Official Title: LCI-HEM-MYE-KRdD-001: Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide and Dexamethasone in Newly Diagnosed Multiple Myeloma
NCT*04113018*
IRB-Approved Date: 11/21/2022

ATRIUM HEALTH
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Sponsor / Study Title:	**Levine Cancer Institute / Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma**
Protocol Number:	**LCI-HEM-MYE-KRdD-001**
Principal Investigator: (Study Doctor)	**Manisha Bhutani, MD**
Telephone:	[redacted]
Address:	**Levine Cancer Institute** [redacted]

Please read this form carefully. Take time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. You will discuss the Informed Consent Form with the study staff and the study doctor in person, during a telephone call, or via a secure video conference call.

You cannot take part in this research study until you sign and date this form. If you agree to take part in the study, you will sign and date the Informed Consent Form either by signing and dating a copy of the printed paper form or by signing and dating electronically using the Florence eConsent platform. Written consent can be done in person or remotely using electronic consent.

After you have signed and dated this paper or electronic Informed Consent Form, you will be given a paper copy or be able to save an electronic copy for your records and/or email a copy to yourself.

This form is for use in a research study that may involve subjects who may or may not have the capacity to consent to take part in the study. Accordingly, when the subject cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the subject rather than the person (legally authorized representative) who is signing and dating this form for the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the subject regains the capacity to consent, informed consent will be obtained from the subject and the subject offered the ability to leave the study if desired.

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INTRODUCTION

The study doctor listed on the first page of this form is asking you to participate in this research study testing the combination therapy of daratumumab, carfilzomib, lenalidomide, and dexamethasone at Levine Cancer Institute and Atrium Health. You are being asked to take part because you have recently been diagnosed with multiple myeloma (MM). The purpose of this study is to determine the efficacy (how well it works) of the study treatment that combines the following drugs: daratumumab, carfilzomib, lenalidomide, dexamethasone in subjects who have a recent diagnosis of multiple myeloma (MM).

Daratumumab and carfilzomib have each been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory MM in combination with standard therapies of lenalidomide and dexamethasone. Daratumumab has also been approved in combination with standard therapies of lenalidomide and dexamethasone for the treatment of patients with newly diagnosed MM. The combination of daratumumab, carfilzomib and dexamethasone has also been approved for the treatment of patients with relapsed or refractory MM. This study will look at how subjects with newly diagnosed MM respond to an investigational combination treatment with the following study drugs: daratumumab, carfilzomib, lenalidomide, and dexamethasone.

This study is being carried out under the sponsorship of Levine Cancer Institute (LCI). Janssen Scientific Affairs, LLC (Janssen) will provide study funding and daratumumab. Amgen will supply carfilzomib, and Celgene will supply lenalidomide.

Taking part in this study is entirely voluntary.

WHY IS THIS STUDY BEING DONE?

Research studies are done to find out the best way to treat subjects. This study is being done because, despite major advances in therapy, MM is still considered an incurable disease.

INFORMATION ABOUT THE STUDY

Normal plasma (blood) cells are found in the bone marrow and are an important part of the immune system. MM is a cancer formed by malignant (cancerous) plasma cells. Daratumumab, one of the study drugs, is a man-made protein that works with your immune system by attaching itself to the cancerous cells. Once daratumumab attaches itself to these cells, it gets your body's immune system to attack and destroy the MM cells. Daratumumab has shown to be effective in subjects with MM when combined with medicines like bortezomib, or lenalidomide + dexamethasone.

This study will be conducted in several parts: Induction, Post Induction/Disease Evaluation Visit, Post-Induction Study Treatment (which may include Consolidation chemotherapy and/or Maintenance/Observation) and Follow-up.

The first part of this study (Induction) will involve treatment with the combination therapy of study drugs (daratumumab, carfilzomib, lenalidomide, and dexamethasone). Your overall health and

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disease status will then be evaluated at the Post Induction/Disease Evaluation Visit to determine your placement into one of the three Post-Induction Study Treatment groups, with Follow-up visits occurring after post-induction study treatment.

You will be one of approximately 39 subjects to participate in this study at the Levine Cancer Institute.

WHAT WILL HAPPEN DURING THE STUDY

To participate in this study, you or your legally authorized representative will need to review, sign and date this consent form and provide authorization for the release of your medical records for research purposes. By doing so, you are giving us permission to determine if you are eligible to participate in this study. To determine if you are eligible, the following will be done. If you have had some of the tests below recently, they may not need to be repeated. Before you begin the study (Baseline):

- A review of your medical and disease history
- Physical examination including weight and vital signs (heart rate, blood pressure, breathing rate, temperature)
- Review of any medicines you are currently taking
- Assessment of your physical activity and ability to perform daily activities
- Pregnancy test (blood) if you are a female of childbearing potential
- Electrocardiogram (ECG) – a measure of your heart's electrical activity
- Echocardiogram (ECHO) a heart test done using sound waves, or MUGA (multigated acquisition scan), a test done to check the pumping action of the heart
- A lung function test if you have chronic obstructive pulmonary disorder (COPD)
- Urine sample for disease evaluation collected over a 24-hour period
- PET/CT scan (positron emission tomography/computed tomography – special types of x-rays) and/or whole body MRI (magnetic resonance imaging – pictures made using strong magnets and a computer). If you have already had a cycle of induction therapy, you may not have to repeat this scan.
- Bone skeletal survey (various X-rays of most bones in the body)
- Bone marrow aspirate (a sample of the liquid portion of the bone marrow) and biopsy (a sample of tissue from the bone marrow and/or a sample of bone) to evaluate your disease
- Blood work to evaluate your disease and to check blood count, blood chemistries, and blood type
- Blood work to test for exposure to the HBV (hepatitis B virus) and for HBV DNA testing. The study doctor may be required by law to report the result of these tests to the local health authority.

A portion of your collected blood and bone marrow samples will be used for correlative (research) studies and to test for Minimal Residual Disease (MRD) throughout the study. MRD can show the extent of any cancerous cells that were not killed/destroyed. A portion of your bone marrow will be collected for MRD testing and sent to an external laboratory, Adaptive Biotech. Only your date of birth and subject ID will be provided to Adaptive Biotech with each sample.

During the study (Intervention; number of visits/cycles):

All study treatment will be given on an outpatient basis. If you are having unfavorable side effects, the study treatment may be stopped for a while, or the dose of the study drug/s may be lowered. Your study doctor will also discuss with you whether it is in your best interest to continue the treatment with the study drugs. You will continue study treatment until your disease progresses or study treatment is interrupted for any other reason.

Induction Phase:

The following will be done prior to each cycle of induction:

- Physical examination including weight and vital signs
- Assessment of your physical activity and ability to perform daily activities
- Pregnancy tests (blood or urine) if you are a female of childbearing potential (this will be done weekly during the first cycle, then monthly)
- Electrocardiogram (ECG) – a measure of your heart's electrical activity
- Blood will be collected to evaluate your disease, check blood counts, blood chemistries and to collect a sample for research at Cycle 1, 3, 5 and 7
- Urine sample for disease evaluation collected over a 24-hour period (only required if your study doctor determines this test is necessary to evaluate how your disease is responding to study treatment)
- If the blood and urine tests for disease evaluation show that your disease is responding and you have a type of myeloma called IgG Kappa, you may have a daratumumab interference blood test done to confirm if the daratumumab is interfering with the blood test disease evaluation result. This type of myeloma may cause one of the disease evaluation blood tests to appear to be "positive" for remaining disease but in fact the positive result can actually be caused by the daratumumab. This test can confirm if this is happening.

