



MULTIPLE MYELOMA
Research Foundation

MULTIPLE MYELOMA IMMUNOTHERAPY

themmrf.org





ABOUT THE **MMRF**

The Multiple Myeloma Research Foundation (MMRF) is the largest nonprofit in the world solely focused on accelerating a cure for each and every multiple myeloma patient. We drive the development and delivery of next-generation therapies, leverage data to identify optimal and more personalized treatment approaches, and empower myeloma patients and the broader community with information and resources to extend their lives.

Central to our mission is our commitment to advancing health equity so that all myeloma patients can benefit from the scientific and clinical advances we pursue. Since our inception, the MMRF has committed over \$500 million for research, opened nearly 100 clinical trials, and helped bring 15+ FDA-approved therapies to market, which have tripled the life expectancy of myeloma patients.

To learn more about the MMRF, visit themmrf.org.

To speak to a patient navigator at the Patient Navigation Center, call **1-888-841-6673** or email patientnavigator@themmrf.org.

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INTRODUCTION

Multiple myeloma is a cancer of the blood cells (specifically, **white blood cells**, which are one of several types of blood cell). Blood cells are formed in the bone marrow (the soft, spongy tissue located inside the long bones of your body).

Myeloma cells grow and crowd out the normal blood cells in the bone marrow, which results in a reduction in the number of normal white blood cells. Having a reduced number of white blood cells in your body makes infections harder to fight off.

The use of the **immune system** to fight cancer—cancer **immunotherapy**—is an exciting area of multiple myeloma research. For myeloma immunotherapy treatments to work, they must be designed to recognize myeloma cells. This has long been a challenge, because myeloma cells—like all cancer cells—have the ability to hide from the body’s normal **immune response**. Myeloma cells also have the ability to weaken the body’s immune response to such an extent that they can continue to grow and thrive. Restoring the immune protection lost to myeloma is believed to be an important potential pathway to new levels of treatment success. Fortunately, there are many types of immunotherapies that can rev up or improve your immune response, including:

- **Antibody**-based treatments
- **Immunomodulatory drugs**
- Cell-based treatments, such as immune cells from the patient or a transplant donor

This booklet is designed to help you better understand the concept and the promise of immunotherapy. Words that may be unfamiliar are **bolded** and defined in the Glossary (page 10).

The information in this booklet is not intended to replace the services or advice of trained health care professionals. Consult with your health care professional regarding specific questions relating to your health, especially questions about myeloma diagnosis or treatment.

THE IMMUNE SYSTEM

If your immune system is primed and ready to attack and kill foreign invaders, why do cancers—like multiple myeloma—still grow and survive? There are a number of reasons why the immune system is ineffective against myeloma.

- Myeloma cells arise from normal **plasma cells** and therefore they may not look like invaders.
- Myeloma cells can fool the immune system by disguising themselves in a way that lets them go unnoticed by immune cells.
- Myeloma cells can actively resist the immune system—they are able to produce substances that inactivate existing immune cells.

Immunotherapy is a therapeutic strategy that is specifically designed to overcome these defensive tactics used by myeloma cells.

For more information about multiple myeloma and its treatment, refer to the companion booklets *Multiple Myeloma Disease Overview*, *Multiple Myeloma Treatment Overview*, and *Newly Diagnosed Multiple Myeloma*, as well as the MMRF website, themmrf.org.

TYPES OF IMMUNOTHERAPY

The excitement that immunotherapy brings to the myeloma community is its unique approach to treatment—immunotherapy works in a manner that is completely different from conventional myeloma therapies, such as **chemotherapy**. In general, immunotherapy selectively targets myeloma cells. Activated immune cells that are programmed to recognize and remember myeloma cells circulate throughout the body, inducing a long-term response to therapy and helping to hold off a myeloma **relapse**.

There are three main types of immunotherapy currently being used or studied in patients with multiple myeloma.

