Understanding EMPLICITI®
(elotuzumab)

A publication of the **International Myeloma Foundation**

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FOUNDATION

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Improving Lives **Finding the Cure**®

INTERNATIONAL MYELOMA FOUNDATION

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 that discussion will be.

This booklet will familiarize you with the drug Empliciti® (known also by its generic name, elotuzumab): How Empliciti works, the results of **clinical trials** with Empliciti, how and when Empliciti is administered, the possible **side effects** of Empliciti, 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 you with some background information 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 Empliciti enlists immune system cells to attack myeloma.

What is Empliciti?

Empliciti is the first immunostimulatory **monoclonal antibody** approved for the treatment of myeloma. It was approved by the United States Food and Drug Administration (FDA) in combination with Revlimid® (lenalidomide) and the **steroid** dexamethasone, because clinical trials demonstrated that the combination is more effective than Revlimid plus dexamethasone without Empliciti. This **antibody** is made in a laboratory rather than inside the human body, and it has been designed to target a particular protein called SLAMF7 (signaling lymphocytic activation molecule F7) that is found on the surface of most myeloma cells. SLAMF7 also appears on the surface of a subset of **white blood cells** (**WBC**, the cells that make up our immune system) called **natural killer (NK)** cells. NK cells are immune system cells that patrol for, and kill, **tumor** cells.

How does Empliciti work?

Both NK cells and myeloma cells have receptors for the SLAMF7 protein. Empliciti attaches to the SLAMF7 receptor on NK cells and stimulates the NK cells to attach to and attack myeloma cells via the SLAMF7 surface receptors on myeloma cells. By attaching directly to myeloma cells, Empliciti "flags" them for destruction by the NK cells. Empliciti thus works via a two-pronged approach:

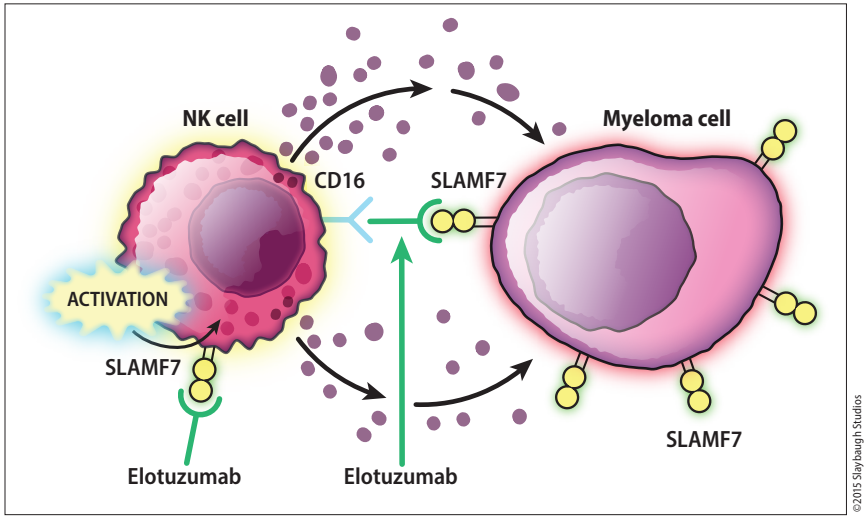
- It provides a docking site for NK cells on myeloma cells.
- It recruits NK cells to attach to that dock and directly attack the myeloma cells from the outside in.

Because Empliciti stimulates these immune system cells to attack myeloma cells, it not only helps to cause myeloma cell death, it also appears to stimulate an ongoing immune response against myeloma.

What were the results with Empliciti in clinical trials?

The randomized, phase III ELOQUENT-2 clinical trial for patients with **relapsed** and/or **refractory** myeloma compared the "control group" of patients receiving Revlimid® (lenalidomide) + low-dose dexamethasone (Rd) to the "experimental group" of patients receiving Empliciti + Revlimid + low-dose dexamethasone (ERd). The data from this clinical trial were submitted to the FDA for approval of Empliciti in combination with Rd. For more information about Revlimid, read the IMF publication

Figure 1. **Using NK (natural killer) cells to attack myeloma with Empliciti (elotuzumab, anti-SLAMF7)**