You will receive 8 cycles, each lasting for 28 days, of the following:

- Carfilzomib – IV (through a vein) over 30 minutes on Days 1, 8, and 15 of all cycles
- Daratumumab +hyaluronidase (daratumumab SC)– (after receiving carfilzomib and dexamethasone) is given subcutaneously – an injection just under the skin in the abdominal area on Days 1, 8, 15, and 22 for cycles 1 and 2, on Days 1 and 15 for cycles 3-6, and on Day 1 only for cycles 7 and 8. The duration of the injection is approximately 3-5 minutes.
- Lenalidomide - 25 mg orally (by mouth) on Days 1 through 21 of all cycles
- Dexamethasone - 40 mg once weekly (Days 1, 8, 15, and 22). You may receive this IV or oral in the infusion center on days when daratumumab is administered. On weeks when you are not receiving daratumumab, you may take this by mouth.

If you received a pre-study cycle of treatment for your multiple myeloma with induction chemotherapy which contained daratumumab and/or carfilzomib, you will only receive 7 cycles of treatment while on study.

If you are at high risk for complications, the study team may contact you within 48 hours after the daratumumab injection to see how you are feeling.

The doses of study treatment you receive may be reduced for side effects after you begin study treatment.

The following will be done every 12 weeks for up to 6 months after the last dose of daratumumab:

- HBV (hepatitis B virus) DNA testing (only if you tested positive for HBV exposure during Screening)

Post-Induction/Disease Evaluation Visit:

The following will be done at the Post-Induction Disease Evaluation Visit**:**

- Physical examination and assessment of your physical activity and ability to perform daily activities
- Electrocardiogram (ECG)
- Blood will be collected to evaluate your disease, check blood counts, blood chemistries and to collect a sample for research
- Urine sample for disease evaluation collected over a 24-hour period (only required if your doctor determines this test is necessary to evaluate how your disease is responding to study treatment)
- Bone marrow aspirate and biopsy to evaluate your disease
- PET/CT scan and/or whole body MRI

NOTE: A Post-Induction Safety Follow-up visit will occur for subjects who discontinue induction early and do not have a Post-Induction visit as noted above. At this Safety Follow-Up visit, the following will occur:

- Physical examination and assessment of your physical activity and ability to perform daily activities
- Blood work to check blood counts and blood chemistries
- Electrocardiogram (ECG)
- If your disease has progressed or relapsed and a bone marrow aspirate is performed as part of clinical care, bone marrow samples will be collected for disease evaluation and research

Post-Induction Study Treatment

The chosen course of your study treatment for post-induction study treatment will be dependent on several factors. Factors include, but are not limited to, how well you did during the induction phase, if you qualify for a transplant, how the disease is affecting your ability to take care of yourself on a day-to-day basis, and your preference.

Relapse is very common with MM, so after the induction phase, the current state of your disease will be evaluated. If assessment reveals that you have achieved a Very Good Partial Response or better as determined by your study doctor, tests on your bone marrow will be performed to assess the extent of any cancerous cells that were not killed/destroyed (minimal residual disease, MRD) because these remaining cancerous cells may cause your MM to come back. The MRD results will be determined to be either positive or negative. If your disease assessment shows that you did not achieve a Very Good Partial Response or better, or if your MRD test could not be performed, you will be considered to be MRD positive (without testing MRD on your bone marrow). The MRD test that will be done is called Next Generation DNA Sequencing (NGS) or Adaptive ClonoSeq Assay. It was recently approved by the FDA, on September 28th, 2018 for monitoring disease burden during and after treatment. The results of this test will be interpreted by your study doctor according to professional guidelines for clinical decision-making. However, the Adaptive ClonoSeq Assay test is not FDA-approved for treatment decisions. That means its use in making decisions about treatment in the context of this study is considered investigational.

Based on these factors and others, you will be part of one of the **3 separate Post-Induction** study treatment groups (Group A, Group B, or Group C) described below:

If you are considered eligible for ASCT (autologous stem cell transplant - where your normal blood stem cells are given back to you after high dose chemotherapy), your normal blood stem cells will be collected (harvested) before you begin post-induction study treatment, or earlier (any time after Cycle 3 during induction) if determined by your study doctor. Your stem cells will be frozen so they are available should you require an autologous stem cell transplant. If the first attempt to collect adequate stem cells fails during or after induction, re-attempts to collect your stem cells may be done at any time during the study if the study doctor feels it is in your best interest.

If you are assigned to Group A:

You will be assigned to this group if you test negative for MRD after induction. Therefore, your post-induction study treatment may involve one or more of the following:

Note: Although your post-induction study treatment will not include ASCT, your study doctor may have your blood stem cells collected and frozen if they feel you might be eligible for ASCT at a later date. If the attempt to collect adequate stem cells during induction or post-induction is not successful, re-attempts at stem cell collection may occur during maintenance therapy per study doctor discretion.

- Lenalidomide - 10 mg orally (by mouth) on Days 1 through 21 (on a 28 day cycle) until your disease comes back, progresses, or you become intolerant to it.
- Or, observation (no further study treatment) at the discretion of your study doctor.

The following will be done prior to each cycle of lenalidomide maintenance/observation:

- Physical examination and assessment of your physical activity and ability to perform daily activities

- Pregnancy test (blood or urine) if you are a female of childbearing potential on Day 1 of each cycle (only if you receive lenalidomide)
- Blood will be collected to evaluate your disease, check blood counts, blood chemistries and to collect a sample for research at Cycle 3, 5, 7, 9, 11 and disease progression (if this occurs)
- Urine sample for disease evaluation collected over a 24-hour period (only required if your study doctor determines this test is necessary to evaluate how your disease is responding to study treatment)
- Bone marrow aspirate and biopsy to evaluate your disease and MRD at 3, 6, and 12 months after the Post-Induction Disease Evaluation Visit; then every 6 months afterward for disease evaluation and yearly for MRD and research samples.
- PET/CT scan or whole body MRI will be performed every 12 weeks from the Post-Induction Visit if your study doctor feels it is necessary to evaluate your disease

After you have been on lenalidomide and/or observation for 12 cycles, these study visits will only be required on Day 1 of every 3 cycles.

If you are assigned to Group B:

You will be assigned to this group if you test positive for MRD after induction and are eligible for transplant. Therefore in this phase, your study treatment will involve the following:

You will undergo ASCT - you will be given a drug called melphalan (high dose chemotherapy) to try and kill/destroy myeloma cells inside your body followed by ASCT (where your own stem cells will be given back to you through a vein). After you recover from the ASCT, you will return for a Post-ASCT Disease Evaluation Visit.

Post-ASCT Disease Evaluation Visit:

The following will be done at the Post-ASCT Disease Evaluation Visit**:**

- Physical examination and assessment of your physical activity and ability to perform daily activities
- Blood work to evaluate your disease and check blood counts and blood chemistries
- Urine sample for disease evaluation collected over a 24-hour period (only required if your study doctor determines this test is necessary to evaluate how your disease is responding to study treatment)
- Bone marrow aspirate and biopsy to evaluate your disease and MRD status (MRD status only if your disease response results show a response of Very Good Partial Response or better)
- Blood work for research will be collected
- PET/CT scan or whole body MRI if your study doctor feels it is necessary to evaluate your disease.
- If your bone marrow samples are MRD-negative after ASCT, you may take lenalidomide 10 mg by mouth on Day 1 through 21 (on a 28 day cycle) or go on observation per your study

doctor's recommendation until your disease comes back or gets worse. Lenalidomide may also be discontinued if you are not able to tolerate it.

