Understanding KYPROLIS®
(carfilzomib) injection

A publication of the **International Myeloma Foundation**

INTERNATIONAL
MYELOMA
FOUNDATION

12650 Riverside Drive, Suite 206
North Hollywood, CA 91607 USA

Telephone:

800.452.CURE
(USA & Canada)

818.487.7455
(worldwide)

Fax: **818.487.7454**

TheIMF@myeloma.org

myeloma.org

u-kypro_en_2018_t8

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®**

Table of contents

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 discusses Kyprolis® (**generic drug name** carfilzomib), the results of **clinical trials** with Kyprolis, how and when Kyprolis is administered, and the possible **side effects** of Kyprolis and how to manage them.

What is Kyprolis?

Kyprolis (pronounced "kye-PRO-lis") is the second drug developed in a new class of drugs called **proteasome inhibitors**. Proteasome inhibitors work by blocking the activity of **enzyme** complexes called **proteasomes**. Both normal **cells** and cancer cells contain proteasomes, which break down damaged and unwanted **proteins** into smaller components. Proteasomes also carry out the regulated breakdown of undamaged proteins in the cell, a process that is necessary for the control of many critical cellular functions. These smaller components are then used to create new proteins required by the cell. Therefore, proteasomes can be thought of as crucial to the cell's "recycling" of proteins.

What are the indications for treatment with Kyprolis?

Kyprolis was first approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of patients with myeloma who have received at least two prior therapies, including the proteasome inhibitor Velcade® (bortezomib) and an **immunomodulatory drug**, Revlimid® (lenalidomide) or Thalomid® (thalidomide). Patients also had to have demonstrated disease progression on or within 60 days of the completion of the last therapy.

In July 2015, the FDA approved Kyprolis given in combination with Revlimid and **dexamethasone** to treat patients with **relapsed** myeloma who have received at least one prior therapy.

In November 2015, the European Commission approved Kyprolis in combination with Revlimid and dexamethasone in the treatment of patients with relapsed myeloma who have received at least one prior therapy. That approval was updated in July 2016, when the European Commission granted an extended indication for Kyprolis to include use in combination with dexamethasone alone for myeloma patients who have received at least one prior therapy.

In January 2016, the FDA approved the supplemental New Drug Application (sNDA) of Kyprolis in combination with dexamethasone or with Revlimid + dexamethasone for the treatment of patients with relapsed or **refractory** myeloma who have received one to three prior lines of therapy. The FDA also approved Kyprolis as a single agent for the treatment of patients with relapsed or refractory myeloma who have received one or more lines of therapy.

In January 2018, the FDA approved the sNDA that adds **overall survival (OS)** data from the phase III ENDEAVOR clinical trial to the label for Kyprolis. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion for recommending a label variation for Kyprolis. As in the US, the new label will include updated OS data from the phase III ENDEAVOR clinical trial.

On October 1, 2018, the FDA approved the supplemental sNDA to expand the prescribing information for Kyprolis to include a once-weekly Kd70 dosing option for patients with relapsed or refractory myeloma. This approval was based on data from the phase III ARROW clinical trial, which demonstrated that Kyprolis administered once-weekly at 70 mg/m^2 (milligram per square meter of body mass) with dexamethasone (once-weekly Kd70) achieved superior **progression-free survival (PFS)** and **overall response rates (ORR)**, with a comparable safety profile, versus twice-weekly Kyprolis administered at a dose of 27 mg/m^2 in combination with dexamethasone (twice-weekly Kd27). The ARROW clinical trial was

conducted in approximately 100 sites worldwide and included 478 patients with relapsed and refractory myeloma who received at least two but no more than three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug. Patients in the clinical trial treated with once-weekly Kd70 achieved a statistically significant 3.7 month improvement in PFS compared to the Kd27 twice-weekly regimen (median PFS 11.2 months for once-weekly Kd70 versus 7.6 months for twice-weekly Kd27). The ORR in patients treated with once-weekly Kd70 was 62.9% versus 40.8% for those treated with twice-weekly Kd27.

