intravenously administered corticosteroid, such as Medrol® (methylprednisone).
- An oral medication to reduce/prevent fever, such as acetaminophen.
- An oral or intravenous (IV) **antihistamine**, such as diphenhydramine.

All patients receive post-infusion medication to reduce the risk of delayed infusion reactions. An oral corticosteroid is given to the patient on the day of and the day after each Darzalex infusion.

If a reaction of any kind occurs during the administration of Darzalex, the infusion will be stopped.

Fatigue

39% of the patients in the registration trials for Darzalex experienced fatigue, all but 2% of which was mild to moderate and did not limit the patients' ability to care for themselves. Caution is advised if you are operating machinery, including automobiles. For more detailed information, please see the IMF publication *Understanding Fatigue*.

Prevention and treatment of fatigue

The effects of fatigue may be minimized by maintaining:

- A moderate level of activity.
- A healthy diet and proper fluid intake.
- A consistent sleeping schedule with enough rest.
- Regularly scheduled visits with your doctor or healthcare provider to discuss issues that may contribute to your fatigue.
- A careful review of the side effects of any other supplements and medications you are taking to ensure that they are not contributing to your fatigue.

Nausea

Approximately one quarter of the patients in the registration trials had mild to moderate nausea. There were no cases of severe nausea.

Prevention and treatment of nausea

Pre- and post-infusion medications help to reduce the occurrence and severity of nausea. Your doctor may order an anti-nausea drug prior to your Darzalex infusion.

Back pain

Treatment-related (rather than myeloma-related) back pain can occur as a result of inflammatory cytokines released in reaction to the monoclonal antibody or may occur because a patient receiving Darzalex has low levels of **white blood cells (WBC)** and develops an infection along with body aches and pains. Of the 25% of patients who experienced back pain in the Darzalex registration trials, only 2% experienced back pain that was severe enough to limit their ability to care for themselves.

Prevention and treatment of back pain

Pre- and post-infusion medications can reduce or prevent infusion-related back pain. Consult your doctor, who will determine if you require medication.

Fever

Fever is defined as an oral temperature greater than 100.4°F (38°C) and it needs to be further evaluated immediately. Fever can be a sign of the interaction of the monoclonal antibody with the immune system, as it may be a flu-like symptom caused by the release of cytokines in an infusion reaction.

Prevention and treatment of fever

You can minimize the effects of fever in the following ways:

- Check your temperature twice a day if you feel warm.
- Notify your doctor immediately if you have a fever greater than 100.4°F (38°C).
- If your doctor's office is closed and you are not able to reach a covering physician, go to an urgent care facility or emergency room.
- Take medications to control the fever as directed by your doctor.
- To avoid dehydration, drink a lot of non-alcoholic and non-caffeinated liquids.

Your treating physician may also do the following:

- Recommend **over-the-counter (OTC) medications** to treat fever related to flu-like syndrome. Do not take any medications without first consulting a doctor familiar with your medical history.
- If you have a fever as a result of an infection, the doctor will prescribe antibiotics. You may also be given a drug that helps to boost the white cell count (a "colony-stimulating factor").

Cough

Cough can be best managed proactively with pre- and post-infusion medications. In general, maintaining good hydration, drinking hot liquids, taking lozenges, avoiding irritants in the air, and breathing warm steam from a shower or humidifier will help relieve your symptoms.

Prevention and treatment of cough

As with the other infusion reaction-related events listed in these pages, cough can be best managed proactively with pre- and post-infusion medications. If you develop a cough as a result of an upper respiratory infection, your doctor will recommend medications, if appropriate, to treat the infection.

Upper respiratory tract infection

20% of the patients in the registration trials for Darzalex had an upper respiratory tract infection (URI); all but 1% were mild to moderate. URIs can be a bacterial or viral infection of the nose, throat, sinuses, or larynx.

Prevention and treatment of URI

Report your symptoms to your doctor immediately. If your infection is serious and your white blood cell count is low, the doctor may hold your Darzalex infusion until you recover or support you with medications to stimulate the production of new white blood cells.

