Understanding VELCADE®
(bortezomib) injection

A publication of the 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 trained specialists who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 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.

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Improving Lives Finding the Cure®
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.

Understanding VELCADE® (bortezomib) injection will familiarize you with Velcade® (also known by the generic drug name “bortezomib”), which plays an important role throughout the myeloma disease course, from induction therapy for those who are newly diagnosed, to a possible role as part of a conditioning regimen for stem cell transplant, to consolidation and/or maintenance therapy, to treatment for those whose myeloma has become refractory to and/or relapsed on previous therapies.

How does Velcade work?

Velcade is the first in a class of drugs called proteasome inhibitors. It was first approved by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory myeloma in May 2003. In June 2008, the FDA expanded Velcade’s approval to include the frontline setting. In January 2012, the FDA approved subcutaneous (SQ, under the skin) administration of Velcade. In August 2014, the FDA expanded the Velcade label to allow for retreatment of patients who previously responded to Velcade and who relapsed at least six months after completing prior Velcade treatment.

Velcade can be used alone, in combination with dexamethasone, or as part of a more complex multi-drug regimen.

Velcade works by inhibiting 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 protein components are then used to create new proteins required by the cell. Proteasomes can be thought of as crucial to the cell’s “recycling” of proteins.

When Velcade inhibits proteasome function, 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, myeloma cells stop dividing. Proteasome inhibition also causes myeloma cells to stop producing chemicals that stimulate other myeloma cells: The autocrine feedback loop is interrupted. Myeloma cells are more sensitive to these effects than normal cells, so myeloma cells die while normal cells can recover.

How is Velcade given?

Velcade comes in the form of a freeze-dried powder, which must be reconstituted before it is administered.

As approved in 2003, Velcade is given as an intravenous (IV, into the vein) infusion injected through either a peripheral IV line (usually in the arm) or a central IV line (usually in the chest, also known as a “central venous catheter”). Velcade is injected over a short period of 3 to 5 seconds.

In January 2012, the FDA approved a second method for administering Velcade to patients. In addition to giving Velcade as an IV infusion, it is possible to receive Velcade as a SQ injection, commonly known as a “shot.” The SQ injection is given at the doctor’s office, at the same dose and on the same schedule as IV Velcade. The SQ injections should be given using a sequential rotation of four injection sites: the left and right sides of the abdomen and the left and right thighs. It is important to note that there is no data from clinical trials to support administration of SQ Velcade in the arm.

Like IV Velcade, SQ Velcade is approved to be administered throughout the myeloma disease course. SQ Velcade causes significantly less peripheral neuropathy (PN) than IV Velcade and may also reduce the occurrence of gastrointestinal (GI) side effects. Other side effects of SQ Velcade are the same as those for IV Velcade. Approximately 6% of patients in clinical trials with SQ Velcade had site reactions (itching, swelling, pain, and/or redness at the injection site). If you have pre-existing neuropathy or GI problems, you should discuss using SQ Velcade with your doctor.

Understanding VELCADE® (bortezomib) injection
When is Velcade given, and at what dose?

In standard protocols, Velcade is given at the doctor’s office or a clinic at 1.3 mg per square meter of body mass, twice per week, for 2 weeks, followed by a 10-day rest period. Patients and their doctors typically choose a Monday + Thursday or Tuesday + Friday schedule. At least 72 hours are needed between doses, so that normal cells have a chance to recover from the effects of the drug. Therefore, changes in the administration schedule must be limited to delaying an injection for a day, rather than moving the injection up one day.

There are situations in which it may be necessary to reduce the dose of Velcade and/or administer it once, rather than twice, per week. Your doctor may order dose reductions and/or treatment schedule changes if you experience side effects. Schedule and dose changes can also be ordered preventively for patients with pre-existing medical problems or for patients who are elderly and frail.

In 2011, IMF International Myeloma Working Group (IMWG) members Dr. Antonio Palumbo and Dr. Kenneth Anderson published a dosing regimen for older and/or frail patients in the *New England Journal of Medicine*. Among that population of patients, Dr. Palumbo recommends that dosages of Velcade and the drugs with which it is commonly combined be adjusted according to the patient’s age and concurrent illnesses and/or tolerance.

