MC1784 / 19-001475

A Phase II Study of Daratumumab and Ibrutinib for Relapsed / Refractory Chronic Lymphocytic Leukemia Treatment (DIRECT)

NCT04230304

Document Date: 05/24/2024

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 24, 2024**
Not to be used after: **May 23, 2025**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1784: A Phase II study of Daratumumab and Ibrutinib for Relapsed / Refractory Chronic Lymphocytic Leukemia Treatment (DIRECT)

IRB#: 19-001475

Principal Investigator: Dr. Sikander Ailawadhi and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to see whether the use of daratumumab in the treatment of CLL patients will enhance the effectiveness of the currently established and approved therapeutic ibrutinib. You have been asked to take part in this research because you have been diagnosed with B Cell chronic Lymphocytic Leukemia.
What's Involved	You will be in the study for approximately 5 years. Study participation involves: • Physical exams • CT scans • Blood and urine tests • SC administrations and oral treatment • Bone marrow biopsies

Key Information	Janssen Pharmaceuticals will pay the institution to cover costs related to running the study. You may not benefit from taking part in this research study. It is for the benefit of research. The information is obtained during this study is very useful scientifically and therefore may be helpful to others with the same condition in the future. The most commonly reported reactions to daratumumab include: neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, muscle spasms, back pain, pyrexia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy and upper respiratory tract infection. Alternative treatments include chemotherapy and/or stem cell transplant in rare cases. This study may not make your health better but what we learn may help future B Cell Chronic Lymphocytic Leukemia patients.
Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

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Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigator:** Dr. Sikander Ailawadhi **Phone:** (904) 953-2000 **Institution Name and Address:** Mayo Clinic Florida 4500 San Pablo Rd Jacksonville, FL 32224
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Participant Advocate (RPA)** **(The RPA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchparticipantadvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

A description of this clinical trial will be available on http://www.mayoclinic.org. This Website will not include information that can identify you. You can search this website at any time.

Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have been diagnosed with B Cell Chronic Lymphocytic Leukemia. The plan is to have about 52 people take part in this study at Mayo Clinic.

Why is this research study being done?

The purpose of this study is to see whether the use of daratumumab in the treatment of CLL patients will enhance the effectiveness of the currently established and approved therapeutic ibrutinib.

Daratumumab is a monoclonal antibody which works with the body's immune system to destroy tumors. Daratumumab was approved by the US Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma. However, daratumumab has not been approved for the treatment of CLL and its use in this study with ibrutinib is considered investigational.

The current commercially approved ways to give daratumumab are by intravenous (IV) infusion or subcutaneous (SC) injection. This study is being amended to give daratumumab and hyaluronidase as a 15 mL subcutaneous (SC) injection for a fixed dose of 1800 mg. This means that daratumumab in liquid form will be injected under the skin, on your abdomen.

Daratumumab SC is approved in the United States for the treatment of patients with multiple myeloma in combination with other therapeutics and for newly diagnosed AL amyloidosis in combination with CyBorD and is currently being evaluated in several other studies.

Information you should know

Who is Funding the Study?
Janssen Pharmaceuticals is funding the study. Janssen Pharmaceuticals will pay the institution to cover costs related to running the study.

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Information Regarding Conflict of Interest:
Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

You will be in the study for approximately 5 years.

What will happen to you while you are in this research study?

If you agree to be in the study, you will be asked to participate in the following:

Screening Visit
During these visits, we will do some tests and procedures to see if you are eligible to take part in this research study. The Principal Investigator will review the results of these tests and procedures. These tests and procedures may be done during a single visit or may be done over two or more visits. If you aren't eligible, the Principal Investigator will tell you why. At this visit we will:

- Ask you about your medical history
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- CT Scans
- EKG or Echocardiogram (if clinically indicated)
- Draw a blood sample
    - This includes testing for Hepatitis B. If your Hepatitis B test result is positive you will need to have a second test done to make sure the results are the same. The researcher will tell you how to find medical help and counseling as needed, and you may not be able to take part in the study. Your health insurer or you will have to pay for the cost of the repeat test, any follow-up medical care, or counseling.

