UNIVERSITY OF MICHIGAN CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: Phase 2 study with Minimal Residual Disease (MRD) driven adaptive strategy in treatment for newly diagnosed multiple myeloma with upfront daratumumab-based therapy (UMCC 2018.056)

Company or agency sponsoring the study: The University of Michigan along with drug and funding support from Janssen Scientific Affairs, LLC

Names, degrees, and affiliations of principal investigator and study coordinator (if applicable):

Principal Investigator:
Matthew James Pianko, MD, Department of Internal Medicine, Hematology/Oncology, University of Michigan

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

You are being asked to be in this study because you have been diagnosed with multiple myeloma (MM). In this study patients will receive daratumumab based therapy. The Food and Drug Administration (FDA) has approved daratumumab in combination with lenalidomide and dexamethasone as induction therapy (first line therapy), or bortezomib and dexamethasone for the treatment of patients with MM who have received at least one prior therapy. Daratumumab is not approved in combination with all three drugs (lenalidomide, bortezomib and dexamethasone). The use of daratumumab combined with all three drugs is thus considered investigational. However, the combination of daratumumab, lenalidomide, bortezomib, and dexamethasone has been used in other clinical trials with published data.

There is the possibility that some multiple myeloma cells remain in the body after a course of therapy is completed. This is referred to as minimal residual disease (MRD). Measuring MRD means counting these cells using the most sensitive method . MRD negativity is the deepest (best) treatment response we can measure as of now. This measurement is done from a bone marrow aspirate.

This count can inform physicians about how well the treatment worked. Measuring MRD after a study intervention treatment can also help to know how deep a patient's remission is and could help figure out how long the remission will last and when the disease might come back again.

The purpose of this study is to test whether the combination therapy of daratumumab, lenalidomide and dexamethasone, followed by the combination therapy of daratumumab, lenalidomide, bortezomib and dexamethasone in patients who are MRD positive after initial treatment, will result in a change in MRD.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Adult men or women who have newly diagnosed multiple myeloma and have received no more than 1 cycle of any chemotherapy.

There are many other inclusion and exclusion criteria which the doctors will use to determine if you can participate in this study. It is important that you discuss your full medical history and all of your medications with your doctor.

3.2 How many people (subjects) are expected to take part in this study?
A total of approximately 57 subjects at several institutions will take part in this study, including approximately 30 subjects from the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?
The study team will explain the research study and answer any questions you have about the study. If you want to participate in the study, the study team will request you sign the consent form prior to any activities occurring that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Many of the procedures that will be performed during the study, including routine blood tests, disease evaluations, physical examinations, vital signs (blood pressure, heart rate, breathing rate, and temperature) and measurement of height and weight, would normally be done as part of your standard of care regardless of study participation. However, some of these may be done more frequently as a result of your participation in this study. Tests and procedures that are done more often than your regular medical care because of your study participation and that are solely for research purposes will be identified below. The study staff will inform you of the types of tests and procedures you have to undergo during the study.

During the study you must:

- Follow the instructions you are given.
- Come to the study center for your visits with the study doctor.
- Tell the study doctor or study staff about any changes in your health and/or medications you are taking.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

Before starting the study: Some exams, tests, and procedures will be required to find out if you can be in this study. If you have had some of the tests recently, they may not need to be repeated. The screening tests and procedures do not have to be completed in one day and you are allowed to take breaks if you have multiple procedures in one day.

The following tests and procedures will be performed during screening and/or at one or more study visits. Refer to the study calendar below for information about which procedures will be performed at certain study visits.

- **Medical history**: including any past treatments, surgeries, infection and autoimmune diseases. You will also be asked about medications, and it is important that you tell your doctor about all of the medications that you have been taking, including over the counter medicines, vitamins or herbal treatments.
- **Vital signs**: could include measurement of your height, weight, blood pressure, heart rate, respiratory rate and temperature.
- **Physical Exam/Performance status**: Your ability to perform day to day activities and care for yourself.
- **Lung Function Test (Spirometry):** You may have this lung function test if you have asthma or COPD (Chronic Obstructive Pulmonary Disease). During this test you will be asked to inhale deeply and then exhale into a device for a few sections.

- **Electrocardiogram (ECG):** An ECG is a recording of the electrical activity of your heart.
- **Echocardiogram**: This procedure captures pictures to assess the heart's function and structures. During an echocardiogram, a wand (like a microphone) sends out sound waves at a frequency too high to be heard. The sound waves bounce or "echo" off of the heart structures and are sent to a computer screen.
- **Routine blood tests (approximately 2 teaspoons)**: Blood will be drawn for tests to check your general health and disease status including blood tests to check the health of your thyroid.
- **HIV and hepatitis testing**
- **Blood and Urine Tests to assess your Myeloma disease process:** These tests will measure proteins and levels of compounds in your blood and urine associated with multiple myeloma.
- **Urine collection**: A urine sample for standard laboratory tests to check your general health.
- **Pregnancy test**: (urine or blood – approximately 1 teaspoon): if you are a woman able to have children.
- **Imaging for Disease Assessment:**
    - **X-rays, MRI (Magnetic Resonance Imaging) or PET/CT scans.** A chest x-ray will be required at baseline to use as a reference in case you develop any cardiac or lung symptoms during the study. This chest x-ray may be done as part of your skeletal survey.
    - **Assessment of plasmacytomas:** Plasmacytomas are masses of plasma cells that can occur anywhere in the body. If such masses are present and measurable by clinical assessment, measurements will be done. If these masses cannot be detected by clinical assessment, your study doctor may ask for imaging studies (x-rays, CT, or MRI).
- **Quality of life questionnaire:** You will be asked to complete a quality of life questionnaire asking about your symptoms and how your disease and symptoms make you feel. You may find some of the questions uncomfortable to answer. You do not have to answer any question you do not want to answer. *This is for research purposes.*
- **Bone marrow aspirate and biopsy:** A bone marrow aspiration is a test involving a thin, hollow needle to withdraw a small amount of bone marrow. *Extra bone marrow aspirate will be collected for this study for research purposes. These samples will be collected at the same time as bone marrow procedures that are done as standard of care. You will not need additional procedures to collect these samples. Depending on the results of the bone marrow biopsy, it is unlikely but possible the procedure will need to be repeated. If unwilling to do this, you will come off the study.*
- **Blood for Biomarkers (approximately 4 teaspoons):** Blood will be drawn for testing for biomarkers (testing of substances such as proteins that tell us how the drug is working in your body). *This is for research purposes.*
- **Stool:** Stool will be collected to check for gut microbioma. If you agree to provide a stool sample, you will also be asked to complete a questionnaire about your antibiotic and probiotic use as well as any surgeries and hospitalizations in the past 60 days. *Both the stool samples and questionnaire are for research purposes and optional.*
- **Minimal Residual Disease (MRD) Assessment:** this assessment involves counting the number of multiple myeloma cells that remain in the body after treatment. This measurement is done from a bone marrow aspirate. *These samples will be collected at the same time as bone marrow procedures that are done as standard of care. You will not need additional procedures to collect these samples.*

Study Intervention (for Research):
If you qualify to participate in the study based on the results of the screening tests and procedures, you will return to the study doctor's clinic.