Dr. Palumbo provides a helpful table for specific dose adjustments recommended for frail patients (see Table 1). His “go-go,” “moderate-go,” “slow-go” three-group system is now in use around the world.

The specific treatment algorithm for Velcade dose reductions within combinations is summarized in Table 2, which includes, at dose level “–2,” a dose reduction of Velcade to once per week (versus twice per week in the standard regimens).

### Table 1: Frail Patient’s Velcade Treatment Algorithm

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age: over 75 years.</td>
</tr>
<tr>
<td>• Mild, moderate, or severe frailty: help needed for household and personal care.</td>
</tr>
<tr>
<td>• Comorbidities and organ dysfunction: cardiac, pulmonary, hepatic, renal.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Go-go</th>
<th>Moderate-go</th>
<th>Slow-go</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level 0</td>
<td>Dose level –1</td>
<td>Dose level –2</td>
</tr>
<tr>
<td>No risk factors</td>
<td>At least one risk factor</td>
<td>At least one risk factor + any G 3–4 non-hematologic AE</td>
</tr>
</tbody>
</table>

### Table 2: Velcade Treatment Algorithm

<table>
<thead>
<tr>
<th>Dose level 0</th>
<th>Dose level –1</th>
<th>Dose level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>Age 65–75 years</td>
<td>Age &gt; 75 years</td>
</tr>
<tr>
<td>1.3 mg/m²; days 1, 4, 8, 11 3 weeks</td>
<td>1.3 mg/m²; days 1, 4, 8, 11 3 weeks or 1.3 mg/m²; days 1, 8, 15, 22 5 weeks</td>
<td>1.0–1.3 mg/m²; days 1, 8, 15, 22 5 weeks</td>
</tr>
</tbody>
</table>

If a Grade 3–4 AE (adverse event, or side effect) occurs: 1. discontinue therapy; 2. wait for a Grade 1 AE; 3. restart at a lower dose

Velcade is frequently given in combination with other anti-myeloma drugs, including dexamethasone, cyclophosphamide, Revlimid® (lenalidomide), thalidomide, and melphalan/prednisone. Velcade is a required component of the FDA-approved combination therapy of Farydak® (panobinostat) + Velcade + dexamethasone for patients who have had one to three prior therapies for myeloma, including Velcade and an immunomodulatory drug such as thalidomide, Revlimid, or Pomalyst® (pomalidomide). Velcade is also being tested in combination with many other agents that are still in clinical trials. Detailed information about Velcade therapy in combination with dexamethasone, thalidomide, Revlimid, or Farydak is discussed in separate IMF booklets.

### Velcade in clinical trials

A wide range of clinical trials has been conducted with Velcade. Studies have demonstrated the efficacy of Velcade therapy for patients in the frontline, conditioning, relapsed/refractory, and maintenance settings.

At the 2015 annual meeting of the American Society of Hematology (ASH), three important myeloma studies were presented that have had profound effects on clinical practice. Each clinical trial involved a regimen containing Velcade in combination with an immunomodulatory drug:

- IMF Chairman Dr. Brian G. M. Durie presented the long-anticipated results of a large, randomized clinical trial known as SWOG 0777 that compared the combination of Velcade + Revlimid + dexamethasone (VRD) to Revlimid + dexamethasone alone (RD) in newly diagnosed myeloma patients who were not candidates for stem cell transplant. The trial results demonstrated that VRD extended both progression-free survival (PFS) and overall survival (OS) by a year longer than RD. These data firmly established the superiority of triplet frontline therapy over two-drug therapy and confirmed...
the efficacy of the combination of a proteasome inhibitor and an immunomodulatory drug. The SWOG 0777 study was published in *The Lancet* in December, 2016, and was named the major “practice-changing” trial for 2016 in *Nature Reviews Clinical Oncology*.