- If your bone marrow samples are MRD-positive (or if your disease evaluation results do not show at least a response of Very Good Partial Response, you will be considered to be MRD positive without testing MRD on your bone marrow) after ASCT, you may receive up to 12 cycles of study treatment with the following study drugs- carfilzomib, lenalidomide and dexamethasone (also known as KRd). The number of cycles you receive will depend on the MRD testing that will be done after completion of cycles 4 and 8. Each cycle will last for 28 days, per the following:
    - Carfilzomib –56 mg/m^2 IV (through a vein) over 30 minutes on Days 1, 8, and 15 of all cycles
    - Lenalidomide – 10-15 mg by mouth on Days 1 through 21 of all cycles
    - Dexamethasone - 20 mg by mouth once every 2 weeks (Days 1 and 15)

Based on your MRD results, the following will happen:

- If you continue to be MRD-positive (based on MRD assessments after the 4th and 8th cycle of KRd), you will continue to receive KRd (maximum of 12 cycles) followed by lenalidomide 10 mg by mouth on Days 1 through 21 until your disease comes back, gets worse, or you are not able to tolerate it.
- If you are determined to be MRD-negative, you will stop receiving KRd but may take lenalidomide 10 mg by mouth on Days 1 through 21 (on a 28 day cycle) or go on observation per your study doctor's decision until your disease comes back or gets worse. Lenalidomide may also be discontinued if you are not able to tolerate it.

If you continue on KRd (this is called consolidation treatment), bone marrow aspirate and biopsy to evaluate your disease, MRD status (MRD status only if your disease response results show a response of Very Good Partial Response or better), and collection of research samples will occur after Cycle 4 and Cycle 8.

During the cycles of KRd, blood work for research will be collected at Cycle 3, and if applicable at Cycles 5, 7, 9, and 11 and disease progression (if this occurs).

If you are assigned to Group C:

You will be assigned to this group if you test positive for MRD after induction and you were found to not be eligible for ASCT based on factors like your age or current medical conditions. Therefore, this phase of your study treatment will involve the following:

Receive up to 12 cycles of chemotherapy with the following study drugs- carfilzomib, lenalidomide and dexamethasone (also known as KRd). The number of cycles you receive will depend on the MRD testing that will be done after completion of cycles 4 and 8.
Each cycle will last for 28 days, of the following:

- Carfilzomib –56 mg/m^2 IV (through a vein) over 30 minutes on Days 1, 8, and 15 of all cycles
- Lenalidomide – 10-15 mg by mouth on Days 1 through 21 of all cycles
- Dexamethasone - 20 mg by mouth once every 2 weeks (Days 1 and 15).

Based on the MRD test results, the following will happen:

- If you continue to be MRD-positive (based on MRD assessments after cycles 4 and 8 of KRd), you will continue to receive KRd (maximum of 12 cycles) followed by lenalidomide 10 mg by mouth on Days 1 through 21 (on a 28 day cycle) until your disease comes back, gets worse, or you are not able to tolerate it.
- If you are determined to be MRD-negative either after cycles 4 or 8 of KRd, you will stop receiving KRd and may take lenalidomide 10 mg by mouth on Days 1 through 21 (on a 28 day cycle) or go on observation per your study doctor's decision until your disease comes back or gets worse. Lenalidomide may also be discontinued if you are not able to tolerate it.

During the cycles of KRd, blood work for research will be collected at Cycle 3, and if applicable at Cycles 5, 7, 9, and 11 and disease progression (if this occurs).

Groups B and C -The following will be done prior to each cycle of KRd:

- Physical examination and assessment of your physical activity and ability to perform daily activities
- Pregnancy test (blood or urine) if you are a female of childbearing potential on Day 1 of each cycle
- Blood work to evaluate your disease and check blood counts and blood chemistries.
- Urine sample for disease evaluation collected over a 24-hour period (only required if your study doctor determines this test is necessary to evaluate how your disease is responding to study treatment)
- Electrocardiogram (ECG) will be performed prior to Cycles 1, 4, and if applicable, 7 and 11.
- After completion of 4 cycles (and again after completion of 8 cycles for subjects who continue consolidation), a bone marrow aspirate and biopsy will be done to evaluate your disease (if your disease response results show a response of Very Good Partial Response or better) and to collect a research sample. If your disease response results do not show a response of at least a Very Good Partial Response, you will be considered to be MRD positive without testing MRD on your bone marrow.
- PET/CT scan or whole body MRI will be performed every 12 weeks from the Post-Induction Visit if your study doctor feels it is necessary to evaluate your disease

After you have completed consolidation study treatment, you will have the following procedures listed below:

Groups B and C only: Post-Consolidation Disease Evaluation:

The following will be done at the Post-Consolidation Disease Evaluation Visit**:**

- Physical examination and assessment of your physical activity and ability to perform daily activities
- Electrocardiogram (ECG)
- Blood work for disease evaluation and to check blood counts and blood chemistries
- Urine sample for disease evaluation collected over a 24-hour period (only required if your study doctor determines this test is necessary to evaluate how your disease is responding to study treatment)
- Bone marrow aspirate and biopsy to evaluate your disease, MRD status (MRD status only if your disease response results show a response of Very Good Partial Response or better), and collection of research samples

After the Post-Consolidation Evaluation visit, bone marrow aspirate and biopsy will be collected for disease evaluation and MRD/research sample at 3, 6, and 12 months after the Post-Consolidation evaluation. After the 12 month sample, bone marrow aspirate and biopsy should be performed for the disease evaluation every 6 months for disease evaluation and annually for MRD and a research sample throughout the lenalidomide/observation period.

If you do not receive consolidation therapy, bone marrow aspirate and biopsy will be collected for disease evaluation and MRD/research sample at 6 and 12 months after transplant.

Groups B and C only: Lenalidomide Maintenance/Observation:

Once you have completed consolidation, you will continue onto lenalidomide or observation per your study doctor's recommendation as indicated above until your disease comes back or progresses. You will come into the clinic for study visits on Day 1 of each 28 day cycle. Study visit procedures for lenalidomide maintenance/observation are listed in the section above labeled "Group A."

After you have been on lenalidomide and/or observation for 12 cycles, these study visits will only be required on Day 1 of every 3 cycles.

During lenalidomide maintenance/observation, blood work for research will be collected on Day 1 of Cycles 1, 3, 5, 7, 9, 11 and at disease progression. Bone marrow aspirate and biopsy will also be collected for disease evaluation every 6 months, with MRD testing and blood for research annually during the lenalidomide maintenance/observation period.

For Groups A, B, and C: After you complete the intervention (Safety Follow-up visit):

An end-of-study treatment visit will be done when you stop study treatment for any reason. The following will be done at this visit:

- Physical examination and assessment of your physical activity and ability to perform daily activities
- Blood work to check blood counts and blood chemistries

Follow Up:

Those who stop study treatment for reasons other than disease progression will continue to have disease assessments per standard of care until relapse or disease progression, start of a new anti-cancer therapy, you withdraw from the study, death, or until the study is complete, whichever occurs first. Follow-up contact will occur approximately every 3 months from the date of last study treatment and may be conducted by telephone.