Before you begin taking the study drugs you will need to take the following drugs to help reduce infusion reactions: acetaminophen, diphenhydramine (anti-histamine), famotidine (antacid) and montelukast. You will also take an antiviral to prevent herpes zoster reactivation on day 1 and continue for 3 months following treatment.

Induction regimen (all subjects 28 day cycles) – Cycles 1-6
You will receive daratumumab given through your vein (IV) in your arm or through an under the skin injection weekly on days 1, 8, 15 and 22 during Cycles 1 and 2 (total of 8 doses), and then every other week on days 1 and 15 for Cycles 3-6 (an additional 8 doses). You will also receive oral lenalidomide on days 1-21 of each cycle. You will also receive dexamethasone orally (by mouth) or IV (given through a vein) in your arm weekly.

- After 3 cycles of the induction regimen:
  - If you are eligible for a transplant, you will have a stem cell collection, which can happen any time after 3 to 6 induction cycles.
  - If you *do not* have a partial response or better, you will move onto the consolidation regimen.
  - If you *do* have a partial response or better, you will continue with another 3 cycles of the induction regimen
- After 6 cycles of the induction regimen:
  - If you *do not* have a complete response or a very good partial response, you will move onto the consolidation regiment
  - If you *do* have a complete response or a very good partial response you will undergo a MRD evaluation. This measurement is usually done from a bone marrow aspirate or a vial of blood.
    - If your MRD status is positive (+) then you will move onto the consolidation regimen.
    - If your MRD status is negative (-) then you will move onto the maintenance regimen.

Consolidation regimen (MRD +, 28 day cycles) – Cycles 7-9
You will receive daratumumab given through your vein (IV) in your arm every four weeks on day 1 of each cycle. You will also receive oral lenalidomide on days 1-21 of each cycle. You will also receive dexamethasone orally (by mouth) or IV (given through a vein) weekly. You will also receive bortezomib injection on days 1, 8, 15 and 22 of each cycle.

After you complete the consolidation regimen:
- If your cancer doesn't respond to the treatment you will be removed from study intervention and your doctor will discuss other treatment options.
- If you *do not* have a complete response or a very good partial response you will move onto a transplant if you are eligible.
- If you *do* have a complete response or a very good partial response you will undergo a MRD evaluation.
  - If your MRD status is positive (+) then you will move onto a transplant if you are eligible.
  - If your MRD status is negative (-) then you will move onto the maintenance regimen.
- After around 100 days after transplant you should move onto the maintenance regimen

Maintenance regimen (all subjects, 28 day cycles) – Cycles 10-22
You will receive daratumumab given through your vein (IV) in your arm every eight weeks, on day 1. You will also receive oral lenalidomide on days 1-21 of each cycle.

You will continue to receive the maintenance therapy for a total of 13 cycles.

After 13 cycles of the maintenance regimen, you will undergo a MRD evaluation and then move onto further maintenance treatment with lenalidomide alone. You will continue to receive lenalidomide alone unless your disease get worse.

The researchers will ask you to complete a drug diary to track when you have taken dexamethasone and lenalidomide. Please bring your drug diary and medication bottles (with extra tablets or empty) with you when you return for each appointment.
If you experience adverse events, you might have to stop taking all of some of the study drugs and if you recover from your adverse events, you may be able to restart the study drugs.

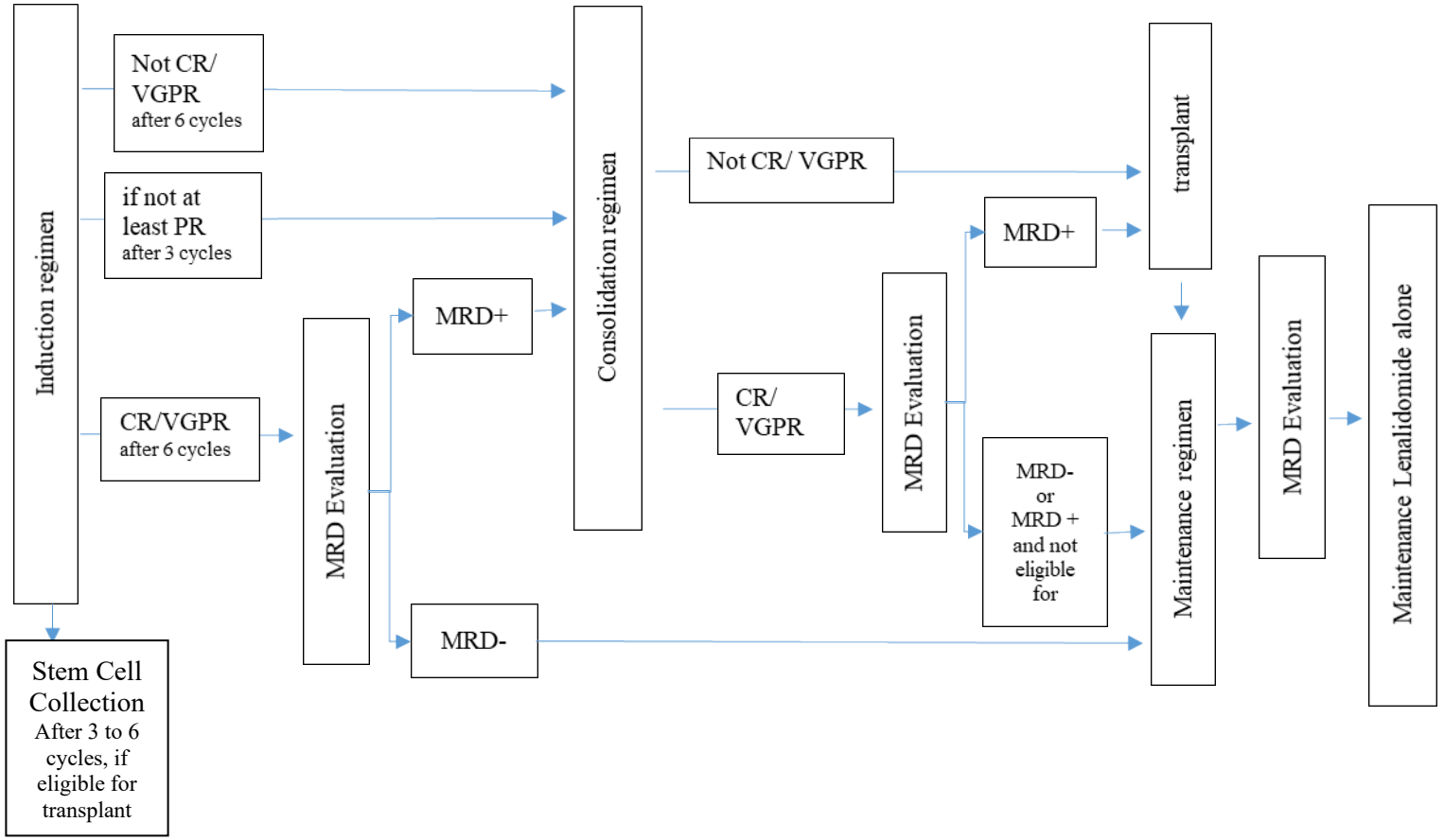
Follow-up:
If you stop the study intervention for any reason you will be asked to return for end of treatment (EOT) visit 28 days after your last dose of study intervention.