Dr. Michel Attal presented the results of the Intergroupe Francophone du Myélome (French myeloma trial group) IFM 2009 clinical trial, which was designed to determine if autologous stem cell transplant (ASCT) is still a necessary component of treatment for newly diagnosed patients in the era of powerful novel therapies. All patients were treated with VRD, and approximately half of them went on to have high-dose melphalan followed by ASCT. Patients in both arms of the study received maintenance therapy with Revlimid. While the trial demonstrated that VRD followed by upfront ASCT provides longer PFS, and data analysis showed higher rates of MRD negativity among those who had upfront ASCT, the 4-year follow-up data presented at the ASH meeting in December 2017 show that OS – the gold standard to demonstrate benefit of one treatment over another – remains the same in the transplant and non-transplant arms. Moreover, survival benefit in MRD-negative patients is the same whether patients were in the transplant arm of the study or achieved their MRD-negativity with VRD and no transplant. The trial investigators will have to follow the survival data out to 10 years or more to see if there is an eventual separation in the survival curves between the transplant and non-transplant arms of the study, but as of this writing in early 2018, the curves continue to overlap.

Dr. Philippe Moreau presented the results of another IFM study that compared the use of triplet therapies with Velcade + thalidomide + dexamethasone (VTD) and Velcade + cyclophosphamide + dexamethasone (VCD) as induction therapy prior to ASCT. The results, subsequently published in *Blood*, demonstrate the superiority of the VTD triplet combining a proteasome inhibitor and an immunomodulatory drug over VCD, which combines a proteasome inhibitor and an alkylating agent.

At the June 2016 annual meeting of the American Society of Clinical Oncology (ASCO), Dr. Antonio Palumbo presented the results of the CASTOR study, which determined that Darzalex® + Velcade + dexamethasone is superior to Velcade + dexamethasone alone. The results of this study were published in the *New England Journal of Medicine* in August 2016, and in November of that year, the FDA approved Darzalex in combination with Velcade + dexamethasone for patients who have had at least one prior therapy. The European Medicines Agency (EMA) followed suit in April 2017. The ASH meetings held in December of 2016 and 2017 featured several important presentations of data from clinical trials in which Velcade was combined safely and effectively with a new therapy plus dexamethasone to treat patients with relapsed/refractory myeloma. The following trials are ongoing:

- Velcade + dexamethasone + and nelfinavir (an approved HIV treatment), now in phase II trials.
- Velcade + dexamethasone + venetoclax (a BCL-2 inhibitor), now in phase III trials.
- Velcade + dexamethasone + selinexor (a selective inhibitor of nuclear export, or SINE®), now in phase III trials.

Because of its effectiveness and broad use in myeloma, Velcade is often used as the standard of care in randomized clinical trials or as a platform drug for novel combination therapies. Velcade is currently in scores of clinical trials, including those evaluating:

- Use of Velcade + high-dose melphalan as conditioning for autologous transplant.
- Use of SQ Velcade as maintenance therapy.
- Use of Velcade + Pomalyst + dexamethasone in relapsed/refractory myeloma.
- Use of Velcade + plerixafor as a stem-cell mobilizer for stem cell harvesting.
- Use of Velcade + Revlimid + Darzalex + dexamethasone in newly-diagnosed myeloma.

**Use of Velcade in clinical practice in 2018**

**In the frontline setting**

Numerous studies have demonstrated the efficacy of Velcade in combination with:

- Melphalan + prednisone (VMP).
- Cyclophosphamide + dexamethasone (VCD, also known as CyBorD).
- Thalidomide + dexamethasone (VTD).
- Revlimid + dexamethasone (VRD and VRD-lite).

It is important to discuss with your doctor the most appropriate combination and strategy in your case. The choice is determined by several factors, including plans for autologous transplantation or not; presence or absence of high-risk chromosome features (t(4;14); t(14;16); t(14;20); del 17p), and the presence or absence of kidney problems or underlying neuropathy. In addition to these medical concerns, personal preference and financial impact are also important considerations.
In other disease settings, including consolidation, maintenance, and relapse

In these settings various combinations and sequences of therapy with Velcade have been demonstrated to be effective. Details should be discussed with your doctor.