Possible adverse reactions to Darzalex Faspro

The most common hematological abnormalities in laboratory tests ($\geq 40\%$) with Darzalex Faspro are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

The most common side effects ($\geq 20\%$) with Darzalex Faspro are:

- **With monotherapy:** Upper respiratory tract infection.
- **With combination therapy:** Fatigue, nausea, diarrhea, shortness of breath, trouble sleeping, fever, cough, muscle spasms, back pain, vomiting, cold-like symptoms (upper respiratory tract infection), peripheral neuropathy (nerve damage causing tingling, numbness, or pain), constipation, and lung infection (pneumonia).

Access to Darzalex and other resources

Janssen Pharmaceuticals has a CarePath program to help support patients who are receiving treatment with Darzalex. Visit darzalex.com or call 844.553.2792. CarePath case coordinators can help you with:

- Access to nurse educators.
- Referrals to independent organizations that provide assistance with costs associated with travel to and from treatment.
- A tool that connects patients and caregivers to national and/or state advocacy groups that offer resources relevant to their needs.
- Personalized, live appointment reminders.

In closing

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine can be reached at InfoLine@myeloma.org or 800.452.CURE or 818.487.7455.

Terms and definitions

Administration-related reaction: An allergic or cytokine-related response to an intravenously administered cancer treatment.

Anemia: A decrease in hemoglobin, a protein which is contained in red blood cells and carries oxygen to the body's tissues and organs. Anemia is usually defined as hemoglobin below 10 g/dL, and/or as a decrease of ≥ 2 g/dL from the normal level for an individual. Over 13–14 g/dL is considered normal.

Antibody: A protein produced by plasma cells in response to an antigen that enters the body. Also see "**Immunoglobulin.**"

Antigen: Any foreign substance that causes the immune system to produce natural antibodies. Examples of antigens include bacteria, viruses, parasites, fungi, and toxins.

Antihistamine: A drug that acts against histamine, a powerful and highly irritant agent released in the body after contact with certain allergens.

Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets. This is the tissue within which abnormal plasma cells build up when myeloma is growing.

Calcium: A mineral found mainly in the hard part of bone matrix (hydroxyapatite). If produced or released in excess, it can build up in the bloodstream. See "**Hypercalcemia.**"

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Clinical trial: A research study of new treatment that involves patients. Each study is designed to find better ways to prevent, detect, diagnose, or treat cancer and to answer scientific questions.

- **Control group** – The arm of a randomized clinical trial that receives the standard treatment or placebo (no treatment).
- **Experimental group** – The arm of a randomized trial that gets the new treatment.
- **Randomized clinical trial** – A research study in which subjects are randomly assigned to receive a particular treatment or not.
- **Arm** – One of the treatment groups of a randomized trial. The majority of randomized trials have two, but some have more.
- **End point** – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.
- **Double blind** – Aspect of a randomized trial in which neither the participant nor the investigator knows the arm of the trial to which the patient is assigned. The purpose is to eliminate any bias in the reporting of results.
- **Phase I trial** – A trial designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual

elements may already have been well tested. Patients in phase I trials generally have advanced cancer that is refractory to all standard treatment. In a typical phase I trial, successive groups (“cohorts”) of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.

- **Phase II trial** – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment. In addition, patients must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may be approved based on phase II trial results.
- **Phase III trial** – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don’t choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.
- **Phase IV trial** – Even after a drug has been approved by the United States Food and Drug Administration (FDA) for use in a particular indication, there may be need for additional studies. Phase IV clinical trials may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons. For example, safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than was possible during the phase I–III clinical trials.

Complement proteins: A complex system of more than 30 proteins that act in concert to help eliminate infectious microorganisms. The complement system causes the lysis (bursting) of foreign and infected cells, the phagocytosis (ingestion) of foreign particles and cell debris, and the inflammation of surrounding tissue.

Cytokine: Cytokines are proteins secreted by cells which can stimulate or inhibit growth/activity in other cells. Cytokines are produced locally (for myeloma, in the bone marrow) and circulate in the bloodstream. Cytokines are normally released in response to infection.

Electrophoresis: A laboratory test in which a patient’s serum (blood) or urine proteins are subjected to separation according to their size and electrical charge. For myeloma patients, electrophoresis of the blood or urine allows both the calculation of the amount of myeloma protein via serum or urine electrophoresis (SPEP or UPEP), as well as the identification of the type of M-spike for each patient (immunoelectrophoresis, IFE). Electrophoresis is used as a tool both for diagnosis and for monitoring.