Kyprolis + Revlimid + low-dose dexamethasone (KRd) and Kyprolis + low-dose dexamethasone (Kd) are listed on the National Comprehensive Cancer Network (NCCN) guidelines for treatment of myeloma as "Preferred Regimens," category 1 (highest level of evidence) treatment option, for patients with relapsed disease. KRd is listed as an "Other Recommended Regimen," category 2A, option for treatment of newly diagnosed patients.

How does Kyprolis work?

Kyprolis forms an irreversible bond with the proteasome in the nucleus of each myeloma cell. When Kyprolis inhibits proteasomes, the normal balance within a cell is disrupted. This disruption results in a number of effects on the cell, some of which are still being studied. When proteasomes are inhibited in laboratory tests, cancer cells stop dividing and undergo **apoptosis** (cell death). They also stop producing chemicals to stimulate other cancer cells. Cancer cells are more sensitive to these effects than normal cells, so the cancer cells die while normal cells are able to recover.

What were the results with Kyprolis in clinical trials?

The 003 A1 clinical trial

Kyprolis was originally approved as a third-line therapy for myeloma based on the results of the phase II 003 A1 study that were reported in July 2012 in the journal *Blood*. In that study, Kyprolis was given at a dose of 20 mg/m^2 for the first two days of the first cycle, and at 27 mg/m^2 for all subsequent doses.

The ASPIRE clinical trial

In July 2015, the results of the 792-patient, randomized, phase III ASPIRE clinical trial of Kyprolis + Revlimid + dexamethasone (KRd) versus Revlimid + dexamethasone (Rd) led to the expanded FDA approval of KRd as second-line treatment of myeloma. The results of the ASPIRE clinical trial were published in the *New England Journal of Medicine* in January 2015.

In this clinical trial, as in the 003 A1 clinical trial, Kyprolis was administered at a dose of 20 mg/m^2 for the first two days of the first cycle and at 27 mg/m^2 for all subsequent doses. The KRd regimen improved PFS, or duration of **response**, to 26.3 months versus 17.6 months with Rd alone. However, the gold standard for measuring treatment efficacy, the OS of patients in the clinical trial, requires longer follow-up.

In July 2017, two years after the initial approval of KRd as second-line treatment, the final ASPIRE clinical trial data were reported. These data revealed that the clinical trial did meet the endpoint of improved OS, demonstrating that KRd reduced the risk of death by 21% over Rd alone. The median OS was 48.3 months for KRd versus 40.4 months for Rd. Patients received 18 cycles of KRd before continuing with Rd alone until disease progression. The OS data from the ASPIRE clinical trial will be submitted to a future medical conference, to a medical journal for publication, and to regulatory agencies worldwide to support a potential label update.

The ENDEAVOR clinical trial

Results of the phase III ENDEAVOR clinical trial comparing Kyprolis + dexamethasone (Kd) to Velcade + dexamethasone (Vd) in patients with relapsed or refractory myeloma were first released in March 2015. The dose of Kyprolis in the ENDEAVOR clinical trial, 56 mg/m^2 twice weekly, was more than twice the FDA-approved dose used in the 003 A1 and ASPIRE clinical trials. PFS in the Kd arm of the study was twice that of the Vd arm. The PFS benefit was seen both in patients who had prior exposure to Velcade and in those who had no prior Velcade, as well as across all age groups and regardless of high-risk mutations or the number of prior lines of therapy. The three-year OS data from the ENDEAVOR clinical trial were presented in 2017 at the 16th International Myeloma Workshop (IMW), demonstrating that Kd reduced the risk of death by 24% compared with Vd, with a 9-month longer median overall survival benefit than Velcade + dexamethasone. The OS benefit was consistent regardless of prior Velcade therapy.

How is Kyprolis given?

Kyprolis is a freeze-dried powder, which must be reconstituted (dissolved) before it is administered. Kyprolis is administered intravenously (IV) at a doctor's office, hospital, or clinic. Hydration (250–500 mL of normal saline given by IV) should be given with each dose of Kyprolis at the discretion of the treating physician, based upon the patient's tolerance of Kyprolis, the dose of Kyprolis, and the duration of **infusion** time. Caution must be exercised to avoid fluid overload.

What are the dose and schedule of Kyprolis?

