Understanding the VRd Regimen for Newly Diagnosed Myeloma
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.
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 with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful those discussions will be.

The Understanding the VRd Regimen booklet discusses a combination therapy for treating newly diagnosed myeloma that consists of three drugs: Velcade® (generic drug name bortezomib), Revlimid® (generic name lenalidomide), and dexamethasone (which is a generic name; there are many branded products). VRd combination therapy is sometimes written as “VRD,” “RVD,” or “RVd.”

This booklet will familiarize you with the way this combination therapy works, how it has been tested in clinical trials, the indication for which it is approved, how and when it is administered, its possible side effects and their management, and special precautions you need to take while taking VRd.

As a newly diagnosed patient, you may also want to read the IMF’s Patient Handbook, which will introduce you to myeloma and help you better understand this complex disease.

What is VRd?

The VRd regimen is based on the highly effective combination of a proteasome inhibitor (Velcade), an immunomodulatory drug, or “IMiD,” (Revlimid), and a steroid (dexamethasone). Each of these classes of drugs has a different way of attacking myeloma, and each drug enhances the activity of the others. This triplet regimen has proven to be both highly effective and well tolerated in newly diagnosed myeloma patients.

The SWOG 0777 study

VRd was approved based on the data from the phase III SWOG (Southwest Oncology Group) 0777 study, in which 539 newly diagnosed patients from 139 institutions were randomly assigned to receive either VRd or Revlimid + dexamethasone (Rd). VRd was given as eight 21-day cycles; Rd was given as six 28-day cycles. After completion of frontline therapy, all patients received ongoing Rd maintenance therapy. At a median follow-up of 55 months, the study met its primary objective of showing that the addition of Velcade to Rd significantly improved progression-free survival (PFS), which was 43 months with VRd and 30 months with Rd. The median overall survival (OS) was also significantly improved in the VRd group (75 months vs 64 months in the Rd group). Treatment-related side effects were well balanced between the two treatment groups. See below for a discussion of side effects and their management.

The standard dose and schedule of VRd

- Velcade is given at 1.3 mg per square meter of body mass (1.3 mg/m²) on days 1, 4, 8, and 11 of a 21-day cycle.
- Revlimid is given at 25 mg per day on days 1–14 of a 21-day cycle.
- Dexamethasone is given at 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.

Velcade was approved in 2003 as an intravenous infusion. In 2012 it was also approved as a subcutaneous (“SQ,” beneath the skin) injection, commonly known as a shot. You may receive Velcade by either method:

- IV infusions are injected through a peripheral IV line (usually in the arm) or a central IV line (usually in the chest). Velcade is injected over a short period of 3–5 seconds.
- SQ injections should be given using a sequential rotation of four sites: the left and right sides of the abdomen and the left and right thighs. (There is no data from clinical trials to support SQ injections given in the arm.)

If needed, your doctor can reduce your dose of Velcade and/or can administer Velcade only once, rather than twice, per week.

Revlimid is taken orally as a capsule that is swallowed with water. Revlimid comes in a range of lower-dosage capsules as well as standard 25-mg capsules. You doctor may reduce your Revlimid dose if needed.
Dexamethasone is taken orally as pills that are swallowed with water. To avoid irritation of the stomach, dexamethasone should be taken with food or after a meal. Your doctor may reduce your dose of dexamethasone as needed.

The “VRd-lite” regimen for older or frail patients includes weekly dosing of Velcade and reducing the starting dose of Revlimid from 25 to 15 mg.

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

Side effects of VRd that occurred in 10% or more of patients include fatigue, damage to the nerve cells, particularly in the hands and feet (peripheral neuropathy), anemia, low levels of certain types of white blood cells called lymphocytes and neutrophils, and low levels of blood cells called platelets, or thrombocytes. Your blood counts will be monitored frequently, especially during your first two cycles of therapy. Dose interruptions or reductions may be required.

**Fatigue**

Fatigue is commonly associated with cancer and with cancer therapy. Fatigue that is related to cancer and its treatments is different from and more severe than normal fatigue, tends to last longer, and includes the feeling of overall weakness (the medical term for this is asthenia). For more information about this debilitating side effect, please refer to the IMF publication *Understanding Fatigue*.

**Prevention and treatment of fatigue**

Let your doctor and/or nurse know how you feel. Your doctor may prescribe a medication to minimize your fatigue. The effects of fatigue may also be minimized by maintaining the following:

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

**Peripheral neuropathy**

Peripheral neuropathy (PN) is a serious condition in which treatment affects nerves 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 let your doctor know. S/he may start your Velcade at a reduced dose. 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.