If it is confirmed by your study doctor that your disease has progressed or you have started new anticancer therapy, you will be contacted by phone once every 3 months from the date of the last study treatment until you can no longer be reached for follow-up, death, or until the study is complete.

YOUR ROLE IN THE STUDY

Taking part in a research study can be an inconvenience to your daily life. Please consider the study time commitments and responsibilities as a research subject when you are deciding to take part. Your responsibilities as a study subject include the following:

- Tell the truth about your medical history and current conditions.
- Tell the study doctor if you have been in a research study in the last 30 days or are in another research study now.
- Tell the study doctor about any problems you have during the study.
- Take the study drugs as directed by the study doctor and study staff.
- Do not share the study drugs with anyone else. Keep the study drugs out of the reach of children and persons of limited capacity to read or understand.
- The study doctor or study staff will talk to you about any food or medicines that you should not take while in this study.
- Use care when driving or using machinery while you are taking the study drugs.
- Accurately fill out your study diaries and return them.

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RISKS OF THE STUDY

As with all research studies, the study drugs and study procedures may involve unknown risks. Any medication can have temporary or permanent side effects and can cause unforeseen adverse reactions.

You may have side effects while on the study. Everyone taking part in the study will be monitored carefully for any side effects. Side effects may be mild or very serious. Your study doctor may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away.

Any drug has risks and side effects which may vary from person to person. Side effects may be mild or very severe. Side effects seen on research studies can result from a subject's disease, the drug under study, other drugs you are taking, other diseases you have, or a combination of these.

Daratumumab

This section gives you the information known so far about side effects seen with daratumumab. As of November 15, 2021, approximately 5839 clinical trial subjects have been enrolled in studies using daratumumab via intravenous (IV, directly into the vein) infusions or SC (subcutaneous – injected into the skin) alone or in combination with other therapies. Of these 5839 subjects, about 1878 received daratumumab alone, and about 3961 subjects received daratumumab in combination with other therapies. Daratumumab is commercially approved for the treatment of multiple myeloma and AL amyloidosis. This study has been revised to give daratumumab as a 15 milliliter subcutaneous (SC) injection for a fixed dose of 1800 milligrams. This means that daratumumab in liquid form will be injected under the skin, on your abdomen. Daratumumab SC is approved in the United States and is currently being evaluated in several other studies.

Not all of the possible side effects and risks related to daratumumab are known. New side effects may happen. You will be watched closely and you will receive appropriate care if side effects happen. Please tell your study doctor if you have any of the side effects described below or any other ones not listed. All serious adverse events will be closely monitored.

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 (IV or 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 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 and 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). 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.

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 study doctor immediately if you experience any of these signs and symptoms.

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 unknown.

The study doctor will continue to monitor infusion-related reactions and make changes to the way daratumumab is administered and/or recommend additional medications as necessary.

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

- You may get medications, including steroids, paracetamol/acetaminophen and antihistamine, before the administration, but this will be per your study doctor's discretion.
- If you have a reaction, the administration will be paused and/or the symptoms treated as needed. Dependent on the reaction, the infusion may continue at a slower rate. If you have a life-threatening reaction, you will need to stop further study treatment with daratumumab and your study doctor will discuss alternative treatments with you.

- If you are considered higher risk for breathing problems (for example COPD, asthma), you may also get medications, including inhaled steroids, after the administration.
- You may stay overnight in the hospital after the administration so medical staff can check you.

Very Common side effects with daratumumab (affects more than 1 in 10 subjects):

- Infection of the upper respiratory tract such as nose, sinuses, throat, or upper airway
- Infection of the lower airway (bronchitis)
- Infection of the lungs (pneumonia)
- Low platelets, which may increase the risk of bleeding and bruising (See separate section "Blood Cell Effects" below)
- Low red blood cells (anemia, including tiredness and weakness)
- Low white blood cells (including neutrophils and lymphocytes), which can make it harder to fight infections
- Decreased appetite
- Sleeplessness (insomnia)
- 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
- Fatigue, or lack of energy
- Weakness, lack of strength
- Fever
- Swelling of hands, feet, or limbs
- Back pain
- Joint pain

Common side effects with daratumumab (affects 1 to 10 in 100 subjects):

- 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 and 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 (sugar) levels
- Low blood calcium levels
- Dehydration (loss of body fluids)
- Irregular heartbeat (atrial fibrillation)
- High blood pressure
- Chills
- Fluid in lungs (pulmonary edema)
- Dizziness
- Fainting
- Inflammation of the pancreas (pancreatitis)
- Itchy skin
- Muscular pain in the chest
- 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

Uncommon side effects with daratumumab (affects 1 to 10 in 1,000 subjects):

- Cytomegalovirus infection (see separate section on infections below)
- Liver infection (hepatitis) in those subjects who are carriers of the hepatitis B virus
- Covid-19 infection

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.

Infection
Different kinds of infection have been seen in patients receiving daratumumab. Most of them are upper 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 infections such as pneumonia and sepsis have 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 study 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

study treatment and until 6 months after the last dose of daratumumab, and you will be treated, if appropriate, by your study doctor. The study doctor may be required by law to report the result of these tests to the local health authority.

Blood transfusions:
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 subject 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.

Carfilzomib

You will be told about the known risks, which are the side effects reported previously by others who took carfilzomib. However, your study doctors do not know all the side effects that you may experience. As with all investigational drugs, all risks may not have been identified at this time. There may be serious unexpected or unforeseen risks while taking carfilzomib, including death. It is known that nearly everyone who takes carfilzomib will have some side effects while on the study drug. Many of these side effects may be mild but some side effects can be serious and even fatal.

As of 19 January 2022, approximately 5209 subjects have received carfilzomib in research studies.

As of 19 January 2022, since it was first approved for sale in July 2012, approximately 235,646 patients have been prescribed carfilzomib (Kyprolis®) for treatment.

Before you take carfilzomib, your study doctor needs to know if you have any:

- Heart problems, including a history or chest pain, heart attack, heart failure, high blood pressure, irregular heartbeat, or if you have ever taken a medicine for your heart
- Lung problems, including a history of shortness of breath at rest or with activity
- Kidney problems, including kidney failure or if you have ever received dialysis
- Liver problems, including a history of hepatitis; particularly previous hepatitis B virus infection, fatty liver, or if you have ever been told your liver is not working properly
- Unusual bleeding, including easy bruising, bleeding from an injury, such as a cut that does not stop bleeding in a normal amount of time, or internal bleeding, which can indicate you have low platelets
- Blood clots in your veins
- Any other major disease for which you were hospitalized or received medication

Talk to your study doctor if any of these apply to you before using carfilzomib. You may need extra tests to check that your heart, kidneys and liver are working properly.

Tell the study doctor or the study staff about any drugs you are taking, have recently taken, or are planning to take, including herbal remedies, supplements, and drugs you take without a prescription.

The side effects of using carfilzomib in combination with other drugs are unknown at this time. Please discuss any concerns you may have with the study doctor.