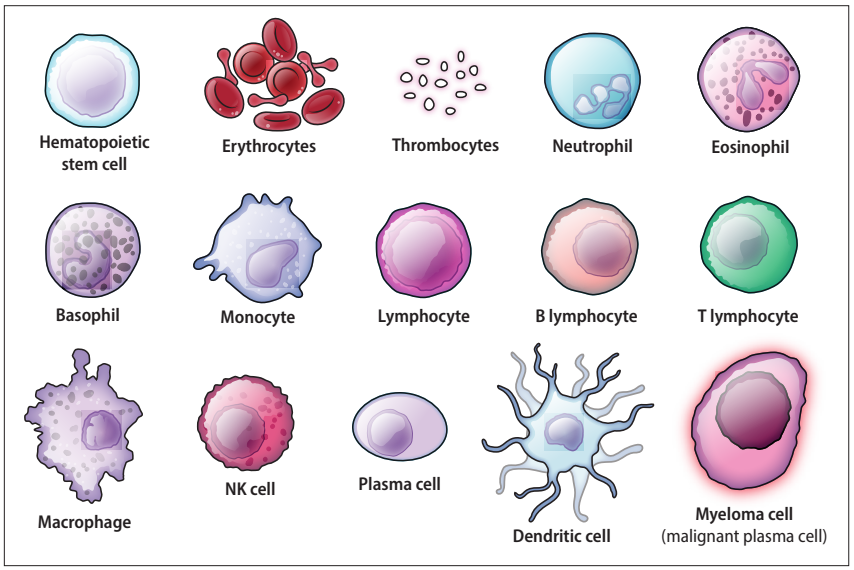


Understanding REVLIMID® (lenalidomide). For more information about dexamethasone, read the IMF publication *Understanding Dexamethasone and Other Steroids*.

In the ELOQUENT-2 clinical trial, 646 patients were enrolled at 224 study sites across 21 countries. Enrolled patients were randomly assigned: 321 patients to the experimental group and 325 to the control group. All patients had received from 1 to 3 prior therapies and were still able to respond to Revlimid. Nearly 1/3 of the patients had **high-risk myeloma**, and more than 1/3 were refractory to their last therapy. Patients were treated until their myeloma progressed or until they were unable to tolerate the therapy.

In the ELOQUENT-2 clinical trial, the addition of Empliciti to Rd resulted in a 30% reduction in the risk of **disease progression**. There was a median remission duration, or **progression-free survival (PFS)**, of an additional 4.5 months with ERd (19.4 months) versus Rd alone (14.9 months). PFS was reported at 24.5 months, with 41% of patients who had received ERd still in remission at that point compared to 27% of patients in the control group. The **overall response rate (ORR)** in the Empliciti group was 79%, versus 66% in the control group. At 24.5 months after the start of the clinical trial, 35% of the patients in the Empliciti arm were still on the study, as compared to 21% of the patients who were in the control arm.

Figure 2. **Immune system cells that play a role in myeloma**



Important note: Over time, the difference between the PFS of patients treated with ERd and those treated with Rd became greater. This increasing duration of **response** among patients who received Empliciti suggests that the addition of the monoclonal antibody to Rd boosts patients' ongoing immune response against myeloma.

Just as Empliciti improves patients' response to Rd by enlisting the help of immune system cells, the reverse is true as well: Revlimid improves patients' response to Empliciti. The results of earlier myeloma clinical trials with Empliciti alone, as compared to those that included Rd, demonstrated that Revlimid is a necessary part of the therapy. Without the **immunomodulatory drug** (Revlimid), Empliciti was only minimally effective against myeloma. Revlimid has its own effect on the NK cells, enabling them to kill myeloma cells more effectively. Revlimid also triggers chemical messengers called **cytokines** that both activate NK cells and shut down another cytokine called Interleukin-6 (IL-6), a **growth factor** for myeloma cells.

The ELOQUENT-2 clinical trial demonstrated that the combination of a monoclonal antibody to SLAMF7 (Empliciti), an immunomodulatory drug (Revlimid), and an anti-inflammatory agent (dexamethasone), itself a modulator of immune activity, is an effective treatment for relapsed/refractory myeloma. In the ELOQUENT-2 clinical trial, the benefit for PFS was consistent even among elderly and high-risk patients. Another benefit was that the addition of Empliciti to Rd did not increase the incidence of negative side effects when compared to Rd alone.