After you complete the end of treatment visit you will have an office visit or be contacted by a member of the study team approximately every 3 months until the study ends (your total participation in this study including treatment and follow-up could be up to 60 months). The study team also plans to contact your healthcare providers to obtain tumor imaging and health records for the purpose of assessing study outcomes.

See the below diagram and table for a summary of the study intervention and procedures

Study Intervention Diagram

MRD = Minimal Residual Disease
CR = complete response
VGPR = very good partial response



Study Procedures Table:

	Screening	Treatment																	Follow-up
		Induction Regimen (28 day cycles)						Stem Cell Collection	MRD 1	Consolidation Regiment (28 day cycles)				MRD 2	Transplant	Maintenance regimen (28 day cycles)	MRD 3	Lenalidomide Alone Regimen	End of Intervention Visit	
		Cycles 1-2				Cycles 3-6				Cycles 7-9						Cycles 10-22		Cycle 23+		
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15			Day 1	Day 8	Day 15	Day 22			Day 1		Day 1		
Medical history	X																			
Physical Exam / Performance Status / Vital Signs	X	X				X				X						X		X	X	
Lung Function Test	X																			
Heart Tests (ECG, ECHO)	X																			
Routine Blood Tests	X	X	X	X	X	X	X			X	X	X	X			X		X	X	
HIV & hepatitis testing	X																			
Routine Urine tests	X																			
Blood or urine test for pregnancy	X	X				X				X						X		X	X	
Blood tests to assess myeloma disease	X	X				X				X						X		X	X	
Urine tests to assess myeloma disease	X	X				X				X						X		X	X	
Bone Marrow aspirate and biopsy	X								X					X			X		X	
Blood, Stool, BM Sample Collection for Research testing	X								X					X		Every 6 cycles	X	Every 6 cycles	X	
Imaging for Disease evaluation	X								X					X			X			
Stem Cell Collection								X												
Transplant															X					

	Screening	Treatment																	Follow-up
		Induction Regimen (28 day cycles)						Stem Cell Collection	MRD 1	Consolidation Regiment (28 day cycles)				MRD 2	Transplant	Maintenance regimen (28 day cycles)	MRD 3	Lenalidomide Alone Regimen	End of Intervention Visit	
		Cycles 1-2				Cycles 3-6				Cycles 7-9						Cycles 10-22		Cycle 23+		
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15			Day 1	Day 8	Day 15	Day 22			Day 1		Day 1		
Quality of life questionnaire	X	X				X				X						X		X	X	
COVID-19 Survey	X								X					X			X			
Survival Follow-up																				X

OPTIONAL Research Samples Stored for Unspecified Future Research:
Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or blood, stool or bone marrow aspirate and biopsy samples. We would also like your permission to keep some of your blood, stool, bone marrow aspirate and biopsy and medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in the main study even if you decide not to let us keep your blood, stool, bone marrow aspirate and biopsy and medical information for future research.

If you give us permission, we will use your blood, stool, bone marrow aspirate and biopsy and medical information for future research. Even if you give us permission now to keep some of your blood, stool, bone marrow aspirate and biopsy and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your blood, stool, and bone marrow aspirate and biopsy, we may not be able to take the information out of our research.

We may share your blood, stool, bone marrow aspirate and biopsy and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your blood, bone marrow aspirate and biopsy and medical information with other researchers, we will not be able to get it back. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your blood, stool, and bone marrow aspirate and biopsy samples. Allowing us to do future research on your blood, stool, bone marrow aspirate and biopsy and medical information will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

Your identifiable private information or identifiable blood, stool, bone marrow aspirate and biopsy specimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the future research on your blood, stool, bone marrow aspirate and biopsy and medical information. You will not have rights to these discoveries or any proceeds from them.

You can make your choice about whether to participate in the Optional substudy (storage of research samples for future use) in Section 12 of the consent.

4.2 How much of my time will be needed to take part in this study?
The initial screening visit will take approximately 3-5 hours. Each study visit is expected to take approximately 4-6 hours. After you complete the study intervention, you will need to return to the clinic for follow-up visits every 3 months until disease progression. After disease progression, you may be contacted by the study team to assess

your general health until the end of the study (your total participation in this study including treatment and follow-up could be up to 60 months).