Very Common Side Effects (may affect more than 1 in 10 people):

- Low red blood cell count, which may cause tiredness
- Low platelets, which may cause easy bruising or bleeding
- Low white blood cell count, which may decrease your ability to fight infection
- Shortness of breath, cough with phlegm (mucus)
- Diarrhea
- Queasy/feeling like you need to throw up (Nausea)
- Constipation
- Vomiting
- Tiredness (fatigue)
- Fever
- Swelling of the hands, feet or ankles
- General weakness
- Respiratory (breathing) tract infection
- Pneumonia (lung infection)
- Bronchitis (infection of the tubes in the lungs)
- Inflammation of the nose and throat
- Decreased appetite
- Back pain, joint pain, pain in limbs, hands, or feet
- Muscle spasms
- Headache
- Dizziness
- Numbness
- Insomnia (difficulty sleeping)
- Changes to blood tests (decreased blood levels of potassium, increased blood levels of creatinine)
- High blood pressure (hypertension)

Common Side Effects (may affect up to 1 in 10 people):

- Fever associated with low white blood cell count
- Heart failure, and heart problems including rapid, strong or irregular heartbeat (The risk of developing heart failure when receiving carfilzomib is higher if you are 75 years of age or older. This risk is also higher if you are Asian.)
- Heart attack
- Blood clots in the lungs

- Fluid in the lungs
- Nosebleed
- Change in voice or hoarseness
- Pain in throat
- Wheezing
- Blurred vision
- Cataract (clouding of the lens of the eye)
- Stomach pain
- Indigestion
- Toothache
- Chills, pain, feeling unwell
- Pain, swelling, irritation or discomfort where you received the injection into your vein
- Infusion site reactions such as pain, swelling, irritation or discomfort where you received the drug injection into your vein
- Liver problems including an increase in your liver enzymes in the blood
- Runny nose or nasal congestion
- Urinary tract infection
- Flu-like symptoms (influenza)
- Serious infection in the blood (sepsis)
- Viral infection
- Infection and/or irritation of your stomach and bowels (intestines)
- Lung infection
- Dehydration (lack of fluids)
- Bone and muscle pain
- Chest pain
- Muscle weakness
- Aching muscles
- Abnormal sensation such as tingling or decreased sensation in arms and/or legs
- Anxiety
- Kidney problems, including decreased ability to make urine, and kidney failure needing dialysis (filtering of blood outside the body)
- Rash, itchy skin, redness of the skin
- Increased sweating
- Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of sugar, calcium, uric acid, potassium, bilirubin, or c-reactive protein)
- Low blood pressure (hypotension)
- Blood clot in the veins
- Ringing in the ears
- Flushing (skin or face become red and hot)

Uncommon Side Effects (may affect up to 1 in 100 people)

- Sudden loss of heart function
- Reduced blood flow to the heart
- Abnormal amount of fluid between the heart and the lining around the heart
- Heart muscle disease which may cause shortness of breath and tiredness
- Bleeding in the lungs
- Bleeding in the stomach and bowels
- Blockage of the intestines
- Inflammation of the pancreas gland
- Multi organ failure
- Liver failure
- Itchy skin, yellow skin, very dark urine and very pale stools which may be caused by a blockage in the flow of bile from the liver (cholestasis)
- Severe infection of the blood causing low blood pressure and low blood flow to the different organs
- Bleeding in the brain
- Allergy to carfilzomib
- Stroke
- Bleeding

Rare (may affect up to 1 in 1000 people)

- Swelling and irritation of the lining around the heart
- Swelling of the throat
- Hole in the stomach, small intestine, or large bowel
- Infection of the back of the eye (cytomegalovirus)

Other conditions/side effects to watch for:

You must look out for certain symptoms while you are taking carfilzomib to reduce the risk of side effects. Carfilzomib can make some conditions worse or cause serious side effects. Tell your study doctor or the study staff as soon as possible if you get any of these:

- Chest pains, shortness of breath, or if there is swelling of your ankles and feet, which may be symptoms of heart problems
- Difficulty breathing, including shortness of breath at rest or with activity, rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung problems.

- Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, queasy/feeling like you need to throw up, vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis.
- Shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension.
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure
- Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, a condition that can occur after treatment of a fast-growing cancer. As tumor cells die, they break apart and release their contents into the blood. This causes a change in certain chemicals in the blood, which may cause damage to organs, including the kidneys, heart and liver.
- A reaction to carfilzomib infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, flushing or swelling of the skin, swelling of the throat, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain.
- Unusual bruising or bleeding, such as a cut that does not stop bleeding in a normal amount of time or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools
- Leg pain (which could be a symptom of blood clots in the deep veins of the leg), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)
- Yellowing of your skin and eyes, stomach pain or swelling, queasy/feeling like you need to throw up, or vomiting, which could be signs of liver problems, including liver failure. If you have previously had hepatitis B virus infection, treatment with Kyprolis may cause your hepatitis B virus infection to become active again.
- Bleeding, bruising, weakness, confusion, fever, queasy/feeling like you need to throw up, vomiting, diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombotic Microangiopathy (including Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS).
- Headaches, confusion, seizures, blindness, and high blood pressure (hypertension), which may be symptoms of a brain condition known as Posterior Reversible Encephalopathy Syndrome (PRES).
- Blurred or double vision, vision loss, difficulty speaking, weakness in an arm or a leg, a change in the way you walk, problems with your balance, persistent numbness, decreased sensation or loss of sensation, decreased alertness, memory loss or confusion which may be symptoms of a central nervous system infection known as Progressive Multifocal Leukoencephalopathy (PML)

The following side effects have been seen in people who received carfilzomib. It is unknown if they were caused by carfilzomib, you may or may not experience these side effects:

- Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia MDS/AML)
- Tenderness of pain in the abdomen that gets more intense with motion or touch, abdominal bloating or distention, queasy/feeling like you need to throw up, vomiting, diarrhea, constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs

Driving and Using Machines
You may experience fatigue, dizziness, fainting, and/or a drop in blood pressure after study treatment with carfilzomib. This may impair your ability to drive or operate machinery. If you have these symptoms, you should not drive a car or operate machinery.

Hydration Risks
There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your study doctor's instructions regarding how much water or other fluids you should drink. Over hydration can cause side effect to your heart, lungs, and kidneys.

Dexamethasone

The potential side effects include the following:

Likely (occurring in greater than or equal to 30% of subjects):
- Difficulty sleeping
- Fatigue

Less Likely (occurring in 10%-29% of subjects):
- Low red blood cells or platelets
- Blurred vision
- Constipation or diarrhea
- Upset stomach or heartburn
- Fever
- Swelling of the arms or legs
- Upper respiratory tract infection
- Decreased weight
- High blood sugar
- Poor appetite
- Muscle cramps
- Bone pain or back
- High blood pressure, swelling, headache
- Sores in your mouth or gut, and a high risk of getting infections

- High blood sugar, muscle weakness
- Increased bleeding and bruising
- Weight gain, increase in appetite, and nausea
- Change in your mood, your spirit to be high, or cause you to have trouble sleeping
- Vision problems
- Gastrointestinal problems
- Acne
- Dizziness

Infrequent but Serious (occurred in less than 10% of subjects):

- Low white blood cell counts
- Vomiting
- Abdominal pain
- Swelling
- Pneumonia
- Low blood potassium
- Pain in the arms or legs
- Tremor
- Altered taste sensation
- Numbness in the hands or feet
- Bronchitis
- Inflammation of the nose or throat

Other side effect to watch for:

- Osteoporosis which could lead to bone fractures

Lenalidomide

Lenalidomide has been studied in healthy volunteers and in subjects with cancer of the blood and other organs of the body as well as in subjects with other diseases. As with any other investigational treatment, there may be side effects or risks associated with lenalidomide, some of which are not yet known.