Types of immunotherapy.

Monoclonal antibodies

Immunomodulatory drugs

CAR T cells

MONOCLONAL ANTIBODIES

A **monoclonal antibody** is produced in a laboratory and engineered to bind to a specific protein found on the surface of a myeloma cell. In antibody therapy, monoclonal antibodies are injected or infused into the body to attack the myeloma cells. Several different types of monoclonal antibodies are used in antibody therapy. The different types are:

1. **Naked antibodies**
2. **Antibody–drug conjugates (ADCs)**
3. **Bispecific antibodies**

When used on their own as a therapy, monoclonal antibodies are referred to as naked antibodies. As noted, naked antibodies recognize and target a specific protein on the surface of myeloma cells, which enables them to help your immune system identify and eliminate the targeted myeloma cells. Darzalex (daratumumab), Sarclisa (isatuximab), and Empliciti (elotuzumab) are naked antibodies that are currently approved for use in patients with multiple myeloma.

Darzalex and Sarclisa target a protein called CD38 that is found on the surface of myeloma cells.

Empliciti works in two ways. Like Darzalex and Sarclisa, it targets and binds to a protein found on the surface of myeloma cells (in this case, a protein called SLAMF7). However, Empliciti also activates a particular group of cells of the immune system—the **natural killer (NK) cells**. These activated NK cells seek out and destroy myeloma cells.

Another type of antibody-based treatment uses a monoclonal antibody that is coupled to a cancer drug or a **toxin**; this type of agent is called an antibody–drug conjugate or ADC. The antibody part of the conjugate binds to a myeloma cell—just as naked antibodies do—and the attached cancer drug kills the myeloma cell. Several ADCs that target a protein called **B-cell maturation antigen (BCMA)** are in **clinical trials** for treatment of myeloma.

BCMA is a unique cell surface protein that is found on all myeloma cells, making it an attractive target for drug therapy. Many immunotherapies in development for multiple myeloma target BCMA, including ADCs, bispecific antibodies, and CAR T cells.

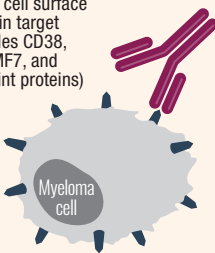
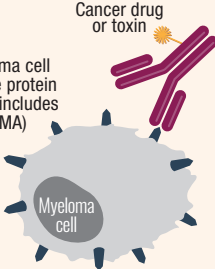
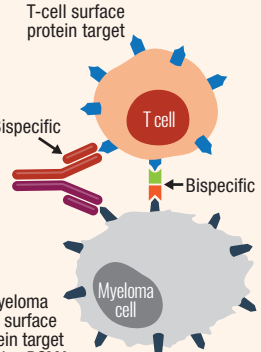
Other antibody-based therapies being studied in myeloma are bispecific antibodies. Bispecific antibodies are made from portions of two different antibodies that have been fused together to make a single antibody that recognizes two different targets. The way that bispecific antibodies work is that one part targets myeloma cells and one part targets T cells, making it easier for T cells to find and kill myeloma cells.

Tecvayli (teclistamab) is a BCMA-directed bispecific antibody that is approved for patients with relapsed or **refractory** myeloma. Several of the bispecific antibodies currently in clinical trials also target BCMA (other bispecific antibodies target different surface proteins) and bind to a protein called CD3 that is found on the surface of **T cells**. Patients have been found to experience a common side effect called **cytokine release syndrome (CRS)**, which is an infection-like syndrome in which a patient experiences fevers, chills, and low blood pressure after receiving treatment. The cause of CRS is thought to be from a surge in the immune response, which is mainly driven by a **cytokine** (a protein produced by immune cells) called interleukin-6 (IL-6). Fortunately, there is a drug called tocilizumab that interferes with IL-6 and can stop CRS. Use of bispecific antibodies is also associated with an increased risk of serious infection. Your doctor may prescribe medication to help prevent certain infections.

