LEUKEMIA & LYMPHOMA SOCIETY®

Immunotherapy

No. 9 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Immunotherapy is a type of cancer treatment that uses a person's immune system to help fight cancer.
- There are several types of immunotherapies, and each works to help the immune system in different ways. Some boost the body's immune system. Others help train the immune system to attack specific cancer cells.
- Immunotherapy can cause side effects. Each type of immunotherapy has different side effects that range from mild to life-threatening. Most are manageable if treated early.
- While great strides have been made in understanding the role of the immune system in cancer, the science is still new compared with other cancer treatments, such as chemotherapy. Research in clinical trials is ongoing to develop new ways to use and improve immunotherapy.

Introduction

Immunotherapy is a type of cancer treatment that uses a person's immune system to help fight cancer. The immune system is the body's defense against infection and disease, including cancer. The immune system is made up of cells and organs that work together to protect the body.

Doctors and researchers are working to boost and train the immune system to attack and destroy cancer cells. These processes can create effective treatments for blood cancers.

This fact sheet gives an overview of several types of immunotherapies and each one's role in treating blood cancers. A brief introduction to the body's immune system and cancer is included to help you understand the immunotherapy information in this fact sheet.

The Body's Immune System

The immune system is the body's primary defense against infection and cancer. It is made up of a complex network of cells, molecules, organs and lymph tissues working together to defend the body against microorganisms, such as bacteria, viruses and fungi, as well as against cancer cells. To do this, the immune system must distinguish between cells that naturally belong in the body (self) and foreign cells (non-self). Antigens are substances the immune system recognizes as toxic and stimulate an immune response; in other words, they are non-self and do not belong in the body. An antigen may be a substance from the environment (such as bacteria, viruses, or pollen), or it may be from inside the body (such as cancer cells).

Once the immune system determines that a cell is foreign (does not belong) in the body, it begins a series of reactions to identify, target and eliminate the foreign cell. White blood cells play an important role in the immune system. Some types of white blood cells, called lymphocytes, help the body fight viruses, bacteria and cancer. There are three major types of lymphocytes:

- **B lymphocytes (B cells):** B lymphocytes make antibodies that recognize and target antigens. They are found in the bone marrow and other parts of the lymphatic system.
- **T lymphocytes (T cells):** T lymphocytes have several functions. They help B lymphocytes make antibodies that recognize and fight against invasive microbes and kill invading or infected cells in the body. T cells are the immune system's main cancer fighters.
- **Natural killer (NK) cells:** Natural killer cells also attack cancer cells and eliminate viruses.

When the immune system functions normally, lymphocytes travel through the body looking for and getting rid of anything that does not belong, including bacteria, viruses, and even cancer cells. These immune cells search for foreign cells by using their receptors to scan for antigens on the surface of the cells. Once the immune system discovers an antigen, it produces antibodies to attack the foreign cells, or it activates T cells to destroy them.

Cancer and the Immune System

Many cancers are likely prevented by the immune system's ability to recognize and destroy abnormal cells before they become cancer. Immunosurveillance is a term used to describe how the immune system patrols the body for pre-cancerous conditions, such as cancer-causing proteins on the surface of cells. Immunosurveillance removes these cells before they can build up to a critical mass and develop into cancer.

However, even a healthy immune system cannot always prevent cancers from forming. Some cancer cells can develop and grow even in the presence of a healthy immune system. Immunoediting is the process by which cancers can evade the immune system and multiply. The three phases of immunoediting are elimination, equilibrium and escape.

- **Elimination.** Also known as immunosurveillance, elimination involves the immune system finding and killing cancer cells, eliminating them from the body. However, while most cancer cells are destroyed in this phase, some survive and can reach equilibrium with the immune system.
- **Equilibrium.** The immune system is unable to eliminate all the cancer cells completely, and the cells remain present without progressing or multiplying. During equilibrium, the immune system can keep the cancer cells in check but is unable to eliminate them completely. The interactions between the cancer cells and the immune system may lead to the ability of the cancer cells to undergo genetic changes that allow them to avoid being detected and destroyed by the immune system.
- **Escape.** Cancer cells in the escape phase have acquired the ability to avoid immune recognition and destruction, which leads to their growth and progression. In the escape phase, cancerous cells use several methods to alter the body's immune response in a way that allows them to grow.