The following is a list of side effects reported in completed and ongoing studies considered to be related to lenalidomide. In some cases, side effects can be serious, long-lasting, may never go away, or can cause death. Your study doctor will answer any questions you might have about these side effects and provide you with more information.

Very common side effects (**occurred in greater than or equal to 10% of subjects**):

- Low number of white blood cells (with or without fever) known as leukocytes, neutrophils, granulocytes or lymphocytes
- Decrease in platelets (cells that help your blood clot)

- Low red blood cells (anemia)
- Blurred vision
- Blood clot in lower extremities (legs) and in the lungs (pulmonary embolism)
- Diarrhea
- Indigestion
- Nausea
- Vomiting
- Feeling weak and unwell
- Fatigue, lack of energy
- Constipation
- Swelling
- Difficulty sleeping (insomnia)
- Pain including muscles and joints
- Pain in the stomach/abdomen
- Fever
- Chills
- Pneumonia
- Influenza (flu)
- Upper respiratory tract infections
- Sinus infection
- Urinary tract infection
- Infection in the stomach and intestines
- Kidney failure
- Sore throat
- Stuffy nose
- Weight loss
- Decreased appetite
- High blood sugar
- Imbalance in blood chemicals (decrease in potassium and decrease in calcium)
- Abnormal liver function tests
- Cough
- Rash
- Dry skin
- Itching
- Shortness of breath
- Nosebleed
- Dizziness
- Altered state of taste
- Headache
- Cataract (clouding of the lens of the eye)

- Tingling of skin
- Abnormal decrease in sense of touch
- Pain sensation in nerves (neuropathy)
- Shaking (tremor)
- Feeling sad (depression)
- Sudden increase in tumor size
- Back pain
- Abdominal pain
- Muscle spasms
- Bone pain
- Pain in the arms and legs, hands and feet

C**ommon side effects** (**occurred in between 1 and less than 10% of subjects**):

- Abnormally low number of all blood cells
- Destruction of red blood cells
- Sudden loss in kidney function
- Heart attack
- Abnormal rapid heart beats
- Heart stops working well (cardiac failure)
- Low oxygen to heart tissue
- Lung inflammation causing chest pain
- Viral infections such as cold sores/genital herpes, and/or shingles
- Cellulitis (infection under skin surface)
- Bacterial infection in the skin
- Meningitis (infection of membranes surrounding brain and spinal cord)
- Lung infection
- Respiratory tract infection
- Blood infections (sepsis and/or bacteremia)
- Infection of the joints (arthritis)
- Dry mouth
- Bile flow from liver slowed or blocked
- Gout (inflammatory arthritis caused by high levels of uric acid in the blood)
- Falling
- Bruising
- Lethargy
- Increase in liver lab tests
- Increased CRP (C-reactive protein) indicating inflammation
- Dehydration (lack of fluids)
- Diabetes
- High uric acid in the blood

- Iron build up in the body
- Decrease in magnesium, phosphate and sodium in the blood
- Increase in calcium in the blood
- Muscle weakness
- Cancer (acute myeloid leukemia, basal cell carcinoma, squamous cell carcinoma, T-cell acute leukemia)
- Stroke
- Decreased sensation in nerves (peripheral neuropathy)
- Fainting
- Vertigo (problem with inner ear that causes spinning sensation)
- Pain including non-heart related chest pain
- Mood altered
- Low oxygen level in blood which might cause lightheadedness
- Breathing disorder
- Excessive sweating, night sweats
- Skin redness
- Swelling of skin filled with blood (hematoma)
- Swelling of blood vessels (vasculitis)
- High or low blood pressure
- Blood clot in vein
- Tumor lysis syndrome - disturbances of your electrolytes which is caused by rapid killing of cancer cells in the blood. This may be seen after initiation of cancer treatment, and may result in kidney damage and heart problems such as an abnormal heartbeat
- Myelodysplastic Syndrome (blood cancer that causes decreased number of red and white blood cells and platelets because they do not develop normally)

Uncommon side effects (**occurred in between 0.1 and less than 1% of subjects**):

- Hypersensitivity to lenalidomide
- Fever, and/or swollen glands
- Infection of the appendix
- Infection of a sac in the tissue filled with fluid (bursa)
- Infection of the colon caused by the bacteria Clostridium difficile
- Infection causing a chronic breathing condition
- Infection of the kidneys

The following side effects have been reported and are considered by Celgene to be related to lenalidomide:

- Inflammation of the lungs (pneumonitis)
- Over and under active thyroid
- Severe allergic conditions including:

  - Swelling under skin
  - Severe skin reactions involving lining of the nose, mouth, stomach and intestines (Steven-Johnson syndrome) or rash leading to the separation of the top layer of skin (toxic epidermal necrolysis)
  - Skin reaction, elevated level of eosinophils (type of white blood cell), fever, and/or swollen glands with other organ complications (inflammation of liver, inflammation of kidney nephrons, infection of lungs, inflammation of the heart and/or inflammation of the sac surrounding the heart
- Reactivation of viruses including hepatitis B or herpes zoster (shingles)
- Tumor lysis syndrome – with initiation of cancer therapy, cancer cells can break down and release large amounts of chemicals such as potassium, phosphate, and uric acid into blood circulation, which may then lead to kidney failure
- Acute Graft versus Host Disease – after a bone marrow transplant, new cells attack the body which can result in abdominal pain or cramps, nausea, vomiting, diarrhea, jaundice (yellowing of the skin), or skin rash
- Solid organ transplant rejection – after organ transplant the body rejects the transplanted organ which can result in flu-like symptoms (fever, chills, body aches, nausea, cough, shortness of breath, feeling unwell or tired), pain at the transplant area, less urine, sudden weight gain, or other possible symptoms specific to the type of transplant
- Progressive multifocal leukoencephalopathy (PML) - infection of the brain with symptoms including vision changes, difficult speaking, weakness in limbs (arms/legs), change in gait or balance, persistent numbness, decreased or loss of sensation, and memory loss or confusion

Second new cancers

In clinical trials of newly diagnosed multiple myeloma, an increased rate of second new cancers have been seen in subjects receiving lenalidomide compared with subjects in the other arm (not receiving lenalidomide). These new cancers including acute leukemia (blood cancers), lymph node cancers, and solid tumors were seen in subjects receiving lenalidomide taken together with melphalan or immediately after high dose melphalan and stem cell transplantation. An increase of blood and lymph node cancers was also seen in the clinical trials where subjects received lenalidomide after stem cell transplant. When lenalidomide is given with dexamethasone, a higher number of skin cancers and solid tumors have been reported.

In chronic lymphocytic leukemia clinical trials, acute leukemia of the B cell type was observed more frequently as second new cancers in subjects receiving lenalidomide compared with subjects in the control arm who did not receive lenalidomide. The majority of subjects who developed leukemia of the B cell type received an alkylating agent before treatment with lenalidomide.

You should make your study doctors aware of your medical history and any concerns you may have regarding your own increased risk of other cancers. Your study doctor will be checking you for any possible new cancers that may develop during your study treatment.