If you are treated with bispecific antibodies, you may experience nervous system side effects, which are referred to as **immune effector cell-associated neurotoxicity syndrome (ICANS)**. Usually, these side effects are mild and result in symptoms like confusion, but in some cases more severe symptoms like delirium or seizures can occur. These side effects are less common—and less understood—than CRS, and most resolve over time. However, these nervous system side effects remain an issue and are under study.

You will need to be hospitalized to monitor for signs of these side effects for several days after receiving the first few doses of Tecvayli.

Types of monoclonal antibodies.

	Type of antibody	Myeloma cell surface protein	Targeted antibody
NAKED	<p>Myeloma cell surface protein target (includes CD38, SLAMF7, and checkpoint proteins)</p> 	CD38	<ul style="list-style-type: none"> • Darzalex (daratumumab) • Sarclisa (isatuximab)
		SLAMF7	<ul style="list-style-type: none"> • Empliciti (elotuzumab)
ADC	<p>Myeloma cell surface protein target (includes BCMA)</p> <p>Cancer drug or toxin</p> 	BCMA	<ul style="list-style-type: none"> • CC-99712*
Bispecific	<p>T-cell surface protein target</p> <p>Bispecific</p> <p>← Bispecific</p> <p>Myeloma cell surface protein target (includes BCMA, GPRC5D, and FcRH5)</p> 	BCMA	<ul style="list-style-type: none"> • Alnuctamab* • Cevostamab* • Elranatamab* • Linvoseltamab* • Tecvayli (teclistamab) • Talquetamab*

*Not yet approved by the Food and Drug Administration

CAR T-CELL THERAPY

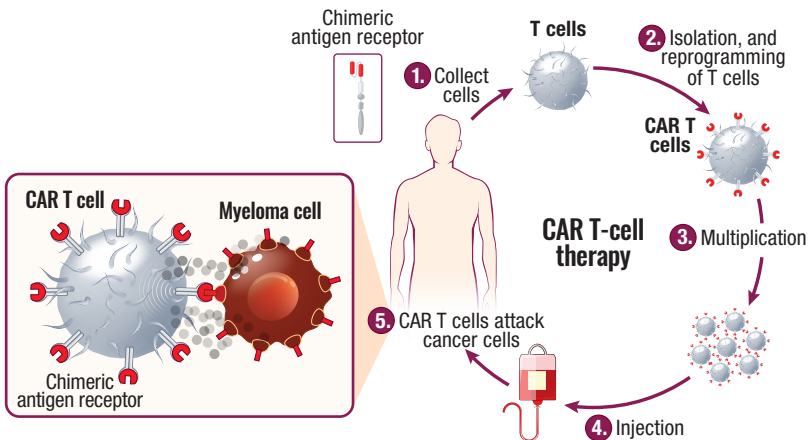
Immune cell therapy—also known as cell-based therapy, cellular therapy, or adoptive cell therapy—is the process of collecting your own immune cells (mostly T cells), engineering them in a lab so they are better able to identify and attack myeloma cells, and then returning them to you.

One form of cellular therapy called **chimeric antigen receptor (CAR) T-cell therapy** is capturing headlines because of its ability to induce responses in most patients—even those who have relapsed from many prior therapies. Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) are both approved for patients with relapsed or refractory myeloma.

Cancer cells have found ways to “hide” from T cells. In CAR T-cell therapy, however, regular/normal T cells are “supercharged,” which helps them see myeloma cells—even when they’re hiding.

The process of supercharging T cells involves collecting them from your blood, making genetic changes to them in a lab (turning them into more effective myeloma detectors and killers), and then re-infusing them back into you. Once back inside your body, the improved T cells (that is, the CAR T cells) resume their search-and-destroy mission against myeloma cells.

Chimeric antigen receptor (CAR) T-cell therapy.