4.3 When will my participation in the study be over?
The maximum time you will be in the study will depend on how your disease responds to the study intervention and how well you tolerate the study intervention and can be up to 60 months. Your participation may end sooner if you decide to no longer participate, your study doctor feels it is in your best interest to stop your study participation, your disease progresses or the study is ended. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

4.4 What will happen with my information and/or blood, stool, bone marrow aspirate and biopsy samples used in this study?
Your blood, bone marrow aspirate and biopsy samples and collected information may be shared with Janssen Scientific Affairs, LLC. With appropriate permissions, your blood, stool, bone marrow aspirate and biopsy samples and collected information may also be shared with other researchers, here, around the world, and with companies. Your identifiable private information or identifiable blood, stool, bone marrow aspirate and biopsy samples may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The drugs used in the study may cause certain side effects and discomforts. You may have all, some, or none of the known side effects. There is also a risk that other rare or unknown side effects may occur. Your doctors and nurses will check you closely for side effects and may give you medicines or other treatments to stop or reduce some of these effects. Some side effects may go away soon after the study medication is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent. There is even a chance that a side effect may cause death. If you have any side effects, it is important that you report them to your study doctor or research staff.

These risks will be minimized by monitoring you carefully. We will provide the usual supportive care that would be routinely given to someone with your condition. If you have side effects from the study intervention, we will make appropriate adjustments as defined by the study protocol. You may need to discontinue the study intervention if the side effects are too serious.

The known or expected risks are:

Side Effects ASSOCIATED WITH DARATUMUMAB (DARZALEX®)

As of November 15, 2022, approximately 5,944 clinical trial patients with multiple myeloma and other various conditions, have been treated with daratumumab IV (intravenous, directly into the vein) or subcutaneous (SC) (subcutaneous, underneath the skin of the abdomen). Of these 5,944 patients about 1936 received daratumumab alone, and about 4008 patients received daratumumab in combination with other therapies.

Daratumumab is commercially approved for the treatment of multiple myeloma and AL amyloidosis. For AL amyloidosis it is currently approved by the FDA in combination with bortezomib, cyclophosphamide and dexamethasone.

Not all 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. You will be told of any new findings that may affect your decision to continue in this study.

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 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 and is currently being evaluated in several other studies.

You will either begin the study receiving daratumumab through an injection or you will be transitioned from receiving daratumumab through an intravenous infusion to an injection.

The following side effects were observed when daratumumab was given to patients, either alone or in combination with other drugs.

Very common side effects seen in more than 1 in 10 people treated with daratumumab:

- Infection of the upper respiratory tract, such as nose, sinuses, throat, or upper airway
- Infection of the lower airway (bronchitis)
- Infection of the lung (pneumonia)
- 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); may increase the risk of getting an infection

- Decreased appetite
- Abnormal sensation including numbness/tingling of hands, feet, or limbs (sensory neuropathy, paresthesia)
- Headache
- Cough
- Shortness of breath, including wheezing
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Rash, a noticeable change in 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
- Sleeplessness (insomnia)
- Joint pain

Common side effects seen in 1 to 10 in 100 people treated with daratumumab:

- 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 levels
- Low blood calcium levels
- Loss of body fluids, also known as dehydration
- Fainting
- Irregular heartbeat (atrial fibrillation)
- High blood pressure
- Chills
- Fluid in lungs (pulmonary edema)
- Dizziness
- 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 seen in 1 to 10 in 1,000 people treated with daratumumab:

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

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 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), 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 anaphylactic reaction, the worst case of allergic reaction.

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.

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.

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

The Sponsor 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 reactions:

- You will get medications, including steroids, acetaminophen, and antihistamine, before the administration.
- If you have a reaction, the administration will be paused, and/or the symptoms treated as needed. Dependent on the reaction, the administration may continue at a slower rate. If you have a life-threatening reaction, you will need to stop further treatment with daratumumab and your doctor will discuss alternative treatments with you.
- If you are considered higher risk for breathing problems (for example, COPD or asthma), you may also get medications, including inhaled steroids, after the administration.
- You may stay overnight in hospital after the administration so medical staff can check you.

Blood Cell Effects

Daratumumab can decrease white blood cell counts which help fight infections, and blood cells called platelet 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 people 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 observed infections so far were mild or moderate. Severe infection such as pneumonia from bacteria, influenza virus, respiratory syncytial virus, and COVID-19, and sepsis have also been reported. Your doctor may also recommend other medications to potentially prevent or reduce the risk of COVID-19 infection or severe infection. It is important to tell your study doctor right away if you are diagnosed with COVID-19 (even if you have no or only minor symptoms) or have been exposed to someone with COVID-19 infection. It is also important to continue general infection prevention practices such as washing hands, wearing masks, social distancing, and avoiding public transportation or travel as much as possible.

Certain infections with viruses, such as shingles (Herpes Zoster virus) and cytomegalovirus and liver infection (hepatitis B virus) have been observed with daratumumab. Your doctor will tell you how to prevent the Herpes Zoster Virus infection. 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.

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 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.

Side Effects ASSOCIATED WITH LENALIDOMIDE (REVLIMID)

You may need to stop lenalidomide due to risks listed below. Your study doctor will discuss with you and the sponsor if it is in your best interest to continue or stop some or all other treatments.

VERY COMMON May affect more than 1 in 10 people
• Low white blood cells (neutropenia, increasing risk of getting an infection), low platelets (thrombocytopenia, increased risk of bruising or bleeding) have been observed which may require reduction or interruption of the dose of Lenalidomide that you receive. • Diarrhea • Fatigue, lack of energy • Low red blood cells (anemia) • Constipation • Swelling of hands, feet or limbs • Muscle cramp/spasms • Pain: back, bone, abdominal and joint

VERY COMMON May affect more than 1 in 10 people

• Nausea
• Fever
• Infection of the upper respiratory tract, including nose, sinuses, and/or throat
• Cough
• Rash
• Difficulty sleeping
• Shortness of breath
• Dizziness
• Decreased appetite/decrease in weight
• Tremor; shaking or trembling
• Infection of the lung
• Bronchitis – infection of the lower airways
• Blood clots; you need to seek medical care if you experience shortness of breath, chest pain, or arm or leg swelling
  ○ Pain or swelling in your legs, especially in your lower leg or calves due to blood clots in the veins of your leg (deep vein thrombosis)
  ○ Sudden pain in your chest or difficulty breathing due to blood clots in the arteries leading to your lungs (pulmonary embolism)
• Bleeding disorder
• High blood sugar
• Decreased calcium in the blood
• Depression
• Headache
• Numbness/tingling of hands, feet or limbs (neuropathy)
• Bleeding from the nose
• Inflammation of stomach and/or intestines
• Vomiting
• Itch
• Renal failure (including acute) – kidney failure which results in a buildup of waste products in the body
• Influenza like illness
• Dry skin
• Decreased potassium in the blood
• Liver disorders
• Distortion of taste

Allergic reaction and tumor lysis syndrome have been reported. Tumor lysis syndrome refers to 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 heart beat.