Immunotherapy seeks to boost or change how the immune system works to find and destroy cancer cells that have escaped immune detection. Several types of immunotherapies are approved by the FDA or are under study (in clinical trials) to determine their effectiveness in treating various types of blood cancer.

Types of Immunotherapy

Immunotherapies for blood cancer that are in use or under study include:

- Adoptive cell transfer, such as chimeric antigen receptor (CAR) T-cell therapy
- Monoclonal antibodies
- Immune system modulators
- Immune checkpoint inhibitors

Visit **www.LLS.org/booklets** to view disease-specific booklets so you can learn more about immunotherapies by diagnosis.

Adoptive Cell Transfer. Adoptive cell transfer is a type of immunotherapy in which immune cells are transferred into a patient to help fight cancer. Depending on the type of cellular therapy, the immune cells may be from the patient or a donor. The immune cells may also be modified in a laboratory to better target and kill cancer cells before they are returned to the patient's body. Several types of adoptive cell transfer therapies are under study. However, as of today, the one that has advanced the furthest in clinical development is chimeric antigen receptor (CAR) T-cell therapy.

Chimeric antigen receptor (CAR) T-cell therapy. In CAR T-cell therapy, T cells are taken from a patient's blood and sent to a laboratory. There, technologies are used to genetically engineer the T cells to express a particular chimeric antigen receptor, which allows the modified T cells to identify, attack and kill cancer cells. The CAR T cells are then grown and multiplied in a laboratory. These modified cells are frozen and sent to the patient's treatment center. Later, they are infused into the patient's bloodstream, where they can seek out and kill cancer cells. (See **Figure 1**, on page 3.)

Side Effects. While many patients have only reported mild to moderate side effects, CAR T-cell therapy is sometimes associated with serious side effects. Most side effects resulting from CAR T-cell therapy will either resolve on their own or can be managed with appropriate treatment. Some of the most common potential side effects of CAR T-cell therapy include:

- **Cytokine release syndrome (CRS):** The most common side effect of CAR T-cell therapy is cytokine release syndrome, also known as a "cytokine storm." It is caused by a large, rapid release of cytokines (immune-stimulating molecules) into the blood from immune cells affected by immunotherapy. Signs and symptoms of cytokine release syndrome include fever, nausea, headache, rapid heartbeat, low blood pressure and difficulty breathing. Most patients have a mild reaction, but severe cytokine release syndrome can be life-threatening.
- **Neurologic side-effects, also called "immune effector cell-associated neurotoxicity syndrome (ICANS)":** CAR T-cell therapy can cause neurologic problems affecting the brain or peripheral nervous system. Symptoms may include problems remembering words, handwriting changes, difficulty speaking, hallucinations, being less alert, being confused and changes in sleep patterns. Neurotoxicity has been reversible in most cases, and the symptoms have resolved over several days without intervention or apparent long-term effects.