Data from the phase II ELOQUENT-3 clinical trial comparing Empliciti + Pomalyst® (pomalidomide) + dexamethasone (EPd) versus Pomalyst + dexamethasone (Pd) for treatment of relapsed/refractory myeloma were presented at the European Hematology Association (EHA) meeting in June 2018. Clinical trial participants included 117 patients who had at least two prior lines of therapy and whose myeloma progressed despite treatment that included Revlimid and a **proteasome inhibitor** (Velcade®, Ninlaro®, or Kyprolis®). Patients treated with EPd had a longer remission duration than patients treated with Pd (10.3 vs 4.7 months), and the treatment had an acceptable safety profile. The ORR was 53% with EPd and 26% with Pd. Based on these clinical trial data, the FDA granted priority review of the application to approve the combination of EPd for treatment of patients with relapsed or treatment-resistant myeloma.

What is the indication for use of Empliciti?

In November 2015, the FDA approved Empliciti in combination with Revlimid + dexamethasone for the treatment of myeloma patients who have received 1 to 3 prior therapies.

In May 2016, the European Commission granted a marketing authorization valid throughout the European Union for Empliciti, indicating Empliciti in combination with Revlimid + dexamethasone for the treatment of myeloma in adult patients who have received at least 1 prior therapy.

How is Empliciti given?

Empliciti is given as an intravenous (IV, or into the vein) infusion. Medication is given before the infusion to help prevent an **infusion reaction**.

What are the dose and schedule of Empliciti + Revlimid + dexamethasone?

Empliciti dosing is determined by a patient's weight. It is given at a dose of 10 milligrams (mg) for every kilogram (kg) of body weight (thus, someone who weighs 60 kg would receive 600 mg of Empliciti). Empliciti is infused very slowly at first (0.5 mg/minute), to ensure tolerance, and subsequently can be given at 2 mg/minute. By the third cycle of treatment, the rate of infusion may increase to 5 mg/minute, at the doctor's discretion.

Each dosing cycle of ERd is 28 days long. For the first two cycles, patients receive their Empliciti dose once weekly, on Days 1, 8, 15, and 22 of each cycle. After the first two cycles, patients receive Empliciti every other week, on Days 1 and 15, repeated every 28 days.

Revlimid is given orally at a dose of 25 mg on Days 1–21 of each cycle, and dexamethasone is given orally at a dose of 40 mg on Days 1, 8, 15, and 22 of each cycle.

What are the possible side effects of Empliciti + Revlimid + dexamethasone, and how are they managed?

Side effects were nearly equal in the experimental and control arms of the ELOQUENT-2 clinical trial, demonstrating that Empliciti adds little or no toxicity over that of Rd. Of the common side effects that occurred in 30% or more of the patients who participated in the ELOQUENT-2 clinical trial, adverse events affecting the blood cells were most prevalent. Almost all the patients in both the ERd experimental group and the Rd control group had low counts of white cells known as **lymphocytes** (99% of the patients in the experimental group and 98% in the control group had **lymphocytopenia** or low lymphocyte counts). 96% in the experimental arm and 95% in the control arm had **anemia** (low red blood cell count). **Neutropenia** (low count of white blood cells called neutrophils) and **thrombocytopenia** (low count of platelets or thrombocytes that enable blood to clot) were also frequent. The most serious blood cell-related side effects – those that led to hospitalization and/or were life-threatening – were low white cell counts, which occurred similarly in both the experimental and control arms of the clinical trial.

Among side effects other than low blood cell counts, infections were most common, pneumonia in particular. Approximately 25% of the patients in both arms of the clinical trial had infections of grade 3 or grade 4, meaning that they were ill enough to be hospitalized, and that the most severe cases (grade 4) were life-threatening.

Fatigue and diarrhea were the next most common adverse events. Both occurred in 47% of patients, although fewer than 9% of the cases of fatigue and 5% of the cases of diarrhea were serious enough to prevent the patients from performing the activities of daily living. The next most common adverse events were fever (which occurred in 37% of patients), constipation (36%), cough (31%), and muscle spasms (30%).