Most of the cells used in the CAR T-cell therapies being studied have been genetically changed to latch onto a specific protein (BCMA) found on the surface of most myeloma cells.

In clinical trials, all the BCMA-modified CAR T-cell therapies being studied in myeloma patients have produced high response rates; that is, most patients respond to the treatment. However, CRS and ICANS are common side effects seen with CAR T therapy.

Many studies are ongoing, as researchers compare different agents in an attempt to determine how long responses last, the maximum number of cells that need to be infused into patients, and whether certain agents are associated with less CRS and fewer nervous system side effects.

Currently, CAR T-cell therapy is limited to myeloma patients whose disease relapses after, or is refractory to, prior treatments. Eligibility for CAR T-cell therapy depends on **comorbidities**, risk factors, and your ability to perform certain daily activities without help (**performance status**).

CAR T-cell therapy is a specialized treatment that is only available at cancer centers that have experts in this therapy on staff. Because this treatment is in high demand, you may need to get on a waiting list before you can begin this therapy.

Though immunotherapy as a treatment option is an exciting and fast-developing area of myeloma management, some immunotherapies are not approved for use in myeloma patients; not all experimental immunotherapies are appropriate for all myeloma patients—talk with your health care team about your disease and what options are best for your care.

The MMRF would like to thank Jesus G. Berdeja, MD, Director of Multiple Myeloma Research and Senior Investigator, Hematologic Malignancies at the Sarah Cannon Research Institute in Nashville, Tennessee, and our patient advocate Mary Elizabeth Graft of Scottsdale, Arizona, for their contributions to this booklet.

MMRF PATIENT SUPPORT AND RESOURCES

The MMRF is dedicated to supporting the myeloma community by providing a broad range of resources for myeloma patients and their family members and caregivers. The MMRF is available to help guide you through your multiple myeloma journey every step of the way.



YOUR QUESTIONS ANSWERED

Speak to an MMRF patient navigator at the Patient Navigation Center for answers to your questions about disease management, treatments, clinical trials, and assistance with finding financial and other available resources.

Telephone: 1-888-841-6673

Monday–Friday, 9:00 AM to 7:00 PM ET

Email: patientnavigator@themmrf.org

Connect with an MMRF Myeloma Mentor™:

themmrf.org/resources/myeloma-mentors

This is a phone-based program offering the opportunity for patients and/or caregivers to connect one-on-one with a trained patient and/or caregiver mentor to share their patient journeys and experiences.

FIND AND PARTICIPATE IN A CLINICAL TRIAL

Search for a clinical trial in your area or let an MMRF patient navigator help guide you through the process.

Clinical Trial Finder: themmrf.org/resources/clinical-trial-finder

The MMRF has partnered with Lazarex Cancer Foundation to help patients access clinical trials by helping with travel expenses. Patients who qualify will be reimbursed for out-of-pocket travel expenses for themselves and a travel companion. To learn more about this program, contact the MMRF Patient Navigation Center (1-888-841-6673 or patientnavigator@themmrf.org).

SUPPORT THE MMRF

Help support the MMRF's efforts to accelerate research and find a cure! Participate in an event or donate today.

Telephone: 1-203-229-0464

Donate now/Take action: Visit themmrf.org/get-involved

GLOSSARY

adaptive immunity The part of the immune system that is composed of highly specialized cells designed to recognize foreign invaders and attack them any time they enter the body

antibody Protein produced by plasma cells that helps protect the body from infection and disease (also called *immunoglobulin*; see also *monoclonal antibody*)

antibody-drug conjugate (ADC) Monoclonal antibody that is coupled to an anti-tumor agent (such as a toxin, a radioactive isotope, or a drug)