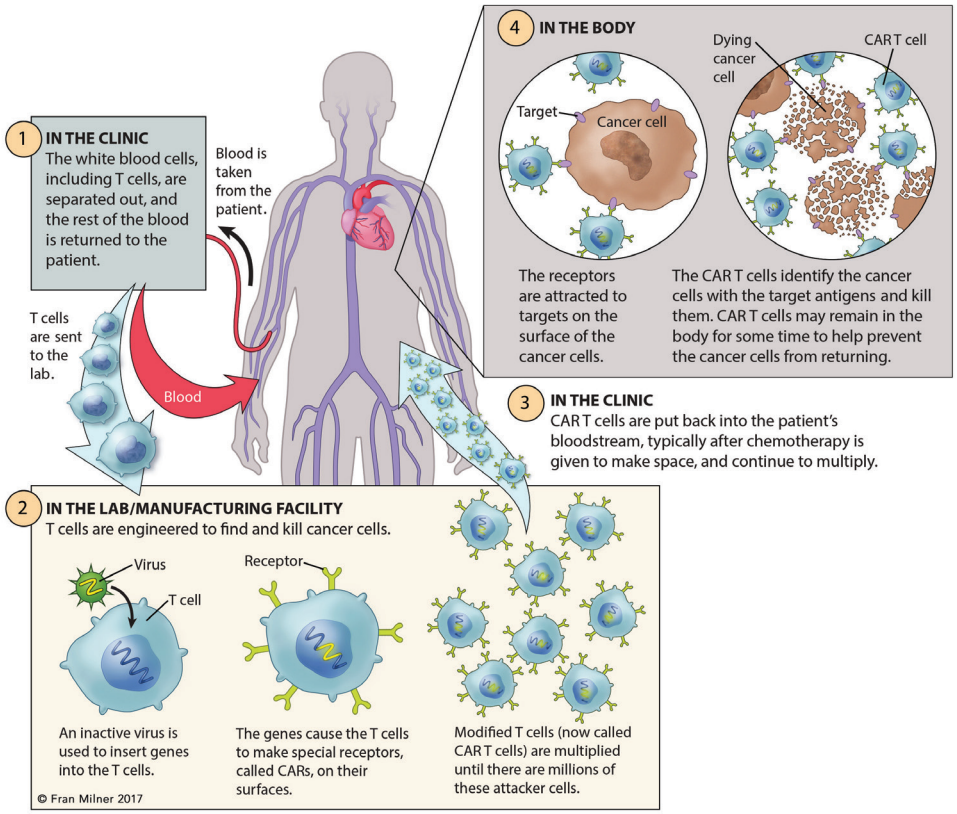

Figure 1. Chimeric antigen recepto (CAR) T-cell therapy

- **Tumor lysis syndrome (TLS):** This syndrome is another known side effect of CAR T-cell therapy. It is a group of metabolic complications that can occur due to the breakdown of dying cancer cells. Tumor lysis syndrome can cause damage to organs, such as the kidneys, and it can be a life-threatening complication of any treatment that involves the breakdown of cancer cells. Tumor lysis syndrome is managed by standard supportive therapy, including hydration (water and fluids) and medications to manage uric acid levels in the body.
- **Low white blood cell counts**: A low white blood cell count can result in serious bacterial, viral or fungal infections.

All treatment centers certified to infuse CAR T cells employ evidence-based strategies to minimize and treat these side effects. Before starting therapy, the patient should speak to their healthcare team about side effects and what to do if they experience them.

For more information about CAR T-Cell therapy, visit www.LLS.org/booklets for the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy.*

Monoclonal Antibodies. One way the immune system attacks foreign invaders is by producing billions of different kinds of antibodies. An antibody is a protein that sticks to an antigen (a substance from the environment, such as a bacteria or virus, or from inside the body, such as a cancer cell). Antibodies circulate throughout the body until they find and attach to a particular antigen for which the antibody has receptors. Once attached, the antibody can recruit other parts of the immune system to destroy the foreign cells that contain the offending antigen. For cancer treatment, researchers can design antibodies in the laboratory that specifically target a certain antigen, such as those found most often on cancer cells. Having the ability to identify and target such antigens would minimize damage to normal cells.

Monoclonal antibodies "mark" cancer cells so that they can be better detected and destroyed by the immune system. Monoclonal antibodies work as target-seeking missiles to find and attach to tumor-specific antigens and then deliver the toxic substance into the cancer cell.

There are three different types of monoclonal antibodies:

- **Naked monoclonal antibodies.** These treatments work by themselves. They have no drugs or radioactive material attached to them. Most naked monoclonal antibodies attach to antigens on cancer cells, but some work by binding to agents on other non-cancerous cells.