- If the Hepatitis B test results are positive, it is the state law that they be reported to the State Department of Health. The test results will also be put in your medical record.

- Bone marrow aspirate/biopsy
- Test your urine and/or blood for pregnancy if you are a female able to become pregnant

Cycle 1, Day 1 (Each cycle = 28 days)

- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample
- Additional blood (15ml) will be collected for research purposes

Cycle 1, Day 15

- Draw a blood sample

Cycles 2 and beyond, Day 1

- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample
- Bone marrow aspirate/biopsy

After you complete Cycle 7, you may be asked to return every 3 cycles for clinical evaluations until the end of your treatment. Daratumumab subjects will need to return every cycle to get their dara injections. Your study doctor will determine if this option is appropriate for your care. If your study doctor feels this is not the best option for your care, you will come every cycle until the end of your treatment.

End of treatment

- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- CT Scans (if clinically indicated)
- Draw a blood sample
- Bone marrow aspirate/biopsy

Study Treatment

Daratumumab will be tested in combination with ibrutinib. There are 2 treatment arms. If you have current or previous treatment with ibrutinib, you will be assigned to Cohort 1. If you have no current or previous treatment with ibrutinib, you will be assigned to Cohort 2. Your study

doctor will confirm which treatment arm you will be enrolled into based on your treatment history. Each treatment cycle is 28 days. Your treatment will be as follows:

For Cohort 1 only
If you are eligible for the study and your study doctors assigns you to Cohort 1, we will ask you to stop taking ibrutinib for 1 week prior to cycle 1.

This "washout period" allows your regular medications to leave your body before you begin taking the study drug. Without your regular medications, your CLL may get worse. If this happens, please call the Principal Investigator at the number provided in this consent form.

For Cohort 1 and 2
In Cycle 1, you will be given daratumumab weekly on days 1, 8, 15, and 22 by SC injection. In Cycle 2, you will be given daratumumab weekly on day 1, 8, 15, and 22 by SC injection on the abdomen and you will take ibrutinib (capsules) by mouth on days 1-28.

During cycles 3-6, you will be given daratumumab every 2 weeks on days 1 and 15. You will continue ibrutinib (capsules) by mouth on days 1-28.

During cycles 7 and beyond, you will be given daratumumab every 4 weeks on day 1. You will continue ibrutinib (capsules) by mouth on days 1-28.

Management of Infusion Reactions
In order to prevent administration related reactions, you may receive the following medications 1-3 hours prior to your administration:

- Acetaminophen
- Diphenhydramine
- Dexamethasone

You will be monitored for administration related reactions by trained study staff after each infusion. If a reaction is suspected, your study drug administration may be interrupted and appropriate medical measures will be taken such as administration of antiemetics, antihistamines, analgesics, corticosteroids, oxygen, epinephrine, or any other measure deemed necessary by the study team.

Patient Medication Diary
You will be given a patient medication diary based on your treatment arm to record your daily study medication intake. Please complete the diary on a daily basis. Instructions on how to complete the diary will be included. The study staff will collect your medication diary on Day 1 of each cycle starting on Cycle 2. If your study doctor decides you are eligible to come every

other cycle after Cycle 6, study staff will contact you by phone to collect this information for the cycles you are not visiting the clinic.

Your last entry will be collected at the End of Treatment visit.

Research Results
Tests done only for research purposes are not meant to provide clinical information or help care for you. The results are only important for research. Therefore, the results of tests done with your information and samples will not be provided to you. In the rare event that a finding might affect the health of you or your family, we will contact you and you can choose whether to receive or refuse the information. If you decide to follow up and further medical testing or care is needed, the costs will be billed to you or your insurance.

What are the possible risks or discomforts from being in this research study?