Infusion Reactions

Monoclonal antibodies entered the cancer-fighting armamentarium over a decade ago, but they are new to myeloma. Empliciti, like other monoclonal antibodies, is well tolerated and has no significant side effects that overlap with Rd. However, like many other monoclonal antibodies, Empliciti may cause infusion reactions, giving rise to a range of responses that may be caused by the release of cytokines. Infusion reactions, which can happen during the infusion or within 24 hours after an infusion of Empliciti, occurred in 10% of the patients who received Empliciti in the ELOQUENT-2 clinical trial, although 70% of those infusion reactions occurred only with the first dose. Infusion reactions with Empliciti, which are likely to be cytokine-mediated, subside with each subsequent dose. The most common infusion reactions were fever, chills, and elevated blood pressure (hypertension). There were no infusion reactions that were serious enough to require hospitalization, and only 2 out of 321 patients dropped out of the ELOQUENT-2 clinical trial because of an infusion reaction.

Prevention and treatment of infusion reactions

Tell your healthcare provider to get medical help right away if you have any of these symptoms after your infusion of Empliciti:

- Fever.
- Chills.
- Rash.
- Trouble breathing.
- Dizziness.
- Light-headedness.

Premedications are given with each dose of Empliciti to reduce the risk of infusion reactions. Reactions can also be managed by pausing the infusion and/or restarting the infusion at a slower rate.

Lymphocytopenia and Neutropenia

Patients may experience conditions called lymphocytopenia and neutropenia, which reflect a lowered level of lymphocytes and neutrophils. White blood cells help to fight infection. Too few white blood cells can lead to infections.

Prevention and treatment of lymphocytopenia and neutropenia

Inform your physician immediately if you experience fever, sore throat, or mouth sores. Fever is the symptom that usually indicates infection in a person who has low neutrophils. Fever is an important sign that immediate medical attention is needed.

The treatment for lymphocytopenia and neutropenia depends on cause and severity. Sometimes the bone marrow (where new blood cells are made) recovers by itself without treatment. The neutropenia accompanying viral infections (such as influenza) may be transient and resolve after the infection has cleared. Mild neutropenia generally has no symptoms and may not need treatment.

Anemia (low red blood cell count)

Red blood cells contain hemoglobin, a protein that contains iron and transports oxygen from the lungs to the body's organs and tissues. When a patient has anemia, the result is low levels of oxygen in the body, which may cause shortness of breath and feelings of exhaustion. Anemia is not an immediate effect of Empliciti + Revlimid + dexamethasone, but one that may appear with duration of treatment.

Prevention and treatment of anemia

Your healthcare providers will determine which treatment regimen for anemia is best suited to your needs and safest for you. The following are options for treatment of anemia:

- Adjusting medications.
- Blood transfusions.
- Erythropoietic (red blood cell-making) agents.

Thrombocytopenia

Thrombocytopenia is a lowered level of platelets in the blood. Platelets help blood to clot; fewer platelets can lead to bruising, bleeding, and slower healing.

Prevention and treatment of thrombocytopenia

You should inform your physician if you experience excessive bruising or bleeding. Management may include platelet transfusions or a thrombocyte growth-stimulating agent, at the discretion of your physician.

Fatigue

Fatigue is commonly associated with cancer and with cancer therapy. 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

Management of fatigue may include treatment, as determined by your physician. 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 fatigue issues.
- A careful review of the side effects of all the other supplements and medications you are taking, in addition to Empliciti + Revlimid + dexamethasone, to ensure that they are not contributing to your fatigue.

Diarrhea

Diarrhea may occur while taking Empliciti + Revlimid + dexamethasone. Dizziness, light-headedness, or fainting may occur due to dehydration caused by either excessive or persistent diarrhea.

Prevention and treatment of diarrhea

Precautions should be taken to prevent dehydration caused by either excessive or persistent diarrhea. You should maintain a proper level of hydration by drinking a sufficient amount of water and seek medical advice if you experience dizziness, light-headedness, or fainting. Your physician may administer antidiarrheal medication or IV hydration, as required.

Fever

Fever is defined as an oral temperature greater than 38°C or 100.4°F in a 24-hour period, or one temperature greater than 38.5°C or 101.3°F. When the white cell count is low, the body's normal defenses against infections are down, and fever needs to be further evaluated immediately. In clinical trials with Empliciti, fevers likely arose from two causes: as a reaction to medication (from the release of cytokines, an immune response that causes flu-like symptoms) and/or from a bacterial or viral infection (from a low white cell count resulting in impaired immune response).