- **Conjugated monoclonal antibodies.** These antibody drugs have a chemotherapy drug, other anti-cancer drug or a radioactive material attached to them. The antibody targets and attaches to an antigen on the cancer cells to deliver the treatment directly to the cancer cells.
  - o Conjugated monoclonal antibody therapy in which a monoclonal antibody is linked to a radioactive isotope is called "radioimmunotherapy." (See **Figure 2** and **Figure 3** below.)
  - o Conjugated monoclonal antibody therapy in which a monoclonal antibody is linked to a chemotherapy drug is called "chemoimmunotherapy."
- **Bispecific monoclonal antibodies.** These treatments are composed of two different monoclonal antibodies and can attach to two different targets at the same time.
  - o **Bispecific T-cell Engager (BiTE®).** A type of bispecific antibody, BiTE molecules bind to 2 antigens: the immune cell (T cell) and the cancer cell target. By binding onto both, the drug brings the cancer cells and immune cells together, which is thought to cause the T cells to be activated and attack the cancer cells. (See **Figure 4,** on the right.)

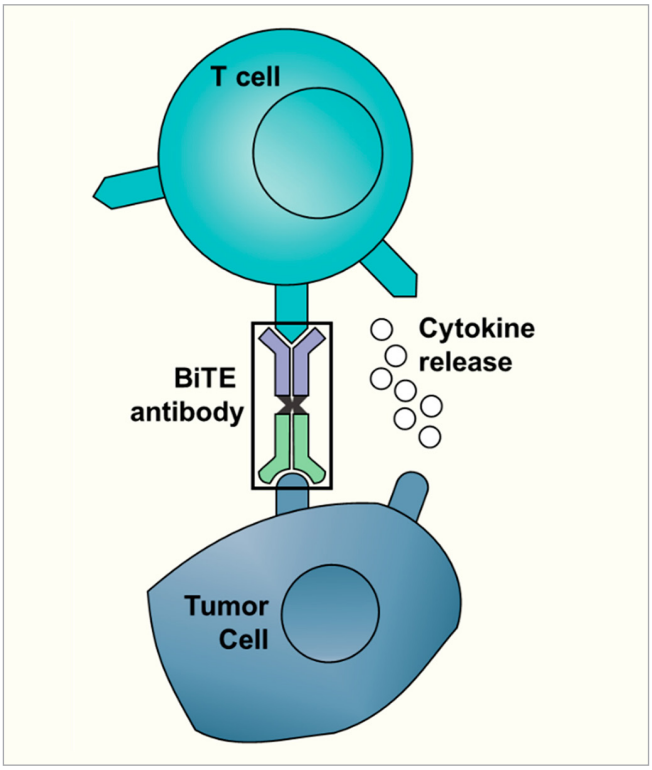

Figure 4. A schematic representation of the Bispecific T-cell Engager (BiTE) technology.

Source: Adapted from Marayati R, Quinn CH, Beierle EA. Immunotherapy in Pediatric Solid Tumors-A Systematic Review. Cancers (Basel). 2019;11(12):2022. Published 2019 Dec 14. doi:10.3390/cancers11122022© 2019 by the authors.

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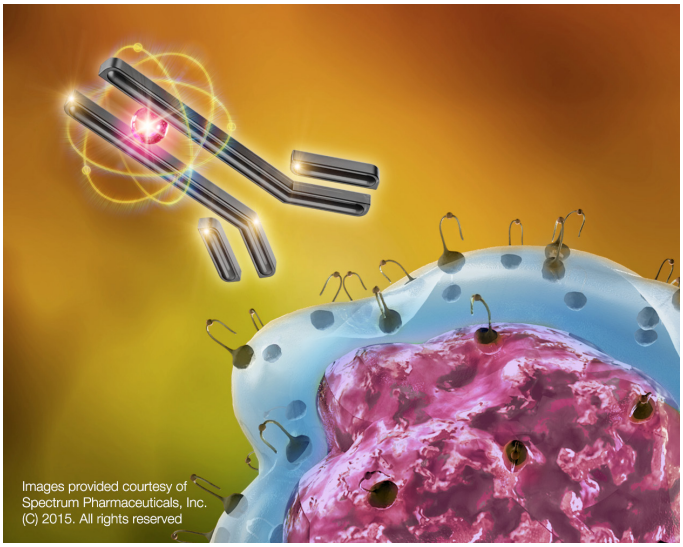

Figure 2. Radiolabeled Yttrium-90-ibritumomab tiuxetan binds to CD20 molecules on the surface of lymphoma cells.