Other risks

Lenalidomide has been shown to increase the level of digoxin in the blood in some subjects; please tell your study doctor if you are taking digoxin.

Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence (sleepiness), vertigo, and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females must not become pregnant while taking lenalidomide. You have been informed that the risk of birth defects is unknown. If you are a female of childbearing potential, you agree not to become pregnant while taking lenalidomide.

Before you consent to participating in this study, your study doctor will discuss with you the full requirements of the pregnancy precautions within the Lenalidomide Information Sheet that you have received and must agree to follow.

Since you will take lenalidomide and dexamethasone for this study please note that:

Subjects who take lenalidomide and dexamethasone have a greater chance of having blood clots. Because of this, it is recommended that you do not take birth control pills or hormone replacement therapy before discussing with the study doctor and considering the risks and benefits of these choices.

There are additional side effects that have been seen in subjects that have taken lenalidomide. Please ask your study doctor for information regarding these side effects.

OTHER POSSIBLE RISKS

Blood Draw/IV Risks

You may have pain or bruising at the site where the blood is drawn or IV is inserted. You may feel faint. An infection at the site of the blood draw or IV insertion is possible.

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Bone Marrow Aspirate/Biopsy Risks

A bone marrow aspirate and biopsy is a procedure in which a small sample of bone marrow (soft, sponge-like tissue in the center of most bones) and bone is removed. A small area of skin and the surface of the bone underneath are numbed with an anesthetic, a special wide needle is pushed into the bone, and a sample of liquid bone marrow is removed with a syringe attached to the needle. The syringe is then removed and the needle is rotated to remove a sample of the bone and the bone marrow. Both the bone marrow and bone samples are sent to a laboratory to be looked at under a microscope.

If you have a bone marrow aspirate/biopsy, you may experience pain and/or discomfort at the site where the needle is inserted. The amount of pain and/or discomfort will depend on your pain tolerance, which is different for each person. Some people describe a sharp pain in the bone where the needle is inserted. Other people describe it as a long, hard punch or kick. This pain and/or discomfort only lasts a few seconds during the procedure. Tenderness over the area may last for a few days. Bleeding from the site or infection may occur but is rare. You may have an allergic reaction to the anesthetic.

MRI

There are risks with an MRI if you are pregnant or have one of the following: an artificial heart valve, metal plate, pin or other metallic objects in your body (including a bullet or shrapnel). During an MRI, you will have to lie still on your back in the MRI scanner in a tight space. This may make you anxious. The MRI scan does not cause any pain and does not expose you to x-ray radiation. Sometimes a dye is used to help make the pictures clearer. The dye is injected into your veins by an IV catheter (a small plastic tube inserted into a vein). The dye may cause you to get a metallic taste in your mouth and to feel warm. Rarely, it causes nausea and vomiting. The dye can also cause damage to the kidneys, which may lead to kidney failure. This is of particular concern if you have poor kidney function. Rarely, the dye can cause a life-threatening allergic reaction.

CT Scan

A CT scan is a computerized x-ray picture of your internal organs. You may feel some discomfort or anxiety when lying inside of the CT scanner. The contrast material (dye) that is injected into your body may cause you to get a metallic taste in your mouth and to feel warm. Rarely, it causes nausea and vomiting. The dye can also cause damage to the kidneys, which may lead to kidney failure. This is a concern if you have poor kidney function. Rarely, the dye can cause a life-threatening reaction.

PET Scan

During a positron emission tomography (PET) scan, your body's tissue will be exposed to a radioactive tracer injection. The risks associated with this exposure include:

- Pain, redness or swelling at the injection site
- Radiation exposure to the fetus of a pregnant woman or the child of a breast feeding woman. If pregnant or breast feeding you are not eligible to participate in this study
- Allergic reaction to the radioactive glucose (rare)
- Tissue damage because of the radiation that might trigger a future cancer (very rare)

X-ray

X-rays involve exposure to radiation. The amount of radiation exposure you may receive from these standard diagnostic tests is considered small and will not adversely affect the treatment of your disease. You may be exposed to more radiation because you are taking part in the study. At exposure levels much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the exposure level you will receive in this study, it is very likely that you will see no effects at all.

ECHO (ultrasound)

An echocardiogram is an ultrasound to take pictures of your heart. The technician will place a jelly-like substance on the left side of your chest and then use a device called a transducer to take pictures of the heart. The transducer is a part of the ultrasound machine that is placed on your chest in the area that the jelly was placed and then moved around the chest to take pictures. When ultrasound enters the body, it heats the tissues slightly. Even though there are no known risks of ultrasound imaging, the long-term effects of tissue heating are not known.

MUGA

A MUGA scan takes video of the blood pumping through your heart. An ECG will be done at the same time to trace your heartbeat. You will be given two injections into a vein 15-20 minutes apart. The first injection prepares your red blood cells for the second injection, which will contain a small amount of radioactivity. You may experience some local discomfort from the injections. After the second injection you will be required to lie on a narrow bed with your hands above your head. A special camera (called a gamma camera) will be placed next to your heart and will take video of your heart beating for 10-20 minutes. Once completed you will be able to leave the study clinic and resume your normal activities. There is a small amount of radiation used for this test and it is considered roughly equivalent to that which you receive from natural background radiation in about 24 months. The radioactivity leaves your body quickly and will not make you feel unwell. Female subjects who are or might be pregnant, or who are breastfeeding, should not have this test done. Although the level of radiation is small, you're advised to avoid close contact with pregnant women, babies, and children for 12 hours after the test.

ECG

An ECG traces the electrical activity of the heart. You may have mild irritation, slight redness, or itching at the sites on your skin where the recording patches are placed.

Reproductive Risks:

Women Who Can Get Pregnant or Are Breastfeeding

You may not take part in this study if you are breastfeeding, are pregnant, think that you may be pregnant, or are trying to get pregnant. If you are pregnant or breastfeeding, there may be risks to you and the baby that are not known at this time. Women who can get pregnant will be tested for pregnancy during the study.

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You must avoid getting pregnant in order to take part in this research study. You should not have sexual intercourse or you must use **at least one** highly effective birth control method **plus a second** birth control method which can be either a "highly" effective method or an acceptable method from the time of informed consent until 3 months after stopping all study drugs. Examples of "highly" effective birth control measures are:

- Oral, intravaginal or transdermal combined (estrogen and progestogen containing) hormonal contraception.
- Oral, injectable or implantable progestogen-only hormonal contraception.
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Vasectomized partner and testing to show there is no more sperm in the semen
- Sexual abstinence (not having sex)

Examples of acceptable birth control measures are:

- Progestogen-only oral hormonal contraception
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide

It is important for you to tell the study doctor at once if you get pregnant or think that you might be pregnant while you are in the research study. If this happens, the study doctor will discuss with you what you should do. If you get pregnant, you will be asked to stop taking part in the study. You may also be asked questions about the outcome of your pregnancy and the baby. You must not donate eggs during the study and for 6 months after your last dose of study drugs.

Men

The effect of the study drugs on male sperm is unknown. In rare cases, study drugs may damage sperm in ways that affect a child that is fathered. Affected sperm may be present in the semen for about 2 months. Therefore, it is recommended to avoid fathering a child for 3 months after your last dose of all study drugs. You also must not donate sperm during the study and for 3 months after your last dose of all study drugs.