Lenalidomide will hurt unborn babies. The manufacturer of this drug has a pregnancy prevention program for any individual, male and female, who takes this drug. Your doctor can explain to you such a program.

In order to participate in this study, you must register in and follow the requirements of the Revlimid Risk Evaluation and Mitigation Strategy (REMS) ™ program (formerly known as RevAssist® program) of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots, and reduced blood counts due to the use of lenalidomide.

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

Side Effects ASSOCIATED WITH DEXAMETHASONE

More common risks:	
• Increased appetite • Aggression • Agitation • Anxiety • Blurred vision • Decrease in the amount of urine • Dizziness • Fast, slow, pounding, or irregular heartbeat or pulse • Headache • Irritability • High blood pressure • High blood sugar • Increased bleeding and bruising • Vision problems (for example, elevated eye pressure, cataracts)	• Mental depression • Mood changes • Nervousness • Noisy, rattling breathing • Numbness or tingling in the arms or legs • Pounding in the ears • Shortness of breath • Swelling of the fingers, hands, feet, or lower legs • Trouble thinking, speaking, or walking • Troubled breathing at rest • Weight gain • Sores in mouth/gut • High risk of getting infections • Delayed wound healing • Gastrointestinal problems (for example, indigestion, stomach ulcers)

Other risks:	
• Abdominal cramping and/or burning (severe) • Abdominal pain • Backache • Bloody, black, or tarry stools • Cough or hoarseness • Darkening of the skin • Decrease in height • Decreased vision	• Lower back or side pain • Menstrual irregularities • Muscle pain or tenderness • Muscle wasting or weakness • Nausea • Pain in back, ribs, arms, or legs • Painful or difficult urination • Skin rash

Other risks:	
• Diarrhea • Dry mouth • Eye pain • Eye tearing • Facial hair growth in females • Fainting • Fatigue • Fever or chills • Flushed, dry skin • Fractures • Fruit-like breath odor • Full or round face, neck, or trunk • Heartburn and/or indigestion (severe and continuous) • Increased hunger • Increased thirst • Increased urination • Loss of appetite • Loss of sexual desire or ability	• Sleeplessness • Sweating • Trouble healing • Trouble sleeping • Unexplained weight loss • Unusual tiredness or weakness • Vision changes • Vomiting • Vomiting of material that looks like coffee grounds • Abnormal fat deposits on the face, neck, and trunk • Acne • Dry scalp • Lightening of normal skin color • Red face • Reddish-purple lines on the arms, face, legs, trunk, or groin • Swelling of the stomach area • Thinning of the scalp hair

There may be additional side effects that have been seen in patients that have taken dexamethasone. Please ask your study doctor for information regarding these side effects.

Side Effects ASSOCIATED WITH BORTEZOMIB (VELCADE)

VELCADE should not be taken if you have ever had a serious allergic reaction to bortezomib (VELCADE), boron, or mannitol. You face some risks or discomforts when you are treated with the study drug, VELCADE. You face some risks or discomforts when you are treated with bortezomib. You are at risk of experiencing all, some, or none of the symptoms below, and they may vary in severity. The severity may be mild, moderate or severe, up to and including death. Any symptoms or conditions that you have before you start bortezomib may worsen. Also, there is always a chance that a rare or previously unknown risk may occur. If any of these symptoms occur, you must tell your doctor who may give you other drugs to ease discomforts you are experiencing. Your doctor may decrease or withhold the dose of bortezomib. In addition, if a very bad reaction to bortezomib occurs, your doctor may permanently stop the study treatment.

Other medications and supplements may affect the way VELCADE works. Tell your doctor about all drugs and supplements you are taking while participating in this study.

Most Common VELCADE Risks:

- The following side effects of VELCADE are very common (may affect more than 1 in 10 people):Feeling weak, tired, and generally uncomfortable

- Gastrointestinal effects such as constipation, diarrhea, nausea, vomiting, and loss of appetite. These may result in dehydration and/or weight loss
- Fever commonly with shaking chills
- Painful feelings or numbness and tingling in hands and feet which may not get better after stopping VELCADE.Rarely, the nerves that control things like your heart rate, gut movement and urinary bladder may be affected
- Lowered platelets (thrombocytopenia); that may increase the chance of bleeding
- Lowered red blood cells (anemia) which may make you feel tired
- Lowered white blood cells (neutropenia) which may increase the chance of infections.
- Pain of bones and muscles

Very Common VELCADE Risks:

The very common risks are those that have occurred in 10-29% of patients who have received VELCADE:

- lowered white blood cells called neutrophils that may increase your risk of infection and is uncommonly associated with fever; commonly you may have lowered white blood cells called lymphocytes or have lowered red blood cells, white blood cells and platelets at the same time.
- flu-like symptoms and other upper respiratory tract infections, such as chills, sore throat, and runny nose and sinus and throat infections
- abdominal (belly) pain
- Aches and pains in muscles and joints pain in bones and in arms and legs
- swelling or fluid buildup in the arms and legs and feeling dizzy and weight gain. You should not drive or operate any dangerous tools or machines if you have these or any other symptoms
- cough, feeling short of breath, lung infections including pneumonia and commonly bronchitis
- headache
- skin rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with skin peeling and mouth sores.
- Herpes Zoster/shingles and herpes simplex virus that can sometimes cause local pain that does not go away for a while. Shingles can sometimes spread over large parts of the body. Both may also affect the eyes or brain, but this is uncommon
- feeling anxious
- problems sleeping (insomnia)

Common VELCADE Risks:

Common risks are those that have occurred in 1-9% of patients who have received VELCADE:

- lowered blood pressure that can commonly cause you to feel light-headed or faint when you stand up. If you have a history of fainting, you may be at higher risk.
- changes in heart rate and heart beat that can cause you to possibly feel light-headed, dizzy, faint, short of breath, and/or have chest pain. This may also cause you to feel confused. An uncommon risk is a possible life-threatening abnormal heart beat.
- new or worsening heart failure, that can show up as feeling short of breath, swelling in the legs, and/or chest pain, or decreased heart function and can uncommonly be severe. If you have heart failure or other diseases that put you at risk of getting heart failure, you should tell your doctor.
- fluid buildup around the lungs
- infection and/or inflammation of the eye or eyelids
- blurred vision
- painful sores of the mouth and/or throat, which may make swallowing difficult