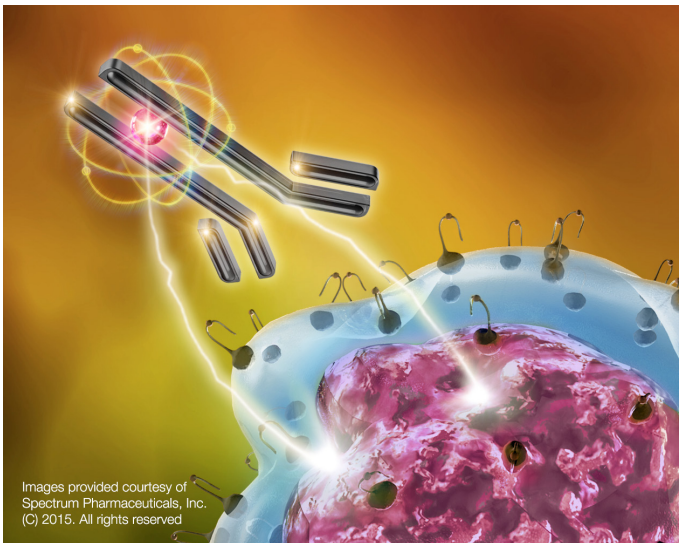

Figure 3. Beta particles emitted from the yttrium-90 irradiate and kill the lymphoma cell.

Side Effects. Monoclonal antibodies are given by infusion into a vein (called "intravenous" and abbreviated IV). The antibodies are proteins that can sometimes cause allergic reactions. This reaction is most likely to happen during or soon after treatment. Symptoms of an allergic reaction may include fever, chills, rash, dizziness, muscle aches, backaches, headaches and breathlessness. Naked monoclonal antibodies tend to have fewer serious side effects than chemotherapy drugs. However, side effects can occur, depending on which drug is given. Aside from allergic reaction, other more general side effects of monoclonal antibodies may include:

- Fatigue
- Weakness
- Flu-like symptoms, such as fever and muscle aches
- Headache
- Diarrhea
- Rash
- Dizziness
- Nausea/vomiting
- Low blood cell counts

Immune System Modulators. Immune system modulators enhance the body's immune response against cancer. Some of these agents affect specific parts of the immune system, and some affect the immune system in a more general way.

Two types of immune system modulators that are used to treat blood cancers include:

- **Immunomodulatory drugs.** These drugs, also called "biological response modifiers," boost the immune system by causing cells to release interleukin-2 (IL-2), a protein that increases the growth and activity of white blood cells. The drugs also have an "angiogenesis" effect, which means they stop tumors from forming new blood vessels that tumors need to grow. The immunomodulatory drugs used for blood cancer treatment are oral medications.
- **Cytokines.** Cytokines are proteins made by white blood cells that play an important part in the body's immune response and affect the growth of all blood cells. An example of cytokines used in blood cancer treatment include:
    - **Interferon.** Interferons are a natural substance that supports the body's immune system. A specific type of interferon, called "interferon-alfa (INF-alfa)," when made in a lab, can be used in cancer treatment to boost white blood cells and attack cancer cells. Interferon can also slow cancer cell growth and cause tumor angiogenesis. Interferon is given as an injection.

Side Effects. Depending on the type of immune system modulator, side effects vary. Most side effects are mild to moderate and reversible if detected early and addressed promptly. Patients should watch and report any new or worsening symptoms to their treatment team. In general, immune system modulators can cause:

- Fevers
- Chills
- Nausea and/or vomiting
- Diarrhea
- Constipation
- Mouth sores
- Decreased appetite
- Join pain
- Fatigue
- Numbness or tingling in the hands or feet (peripheral neuropathy)
- Low blood cell counts
- Blood clots, which can lead to serious complications

Cytokines can also cause serious side effects, including:

- Trouble breathing
- Low or high blood pressure
- Cognitive (thinking) changes
- Rash
- Organ damage

Interferon can also cause hair loss.