It is important to note that Velcade is active and well-tolerated in patients with relapsed myeloma with varying degrees of renal (kidney) insufficiency. Efficacy/safety in clinical trials were not substantially affected by severe-to-moderate versus none-to-mild kidney impairment. Several trials have confirmed the safety and efficacy of Velcade for patients with renal impairment.

In addition, several clinical trials using various treatment strategies incorporating Velcade have shown that Velcade can help overcome poor-risk genetic mutations, t(4;14) in particular, and significantly improve OS. Clinical trials with Velcade have also demonstrated its ability to help prevent bone loss in myeloma patients.

There is low risk of venous thromboembolism (VTE) with Velcade, and Velcade may even provide a protective effect against VTE in combination with IMiD-based regimens.

**What are the possible side effects of Velcade?**

Most of the side effects associated with Velcade are manageable and predictable. The most important and most frequently occurring side effects are described below. Your doctor or nurse 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.

**Peripheral neuropathy**

Peripheral neuropathy (PN) is a serious condition in which treatment affects nerves in the hands, feet, legs, and/or arms. Symptoms of PN include numbness, tingling, or even pain in the hands, feet, legs, and/or arms. Some patients may have experienced PN from the effects of the myeloma monoclonal protein itself and/or from previous treatments for myeloma. If you begin taking Velcade with this pre-existing condition, it is especially important that you pay particular attention to the extent of your discomfort, so that you can rapidly report a worsening of your condition to your doctor. If detected and managed appropriately, the neuropathy is often reversible.

SQ Velcade causes significantly less PN than IV Velcade. In a French trial that compared SQ to IV Velcade, patients who received SQ Velcade had an incidence of PN of any severity of 38%, while those who received IV Velcade had a 53% incidence of any grade of PN. Only 6% of the patients who received SQ Velcade had PN of Grade 3 or 4 (on a scale where 1 is the lowest and 4 the highest grade), while 16% of the IV patients had Grade 3 or 4 PN. SQ Velcade may also have reduced side effects on the gastrointestinal system (nausea, constipation, diarrhea).

**Prevention and treatment of PN**

You are strongly advised to contact your doctor if you experience new or worsening symptoms of PN, as early detection and dose modification may prevent progression of this condition. Notifying your doctor also allows for appropriate modifications of the Velcade dose and/or schedule.

You should be aware that very detailed recommendations for Velcade dose and schedule modifications are available (see Tables 1 and 2). These are the key principles:

- Avoid progressive PN, especially if any significant pain develops (what is called Grade 2). Although PN can be reversible, it may be partly but not fully reversible. Prevention is the best approach. This requires early, proactive dose and/or schedule modifications.

- Discuss options for dose/schedule/method of administration changes with your doctor. The main types of modification are:

  1. **Dose reduction.** This is done in stepwise fashion:
     - Full dose: 1.3 mg/m² of body surface area.
     - First dose reduction: 1.0 mg/m².
     - Half dose: 0.7 mg/m².
  
  2. **One day per week option.** Several recent studies have shown that using Velcade 1 day/week instead of the standard 2 day/week schedule can retain full efficacy (with some of the major combinations now used) and significantly reduce the risk of neuropathy of Grade 2 or higher.

  3. **SQ administration option.** SQ Velcade causes significantly less peripheral neuropathy than IV Velcade.

**Fatigue**

Fatigue is a common side effect associated with Velcade therapy. Although fatigue is generally not severe, caution is advised if you are operating machinery, including automobiles. Please see the IMF publication *Understanding Fatigue* for further information on this debilitating side effect and how to manage it.
Prevention and treatment of fatigue
Management of fatigue may include supportive care as determined by your doctor. The effects of fatigue may be minimized by maintaining:
- A moderate level of daily activity.
- A healthy diet and proper fluid intake.
- A consistent sleeping schedule with enough rest at night.
- Regularly scheduled visits with your doctor or healthcare professional.

Nausea
Nausea may occur while taking Velcade and may be associated with dizziness, light-headedness, or fainting if it leads to dehydration. Medical treatment may be required for dehydration.