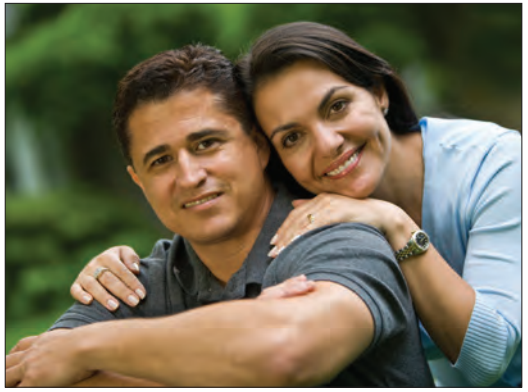
In addition to the once-weekly Kd70 dosing option explained on page 5, Kyprolis can be administered twice-weekly at a dose of 27 mg/m^2 in combination with dexamethasone (twice-weekly Kd27) for three weeks out of every four-week cycle, given on days 1 and 2, days 8 and 9, and days 15 and 16, followed by a 12-day rest period on days 17–28.

Kyprolis was originally approved at a dose of 20 mg/m^2 for the first two days of cycle 1 at and at a dose of 27 mg/m^2 (if the 20 mg/m^2 dose was well tolerated) from day 8 of cycle 1 onward.

Kyprolis is given as an IV infusion over 10 minutes, but your doctor may choose to give it to you more slowly. If Kyprolis is given as part of a combination therapy or at doses higher than 27 mg/m^2, it should be administered as a 30-minute infusion.

As mentioned on page 7, the 56 mg/m^2 dose of Kyprolis was safely used in the ENDEAVOR clinical trial comparing Kyprolis + dexamethasone and Velcade + dexamethasone. In January 2016, based on the safety data from this clinical trial, the FDA amended the dosing information for Kyprolis to include the following:

- When Kyprolis is given as a *single agent*, it may be administered at a dose of 20 mg/m^2 for the first two days of cycle 1, and if tolerated, may be given at a dose of 56 mg/m^2 for the rest of cycle 1 and all subsequent cycles.
- When Kyprolis is given *in combination with dexamethasone*, it may be administered at a dose of 20 mg/m^2 for the first two days of cycle 1, and if tolerated, may be given at a dose of 56 mg/m^2 for the rest of cycle 1 and all subsequent cycles.
- When Kyprolis is given *in combination with Revlimid and dexamethasone*, the recommended starting dose is 20 mg/m^2 for the first two days of cycle 1, and if tolerated, it may be given at a dose of 27 mg/m^2 from day 8 of cycle 1 on. From cycle 13 on, the day 8 and day 9 doses of Kyprolis should be omitted. Kyprolis should be discontinued after cycle 18.



Your doctor will evaluate your disease, your response to Kyprolis, and your tolerance of your medications to determine how many cycles of treatment are right for you, and will make any dose or schedule adjustments as necessary. It may be necessary to reduce the dose of Kyprolis or stop treatment temporarily until a side effect improves, and then resume again. Caution should be exercised with higher doses of Kyprolis. A member of your healthcare team should monitor you carefully for infusion reactions when the Kyprolis is administered. It is very important that you promptly report to your healthcare team any side effects that you experience in the days after your infusion.

Additional precautions:

- Patients should be pre-treated with dexamethasone prior to all cycle 1 doses and if **infusion reaction** symptoms develop or reappear.
- Patients should drink water at a rate of 30 milliliters (1 ounce) for every kilogram (2.2 pounds) of their body weight at least 48 hours before their first infusion.
- Patients should receive appropriate medication to prevent blood clots if they are taking Kyprolis in combination with dexamethasone or with Revlimid + dexamethasone. The medication chosen should be based on an assessment of individual risk factors for blood clot.
- Patients should receive antiviral therapy to decrease the risk of herpes zoster reactivation (shingles).
- Patients who are receiving hemodialysis for kidney failure should receive Kyprolis after the hemodialysis procedure.

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

The most common side effects, those seen in 30% or more of the patients who received Kyprolis in clinical trials, include fatigue, **anemia** (low **red blood cell** count), nausea, **thrombocytopenia** (low **platelet** count), dyspnea (shortness of breath), diarrhea, and fever. Kyprolis may also cause dizziness, fainting, and/or a drop in blood pressure, so caution is advised if you are operating machinery, including automobiles.