Immune Checkpoint Inhibitors. Checkpoints are molecules found on T cells, a type of white blood cell. These checkpoint molecules act as "brakes." T cells circulate throughout the body looking for signs of infection and diseases, including cancer. When a T cell comes near any cell, it probes (looks for) specific proteins on the cell's surface. If the T cell determines that it is a normal, healthy cell, it moves on to check other cells. If the proteins indicate that the cell is foreign or cancerous, the T cell attacks it. But cancer cells can sometimes send misleading signals to these checkpoints, telling the T cells that they are not harmful. Checkpoint inhibitors work by "taking the brakes off" T cells so that the T cells can now attack the cancer cells.

Immune checkpoint inhibitors are given intravenously. The treatment period typically lasts 30 to 60 minutes, but the number of sessions may vary depending on the type of cancer and the drug given.

Side Effects. In general, immune checkpoint therapies are better tolerated than chemotherapy. Most side effects are mild to moderate and reversible if detected early and addressed promptly. Patients need to mention their side effects to their treatment team. Side effects of checkpoint inhibitor treatment can arise anytime during treatment—and sometimes may arise months after treatment. Patients should report any of the following symptoms to their treating doctor:

- Fatigue
- Rash
- Diarrhea
- Abdominal pain
- Nausea/vomiting
- Cough
- Shortness of breath
- Headache
- Confusion
- Muscle weakness or muscle pain

Side Effects of Immunotherapies

Immunotherapy can cause side effects that range from mild to life-threatening. The side effects of immunotherapy are different from those seen with traditional cancer treatments, such as chemotherapy. Unlike other cancer treatments, immunotherapy side effects occur due to overactivation of the immune system. When this happens, the immune system starts attacking healthy cells. The doctor should review any potential side effects for each treatment the patient is receiving.

Side effects can sometimes occur weeks or even months after treatment stops. Some patients have a lifetime risk of late side effects caused by immunotherapy. It is important for patients to be vigilant about potential side effects. The organs most susceptible to an overactive immune system caused by immunotherapies are the liver, skin, lungs, kidneys, gastrointestinal tract and endocrine organs. Without a proper diagnosis and early treatment, an autoimmune response could lead to irreversible and life-threatening conditions. Many, but not all, of these can be reversed or minimized with steroids or stopping treatment.

If a patient becomes ill at home and needs to be seen by a doctor outside of the patient's cancer team, it is important for the patient or caregiver to alert any doctor seen that the patient is receiving immunotherapy. The Oncology Nursing Society (ONS) provides an "ONS Immunotherapy Patient Wallet Card" online at **https://www.ons.org/store/product/immunotherapy-wallet-cards.** This Wallet Card form can be printed, filled in and carried by the patient in a wallet or purse at all times. When completed (by the patient, with help from the primary oncologist-hematologist, if needed), the ONS card is intended to communicate information about the patient's immunotherapy treatment with healthcare providers who are not involved with a patient's cancer treatment.

Visit www.LLS.org/booklets to view the Side Effects Management series (filter by "side effect management.")

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials, and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (U.S. Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using:
  - A new drug
  - An approved drug to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth (pill), intravenously (IV)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new,

cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients who have been willing to join clinical trials. Anyone interested in participating in a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation, it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit **www.LLS.org/WhatToAsk** for lists of suggested questions)
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes

Clinical trials can be challenging to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome the barriers to enrollment, and provide support throughout the entire clinical trial process.