Prevention and treatment of nausea
Precautions should be taken to prevent dehydration caused by vomiting. You should drink a sufficient amount of water and other fluids and seek medical advice if you experience dizziness, light-headedness, or fainting. Your doctor may administer anti-emetic medication (to prevent vomiting) or IV hydration, as required.

Diarrhea
Diarrhea may occur while taking Velcade. 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 doctor may administer antidiarrheal medication or IV hydration, as required.

Decreased platelet levels
Myeloma patients taking Velcade often experience a condition called thrombocytopenia – a lowered level of platelets in the blood. Platelets help blood to clot; fewer platelets can lead to bruising, bleeding, and slower healing. The platelet level falls 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 doctor if you experience excessive bruising or bleeding. Management may include platelet transfusions at the discretion of your doctor.

Low blood pressure (hypotension)
A drop in blood pressure may occur after receiving Velcade. If you have a history of fainting or low blood pressure or are taking medication that can cause low blood pressure (such as antihypertensive medication, that is, medication to treat high blood pressure), it is important that you tell your doctor about your condition before you begin receiving Velcade. Dizziness, especially when it occurs after rapidly sitting up or standing from a lying-down position, may be a sign of low blood pressure.

Prevention and treatment of low blood pressure
You should seek medical advice if you experience dizziness, light-headedness, or fainting. Caution is advised when operating machinery, including automobiles. You should take precautions to prevent dehydration (drinking plenty of water, for example), and your doctor may administer medication for the treatment of low blood pressure. It is also important to inform your doctor about any additional medications you are taking, particularly for the treatment of hypertension (high blood pressure).

Other side effects of Velcade
Other side effects that may occur with Velcade include headache, insomnia, occasional rash, fever, cough, back pain, and muscle cramps. Velcade has been shown to increase the incidence of reactivation of the herpes zoster virus, which is known to cause shingles (a painful, itchy rash usually located on one side of the body). Patients with myeloma have a higher risk for developing shingles because myeloma compromises the immune response. Please talk to your doctor about taking an anti-viral medication to reduce your risk for shingles while you are receiving Velcade and remember to discuss ANY changes in your health with a doctor or nurse on your healthcare team.

Will a reduction in dose of Velcade change the effectiveness of treatment?
It is important to communicate openly with your doctor or healthcare professional and keep regular appointments to maintain your Velcade treatment schedule. Your doctor may choose to lower your dose of Velcade as part of an overall plan to manage a particular side effect you experience. The recommended initial dose of Velcade is 1.3 mg/m². However, a lower dose of 1.0 mg/m², which is the first dose reduction your doctor is likely to try, has also been proven to have efficacy against myeloma. In the small study that examined both of these doses, there was no significant difference in effectiveness between the two doses. Your doctor may also choose to skip a scheduled dose to reduce the severity of a side effect before continuing treatment.
Studies have shown that administration of Velcade on a weekly schedule in combination with other anti-myeloma agents is associated with a reduction in side effects, particularly peripheral neuropathy, without significant reduction in efficacy.

**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**

**Autocrine:** The process whereby a growth factor is both produced by a cell (such as a myeloma cell) and can also stimulate the cell to grow, creating a positive feedback loop. Also see “Paracrine.”

**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, and in addition, they 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.

**Conditioning:** A treatment regimen given to a patient to destroy cancer cells prior to stem cell transplant. The most common conditioning regimen given to myeloma patients is 200 mg of melphalan per square meter of body mass.

**Deep vein thrombosis (DVT):** A condition that occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body, usually in the legs. Deep vein thrombosis can cause leg pain or swelling, but may occur without any symptoms.
**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:** See “**Induction therapy**.”

**Gastrointestinal side effects:** Side effects of medication that affect the digestive tract, such as nausea, vomiting, diarrhea, and constipation.

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

**Induction therapy:** The initial treatment used in an effort to achieve remission in a newly diagnosed myeloma patient. Sometimes called “frontline” therapy.