Serious side effects (also called "serious adverse events") were reported to the FDA by researchers during clinical trials. They included cardiac failure events (e.g., **congestive heart failure**, pulmonary edema, decreased heart ejection fraction), reported in 7% of patients; pulmonary arterial hypertension (abnormally high blood pressure in the arteries of the lungs) in 2% of patients, and liver failure, including fatal cases, in less than 1% of patients. Death due to cardiac arrest has occurred within a day of Kyprolis administration. Patients with pre-existing heart conditions may be at greater risk for cardiac complications. Although underlying heart disease does not exclude use of Kyprolis, patients with New York Heart Association (NYHA) Class III and IV congestive heart failure, as well as those with uncontrolled conduction abnormalities or a history of heart attack within the previous six months, were excluded from clinical trials. Prescribing information for Kyprolis recommends that patients be monitored for cardiac complications and managed promptly.

Kyprolis can cause other rare but serious side effects. You must report any changes in your health promptly to your medical team so that they can monitor your signs and symptoms. Call your doctor immediately if you experience any of the following: fever, chills, shivering, chest pain, cough, swelling of the feet or legs, bleeding, bruising, weakness, headaches, confusion, seizures, loss of sight, shortness of breath, dizziness, light-headedness, fainting spells, or any other side effect that bothers you or doesn't go away.

Kyprolis can cause harm to a fetus if it is administered to a pregnant woman. Women should avoid becoming pregnant during treatment with Kyprolis.

Infusion reactions (a spectrum of complications including fever, chills, joint pain, muscle pain, facial flushing, facial swelling, vomiting, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain) can occur immediately following an infusion of Kyprolis or up to 24 hours after. Administration of dexamethasone prior to the infusion of Kyprolis reduces the incidence and severity of infusion reactions.

Any concerns or questions about these issues should be discussed with your doctor or nurse, who can provide more information in greater detail about these and other possible side effects. Speak with your doctor or nurse if you notice ANY changes in your health while you are taking Kyprolis or any other medication.

Fatigue

Fatigue is the most common side effect associated with Kyprolis therapy, one that can appear with increasing severity over time. See the IMF publication, *Understanding Fatigue*, for further information about this topic and about anemia.

Prevention and treatment of fatigue

Management of fatigue may include supportive care as determined by your physician. The effects of fatigue may be minimized by maintaining:

- A moderate level of activity, neither too much nor too little.
- A healthy diet and proper fluid intake.
- A consistent sleeping schedule with enough rest.
- Regularly scheduled visits with your doctor or healthcare professional.

Anemia

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 side effect of Kyprolis, but one that can appear with duration of treatment.

Prevention and treatment of anemia

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

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

Nausea

Nausea may occur while taking Kyprolis, but is typically not severe. If vomiting occurs and leads to dehydration, the patient may experience dizziness, light-headedness, or fainting. Medical treatment may be required for dehydration.

Prevention and treatment of nausea

Precautions should be taken to prevent dehydration caused by vomiting. Drink a sufficient amount of water and other fluids. Seek medical advice if

you experience dizziness, lightheadedness, or fainting. Your physician may administer anti-emetic medication (to prevent vomiting) or intravenous hydration, as required.

Thrombocytopenia (decreased platelet levels)

Patients taking Kyprolis often experience thrombocytopenia – a lowered level of platelets in the blood. Platelets help blood to clot; fewer platelets can lead to easier bruising, bleeding, and slower healing. The platelet level decreases with treatment but, after the required interval between doses, should return to the baseline level by the beginning of the next cycle.

Prevention and treatment of decreased platelet levels

You should inform your physician if you experience excessive bruising or bleeding. Management may include platelet transfusions at the discretion of your physician. A baseline low platelet count does not necessarily preclude treatment with Kyprolis since a platelet transfusion can rectify the situation.

Dyspnea (shortness of breath)

If there is a sudden change in your breathing, it is urgent that you contact your doctor immediately. There have been reports of heart and lung disorders in patients receiving Kyprolis, so shortness of breath can be a sign of a serious problem and must be reported to your doctor promptly.