Enzyme: A protein molecule manufactured by a cell. An enzyme acts as a catalyst that increases the rate of a specific biochemical reaction in the body.

Frontline therapy: A general term for the initial treatment used in an effort to achieve response in a newly diagnosed myeloma patient. See “**Induction therapy**” and “**Response.**”

Generic drug name: A generic drug name refers to the chemical makeup of a drug rather than its brand name. A generic name is given to a drug before it is approved and given a brand name. After a drug goes off patent, other manufacturers may make generic versions of the drug. For example: ibuprofen is the generic name for drugs brand-named Advil® and Motrin®.

Glycoproteins: Proteins on the outer surface of cells that have sugars (carbohydrates) attached to them. They function as receptor sites where other molecules may attach to the cell.

Herpes zoster: The virus that causes chicken pox. When reactivated, the herpes zoster infection frequently affects nerves. This condition is also called “shingles.”

Hypercalcemia: A higher than normal level of calcium in the blood. In myeloma patients, it usually results from bone breakdown with release of calcium from the bone into the bloodstream. This condition can cause a number of symptoms, including loss of appetite, nausea, thirst, fatigue, muscle weakness, restlessness, and confusion. See “**Calcium.**”

Immune system: The body’s defense system from pathogens and foreign substances that destroys infected and malignant cells and removes cellular debris. The immune system includes white blood cells and organs and tissues of the lymphatic system.

Immunofixation electrophoresis (IFE): An immunologic test of the serum or urine used to identify proteins. For myeloma patients, it enables the doctor to identify the M-protein type (IgG, IgA, kappa, or lambda). The most sensitive routine immunostaining technique, it identifies the exact heavy- and light-chain type of M-protein.

Immunoglobulin (Ig): A protein produced by plasma cells; an essential part of the body’s immune system. Immunoglobulins attach to foreign substances (antigens) and assist in destroying them. The classes (isotypes) of immunoglobulins are IgG, IgA, IgD, IgE, and IgM. Also see “**Antibody.**”

Immunomodulatory drug: An agent that affects, enhances, or suppresses the immune system. Sometimes called an IMiD® compound.

Induction therapy: A specific term used for the initial treatment given to a patient in preparation for an autologous stem cell transplant (ASCT). See “**Frontline therapy**” and “**Line of therapy.**”

Line of therapy: A term used to calculate the number of therapies a patient has received. Induction therapy + an autologous stem cell transplant (ASCT) is considered a single line of therapy. See “**Induction therapy.**”

Lymphopenia: Low levels of B cells, T cells, and natural killer (NK) cells. Also called “lymphocytopenia.”

Macrophage: A macrophage is an immune system cell whose job it is to engulf and devour any cell (including a cancer cell) that does not have proteins on its surface that identify it as a healthy body cell.

Minimal residual disease (MRD): The presence of residual tumor cells after treatment has been completed and complete remission (CR) has been attained. Even patients who have attained a stringent complete response (sCR) may have MRD. Very sensitive new testing methods are now able to detect 1 myeloma cell among 1,000,000 sampled cells in blood or bone marrow. See "**MRD-negative.**"

Molecule: The smallest particle of a substance that retains all the properties of the substance. A molecule is an electrically neutral group composed of two or more atoms held together by chemical bonds.

Monoclonal antibody: An antibody manufactured in a lab rather than produced in the human body. Monoclonal antibodies are specifically designed to find and bind to cancer cells and/or immune system cells for diagnostic or treatment purposes. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to tumor cells.

MRD-negative: Minimal residual disease-negative; not even one myeloma cell found in 100,000 or 1,000,000 bone marrow plasma cells sampled (depending on the test). See "**Minimal residual disease.**"

Multiple myeloma: A cancer of the bone marrow plasma cells, white blood cells that make antibodies. The cancerous plasma cells are called myeloma cells.

Natural killer (NK) cell: A lymphocyte (type of white blood cell) that is a component of the innate immune system. NK cells are responsible for tumor surveillance and are able to induce strong responses against tumors through the release of cytokines.

Neutropenia: A reduced level of neutrophils, a type of white blood cell necessary to combat bacterial infection.

Over-the-counter (OTC) medications: OTC medications can be purchased without a prescription.

Progressive disease: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of $\geq 25\%$ from the lowest confirmed response value in the myeloma protein level and/or new evidence of disease.