Prevention and treatment of fever

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

- Notify your healthcare team immediately if you have a fever greater than 38.5°C or 101.3°F.
- 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 to have the fever worked up.
- Check your temperature twice a day if you feel warm.
- To avoid dehydration, drink a lot of non-alcoholic and non-caffeinated liquids.
- Take medications to control the fever as indicated.

Your treating physician may also do the following to control fever and treat its cause:

- Tell you to use over-the-counter (OTC) medications that you can buy without a prescription, such as acetaminophen, to treat fever related to flu-like syndrome. Do not take more than the recommended amount of acetaminophen in a 24-hour time frame. There are other drugs used to reduce fever that may be an option, but you should 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, or you may need to receive intravenous antibiotics in the hospital. You may also be given a **colony-stimulating factor (CSF)**, a drug that helps to boost the white cell count.

Constipation

Prevention is the key to managing constipation, which is defined as having fewer than three bowel movements a week. Chronic constipation is defined as infrequent bowel movements or difficult passage of stools that persists for several weeks or longer.

Prevention and treatment of constipation

These strategies may help alleviate constipation:

- Drink at least eight 8-ounce glasses of fluid daily.
- Add plenty of dietary fiber every morning, such as prune juice, apple juice, or bran.
- Get some exercise daily, even if it's just walking. Moving your body increases peristalsis, the rhythmic contractions that move food through the digestive system.
- Report the problem to a member of your healthcare team, who may recommend a stool softener or laxative.

Infections

Infections as mild as a cold (an upper respiratory tract infection) or as severe as pneumonia can occur in people who receive Empliciti + Revlimid + dexamethasone. Cough, runny nose, and sore throat are all common side effects experienced by patients taking Empliciti + Revlimid + dexamethasone and may be signs of an upper respiratory tract infection. The signs and symptoms of pneumonia vary depending on what is causing the infection. Mild signs and symptoms are similar to those of a cold or flu, but they last longer.

Tell your healthcare provider immediately if you have any signs and symptoms of an infection, including:

- Fever.
- Flu-like symptoms (body aches, sweating, chills, fatigue).
- Cough (which may produce phlegm).
- Shortness of breath.
- Chest pain when you breathe or cough.
- Burning with urination.
- A painful skin rash.
- Nausea, vomiting, or diarrhea.

Prevention and treatment of infections

You should report your symptoms to your healthcare team, who will determine how the symptoms should be managed, and if you need to receive an antibiotic or other medications. If your doctor or another doctor covering the practice is not available to diagnose or rule out pneumonia, which can be a severe infection, you should go to an urgent care or emergency facility.

Muscle spasms

Muscle spasms occur when a skeletal muscle contracts forcefully and involuntarily and does not relax. Leg muscles, especially the thighs, hamstrings, and calves, are most likely to contract, but any skeletal muscle in the body can cramp. Dehydration, **electrolyte** imbalance, and physical deconditioning may all cause muscle spasms, but they may also be related to neuropathy caused by treatment or arising from the myeloma itself.

Prevention and treatment of muscle spasms

If you have frequent, painful muscle spasms and cramps that interfere with your sleep or your ability to perform the activities of daily living, you should report the problem to your healthcare provider. You may need a referral to a neurologist to help determine the origin of the problem, and if it is neurologic, to treat the neuropathy.

Some non-neurologic causes of muscle spasms can be prevented by drinking adequate amounts of non-alcoholic and non-caffeinated liquids and getting some light daily exercise. If any of your electrolytes (e.g., sodium, potassium, calcium, magnesium, chloride, phosphate, bicarbonate) are low, your doctor may need to oversee an increase or decrease in your fluid intake and/or prescribe oral or intravenous mineral supplements.

Decreased appetite

There are many causes for loss of appetite during treatment, including side effects of treatment such as diarrhea and constipation. Lack of exercise, anxiety, depression, and pain can also be at the root of the problem. Good communication with members of your healthcare team will help them understand how you're feeling physically and mentally, and may help determine the source of your appetite loss.

Prevention and treatment of decreased appetite

- Managing your gastrointestinal health and controlling diarrhea or constipation while on Empliciti + Revlimid + dexamethasone is an important step in maintaining your appetite.
- If you are losing weight, your doctor or nurse may refer you to a nutritionist or suggest a nutritional supplement to provide more calories.
- If appropriate, your doctor may also refer you to a mental health counselor to help you with depression and/or anxiety.