You should not have sexual intercourse or you should use a method of birth control that is acceptable to you and the study doctor. If you think that you have gotten a woman pregnant, you must tell the study doctor at once. If your partner gets pregnant during the study, you may be asked questions about the pregnancy and the baby.

<u>Unknown Risks</u>

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

ALTERNATIVES TO BEING IN THE STUDY

You do not need to take part in this research study. You may choose not to take part in this study and receive other available treatments for multiple myeloma as recommended by your study doctor, such as standard chemotherapy, standard radiation therapy, stem cell transplantation, other medications, or you may be eligible for other experimental treatments for multiple myeloma. As an alternative to taking part in this study, you may receive treatment to just control the symptoms you are having because of your disease. You can also choose to have no treatment at all. Your study doctor can discuss the alternatives and the risks and benefits of these alternatives with you.

POTENTIAL BENEFITS OF BEING IN THE STUDY

Taking part in this study may or may not improve the symptoms of your condition. There may be no benefit to you and your condition may not improve. While you are in this study, your study doctor will follow your condition closely. By taking part in the study you may help future patients.

COSTS OF BEING IN THE STUDY

You or your insurance company will be charged for routine medical care and/or hospitalization in the usual manner. You or your insurance company will not be charged for procedures that are being performed for research purposes only. The study drugs (daratumumab, carfilzomib, and lenalidomide) will be provided at no cost to you. Some health insurance plans may not cover certain procedures and medical treatments. You may wish to discuss coverage with your insurance company before agreeing to participate in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage You can print a copy of the "Clinical Trials and Insurance Coverage" information from this web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

YOUR PAYMENT FOR BEING IN THE STUDY

You will not be paid for being in this study. You will also not be paid or reimbursed for time and transportation costs for traveling to and from the clinic.

STUDY STAFF PAYMENT/FINANCIAL DISCLOSURE

None of the doctors asking you to participate in this study has received or will receive money or other benefits for personal use from the companies (Amgen, Inc.; Celgene Corporation, and Janssen) that developed some of the drugs used in this study. However, Janssen will give money or other benefits to a research fund, foundation, educational institution, or other organization with which the study doctor or study staff is associated.

Affix Participant Barcode Label Here

COMPENSATION FOR INJURY

In the event that you are injured as a result of your participation in this study, we will provide or arrange for treatment as necessary. This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner. You will be responsible for deductibles, co-payments, and co-insurance. There are no plans to pay or give you other compensation for the injury. You do not waive any legal rights by signing this consent form.

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

For insurance or other payment reporting purposes, we may need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because we may have to check to see if you receive Medicare and if you do, report the payment we make to Medicare.

In no way does signing this consent form waive your legal rights nor does it relieve the investigators, Sponsor, or involved institutions from their legal and professional responsibilities.

CONFIDENTIALITY

The records of this study will be kept private. If any report about this research is published, we will not include any information that will make it possible to identify you. However, there is some risk that de-identified data might be re-identified. Also, your record for this study may be reviewed and/or photocopied, by Atrium Health, or by representatives of the Food and Drug Administration or other government agencies.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

Affix Participant Barcode Label Here

AUTHORIZATION TO USE AND DISCLOSE YOUR PROTECTED HEALTH INFORMATION

If you wish to participate in this research study, you _____
Printed Name of Research Subject

must sign this Authorization. By signing this Authorization, you give all healthcare providers, including Atrium Health, permission to use or disclose (release) your protected health information, both past and present, for the research study described here:

LCI-HEM-MYE-KRdD-001: Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma

The protected health information that we may use or disclose (release) for this research may include all information in your medical record, such as results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition.

The health information listed above may be used by and/or disclosed (released) to:

- Study investigator and research staff
- Study sponsor and/or its associated companies
- Regulatory or other governmental authorities of the United States or other countries based on this study
- Other persons or agents authorized by the study sponsor
- Atrium Health employees
- Other persons or agencies as required by law or allowed by federal regulations
- Advarra Institutional Review Board (Advarra IRB) or Data Safety and Monitoring Boards.

Atrium Health is required by law to protect your protected health information. By signing this Authorization, you authorize Atrium Health to use and/or disclose (release) your protected health information for this research study. Those persons who receive your protected health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your protected health information with others without your permission, if permitted by laws governing them. Your protected health information may then no longer be protected by the Privacy Rule.

Please note that you do not have to sign this Authorization, but if you do not, you may not receive research-related treatment through this study. However, Atrium Health may not condition (withhold or refuse) your other Atrium Health providers treating you on whether you sign this Authorization. You may change your mind and withdraw (take back) this Authorization at any time, except to the extent that Atrium Health or the Sponsor has already used or disclosed your protected health information based on this Authorization. To withdraw this Authorization, you must write to the Study Doctor at the address listed on the first page of this form.

Affix Participant Barcode Label Here

No publication or public presentation about the research described above will reveal your identity without another Authorization from you. If all protected health information that does or can identify you is removed, the remaining information will no longer be subject to this Authorization or federal rules (such as the Privacy Rule) and may be used or disclosed for other purposes.

When the research for which the use or disclosure is made involves treatment and is conducted by Atrium Health: To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete.

At the conclusion of the research study and at your request, you generally will have access to your protected health information. Access to your protected health information in a medical record is described in the Notice of Privacy Practices provided to you by Atrium Health.

When conducting research, the data and results may be used or disclosed for further treatment outcomes research or to research a secondary result. This Authorization will remain in effect after the end of the current study, and any future related secondary study unless it is revoked by you in writing as described above.

_____

Signature of Research Subject or Research Subject's Legally Authorized Representative

_____

Printed Name of Research Subject or Research Subject's Legally Authorized Representative

_____

Date

Affix Participant Barcode Label Here

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the phone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By **mail**:
  Study Subject Adviser
  [redacted]
- or call **collect**: [redacted]
- or by **email**: [redacted]

Please reference the following number when contacting the Study Subject Adviser: Pro00037709

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

BEING A STUDY VOLUNTEER AND WITHDRAWING FROM THE STUDY

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Atrium Health. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Atrium Health. If you choose to withdraw from the study, please notify the study doctor on page 1 of this consent form.

Any specimens which may have been collected but have not yet been processed may be destroyed upon your written request. No specimens will be returned to you. If you leave the study for any reason, you will be asked to have the procedures completed for the final visit.

Your part in the research may stop at any time for any reason, such as:

- The sponsor or the study doctor decides to stop the study.
- The sponsor or the study doctor decides to stop your part in the study for your safety.
- You need additional medicine.
- You do not follow the study rules.
- You have a new injury or illness.
- You decide to stop.

You may be asked to stop the study even if you do not want to stop.

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NEW INFORMATION ABOUT THE STUDY
Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. **I am not giving up any of my legal rights by signing this form.**

_____ ____/____/____ _____
Signature of Research Subject Date Time

_____
Printed Name of Research Subject

_____ ____/____/____ _____
Signature Of Legally Authorized Representative (if applicable) Date Time

_____
Printed Name of Legally Authorized Representative (if applicable)

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject or the subject's legally authorized representative the nature and purpose of the above study. There has been an opportunity for the subject or the subject's legally authorized representative to ask questions about this research study. I have been available to answer any questions that the subject or the subject's legally authorized representative has about this study.

_____ ____/____/____ _____
Signature of Person Explaining Consent Date Time

_____
Printed Name of Person Explaining Consent

Affix Participant Barcode Label Here