Proteasome inhibitor: Any drug that interferes with the normal function of the proteasome, an enzyme complex responsible for breaking down and recycling unwanted proteins in both normal cells and cancer cells.

Proteins: Substances composed of amino acids. Proteins are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, collagen, etc., as well as enzymes and antibodies.

Refractory: Disease that is no longer responsive to standard treatments. Patients with refractory myeloma have had progressive disease either during treatment or within 60 days following treatment. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Registration trial: A well-controlled clinical trial intended to provide the substantial evidence of safety and efficacy required by a governmental regulatory agency to be completed as a prerequisite to approval and sale of a product. For drugs sold in the United States, the regulatory agency is the US Food and Drug Administration (FDA). For drugs sold in the European Union, it is the European Medicines Agency (EMA).

Relapse: The reappearance of signs and symptoms of a disease after a period of improvement. Patients with relapsed disease have been treated, then developed signs and symptoms of myeloma at least 60 days after treatment ended. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Response or remission: Complete or partial disappearance of the signs and symptoms of cancer. Remission and response are interchangeable terms.

- **Stringent complete response (sCR)** – sCR is CR (as defined below) plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
- **Complete response (CR)** – For myeloma, CR is negative immunofixation on serum (blood) and urine, and disappearance of any soft tissue plasmacytomas, and $\leq 5\%$ plasma cells in bone marrow. CR is not the same as a cure.
- **Very good partial response (VGPR)** – VGPR is less than CR. VGPR is serum M-protein and urine M-protein detectable by immunofixation but not on electrophoresis, or 90% or greater reduction in serum M-protein, plus urine M-protein less than 100 mg per 24 hours.
- **Partial response (PR)** – PR is a level of response in which there is at least a 50% reduction in M-protein, and reduction in 24-hour urinary M-protein by at least 90% (or to less than 200 mg per 24 hours).

Side effect: Unwanted effect caused by a drug. Also known as “adverse reaction” or “adverse event (AE).”

Smoldering multiple myeloma (SMM): SMM is a higher level of disease than MGUS, but is still not active myeloma with CRAB features indicating organ damage. Patients with standard-risk SMM do not require treatment, but should be observed at regular intervals by a hematologist-oncologist. Patients with high-risk SMM may choose to participate in a clinical trial.

Subcutaneous injection or “shot”: A method of administering medication under the skin by a short needle that injects a drug into the tissue layer between skin and muscle.

Thrombocytopenia: A low number of platelets in the blood. “Normal” levels vary from laboratory to laboratory. The normal level at the Mayo Clinic is 150,000–450,000. If the platelet count is less than 50,000, bleeding problems could occur. Major bleeding is usually associated with a reduction to less than 10,000.

White blood cells (WBC): General term for a variety of cells responsible for fighting invading germs, infection, and allergy-causing agents. These cells begin their development in bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, basophils, eosinophils, lymphocytes, and monocytes.



You are not alone. The IMF is here to help.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments.

The IMF produces a library of publications to help arm you with an important weapon in the fight against myeloma: INFORMATION. The following is a partial list of materials available in English. Selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding DARZALEX® (daratumumab) intravenous infusion and DARZALEX FASPRO™ (daratumumab + hyaluronidase-fihj) subcutaneous injection*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding FARYDAK® (panobinostat) capsules*
- *Understanding Fatigue*
- *Understanding Freelite® and Hevlyte® Tests*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib) injection*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding Peripheral Neuropathy in Myeloma*
- *Understanding POMALYST® (pomalidomide) capsules*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding the Role of Vertebroplasty and Kyphoplasty*
- *Understanding SARCLISA® (isatuximab-irfc)*
- *Understanding Thalidomide Therapy*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib) injection*
- *Understanding the VRd Regimen for Newly Diagnosed Myeloma*
- *Understanding XPOVIO™ (selinexor)*
- *Understanding Your Test Results*

IMF publications are free of charge. Subscribe at [subscribe.myeloma.org](https://www.internationalmyeloma.org/subscribe) and read, download, or order printed copies at [publications.myeloma.org](https://www.internationalmyeloma.org/publications).

As always, the IMF urges you to discuss all medical issues with your doctor, and to contact the IMF's InfoLine with your myeloma questions and concerns.



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