Risks associated with Daratumumab (SC)

Very common side effects with daratumumab ***(events occurring greater than 10% of the time)***

- Infection of the upper respiratory tract such as nose, sinuses throat or upper airway
- Infection of the lung (pneumonia)
- Infection of the lower airway (bronchitis)
- Low platelets; may increase the risk of bleeding and bruising (see separate section "Blood Cell Effects" below)
- Low red blood cells (anemia)
- Low white blood cells (including neutrophils and lymphocytes)
- Decreased appetite
- Abnormal sensation including numbness/tingling of hands, feet or limbs (sensory neuropathy, paresthesia)
- Headache
- Cough
- Shortness of breath (dyspnea), including wheezing
- Constipation
- Diarrhea
- Nausea
- Vomiting

- Rash, a noticeable change in the texture or color of your skin
- Muscle spasms
- Swelling of hands, feet or limbs
- Fatigue, or lack of energy
- Weakness, lack of strength
- Fever
- Back pain
- Joint pain

Common side effects with daratumumab ***(events occurring less than or equal to 10% of the time)***

- Urinary tract infection
- Influenza or flu like symptoms
- Sepsis (a life-threatening condition that arises when the body's response to an infection injures its own tissues or organs
- Hypogammaglobulinemia, a condition with your immune system in which not enough gamma globulin proteins (also known as antibodies) are produced. Decreases in gamma globulin proteins can increase the risk of infections
- High blood glucose levels
- Low blood calcium levels
- Loss of body fluids, also known as dehydration
- Dizziness
- Fainting
- Irregular heartbeat (atrial fibrillation)
- High blood pressure
- Chills
- Infusion-related reaction (see separate section "Infusion-Related Reactions" below)
- Injection site reaction: local reaction reported as mild pain or a burning sensation at the site of injection in the abdominal wall. Redness and hardening of the skin at the injection site was also observed and usually disappeared within a few hours after the administration
- Inflammation of lung tissue (pneumonitis)
- Itchy skin
- Fluid in lungs (pulmonary edema)
- Muscular pain in the chest
- Inflammation of the pancreas (pancreatitis)

Uncommon side effects with daratumumab ***(events occurring less than or equal to 1% of the time)***

- Cytomegalovirus infection
- Liver infection (hepatitis) in those patients who are carriers of the hepatitis B virus

Infusion Related Reactions

An antibody is a large protein that is generated as part of the normal immune system to neutralize foreign objects such as bacteria and viruses. Daratumumab is an antibody designed to specifically target and eliminate a specific harmful object in your body, in this case cancerous plasma cells. A non-local, hypersensitivity reaction to daratumumab that occurs during or shortly after an administration (SC) is called an infusion-related reaction. It usually occurs during or within the first few hours after the start of the first administration. However, delayed reactions can happen up to 3-4 days after the dose administration. These reactions can be life-threatening and fatal outcomes have been reported.

Signs and symptoms of infusion-related reactions may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Most of the observed infusion-related reactions were mild or moderate, and ended by temporarily stopping the administration and/or giving medicines to treat the symptoms. Tell your doctor right away if you have above mentioned symptoms.

If you have a breathing problem now or had breathing problems in the past (like chronic obstructive pulmonary disease (COPD) or asthma), you should tell your study doctor. Also, if you start to have breathing problems while you are on the study you should tell your study doctor right away.

Severe reactions have occurred, including narrowing and obstruction of the respiratory airway (bronchospasm), low level of oxygen (hypoxia), shortness of breath, high blood pressure, swelling in the throat, fluid in the lungs (pulmonary edema), heart attack (myocardial infarction) and complaints of the eyes, such as fluid in the eye (choroidal effusion), blurry vision (acute myopia), and increased pressure in the eye or eye pain (acute angle closure glaucoma). In addition, heart attack (myocardial infarction) has also occurred when daratumumab is given through the vein. Your study doctor and their staff will be ready to treat such a reaction in case it happens. In the future, you should tell any doctor you visit that you received daratumumab (an antibody) in this research study and if you had an allergic reaction including an anaphylactic reaction, the worst case of allergic reaction.

Please inform your doctor immediately if you experience any of these signs and symptoms.

Infection
Different kinds of infection have been seen in patients receiving daratumumab. Most of them are respiratory tract infections. If you have an infection now, have a history of frequent infections, or if you feel sick, you should tell your study doctor right away. The majority of the observed infections so far were mild or moderate. Severe infection such as pneumonia from bacteria, influenza virus, respiratory syncytial virushave also been reported.