- heartburn, acid reflux and stomach bloating
- severe bleeding, including bleeding in the stomach and intestines (gut) that may be linked with low platelet counts, and blood clotting changes. Uncommonly, this bleeding may cause bloody diarrhea and/or bloody vomit.
- nosebleeds
- kidney function that gets worse
- infections of the bladder, sinuses, throat, stomach and intestines (gut), skin and at the area of skin where your catheter is placed
- fungal infections in the mucous membrane such as the mouth and throat and uncommonly in the skin and nails
- life-threatening infections in the blood (sepsis)
- changes in blood sugar have been reported in a few diabetic patients who took oral antidiabetic medicine. If you are taking oral antidiabetic medicines, you may need your blood sugar levels watched more closely.
- blood in the urine
- feeling confused
- changes in the way things taste
- abnormal liver tests and decreased protein in the blood.
- lowered amount of potassium and sodium in your blood and increase in the amount of calcium in your blood
- muscular weakness
- skin pain, redness, swelling or infection in the area where VELCADE is injected under the skin

Uncommon VELCADE Risks:

Uncommon risks are those that have occurred in less than 1% of patients who have received VELCADE:

- inflammation and fluid buildup in the lungs, or pus build up between the layers surrounding the lungs that may cause breathing problems and can be life-threatening or lead to death. Increased blood pressure in the lungs, called pulmonary hypertension, has also been reported. This can cause breathing problems and can be life-threatening. If you have new or worsening breathing problems, you should tell your doctor.
- Inflammation of the layers surrounding your heart or collection of fluid around the heart may cause chest pain or breathing problems and can be life-threatening or lead to death. If you have new or worsening chest pain or breathing problems, you should tell your doctor.
- hepatitis and liver failure (in patients who also receive many drugs and have other serious medical problems).
- pain, redness, swelling or infection in the area of the skin where VELCADE is injected into the vein
- pain in the mouth and throat when swallowing
- loss of hearing
- intestinal obstruction (blockage in the gut) that may get better on its own and not need surgery and inflammation of the intestines, pancreas or stomach
- coughing up blood
- bleeding in the brain and subdural hematoma which is bleeding between the skull and your brain
- fast death of cancer cells that may let toxins into the blood and injure organs, such as the kidneys
- allergic reactions that may include skin swelling and/or swelling of the face or throat and could be severe or life threatening
- severe muscle weakness and paralysis (not being be able to move your arms and legs)
- changes to the brain that may cause convulsions and confusion

- reversible posterior leukoencephalopathy syndrome affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible
- loss of some to all vision affecting one or both eyes, which may be caused by damage to the nerve in the eye. Loss of vision may or may not be reversible.
- Progressive multifocal leukoencephalopathy (PML); PML is a rare, serious infection of the brain that is caused by a virus already in your body at the time of treatment onset. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. Tell your study doctor immediately if you have any of the following symptoms or if anyone close to you notices these symptoms: confusion or problems thinking, loss of balance or problems walking, difficulty speaking, decreased strength or weakness on one side of your body, blurred vision or loss of vision.
- Thrombotic microangiopathy: TTP (blood clots forming in small blood vessels throughout the body, causing low hemoglobin or platelets; these clots can limit or block the flow of oxygen-rich blood to the body's organs, such as the brain, kidneys, and heart) or HUS (when the small blood vessels in your kidneys become damaged and inflamed). This damage can cause clots to form in the vessels. The clots clog the filtering system in the kidneys and lead to kidney failure, which could be life-threatening.

Guillain-Barre Syndrome (GBS), a type of peripheral neuropathy and demyelinating polyneuropathy, including weakness, paralysis, and impaired movements of the arms and legs are rare side effects of VELCADE.

Injection site skin reactions are uncommon. If the skin reaction is severe, your doctor may no longer give VELCADE under the skin. Instead, VELCADE can be given via a vein.

Some of the risk associated with VELCADE are more severe in certain combinations of drugs.

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

Risks of CT Scan

The contrast substance injected during the CT scan may cause pain, burning feeling, sweating and rarely a serious allergic reaction that can be serious. If you know you're allergic to iodine you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated and if you're older. In addition, your thyroid function may be affected. Please inform your doctor if this is the case.

CT imaging uses ionizing radiation, which increases your risk to develop cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation. The estimated additional lifetime risk of developing a fatal cancer from a standard CT scan is approximately 1 in 2,000.

Risks of MRI Scan

Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation.

The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF) As a rare complication in patients with kidney disease that undergo an MRI with contrast material. This causes a thickening of the skin, organs, and other tissues. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

PET-CT Scans
A PET-CT (positron emission tomography-computed tomography) scan is a nuclear medicine imaging test performed with a CT scan. The combined images show the location of abnormal metabolic activity within the body. A small amount of radioactive material (radiopharmaceutical or radiotracer) is injected intravenously before imaging for the PET component of the test. Radioactivity from the radiotracer or radiopharmaceutical is detected by a special camera or imaging device. The CT uses ionizing radiation to obtain pictures of the body. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation. The amount of radiation exposure from the radioactive tracer [18F-2-fluoro-2-deoxy-D-glucose (FDG)] is approximately comparable to 2 years of natural background radiation.

Blood tests
Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include dizziness and fainting.

Bone Marrow Aspirate/Biopsy
You may feel some amount of pain or discomfort during the aspiration or biopsy, including slight, stinging pain with the local anesthetic is injected by needle to numb the area, pressure and full pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness at the biopsy site. If a conscious sedation medication is used, you will not feel pain during the procedure because you will be asleep. Your study doctor will explain the details of the procedure and the risks to you, depending on how the bone marrow aspirate and biopsy will be obtained.

Other risks include redness, swelling, excessive bleeding, bruising or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site.

Risks related to Minimal Residual Disease testing (MRD) change in treatment
MRD is a much more sensitive test compared to routine protein level detection in the blood which is being used in clinic now to assess treatment response. Many studies showed evidence that negative MRD predicts longer remission, however MRD use in treatment decision is still experimental. Since this test is being used to decide options for treatment in this study, there is a risk you could end treatment before you should or stay on treatment longer, compared to routine protein level detection in the blood.

MRD measurement is usually done from a bone marrow aspirate.

Your study doctor can explain this to you in greater detail.