B-cell maturation antigen (BCMA) Protein found on the surface of myeloma cells

bispecific antibody Engineered therapy created by fusing two antibody fragments together; one fragment binds to surface proteins on cancer cells and the other binds to a protein found on the surface of immune cells

chemotherapy The use of drugs to kill rapidly dividing cancer cells

chimeric antigen receptor T (CAR T)-cell therapy Form of immunotherapy in which a patient's immune cells (T cells) are collected, engineered in a lab to be better able to identify and attack myeloma cells, and then returned to the patient

clinical trial Study of the safety and effectiveness of a therapeutic agent using consenting human subjects

comorbidity Disease that is present at the same time as another disease

cytokine Protein produced and secreted by cells of the immune system (for example, interleukins)

cytokine release syndrome (CRS) Common, infection-like side effect following treatment with bispecific antibodies or infusion of CAR T cells in which a patient experiences fevers, chills, and low blood pressure

immune effector cell-associated neurotoxicity syndrome (ICANS) Common side effect of the nervous system observed after certain immunotherapy treatments that can include confusion or delirium, expressive aphasia, motor weakness, tremor, headache, seizures, and reduced level of consciousness

immune response Reaction of the cells and fluids of the body against a substance or agent (for example, bacteria, a virus, or a foreign cell) that is not recognized as part of the body

immune system Network of cells that protect the body from foreign substances and destroys infected and cancerous cells

immunomodulatory drugs Drugs that fight cancer by altering the function of the immune system; examples include Thalomid, Revlimid, and Pomalyst

immunotherapy Prevention or treatment of disease with drugs that stimulate the immune system

lymphocyte Type of immune cell made up of two main types, B cells and T cells

monoclonal antibody Antibody produced in a laboratory that is used to diagnose and treat some diseases

naked antibody Monoclonal antibody that can bind to a cell surface protein and that has no drug or toxin attached

natural killer (NK) cell Type of white blood cell that has granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus

performance status A score that estimates a patient's ability to perform certain daily activities without help

plasma cell Antibody-secreting immune cell that develops from a B cell; in myeloma, it is this cell that has become cancerous or abnormal

refractory Disease that does not respond to therapy

relapse Progression of a disease that has initially responded to therapy

T cell (or T lymphocyte) Type of white blood cell that can be subdivided into two groups, helper and cytotoxic T cells; helper T cells are responsible for *adaptive immunity*; cytotoxic T cells are killers of cells that have been targeted for death

toxin A poisonous substance

white blood cell One of the major cell types in the blood; attacks infection and cancer cells as part of the immune system

NOTES



MMRF RESOURCES IN PERSON OR ONLINE



Attend a Multiple Myeloma Patient Summit

Learn about standard and emerging therapies, including stem cell transplants, promising clinical trials, and more for optimal disease management. Attend a complimentary symposium for all the information you need to make well-informed decisions about your treatment and care.

To register or to view the complete calendar, visit:
themmrf.org/resources/education-programs



View Past Programs on Demand

Access our archive of recorded Patient Summits and webcasts. Hear expert perspectives on key clinical research and the rapidly evolving myeloma treatment landscape.

All available online, and free, at:
themmrf.org/resources/education-programs



Find a Clinical Trial Near You

Clinical trials are critically important to developing new myeloma treatments and better understanding the biology of the disease. The more people who enroll, the faster we can find answers. Patients who enroll in clinical trials have the opportunity to be among the first to receive the newest drugs or drug combinations in development and receive close monitoring.

To find a clinical trial near you, visit:
themmrf.org/resources/clinical-trial-finder

Don't miss out on the latest myeloma updates! Sign up today to receive news updates and notice of educational programs.

Name: _____

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Email: _____

Or sign up at **themmrf.org**

I AM A:

- Myeloma Patient
- Myeloma Patient Caregiver
- Myeloma Patient Family Member (non-caregiver)
- Health Care Professional or Researcher
- Biopharma, Medical Device, or Health Care Technology Industry Professional

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Hours: **Mon–Fri, 9 AM–7 PM ET**
Email: **patientnavigator@themmrf.org**



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