Looking forward

There are many ongoing or soon-to-be enrolling clinical trials with Empliciti in various myeloma disease settings and in combination with a wide variety of other drugs. Among them are:

- Empliciti used in combination with Revlimid as post-transplant maintenance therapy.
- Velcade + Revlimid + dexamethasone (VRd) + Empliciti in newly diagnosed myeloma.
- Empliciti + Revlimid + dexamethasone (ERd) as induction, consolidation, and maintenance therapy for newly diagnosed, transplant-eligible myeloma.
- Umbilical cord blood-derived natural killer (NK) cells with Empliciti + Revlimid and autologous stem cell transplant (ASCT) for patients with high-risk myeloma.
- Empliciti + anti-PD-1 checkpoint inhibitor Opdivo® + Pomalyst in relapsed/refractory myeloma.
- Empliciti + Revlimid + dexamethasone (ERd) in high-risk smoldering multiple myeloma (SMM).

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 specialists can be reached at InfoLine@myeloma.org or 818.487.7455 or 800.452.CURE.

Terms and definitions

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 white blood cells called plasma cells in response to an antigen that enters the body. The medical term for antibody is "immunoglobulin."

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.

Colony-stimulating factor (CSF): Proteins that stimulate the development and growth of blood cells. Neupogen® (filgrastim), Neulasta® (pegfilgrastim), and Leukine® (sargramostim) are colony-stimulating factors that are used to mobilize stem cells from the bone marrow into the bloodstream prior to apheresis. These may also be used after the transplant to hasten blood count recovery, or to treat low white cell count caused by therapy.

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.

Disease progression: See "**Progressive disease**."

Electrolytes: Minerals in your blood and other body fluids that carry an electrical charge and are essential for life. Electrolytes include sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate. They affect the amount of water in the body, the acidity of the blood (pH), nerve and muscle function (including the heart), and other important processes.

Growth factors: Drugs that stimulate blood stem cells to both grow and be released into the bloodstream.

High-risk myeloma: According to the International Myeloma Working Group (IMWG) consensus on risk stratification in myeloma, markers have been identified that can be applied to more than 90% of all myeloma patients to define high-risk myeloma: ISS stage II/III and the pres-ence of either the t(4;14) or 17p13 genetic mutations by FISH testing.

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

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

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

Lymphocytes: B cells, T cells, and natural killer (NK) cells, which together constitute 30% of white blood cells. B lymphocytes and T lymphocytes are responsible for the adaptive immune response, which enables immune system cells to attach to specific antigens on the cell surfaces of infectious organisms, tumors, and other foreign substances.

Lymphocytopenia: Low levels of B cells, T cells, and natural killer (NK) cells.

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.

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.

Overall response rate (ORR): The percentage of patients in a clinical trial whose monoclonal protein decreased by at least 50% in response to treatment.

Overall survival (OS): The median number of individuals in a group who are alive after a particular duration of time. OS is often used as a measure of treatment efficacy in clinical trials. The lengthening duration of OS in myeloma trials makes it a difficult endpoint to use, leading to the effort to validate minimal residual disease status as a new endpoint.

Progression-free survival (PFS): The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to determine how well a new treatment works. Also called PFS. See "**Progressive disease**."

Progressive disease: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of ≥ 25% from 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.

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.

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 ≤ 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).

Steroid: A type of hormone. Synthetic steroids are often given to myeloma patients along with one or more anticancer drugs and typically enhance the anti-myeloma treatment benefit.

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.

Tumor: An abnormal mass of tissue that results from excessive cell division. In myeloma, a tumor is referred to as a plasmacytoma.

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.

INTERNATIONAL MYELOMA FOUNDATION

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 and maintains a library of publications to help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The following is a partial list of publications available in English, and selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding DARZALEX® (daratumumab)*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding Fatigue*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib)*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding POMALYST® (pomalidomide)*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib)*
- *Understanding Your Test Results*

All IMF publications and periodicals are always free of charge. Visit **publications.myeloma.org** to read, download, or order printed copies. Subscribe to IMF periodicals at **subscribe.myeloma.org** or by contacting the IMF.

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

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