Electrocardiogram (ECG)
Up to 12 self-adhesive electrodes (small blunt pieces of metal) will be attached to your skin on your arms, legs and chest. The areas where the electrodes will be placed will be cleaned; some areas may need to be shaved. Some skin irritation can occur where the electrodes are placed. Once the electrodes are placed, the test will begin. The test is completely painless and takes less than a minute to perform. After the test, the electrodes are removed.

Echocardiogram (ECHO)
An ECHO is a test that uses sound waves to create a moving picture of the heart, also called a cardiac ultrasound. This test is done to assess how well your heart functions. You may feel some discomfort due to the specific position you may hold during the exam.

Questionnaires
Filling out the questionnaires could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire. You have the right to refuse to answer any questions.

Research samples/Loss of Confidentiality
Your samples will be coded however there is a risk of loss of confidentiality of your information. If your samples are provided to research collaborators the following information may be made available: your diagnosis and treatments, the time the samples were collected in relation to your study regimen, your disease status, and demographic data (for example gender, race, age, etc.). See section 9 of this document for more information on how the study team will protect your confidentiality.

Pregnancy
The effects of the study intervention on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. If you are a woman of child-bearing potential, taking part in this study might harm your unborn child or breast-fed baby. Thus, you must agree not to become pregnant while you are in this study. Also, you cannot take part in this study if you are pregnant or breastfeeding a child.

WOMEN
If you are a woman of child bearing potential, you must not have sexual intercourse, or you must use at least two reliable forms of birth control from at least 28 days prior to starting the study interventions, throughout the study and for at least 3 months after the last dose of study drug.

If you become pregnant or think you may be pregnant during the study, immediately stop using the study drugs and contact the study doctor's office **immediately**. Please also inform the study doctor if you become pregnant up to 3 months after the completion of the study drug.

If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use two acceptable birth control methods (see below).

You must use acceptable birth control for medical reasons all during the study intervention (including during temporary breaks from the study intervention), and for at least 3 months after lenalidomide (Revlimid) has stopped and 7 months after bortezomib (Velcade) has stopped. You must talk to the doctor before changing any birth control methods you have already agreed to use.

The two methods of reliable birth control must include one highly effective method and one additional effective method. Acceptable methods of contraception are:

Highly effective methods (must include at least one):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin
- tubal ligation
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Additional effective methods (must include at least one in addition to a highly effective method):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (women who have not given birth)
- contraceptive sponge (women who have not given birth)
- male condom or female condom (cannot be used together)

Any birth control method can fail. The reports of birth control failing are more frequent for female patients who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

You must not donate eggs during the study and for 3 months after your last dose of lenalidomide (Revlimid) and 7 months after the last dose of bortezomib (Velcade).

MEN

All men must use an acceptable form of birth control while taking part in the study and for 3 months after the last dose of Revlimid and/or 4 months after the last dose of bortezomib (Velcade) have stopped because the effects on sperm are not known. Acceptable forms of birth control are noted above. Also, men should not donate sperm or semen while taking part in the study and for 3 months after the last dose of lenalidomide (Revlimid) and/or 4 months after the last dose of bortezomib (Velcade) because the effects on sperm are not known.

The study doctor must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you become pregnant during the study, the study doctor or his/her staff will ask to contact you and your pregnancy physician for information about the pregnancy until the child is born and may share this information with the sponsor.

If you are male, you should advise your study doctor if you father a child while participating in this study. The doctor will advise you on medical attention for your partner should this be necessary. We will ask for your partner's permission to collect information about the pregnancy and health of the baby.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may or may not receive any direct benefits from being in this study. However, others may benefit from the knowledge gained from this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
You do not have to be in this study to get treatment for your cancer. Other possible options include:

- Additional treatment such as chemotherapy (i.e. bendamustine, VTD-PACE, cyclophosphamide), novel biologic therapies (carfilzomib, ixazomib,), high dose steroids, radiation therapy or stem cell transplantation. These other treatments/therapies may already be approved for your condition or there may be other studies you can enroll in.
- You could choose not to receive any treatment.

You should talk to your study doctor and your regular physician about each of your options and their risks and benefits before you decide if you want to take part in this study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
If you decide to leave the study early, please notify someone on the study team. They will instruct you on how to stop the study safely and you will be advised whether any additional test may need to be done for your safety.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

Daratumumab will be provided by Janssen free of charge.

You may have multiple tests for Minimal Residual Disease (MRD) over the course of this study. The MRD test will be charged to you or your insurance. It is possible that your insurance will not cover these costs. It is important that you work with the study team to confirm your health plan will cover the costs of the MRD test if you take part in this study.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Lenalidomide, dexamethasone and bortezomib
- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services

You may have multiple tests for Minimal Residual Disease (MRD) over the course of this study. The MRD test(s) is performed by Adaptive Biotechnologies. The MRD test(s) will be billed by Adaptive to your insurance (or you if you don't have insurance). It is possible that your insurance will not cover these costs. It is important that you work with the study team, Adaptive, and your insurance company to determine if you may be responsible for costs of MRD testing if you take part in the study.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

Some health plans will not cover the cost of standard treatments when they are combined with investigational treatments. It is important that you work with the study team to confirm your health plan will cover the costs of the lenalidomide, dexamethasone, and bortezomib if you take part in this study.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you or your

insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will not be paid to take part in this study.

8.3 Who could profit or financially benefit from the study results?
Information obtained from this study may help the supporter Janssen and/or the University of Michigan learn more about the causes, risks, treatments, or how to prevent this and other health problems. Janssen, the University of Michigan, or physicians at the university could profit financially from this information.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
The University of Michigan has rules to protect information about you. Federal and state laws also protect your privacy. Upon enrolling in this study, you will be assigned a unique identification number. All records related to the study will use this identification number instead of your name or other personally identifying information whenever possible. We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

You have the right to request access to your protected health information that is used or shared during this research and that is related to your study treatment for your disease, but you may access this information only after the study is completed. To request this information, please contact the researchers listed in Section 10 “Contact Information” (below).

Genetic Risks:
The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service

Federal employees receiving care through the Federal Employees Health Benefits Plans

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.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease or other communicable disease status
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University of Michigan, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Janssen, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study

- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular University of Michigan medical record.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?
As a rule, the researchers will not continue to use or disclose information about you but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission, or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help the University of Michigan and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa.