Certain infections with viruses, such as shingles (Herpes Zoster virus) and cytomegalovirus and liver infection (hepatitis B virus) have been observed with daratumumab. Patients who have had prior exposure to hepatitis B virus are at increased risk of recurrence of the virus. Your doctor will test you for the hepatitis B virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of infection during daratumumab treatment and until 6 months after the last dose of daratumumab, and you will be treated, if appropriate, by your doctor.

Precautions (safety measures) - Allergic reactions/Anaphylaxis
Daratumumab is an antibody made from a protein. Protein drugs can cause allergic reactions (for example fever or chills, sometimes, it is very difficult to tell the difference with infusion related reactions) in some people.

Anaphylactic reaction
Anaphylactic reaction is a serious allergic reaction that can develop quickly (in minutes to a few hours) and may cause death. Usually, a combination of the following side effects occurs: an itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, and low blood pressure. This type of reaction is for example seen when one is allergic to a bee sting or certain foods like peanuts. Please inform your doctor immediately if you experience any of these signs and symptoms.

Anaphylaxis is the worst type of allergic reaction, it can happen suddenly and often causes the throat to swell, an itchy rash and sometimes the blood pressure to drop. Anaphylaxis has not been seen with daratumumab so far. Your study doctor and their staff will be ready to treat such a reaction in case it happens. If this happens, you will not receive any more daratumumab infusions. You may not be able to be treated again with this type of medication. In the future, you should tell any other doctor you visit that you received daratumumab in this research study and if you had an allergic reaction.

Anaphylactic reactions were rarely reported when commercially available daratumumab was used outside of clinical trials (also called post marketing experience). The reported cases of anaphylactic reaction were believed to be a more severe form of infusion related reactions. More

than 227,000 patients globally have been treated with daratumumab. Anaphylactic reaction has not been reported in clinical studies; therefore, the frequency is not known.

Get emergency medical help if you have any of following: hives; wheezing; difficulty breathing; swelling of your face, lips, tongue, or throat; or pain in chest.

The manufacturer, Janssen Biotech, Inc. has tried different ways of giving the infusions to lessen these reactions. The manufacturer will continue to monitor infusion-related reactions and make changes to the infusions as necessary.

In this study, the following will be done to reduce the chance of a daratumumab infusion related reaction:

- You will get medications, including steroids, acetaminophen and antihistamine, before and after the infusion
  - The infusion may be slowed down or stopped
  - At the discretion of the study doctor, you may stay overnight in hospital after the infusion so medical staff can check on you and to make sure you are monitored and managed appropriately. Your study doctor will discuss with you if an overnight stay is required.

Blood Cell Effects

Daratumumab can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever or any symptoms of decreased platelet counts such as bruising or bleeding.

If you need a blood transfusion, you will have a blood test first to match your blood type. Daratumumab can affect the results of this blood test. These changes can last up to 6 months after your last dose. Your doctor will therefore test your blood type before you start treatment with Daratumumab. The test result will be placed on the patient identification wallet card you will carry for this study. Please tell all your health care providers that you are using Daratumumab before receiving a blood transfusion.

<u>Heart problems in patients with light chain (AL) amyloidosis</u>
Heart problems, in some cases fatal, have occurred. Your study doctor will monitor you closely during treatment with daratumumab. Call your study doctor right away if any of the following symptoms occur: chest pain, feeling faint, swollen legs, shortness of breath, or abnormal heart rhythm.

Risks Associated with Ibrutinib

The most common side effects, occurring in at least 1 of every 5 (≥ 20%), patients have been:

Occurrence or increase in frequency of loose or watery stools (diarrhea)

- Muscle and bone pain (musculoskeletal pain)
- Nausea
- Low white blood cell count (neutropenia, cells that help fight infection)
- Low platelet count (cells that help blood to clot) (Thrombocytopenia)
- Bleeding (Hemorrhage)
- Rash
- Fever (Pyrexia)

Side effects that have bene seen in at least 1 of every 10 (≥ *10%) patients include:*

- Common cold (Upper respiratory tract infection)
- Pneumonia
- Constipation
- Swelling of the hands or feet (Oedema peripheral)
- Muscle spasms
- Vomiting
- Joint aches (arthralgia)
- Sores in mouth (stomatitis)
- Headache
- High blood pressure (hypertension)
- Skin infection
- Weakness, tingling, numbness, and pain from nerve damage, usually in the hands and feet (peripheral neuropathy)
- Dizziness
- Urinary tract infection
- Indigestion (Dyspepsia)