Prevention and treatment of dyspnea

Appropriate measures to prevent and treat shortness of breath depend on the cause of this problem. Your doctor will assess your heart and lungs and order blood tests before deciding upon the correct course of action.

Diarrhea

Diarrhea may occur while taking Kyprolis. Dizziness, lightheadedness, 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, lightheadedness, or fainting. Your physician may administer antidiarrheal medication or IV hydration, as required.

Fever

Fever can signal bacterial or viral infection, an adverse reaction to a drug, or in rare cases, an aggressive myeloma relapse. Since fever can be the sign of a life-threatening condition, you should report this problem immediately. The combination of fever and shortness of breath is of special concern. If this occurs, it is urgent that the patient is seen by a healthcare professional to receive immediate treatment.

Prevention and treatment of fever

Your doctor will perform tests to determine the cause of the fever and will take appropriate action, which may include one or more of the following:

- Antibiotic therapy.
- Antiviral therapy.
- Treatment with acetaminophen.
- Hydration.
- Change in therapy.

Other side effects of Kyprolis

Other side effects can occur with Kyprolis, but they are much less frequent. These side effects include **tumor lysis syndrome (TLS)**, lung disorders, and liver problems. You will be monitored carefully during treatment for any signs of these problems. If you have questions or concerns about any of these potential issues, you should discuss them with your treating physician.

You should contact your doctor immediately if you experience any of the following:

- Shortness of breath.
- Flu-like symptoms (for example, fever, chills, or shivering).
- Chest pain.
- Cough.
- Dizziness, light-headedness, or fainting spells.
- Swelling of the feet, ankles, or legs.
- Pregnancy (women should not receive Kyprolis if they are pregnant).
- Any other side effect that bothers you or does not go away.

Good communication with your healthcare team is essential while you are receiving therapy for myeloma. Ask your doctor for a number you can call if you need immediate help, especially after office hours and on the weekend. An important part of being a good patient is to report side effects promptly and clearly. Your doctor cannot ensure effective treatment with good quality of life unless you play an active role in your own treatment. The IMF is here to help facilitate the best possible dialogue with your healthcare team.

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 de nitions

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.

Apoptosis: A normal cellular process leading to the death of a cell.

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.

Cell: The basic unit of any living organism. Millions of microscopic cells comprise each organ and tissue in 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.

Congestive heart failure: A condition that occurs when the heart's pumping function is weakened, causing a series of events that result in the body retaining fluid and salt. If fluid builds up in the arms, legs, feet, ankles, lungs, or other organs, the body becomes congested.

Dexamethasone: A powerful corticosteroid given alone or with other drugs.

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.

Generic drug name: A generic drug name refers to the chemical makeup of a drug rather than to 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®.

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

Infusion: Delivering fluids or medications into the bloodstream over a period of time.

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

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

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.

Platelets: One of the three major types of blood cells, the others being red blood cells and white blood cells. Platelets plug up breaks in the blood vessel walls and release substances that stimulate blood clot formation. Platelets are the major defense against bleeding. Also called thrombocytes.

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 progression-free survival is one way to see 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: A joined group (or complex) of enzymes that destroy damaged or unwanted proteins and undamaged proteins that require degradation in the cell. This turnover or "recycling" of proteins is important to maintain balance within the cell and helps to regulate several functions including cell growth.

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.

Red blood cells (RBC, erythrocytes): Cells in the blood that contain hemoglobin, deliver oxygen to all parts of the body, and take away carbon dioxide. Red cell production is stimulated by a hormone (erythropoietin) produced by the kidneys. Myeloma patients with damaged kidneys don't produce enough erythropoietin and can become anemic. Myeloma patients can also become anemic because of myeloma cells' effect on the ability of the bone marrow to make new red blood 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).

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 lysis syndrome (TLS): A disorder caused by the break-down products of dying cancer cells, which can overwhelm the kidneys and lead to kidney failure. TLS can occur when a patient responds very quickly and deeply to therapy. TLS is usually treated with allopurinol, a treatment for gout.

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.

818.487.7455 **800.452.CURE** **TheIMF@myeloma.org**