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Matthew James Pianko, MD
Mailing Address: 1500 E. Medical Center Drive, SPC 5848

C365 Med Inn
Ann Arbor, MI 48109-5848

Telephone: 734-647-8901
734-936-4000 (Hospital Operator – 24-hour paging)

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received signed and dated copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

11.2 Additional required information
Because this study requires you to receive an HIV test in order to be a part of the study, the State of Michigan requires information about HIV to be provided to you.

HIV testing information

What is HIV (human immunodeficiency virus) and how is it spread?

- HIV infection is a long-term illness that damages the body's immune system, or its ability to fight off diseases. HIV spreads through blood, semen, vaginal fluids, and breast milk. You can get or give HIV infection by:
    - Having vaginal, anal, or oral sex without a condom.
    - Sharing needles or works when injecting drugs.

- HIV can be passed from mother to child during pregnancy, birth or breastfeeding.
- You cannot get HIV by donating blood or through casual contact such as hugging or shaking hands.

What is AIDS?

- AIDS (Acquired Immunodeficiency Syndrome) is the stage of HIV infection when the body is weakened and less able to fight off germs.

What is an HIV test?

- It is a simple test, done by taking blood or fluid from cells in the mouth, that shows if you have been infected with HIV, the virus that causes AIDS.

Who should have an HIV test?

- The CDC (Centers for Disease Control and Prevention) recommends that everyone between the ages of 13 and 64 get tested for HIV.
- Whatever your age, you should have an HIV test if you are sexually active or have shared needles or works for injecting drugs.
- Women who are pregnant or considering pregnancy should also get an HIV test.

Can anyone make me take an HIV test?

- Under Michigan law, unless you are ordered by a judge, or you are a prisoner entering into a state correctional facility, getting an HIV test is your decision. No one can test you without getting your consent.

Can I change my mind after I consent to the test?

- Yes, you can change your mind at any time before the lab runs the test.
- If you change your mind, you must give the study team a written request saying that you do not want your test to be run. This may mean that you cannot take part in the study.

Can someone under age 18 take the test without their parents' consent?

- Yes. Minors, age 13 and older, have the right to take the test for HIV without their parents' knowledge or consent.

What is the difference between anonymous and confidential testing?

- Anonymous HIV testing means your name is not used and will not be on the test results. To get your test results, you will be given a code number.
- Confidential HIV testing means that your name will be used on your test results.
- If you get an anonymous HIV test, you will not receive a piece of paper with your name and your test results. If you need a copy of your HIV test results, you should take a confidential test.
- In Michigan, you have the right to request an anonymous HIV test.

- Anonymous HIV testing may not be available if the researchers need to know your HIV status for this study. However, your HIV status will remain confidential.

How is HIV testing done?

- Typical HIV tests are done on blood or oral fluids. Specimens are sent to a lab and you get your results in about one week. When testing blood, a needle will be used to draw blood from a vein in your arm. When testing oral fluids, they are collected on a swab from your mouth.
- Rapid test: Some clinics or testing sites offer rapid testing. This is a test done on a small amount of blood from the tip of your finger or from fluid in your mouth. You will get results in that same visit. If your result is reactive (shows possible signs of infection), you will need more testing.

How will this test help me?

- The test will tell you whether or not you have HIV. People can have HIV for years and not know it unless they get tested.
- If you are infected, it can help you get proper treatment and learn how to avoid spreading HIV to other people.
- If you are not infected, it can help you learn how to reduce your risk of getting HIV.

What does a negative (or “non-reactive”) result mean?

- A negative result means you are not infected with HIV,
- OR you have been infected too recently for it to show up on the test.
- If you recently had sex without a condom or shared needles, you should get another test in about six weeks. This is because sometimes HIV tests cannot detect recent infection.

What does a positive result mean?

- A positive result means that you are living with HIV.
- You should see a doctor as soon as possible. The person who gave you your test results can help you find a doctor if you don’t have one.
- If you have HIV, you can pass your infection to other people through sex, sharing needles, or through birth or breastfeeding if you are or will be a mother.
- You should use condoms every time you have sex, to prevent passing the infection to others. The person who gave you your test results can help you plan ways to keep from passing your infection on to others.

Who will know the results of my test?

In Michigan, all HIV test information is confidential, by law.

- This means that there are very strict rules about who is allowed to see that information.
- Health care workers that are involved in your care may see your test results.
- Health insurance companies, Medicare and Medicaid, if they are paying all or part of the cost of your health care, will also see your test results.

- All positive HIV tests are reported to the health department.
- If you have HIV, Michigan law requires that your doctor or someone from the local health department notify all of your known sexual and/or needle-sharing partners that they may have been exposed to HIV. They do this without using your name, or sharing any information about you.
- It is illegal to discriminate against people with HIV.

If I have HIV, will I definitely develop AIDS or get sick?

- No. Today there are many treatments for HIV. These treatments can prevent serious illness, including AIDS. If you get care quickly, you have a good chance for a long and healthy life.

Whom should I tell if I have HIV?

- Current, past and future sexual and/or needle-sharing partners should be notified.
- Your local health department can also help to notify partners. They will do this without using your name or sharing any information about you. Your doctor, health care provider or counselor that performed the test can connect you with the local health department.
- Michigan law requires you to tell any current or future sexual partner that you have HIV before having any kind of sex with them.
- The law also requires that your doctor or someone from the local health department talk to you about this.

What if I have more questions?

- Feel free to ask the health professional who gave you this booklet any questions that you might have.
- Call the Michigan statewide HIV/AIDS information hotline (English 1-800-872-AIDS; Español 1-800-862-SIDA; TDD 1-800-332-0849).

Visit the CDC's HIV/AIDS website for more information (http://www.cdc.gov/hiv/).

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent to Collect and Store OPTIONAL Research Samples for Unspecified Future Research
This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to take part in this optional research. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep and store my blood, bone marrow aspirate, and biopsy samples for future research.

_____ No, I do not agree to let the study team keep and store my blood, stool and bone marrow aspirate, and biopsy samples for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent for Providing Optional Stool Samples

This project involves optional collection of stool samples . In addition, this will allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to provide stool samples. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to provide stool samples.

_____ No, I do not agree to provide stool samples.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

UMCC 2018.056

PERSONAL CENSUS FORM

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]

2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as “Haitian” or “Negro” are sometimes used in addition to “Black” or “African American.”)

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” is sometimes used in addition to “Hispanic” or “Latino.”