Side effects that have been seen in at least 1 of every 100 (≥1%) patients include:

- Sinus infection (Sinusitis)
- Increased level of uric acid in the blood (Hyperuricemia)
- Abnormal heart rhythm (Atrial fibrillation)
- Non-melanoma skin cancer
- Blurry vision (Vision blurred)
- Low white blood cell counts with fever (Febrile neutropenia)
- Severe infection throughout the body (Sepsis)

- Redness of the skin (Erythema)
- Increase in specific white blood cell count (Leukocytosis, Lymphocytosis)
- Breaking of the nails (Onychoclasis)
- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Increased level of "creatinine" in the blood (blood creatinine increased)
- Heart failure (Cardiac failure)
- Indigestion (Dyspepsia)

Side effects that have been seen in less than 1 of every 100 (<1%) patients include:

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures. (Tumor lysis syndrome)
- Itchy rash (Urticaria)
- Inflammation of the fatty tissue underneath the skin (Panniculitis)
- Swollen face, lip, mouth, tongue, or throat (Angioedema)
- High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes, and genitals (Stevens-Johnson syndrome)
- Liver failure (Hepatic failure)
- Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachyarrhythmias).
- Temporary or permanent decrease of brain or nerve function due to reduced blood flow to the brain (mini-stroke or stroke)
- Tender or painful bumps or ulcers on the skin, sometimes with a fever (Neutrophilic dermatosis)
- Bleeding in the eye (Eye hemorrhage)

Most of these side effects listed above have been mild to moderate in severity; however severe side effects have occurred. Some side effects have been severe enough to lead to study drug discontinuation, dose modification or reduction, hospitalization, disability, and sometimes death.

You should be made aware that most of these patients also had illnesses related to their cancers or to other medical problems. However, it is possible that you might have side effects like those seen in patients previously receiving ibrutinib. You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Bleeding
You may experience bruising or nosebleeds during treatment with ibrutinib. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur, sometimes resulting in death. If you take other medicines or supplements that increase your risk of bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or medicines used to prevent or treat blood clots or stroke, ibrutinib may increase this risk. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided while taking ibrutinib. Call your study doctor if you have signs or symptoms of serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.

Effects on the heart
Abnormal rapid and/or irregular heart rhythm (atrial fibrillation, atrial flutter, and/or ventricular tachyarrhythmia) and heart failure, including some fatal events, which could sometimes be sudden, have been reported in patients treated with ibrutinib, especially when they also have heart conditions, increased blood pressure or have diabetes, infections, or had abnormal heartbeat in the past. Tell your study doctor immediately if you have any symptoms of heart problems such as feeling as if your heartbeat is fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, swollen legs, or you faint.

Infections
You may experience viral, bacterial, or fungal infections during treatment with ibrutinib. Some of these infections have led to hospitalization and death. Contact your study doctor immediately if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, vomiting, jaundice, feel tired or feel short of breath - these could be signs of an infection. Your study doctor may start or continue medication to help prevent or treat an infection.

A rare and usually fatal viral disease in the brain, Progressive Multifocal Leukoencephalopathy (PML), has been reported in patients treated with ibrutinib in combination with rituximab and in patients who were previously treated with rituximab. If you experience symptoms such as weakness, paralysis, vision loss and/or impaired speech, you should tell your study doctor immediately.

Lymphocytosis and leukostasis
You may experience an increase in the number of lymphocytes, which is a type of white blood cell, in your blood (lymphocytosis). This may occur in the first few weeks of treatment and you should not assume that this increase in white blood cells means that your disease is worsening. This increase may last for several weeks to months.

In rare cases, increased number of white blood cells in your bloodstream may change the blood flow, resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in patients treated with ibrutinib. Your study doctor will monitor your blood counts and may administer additional therapy as needed. Talk to your study doctor about what your test results mean.