**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 and/or schedule modification may prevent progression of this condition.

You should be aware that very detailed recommendations for Velcade dose and schedule modifications are available. These are the key principles:

- Avoid progressive PN, especially if any significant pain develops. 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 reduces the risk of painful neuropathy.
  3. **SQ administration option.** SQ Velcade causes significantly less peripheral neuropathy than IV Velcade.

**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. A low level of red blood cells results in low levels of oxygen in the body, which may cause shortness of breath and feelings of exhaustion. Many newly diagnosed myeloma patients have anemia; Revlimid can cause anemia or make existing anemia worse.
Prevention and treatment of anemia
Your doctor will determine which treatment regimen for anemia is best suited to and safest for you.

The following are options for treatment of anemia:
- Interruption, reduction, or discontinuation of therapy
- Blood transfusions
- Erythropoietic (red blood cell-making) medication.

Neutropenia (low level of neutrophils) and lymphopenia (low level of lymphocytes)
Neutrophils, the most abundant type of white blood cell, are the body’s “first responders” in fighting bacterial infections. Lymphocytes – B cells, T cells, and NK (natural killer) cells – make antibodies to infection, help kill tumor cells, help control immune responses, and kill cells infected with a virus. Having too few neutrophils and lymphocytes can lead to infection. Fever is the most common sign of neutropenia and lymphopenia. If you have a fever, you need immediate medical attention.

Prevention and treatment of neutropenia and lymphopenia
Your blood counts will be monitored closely during your treatment with VRd. You will also be monitored for signs and symptoms of infection. Call your doctor immediately if you have a fever, and make sure you have an emergency or after-hours number to reach a doctor who is covering the practice. You may be given a prescription for medication if you are showing signs of infection. Your doctor may also give you a white blood cell growth factor (G-CSF, or granulocyte-colony stimulating factor) to increase production of your white blood cells.

Thrombocytopenia (low level of platelets)
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 thrombocytopenia
You should inform your doctor if you experience excessive bruising or bleeding. Management of a low platelet level may include changes in the dose and/or schedule of your medications, interruption or discontinuation of one or more of the drugs in your regimen, or platelet transfusions, at the discretion of your doctor.

Important precautions while taking VRd
All patients taking VRd should receive the following preventive medications:
- An anticoagulant (blood thinner) to prevent blood clotting. The combination of Revlimid and dexamethasone is known to increase the risk for blood clots. The doctor will prescribe aspirin or another medication depending on your medical history and the assessment of your risk for a blood clot.
- Antiviral therapy to prevent shingles, a reactivation of the herpes zoster (chicken pox) virus. Velcade, like all proteasome inhibitors, is known to increase the risk of shingles. Antiviral therapy with acyclovir or valacyclovir are typically prescribed as preventive treatments.

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
Asthenia: A condition in which the body lacks or has lost strength either as a whole or in any of its parts.

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.
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.

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

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

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

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

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

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

**Neutrophil**: A type of white blood cell necessary to combat bacterial infection.

**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 (MRD) 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 PFS is one way to determine how well a new treatment works. See “Progressive disease.”

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

**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).

**Shingles**: See “Herpes zoster.”

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

**Steroid**: A type of hormone. Steroidal hormones are produced by the body and some also have synthetic (man-made) equivalents or analogues. Glucocorticosteroids (e.g., dexamethasone, prednisone, and methylprednisolone) are synthetic steroids that have multiple effects and are used for a large number of conditions, including myeloma.

**Thrombocytes**: See “Platelets.”

**Notes**

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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 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 DARZALEX® (daratumumab) injection
- Understanding Dexamethasone and Other Steroids
- Understanding EMPILIT® (elotuzumab)
- Understanding FARYDAK® (panobinostat) capsules
- Understanding Fatigue
- Understanding Freelite® and Hevylite® Tests
- Understanding High-Dose Therapy with Stem Cell Rescue
- Understanding the Immune System in Myeloma
- Understanding KYPROLIS® (carfilzomib) injection
- Understanding MGUS and Smoldering Multiple Myeloma
- Understanding NINLARO® (ixazomib) capsules
- Understanding Peripheral Neuropathy in Myeloma
- Understanding POMALYST® (pomalidomide) capsules
- Understanding REVLIMID® (lenalidomide)
- Understanding the Role of Vertebraloplasty and Kyphoplasty
- Understanding Thalidomide Therapy
- Understanding Treatment of Myeloma Bone Disease
- Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures
- Understanding VELCADE® (bortezomib) injection
- Understanding the VRd Regimen for Newly Diagnosed Myeloma
- Understanding XPOVIO™ (selinexor)
- Understanding Your Test Results

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.