**Maintenance therapy:** Drugs given to patients in remission to delay or prevent a relapse.

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

**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.

**Paracrine:** In a paracrine loop, factors produced by the microenvironment surrounding myeloma cells can stimulate these cells. Stimulated myeloma cells produce factors that can in turn stimulate microenvironmental cells. Also see “**Autocrine.**”

**Peripheral neuropathy (PN):** Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

**Plasma:** The liquid part of the blood in which red blood cells, white blood cells, and platelets are suspended.

**Plasma cells:** Special white blood cells that produce antibodies (immunoglobulins). Myeloma is a cancer of the plasma cells. Malignant plasma cells are called myeloma cells. In myeloma, malignant plasma cells produce abnormal antibodies that lack the ability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor marker for myeloma. The presence of malignant plasma cells in the bone marrow can lead to organ and tissue damage (anemia, kidney damage, bone disease, and nerve damage).

**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.

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**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.

**Pulmonary embolism (PE):** A condition that occurs when a blood clot in the vein (deep vein thrombosis, or DVT) breaks loose, travels through the bloodstream, and lodges in a lung, blocking blood flow.

**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).

**Transplant (transplantation):** There are several different types of transplantation.

- **Peripheral blood stem cell (PBSC) transplant** – Doctors remove healthy blood-making stem cells from a patient’s circulating blood (not from the bone marrow), which are then frozen and stored. The patient receives high-dose chemotherapy to destroy the cancer cells, but healthy blood cells are also destroyed. The frozen
stem cells are then defrosted and returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment.

- **Autologous transplant** – A procedure in which stem cells are removed from a patient’s blood and then are given back to the patient following intensive treatment.

- **Bone marrow transplant** – This term refers to the process of collecting stem cells from the bone marrow and infusing them into a patient. This term is used less frequently today in myeloma as stem cells are now collected from the peripheral (circulating) blood.

- **Allogeneic (allograft) transplant** – The infusion of bone marrow or stem cells from one individual (donor) to another (recipient). A patient receives bone marrow or stem cells from a compatible, though not genetically identical, donor. An HLA blood test is done to determine if a patient has a potential donor match. A donor may be a family member or may be obtained through a donor registry such as the National Marrow Donor Program (NMDP). Rarely, donor cells may be obtained from an umbilical cord blood bank. The donor’s immune system cells recognize the recipient’s myeloma cells as foreign, and attack them. Unfortunately, the donated cells also attack other tissues in the recipient’s body, causing graft-versus-host disease (GVHD), which may be fatal.

- **Reduced-intensity conditioning (RIC) allo transplant** – A newer and, for myeloma, safer technique than an allogeneic transplant. RIC is a non-myeloablative, reduced-intensity “mini-allo” transplant performed within 180 days after a standard autologous transplant.

- **Tandem transplant** – A term used to indicate two autologous transplants done in succession. Tandem transplants are usually planned with 3-month to 6-month intervals between transplants. Tandem transplantation has become less common in the US in the era of effective novel therapies.

- **Matched unrelated donor (MUD) transplant** – Refers to a stem cell transplantation procedure in which the patient and the stem cells are genetically matched but are not from family members. This procedure is not recommended for myeloma patients because it carries an unacceptably high mortality rate from graft-versus-host disease (GVHD).

- **Syngeneic transplant** – The infusion of bone marrow or stem cells from one identical twin into another.

- **Umbilical cord blood transplant** – Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks. Because multiple cords are needed to provide enough stem cells for an adult transplant, the risk of graft-versus-host disease is increased with this type of transplant, making it even riskier for myeloma patients.

**Venous thromboembolism (VTE):** A condition that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Risk factors include infection, age > 75, cancer, and a history of VTE. See “Deep vein thrombosis (DVT)” and “Pulmonary embolism (PE).”

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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’s library of educational publications will help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The IMF publications listed below are available in English, and selected titles are also available in other languages. All IMF publications are free of charge and can be viewed, downloaded, or ordered at publications.myeloma.org

- 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

In addition, the IMF produces an array of Tip Cards, concise reference tools on a variety of topics of interest, as well as periodicals such as the quarterly journal *Myeloma Today*, the weekly e-newsletter *Myeloma Minute*. Subscriptions to all IMF periodicals are free of charge at subscribe.myeloma.org

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

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