Decreased blood counts
Severe decreases in white blood cells, red blood cells, and platelets (neutropenia, anemia, and thrombocytopenia) were reported in subjects treated with ibrutinib. If you experience symptoms such as fever, weakness, or easy bruising and/or bleeding, you should tell your study doctor immediately.

Allergic reactions
Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life threatening. If you have an allergic reaction to ibrutinib, you might develop a rash, difficulty breathing, wheezing when you breathe, sudden low blood pressure with light-headedness, swelling around the mouth, throat or eyes, a racing heartbeat, and/or sweating.

Before starting the study drug, you must tell your study doctor about any drug allergies. You should tell the study doctor right away if you have any allergy symptoms listed above.

Rash
A maculopapular rash (flat, red areas on the skin with small bumps) has been commonly reported in patients treated with ibrutinib alone or in combination with other drugs. Most rashes are mild to moderate in severity and begin 2 to 3 weeks or longer after starting ibrutinib.

There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction or “SCAR”, involving more than 50% of the body) or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas of the body (Stevens-Johnson syndrome). These skin rashes could be life-threatening. You should notify your study doctor immediately if you develop a rash that spreads quickly, or if you notice peeling of your skin, with or without ulcers or sores in your mouth.

Non-Melanoma Skin Cancer and Other Cancers
Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and may be related to the use of ibrutinib. Other cancers have been reported such as solid tumors and blood cancers; the relationship to the use of ibrutinib is unknown. You should tell your study doctor if you develop a new cancer while in the study.

Tumor Lysis Syndrome (TLS)
Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your study doctor may do blood tests to check for TLS.

Hypertension
Hypertension is also called high blood pressure and has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing, or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly.

You should let your study doctor know if you have any of the symptoms of high blood pressure which may mean that you have developed hypertension or that your hypertension is getting worse. Your study doctor may adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Stroke
Cases of stroke, with and without changes in heartbeat rhythm and/or hypertension have been reported with the use of ibrutinib. Some of these cases have led to death. Seek immediate medical attention if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

Liver Failure
Rare cases of liver failure have been reported in patients treated with ibrutinib. Symptoms of liver failure include yellowing of the eyes and skin (jaundice), itching of the skin, dark colored urine, gray or clay-colored stools, confusion, nausea, loss of appetite, and fatigue or diarrhea. You should tell your study doctor immediately if you have any of these symptoms which may suggest liver disease. Your study doctor may be able to diagnose and provide you required medical care.

Interstitial lung disease
Interstitial lung disease is a group of lung disorders in which the tissues become inflamed and may become damaged. Interstitial lung disease is not associated with infections (e.g., bacteria, viruses, fungi) and has been reported in patients treated with ibrutinib. You should report to your physician if you have cough, any signs of new or worsening respiratory symptoms such as shortness of breath or difficulty breathing.

Interference with other drugs
Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body processes ibrutinib. This interference could cause the amount of ibrutinib in your body to be higher or lower than expected. It is also possible that taking the study drug with your regular medications or supplements, including fish oil, Vitamin E, or other vitamins, may change how your regular medications, or your regular supplements, work. It is very important that you avoid grapefruit juice and Seville oranges and tell the study doctor about all medications, supplements, or herbal medicine like St. John's wort that you are taking during the study. You should notify your study doctor immediately about any side effects to avoid possible harm.

Ibrutinib in combination with intensive chemoimmunotherapy treatments
When ibrutinib is given in combination with certain intensive chemoimmunotherapy treatments, older patients may experience more side effects, which may limit their ability to receive the full course of treatment. If you are 65 years of age or older, your study doctor may recommend a lower dose of ibrutinib, discontinuing ibrutinib, and/or more frequent follow-up visits and tests.

Drug interruption for any surgical procedures
Ibrutinib may increase the risk of bleeding with any surgical procedure. Ibrutinib should be held at least 3 to 7 days before and after surgery depending upon the type of surgery and the risk of bleeding. Please contact your study doctor if you have any planned surgical procedures. For emergency surgical procedures, ibrutinib should be discontinued (stopped) after the procedure until the surgical site is reasonable healed (not oozing fluid).

Please contact your study doctor as soon as possible and your study doctor will tell you when to stop ibrutinib and when to restart it following a surgical procedure.