Our Clinical Trial Nurse Navigators are registered nurses who are experts in adult and pediatric blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you to understand the clinical trial process, including your rights as a patient
- Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health and your medical history—because these might impact whether you can take part in certain clinical trials.
- Help you to understand how your finances, insurance coverage, and support network, as well as your ability and willingness to travel, might impact your choice of a clinical trial
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you participate in a trial
- Support you throughout the clinical trial process

Call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers.*

Questions to Ask Your Doctor About Immunotherapy

People living with blood cancers can use the following questions as a guide to discuss immunotherapy with members of their oncology team:

- Why are you recommending this type of therapy?
- What are the benefits and risks of this therapy?
- How does this therapy work to treat this disease?
- How will this treatment be given and how often?
- How long will I need to be on this treatment?
- How will you know if this therapy is working?
- What are the potential side effects of this therapy?
- Will health plans cover this therapy?
- Will immunotherapy be my only treatment?
  - Will other cancer treatments be needed?
  - If so, will these therapies be given together or at different times?
- Are there any clinical trial options for my diagnosis?

Visit www.LLS.org/WhatToAsk to view a printable list of questions about treatment.

Feedback. Visit **www.LLS.org/PublicationFeedback** to give suggestions about this booklet.

Acknowledgement

The Leukemia & Lymphoma Society appreciates the review of this material by

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ONE-ON-ONE SUPPORT

Information Specialists

Our blood cancer Information Specialists are highly trained oncology social workers and nurses who provide free, personalized assistance to patients, families and healthcare providers. Our Information Specialists offer guidance through blood cancer treatment, financial and social challenges, and give accurate, up-to-date disease, treatment and support information. Visit **www.LLS.org/InformationSpecialists** to chat online or call **800-955-4572**.

Clinical Trial Nurses

Our Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers who conduct comprehensive clinical trial searches and personally assist patients, parents and caregivers throughout the entire clinical trial process. Visit **www.LLS.org/CTSC** to learn more and complete a referral form.

Registered Dietitians

Our registered dietitians have expertise in oncology nutrition and provide patients, parents and caregivers with free nutrition consultations by phone. Visit **www.LLSnutrition.org/consult** or call **877-467-1936** to schedule.

Do you need financial assistance? Call **877-557-2672** or visit www.LLS.org/finances to learn more about financial support programs.

GET INFORMATION AND SUPPORT

We offer a wide variety of free information and services for patients and families affected by blood cancers.

Peer-to-Peer Support
LLS Patient Community
Online Chats
Podcast
Webcasts and Videos
Caregiver Support
Children & Young Adults
Information Booklets
Local Programs
Advocacy

Visit **www.LLS.org/PatientSupport** or call **800-955-4572** to learn more about all our offerings.

LEUKEMIA & LYMPHOMA SOCIETY®

Visit **www.LLS.org/espanol** for information in Spanish.

FREE MOBILE APPS

LLS Health Manager™

Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Also available in Spanish and French Canadian. Visit **www.LLS.org/HealthManager** to download.

LLS Coloring for Kids™

Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit **www.LLS.org/ColoringApp** to download.

Both are available on the App Store and Google Play.

Visit **www.LLS.org/PatientSupport** or call **800-955-4572** to learn more about all our offerings.

LEUKEMIA & LYMPHOMA SOCIETY®

Additional Resources

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam; to airborne hazards and burn pits while serving in Iraq, Afghanistan and other areas of Southwest Asia; to contaminated water at Camp Lejeune between 1953-1987; or to ionizing radiation during service may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: https://www.va.gov/disability/eligibility/hazardous-materials-exposure/

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

World Trade Center Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program.

People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

Mental Health. Caring for your mental health has benefits for cancer patients. Seek medical advice if you are struggling. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov

If you or your loved is experiencing a mental health crisis, call 988 to talk to a trained mental health professional. The 988 Suicide and Crisis Lifeline is free, confidential and always available. For the Crisis Text Line, text HOME to 741741.

Oncology Nursing Society
www.ONS.org

The Oncology Nursing Society created a wallet card for patients to carry that helps doctors and nurses communicate that the patient is being treated with immunotherapy. The ONS Immunotherapy Patient Wallet Card can be accessed online at https://www.ons.org/store/product/immunotherapy-wallet-cards and printed and completed to carry in a wallet or purse.

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