In addition to the risks listed above, there could be unknown or unexpected side effects associated with the use of ibrutinib. You will be told in a timely manner, verbally and in writing, of any new information, findings, or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

You may have all, some, or none of the listed side effects of ibrutinib. Your study doctors and nurses will check you closely for side effects. You may receive medicines or other treatments to prevent or reduce some of these effects. Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think they are related to the study drug.

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Pregnancy Risks

The effect of ibrutinib and daratumumab on a fetus (developing baby still in the womb) is known to cause harm. It is not known whether ibrutinib or daratumumab is excreted in human milk. Because of these risks, women cannot take part in this study if they are pregnant or breastfeeding.

Birth control requirements for female participants

If you are a female, you must have a negative pregnancy test in order to participate in this study unless you cannot become pregnant.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

You must use birth control and not donate eggs for the entire study and for at least 3 months after your last dose of study drug. If you miss a period, or think you might be pregnant during the study, you must tell the Principal Investigator immediately.

Birth control requirements for male participants

If you are sexually active, and able to father a child, you must agree to use one of the birth control methods listed below:

- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Hormonal methods used by your partner, such as birth control pills, patches, injections, vaginal ring, or implants
- Intrauterine device (IUD) used by your partner
- Abstinence (no sex)

You must use birth control and not to donate sperm for the entire study and for at least 3 months after your last dose of the study drug.

Breast-feeding
It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, breast-feeding should be discontinued during ibrutinib treatment.

Risk with Drug Administration
Temporary irritation and bruising may occur at the injection site. There may also be discomfort, pain, or bruising from the needle puncture. In rare cases, an infection may also occur at the site of the needle stick.

Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator, the funding partner, Janssen Pharmaceuticals, Inc., or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you don't follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this research study. It is for the benefit of research. The information that is obtained during this study is very useful scientifically and therefore may be helpful to others with the same condition in the future.

What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. Alternatives to this study for the treatment of your cancer may include other drugs being used for the treatment of cancer, or other experimental drugs. Talk to the Principal Investigator or your doctor if you have any questions about any alternative treatments or procedures for your condition.

What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Study drug and Administration (Daratumumab)

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care. These tests and procedures are:

- Physical Exam
- CT scan
- EKG/ECHO
- Standard of care blood draws

- CBC, Chemistry and Immunoglobulin testing
- Beta 2 microglobulin, Zap-70, CD38, IgHV
- Hepatitis testing
- FISH analysis
- Pregnancy test
- Bone Marrow Aspirate biopsy
- Standard of Care drugs and administration (ibrutinib)
- Post-infusion supportive care medications

You will also be responsible for any co-payments and deductibles.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

Will you be paid for taking part in this research study?

You won't be paid for taking part in this study.

There is a very small chance that some commercial value may result from the use of your sample. This could include new products like a drug or a test to diagnose a disease. If that happens, you will not be offered a share in any profits.

Will your information or samples be used for future research?

Your information or samples collected for this study will not be used or shared for future research studies even if the identifiable information such as your name, Mayo Clinic number or date of birth is removed.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. To protect the data and confidentiality of subject's data, a

code will be used as an identifier. The code will be a registration number assigned specifically to the patient by Mayo Clinic. The correlating Mayo Clinic number and the patient's name for reference will be maintained in a secure database accessible by Mayo Clinic assigned research staff.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private.
However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Your health information may be collected from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- The sponsor(s) of this study and the people or groups hired by the sponsor(s) to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.
If the results of this study are made public (for example, through scientific meetings, reports or media) information that identifies you will not be used.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you.

However, the individuals will not be allowed to record, print, copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 24, 2024**
Not to be used after: **May 23, 2025**

You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
Plummer Building PL 3-02
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Participant Advocate at: researchparticipantadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts until the end of this study, unless you cancel it. The study does not end until all data has been collected, checked (or audited), analyzed, and reported. Because research is an ongoing process, we cannot give you an exact date when the study will end. Sometimes this can be years after your study visits and/or activities have ended.

There is no expiration or end date related to the Sponsor's use of your health information received from Mayo Clinic as part of this study.

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 24, 2024**
Not to be used after: **May 23, 2025**

Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature