Informed Consent Form

Winship4547-18: A Randomized Phase II Study of Daratumumab, Ixazomib, and Dexamethasone vs Daratumumab, Bortezomib (Velcade) and Dexamethasone Followed by Ixazomib-Dexamethasone in Newly Diagnosed Multiple Myeloma (DeRIVE) Study)

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EMORY | WINSHIP CANCER INSTITUTE

A Cancer Center Designated by the National Cancer Institute

You Are Being Asked to Be in a Research Study

What Is a Research Study?

The main purpose of research studies is to gain knowledge. This knowledge may be used to help others. Research studies are not intended to benefit you directly, though some might.

Do I Have to Do This?

No. Being in this study is entirely your choice. If you decide to join this study, you can change your mind later on and withdraw from the research study.

Taking part in a study is separate from medical care. The decision to join or not join the research study will not affect your status as a patient.

What Is This Document?

This form is an informed consent document. It will describe the study risks, procedures, and any costs to you.

This form is also a HIPAA Authorization document. It will describe how your health information will be used and by whom.

Signing this form indicates you are willing to take part in the study and allow your health information to be used.

What Should I Do Next?

1. Read this form, or have it read to you.
2. Make sure the study doctor or study staff explains the study to you.
3. Ask questions (e.g., time commitment, unfamiliar words, specific procedures, etc.)
4. If there will be medical treatment, know which parts are research and which are standard care.
5. Take time to consider this, and talk about it with your family and friends.

Emory University
Consent to be a Research Subject / HIPAA Authorization

Title: A Randomized Phase II Study of **D**a**R**atumumab, **I**xazomib, and Dexamethasone vs Daratumumab, bortezomib (**VE**lcade) and dexamethasone followed by Daratumumab-Ixazomib-Dexamethasone in Newly Diagnosed Multiple Myeloma (**D**e**RIVE** study)

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Sponsor-Investigator: Ajay K. Nooka, MD/MPH

Study-supporter: Ixazomib provided by Millennium Pharmaceuticals, Daratumumab provided by Janssen Scientific Affairs

This study is evaluating products manufactured by Janssen. Dr. Nooka serves as a consultant to Janssen and personally receives compensation for his services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form, you will not give up any legal rights.

You are being asked to participate in this research study which will be testing two different combinations of three study drugs as initial therapy for myeloma among newly diagnosed myeloma patients. The purpose of the study to determine a more tolerable and effective monoclonal antibody combination therapy for newly diagnosed multiple myeloma patients.

Daratumumab and ixazomib have been approved by the U.S. Food and Drug Administration (FDA) to treat relapsed and refractory multiple myeloma, not together but in combination with other drugs, as described below. Daratumumab is approved for transplant ineligible multiple myeloma in combination with bortezomib, melphalan and prednisone (VMP) and in combination with lenalidomide and dexamethasone (Rd). Daratumumab is also currently approved for treating transplant-eligible newly diagnosed myeloma in combination with bortezomib, thalidomide and dexamethasone (VTD).

Ixazomib is not approved for treating newly diagnosed multiple myeloma by the FDA. Therefore, the combination can only be used for those purposes in a research study such as this one. Bortezomib has been approved for treating patients with multiple myeloma by the FDA, as described below. Dexamethasone has been used for treatment of myeloma for several decades.

Other alternative FDA-approved regimens that are effective for the treatment of newly diagnosed myeloma are available if you decide not to participate in the clinical trial. Lenalidomide in combination with dexamethasone is an FDA approved regimen for the treatment of newly diagnosed multiple myeloma patients who are not eligible for autologous stem cell transplant. Bortezomib in combination with melphalan and prednisone (VMP) is another option for patients treated with newly diagnosed myeloma patients who are not eligible for autologous stem cell transplant.

DARZALEX® (daratumumab) alone, as a treatment option is approved for use in the United States and in Canada for patients with multiple myeloma who have received at least 3 prior treatments including a proteasome inhibitor (examples: bortezomib, carfilzomib) and an immunomodulatory agent (examples: thalidomide, lenalidomide, pomalidomide), or did not respond to a proteasome inhibitor and an immunomodulatory agent. Daratumumab was also approved in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. More recently, FDA approved daratumumab in combination with pomalidomide and dexamethasone for the third-line treatment of patients with multiple myeloma who received prior therapy with lenalidomide and a proteasome inhibitor. Daratumumab was recently approved by the FDA for treating newly diagnosed transplant-ineligible multiple myeloma patients in combination with VMP and in combination with lenalidomide and dexamethasone (Rd). Daratumumab is also currently approved for treating transplant-eligible newly diagnosed myeloma in combination with bortezomib, thalidomide and dexamethasone (VTD).

Subjects with a known allergy/intolerance to any of the components of the SC formulation, including sorbitol, will not be eligible to switch to daratumumab SC. Your doctor will discuss with you if you have allergy/intolerance to any of the components of the SC formulation.
On May 1, 2020, the Food and Drug Administration approved daratumumab and hyaluronidase-fihj (DARZALEX FASPRO, Janssen Biotech, Inc.) for adult patients with newly diagnosed or relapsed/refractory multiple myeloma. This new product allows for subcutaneous dosing of daratumumab.

Daratumumab and hyaluronidase-fihj is approved for the following indications that intravenous daratumumab had previously received:

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant,
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy,
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy,

as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

BORTEZOMIB is approved by the FDA for the treatment of patients with multiple myeloma, including with dexamethasone, for patients who have received at least one other treatment for multiple myeloma and who's disease has either not responded to that treatment or the disease has come back. VMP, as described earlier is another option for patients treated with newly diagnosed myeloma patients who are not eligible for autologous stem cell transplant. The safety of daratumumab when given with bortezomib and dexamethasone has been studied in advanced myeloma (patients who have received one other treatment and who's disease has either not responded to that treatment or the disease has come back) but not in patients with newly diagnosed myeloma.

IXAZOMIB combined with lenalidomide and dexamethasone is approved by the FDA for the treatment of patients with multiple myeloma who have received at least one other treatment for multiple myeloma and who's disease has either not responded to that treatment or the disease has come back. Ixazomib is also approved as maintenance therapy post-ASCT in patients with NDMM in Japan and South Korea.

The safety of daratumumab when given with ixazomib and dexamethasone has not been studied in multiple myeloma.

DEXAMETHASONE is taken by mouth as a pill or given as an infusion. Dexamethasone used to the primary therapy for myeloma prior to the availability of all the new myeloma treatments. Now a day, dexamethasone is not used as sole treatment option for myeloma but it is used in combination with other myeloma treatments and allows for achieving better responses.

MELPHALAN (used only in transplant patients) and **CYCLOPHOSPHAMIDE**, the drugs used during stem cell transplant and stem cell collection, respectively, are also approved by the U.S. FDA. Melphalan is an FDA-approved chemotherapy for multiple myeloma and is used as a high-dose conditioning treatment prior to stem cell transplantation. Cyclophosphamide is used, either alone, or in combination with other drugs, to treat multiple myeloma. These drugs have been used in other research studies in subjects with multiple myeloma and information from those other research studies suggests that this combination of therapy may help to treat newly diagnosed multiple myeloma in this research study.

The purpose of this study is to look at what happens (both good and bad) when daratumumab is given with two other drugs called bortezomib and dexamethasone for the first three cycles of treatment and change treatment to receive daratumumab, ixazomib and dexamethasone continuously compared to just giving daratumumab, ixazomib and dexamethasone continuously. Young healthy patients that will be eligible for transplant will still receive a transplant, but the decision of transplant is made before the start of the study.

Ask the study doctor if you have any questions about how the study drugs work.

Taking part in this study is entirely voluntary and up to you to decide. In order to decide if you wish to take part in this study, you should understand enough about its purpose, procedures, risks, benefits and costs to make an informed decision. This process is known as informed consent.

Before you agree to join in this study, it is important for you to understand why the study is being done. What the requirements are for your participation. Please take time to read the following

information carefully and ask questions if anything is not clear. This consent form describes the purpose, procedures, precautions and possible benefits, risks (side effects). Discomforts that go along with your participation in this study. The consent form also outlines your rights as a subject involved in this study. If you agree to join, you will be asked to sign this form.

The consent form also describes the other procedures that are available to you, and your right to withdraw from the study at any time. Please take time to read the following information carefully. Discuss it with your family doctor, friends, and relatives if you wish. Feel free to ask about anything that is not clear or to request additional information. Take as much as you want to decide whether or not you wish to take part. If you decide to take part, you may withdraw from the study at any time.

People invited to join in this study must be 18 years of age or older and, if female, cannot be pregnant. There will be up to 76 subjects enrolled on the study. Emory will enroll all subjects at the Winship Cancer Institute.

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.

What is the purpose of this study?

The purpose of this study is to look at what happens (both good and bad) when daratumumab is given with two other drugs called bortezomib and dexamethasone for the first three cycles of treatment and change treatment to receive daratumumab, ixazomib and dexamethasone continuously compared to just giving daratumumab, ixazomib and dexamethasone continuously. Young healthy patients that will be eligible for transplant will still receive a transplant, but the decision of transplant is made before you enter the study. Since the study is trying to find which is the better treatment, you may be allotted to one of the two groups by a process called 'randomization'. These two groups receive two different treatment plans. Neither you nor the study doctor will have the ability to choose which group you will be in. In order to balance both the groups, the study team has already designed a plan called 'stratification' which puts equal number of high-risk patients (that are determined by the genetics on the bone marrow and blood markers before you start the treatment) and equal number of patients that go for a transplant in both arms.

What will I be asked to do?

If you decide to take part in this research study, you will undergo the following procedures:

Procedures to determine if you are eligible to take part in a research study are called "screening" procedures. For this research study, the screening procedures include those listed below. These procedures may overlap with procedures you would undergo as part of your routine care, and may be done regardless of whether you join this study. They will be done as an outpatient, and will involve 3-4 hours of your time. You will be seen by a physician, nurse practitioner or physician's assistant, nurses and medical technicians. All tests must be completed within 21 days from the day you receive you first treatment (Cycle 1 Day 1), unless otherwise indicated. You must sign this informed consent form before any research procedures may be done.

- A review of your medical history and confirmation of high risk status
- A review of any medication(s) you are currently taking
- Performance status (how well you are able to do your normal activities)

- Vital signs (blood pressure, pulse, and temperature) will be recorded
- A neurologic assessment including a physical evaluation and a questionnaire
- An echocardiogram (ECHO) test or Multi Gated Acquisition Scan (MUGA) (a test that measures how much blood your heart pumps on each beat)
- Pulmonary function tests (a test to assess your lung function by measuring how much air is in your lungs and how forcefully this air can be exhaled.)
- Chest x-ray which is a test to evaluate your lung (and sometimes) heart function.
- Height and weight will be recorded
- Blood samples (about 3 teaspoons) will be taken for routine tests to check your blood counts (numbers of each type of blood cell), chemistries (to evaluate your overall health status by checking things such as your kidney and liver function within 72 hours of starting treatment. Tests to assess your blood clotting will also be done.
- An EKG, or electrocardiogram (a test that measures the rhythm of your heart to make sure your heart is functioning properly)
- If you are a woman capable of having children, you will have another blood test to determine if you are pregnant before entering the study (about 1 teaspoon will be collected within 7 days of starting the study)
- Blood tests to assess the status of your myeloma
- A 24-hour urine collection will be done
- Skeletal survey - x-rays of the skull, long bones, pelvis and chest. This will be done if it has not been done in the past 12 weeks
- Bone marrow biopsy and aspirate

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

After the screening procedures confirm that you are eligible to participate in the research study:

Because no one knows which of the study options is best, you will be “randomized” into one of the two study groups. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor the research doctor will choose what group you will be in.

Initial phase (induction phase):

- Treatment Group A: Patients will receive Daratumumab, Ixazomib and dexamethasone (each cycle is 28 days in length) for a total of 8 cycles.
- Treatment Group B: Patients will receive daratumumab, Bortezomib and dexamethasone for 3 cycles (each cycle is 21 days in length) and will be switched to daratumumab, ixazomib and dexamethasone (each cycle is 28 days in length) for a total of 5 more cycles

After completing the first three cycles, patients eligible for transplant will proceed with stem cell collection and resume induction therapy. After completing the induction phase transplant eligible patients will proceed to autologous stem cell transplantation, followed by maintenance phase. Patients that are not eligible for transplant, will directly move towards maintenance phase.

Maintenance phase:

- Both groups: Patients will receive Daratumumab, Ixazomib and dexamethasone (each cycle is 28 days in length) until the disease is no longer responding or until we stop due to toxicity or for a maximum of 24 months or until your physician or you feel it is not right for you to continue the study.

DESIGN SUMMARY:

Stratification by transplant vs and risk status		
	RANDOMIZATION	
Arm	**Arm A**	**Arm B**
Induction	daratumumab, Ixazomib, dexamethasone (DId) x 8 cycles (28 days)	daratumumab, Bortezomib, dexamethasone (DVd) x 3 cycles (21 days) daratumumab, Ixazomib, dexamethasone (DId) x 5 cycles (28 days)
Stem cell collection	Patients eligible for transplant will proceed to stem cell collection after completing 3 cycles in both arms. Patients not eligible for transplant will continue the induction treatment without interruption	
Transplant	Yes/No (if proceeding for transplant, you receive transplant and move to maintenance. If you are not a candidate for transplant, you proceed to maintenance directly	
Maintenance	daratumumab, Ixazomib, dexamethasone (DId) (28 days) until progression or for a maximum of 24 months, whichever is earlier	

How will my medicine be provided?

The medicine that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the medicine to you. If you have questions about the medicine, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the medicine. The number for the pharmacy is included on your medicine package.

Study Drug(s):

If you take part in this research study, you will be given a study drug-dosing calendar for each treatment cycle with daratumumab, ixazomib and dexamethasone (DId) or daratumumab, bortezomib and dexamethasone (DVd), for your stem cell collection procedures with filgrastim (G-CSF), and/or cyclophosphamide, Mesna, for your stem cell transplant procedure (if you were deemed as a transplant candidate) with melphalan, and for each treatment cycle during maintenance.

Daratumumab will be given in the outpatient treatment center. Daratumumab SC is given through a small needle that goes directly under your skin, called a subcutaneous (SC) injection on Days 1, 8, 15, 22 every 28 days in arm A for a total of 2 cycles. From cycle 3 onwards until you complete the induction therapy (a total of 8 cycles) daratumumab will be given on days 1 and 15 every 28 days. Daratumumab is given on Days 1, 8, 15 every 21 days in arm B for a total of 3 cycles. From cycle 4 onwards until you complete the induction therapy daratumumab will be given on days 1 and 15 every 28 days. . The duration of the SC injection is about 3-5 minutes. The drug will be given in your abdomen and manually

injected by a trained person. As you receive additional daratumumab SC injections your doctor will alternate the side of your abdomen the injection is given in.
You will be observed carefully for SC injection site reactions at the place in the skin where the study drug is given, such as redness or swelling, and for general reactions to the study drug.
Pre-Infusion/Administration medications (for daratumumab)

You will be asked to take montelukast by mouth on the day of your daratumumab SC administration. Your doctor may also ask you to take this medication the day before your SC administration. Montelukast is used to prevent wheezing, difficulty breathing, chest tightness and coughing. It works by blocking the action of substances in your body that might cause these side effects of asthma and allergy. If you are free of these kinds of reactions after your second daratumumab dose, your doctor may choose not to use montelukast for future treatments.
You will also receive dexamethasone (a steroid), acetaminophen and diphenhydramine (an antihistamine) or their equivalents, approximately 1 hour before all study medication administration to prevent or minimize a reaction to the daratumumab SC administration. Your study doctor will explain to you when you will take the pre- administration medications and the dose you will receive.
Post-Infusion/Administration medications (for daratumumab)

Administer post-infusion medication to reduce the risk of delayed infusion related reactions as follows:

- Consider administering low-dose methylprednisolone (≤ 20 mg) or equivalent, the day after the infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the infusion, additional post-infusion steroids are not required, but may be considered by the investigator.
- For participants with a higher risk of respiratory complications (e.g. participants with mild asthma or participants with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history) the following post-infusion medication should be considered:
  - Antihistamine (diphenhydramine or equivalent)
  - Leukotriene inhibitor (montelukast or equivalent)
  - Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol

Control medications for lung disease (e.g. inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for participants with COPD)

Ixazomib will be taken at home by you. It is given as an oral pill on Days 1, 8 and 15 followed by a fourteen-day rest period for a total of 8 cycles in arm A (each cycle is 28 days long). In arm B, Ixazomib will be given as an oral pill on Days 1, 8 and 15 followed by a fourteen-day rest period for a total of 5 cycles (after completing the first 3 cycles of bortezomib).

Only patients in arm B receive bortezomib. Bortezomib will be given in the outpatient treatment center. It is given subcutaneously on Days 1, 4, 8 and 11 followed by a ten-day rest period for a total of 3 cycles (each cycle is 21 days long). Should you develop peripheral neuropathy (a possible treatment side-effect which can cause numbness and pain in the hands/ feet) during the course of treatment, your study doctor makes dose adjustments to reduce the effects of peripheral neuropathy.

Dexamethasone will be taken at home by you. It is given as small oral pills weekly. Should you develop any side effects your study doctor makes dose adjustments to reduce the side effects of the steroids.

IF YOU ARE A TRANSPLANT-ELIGIBLE PATIENT

Autologous peripheral blood stem cell collection:
An autologous peripheral blood stem cell transplant is a procedure in which immature, or undeveloped, "stem cells" (cells which will eventually develop into white blood cells, red blood cells and platelets) are stimulated by a drug called granulocyte colony stimulating factor [G-CSF]. These cells are collected and stored. Sometimes chemotherapy can also be used in addition to the G-CSF for stem cell collection. The participant then receives a high dose of chemotherapy to destroy any myeloma cells, and the participant's own "stem cells" are replaced.

Depending on the response after cycle 3, for both arms, if you received less than a partial response, two to three weeks after completing cycle 3, you will receive the chemotherapy drug cyclophosphamide by IV infusion over 2 hours or a period of time which is in accordance with the policies of your treating hospital. Beginning 24 - 48 hours after your cyclophosphamide infusion, you will receive the drug G-CSF daily by subcutaneous injection (under your skin) until your stem cells are collected. You will also receive a drug called Mesna. This drug is given to reduce the side effects of certain chemotherapy drugs. You may receive Mesna by IV infusion at 30 minutes before your cyclophosphamide infusion, and 3 hours and 6 hours after your cyclophosphamide infusion, and one additional oral dose of Mesna to be taken at 9 hours after your cyclophosphamide infusion. You may also receive Mesna by IV infusion over the period of time during which you receive cyclophosphamide or according to standard hospital procedure.

If you have achieved greater than a partial response after cycle 3, two to three weeks after completing cycle 3, you will receive only the drug G-CSF daily by subcutaneous injection (under your skin) until your stem cells are collected.

Stem cell collection will occur approximately 10 days after your cyclophosphamide infusion or your first G-CSF injection according to standard hospital procedure. We will collect some of your blood cells in a procedure called "leukapheresis". You will have IVs inserted, one in each arm. The blood is taken out of one arm and run through a machine that collects only the cells we want. The rest of your blood is given back to you in the other arm. The whole collection process takes approximately 5 - 7 hours and may last anywhere from 2-5 days.

Autologous peripheral blood stem cell transplant:
After your stem cells are collected, you will be admitted to the hospital for chemotherapy and to return to your system the "stem cells" previously collected from you. This will require you to be hospitalized for approximately 2 - 3 weeks or cared for in a closely monitored outpatient setting.

You will receive the chemotherapy drug melphalan by IV infusion over 30 minutes, either as a single infusion on one day or over the course of two days. After a rest to allow the chemotherapy to completely leave your body, the stem cells that were previously collected from you will be thawed and given to you intravenously, much like a blood transfusion is given. It is given through a central

venous catheter. You will be given pre-medications just prior to the infusion to decrease the risk of a reaction.

During the infusion of the stem cells previously collected from you, you may experience a number of side effects that are caused by the chemical DMSO. DMSO is mixed with your stem cells in order to allow them to be safely frozen and then thawed. You may notice a garlic taste or smell from the DMSO. You will be monitored very closely during the infusion and afterwards to look for these reactions and given medications (including anti-nausea medications) and/or intravenous fluids to minimize these side effects.

Side affects you may experience during your stem cell infusion include nausea, vomiting, headache, flushing, chest tightness and pressure, as well as abdominal cramps. Once the stem cell infusion is completed, the side effects should be gone within several hours.

Beginning the seventh day after the stem cell infusion, and each day thereafter, you will again receive the drug G-CSF daily by subcutaneous injection until your blood counts have recovered to satisfactory levels. You may also receive G-CSF according to standard hospital practice.

During the remainder of your time in the hospital you will be supported with blood transfusions, platelet transfusions, antibiotics, and nutritional support in a manner similar to that during your previous treatment. When you have recovered from the effects of the high-dose chemotherapy you will be discharged from the hospital. After leaving the hospital, medication will be prescribed for you to prevent infections until your immune system has recovered satisfactorily.

Additionally, anti-viral medication will be prescribed for you while you are taking ixazomib or bortezomib

Additional medications such as antibiotics, anti-fungal or other medication may be given to you depending on your side effects as determined by your doctor.

The pre-medications are all FDA-approved drugs that are commercially available. Your doctor may also replace other drugs or dosages for the pre-medications based on preference.

Research study plan:

DId Therapy (Arm A: Cycle 1-2)
Each cycle lasts 28 days

Day	What will happen
Day 1 4-hour clinic and infusion visit for Cycle 1 day 1 and 1-hour visit for subsequent cycles)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • Myeloma Frailty Score http://195.88.6.191/Frailtyscore/Geriatric.aspx • You will receive a supply of ixazomib and dexamethasone • Collection of approximately 3 tablespoons of blood

	• Collection of 24-urine urine sample (collection for 24 hrs prior) • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take ixazomib • You will take dexamethasone • You will be monitored for 3.5 hours after first SC administration of daratumumab
Day 2-7 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 8 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take ixazomib • You will take dexamethasone
Day 9-14 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 15 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take ixazomib • You will take dexamethasone
Day 16-21 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 22 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take dexamethasone
Day 23-28 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period

DVd Therapy (Arm B: Cycle 1-3)
Each cycle lasts 21 days

Day	What will happen
Day 1 4-hour clinic and infusion visit for Cycle 1 day 1 and 1-hour visit for subsequent cycles)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • Myeloma Frailty Score http://195.88.6.191/Frailtyscore/Geriatric.aspx

	• You will receive a supply of dexamethasone • Collection of approximately 3 tablespoons of blood • Collection of 24-urine urine sample (collection for 24 hrs prior) • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will be given bortezomib • You will take dexamethasone • You will be monitored for 3.5 hours after first SC administration of daratumumab
Day 2-3 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 4 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • You will be given bortezomib • You will take dexamethasone
Day 5-7 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 8 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take bortezomib • You will take dexamethasone
Day 9-10 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 11 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • You will be given bortezomib • You will take dexamethasone
Day 12-14 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 15 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take dexamethasone
Day 16-21 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period

DId Therapy (Arm A: Cycle 3-8 and Arm B: Cycle 4-8)
Each cycle lasts 28 days

Day	What will happen

Day 1 (1-hour clinic and infusion visit)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • You will receive a supply of ixazomib and dexamethasone • Collection of approximately 3 tablespoons of blood • Collection of 24-urine urine sample (collection for 24 hrs prior) • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take ixazomib • You will take dexamethasone
Day 2-7 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 8 (No clinic visit)	• You will take ixazomib • You will take dexamethasone
Day 9-14 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 15 (1-hour clinic and infusion visit)	• Vital signs • Collection of approximately 1 tablespoon of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab • You will take ixazomib • You will take dexamethasone
Day 16-28 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period

Stem Cell Collection:
Arm A and Arm B: Stem cell collection will occur approximately two to three weeks after your Cycle 3 of DId or DVd therapy. The entire stem cell collection process will take approximately up to two weeks.

Day	What will happen
Day 1-4 (30-minute clinic visit)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • Consents for collection • Collection of approximately 1 tablespoons of blood • Collection of 24-urine urine sample (collection for 24 hrs prior) • Pregnancy test, by serum (blood) or urine, if applicable. • You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim)
Day 2-3 (No clinic visit)	• You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim)

Day 4	• You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim) • Collection of approximately 1 tablespoon of blood • You may receive additional mobilizing agent 'plerixafor'
Day 5-completion (Hemapheresis)	• You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim) • Vital signs • Collection of approximately 1 tablespoon of blood • You may receive additional mobilizing agent 'plerixafor' • Stem cells will be collected by luekepheresis

For some patients cyclophosphamide may be used for collection. In such case, the schedule will be

Day	What will happen
Day 1 (8-9 hour clinic visit)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • Consents for collection • Collection of approximately 1 tablespoons of blood • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given cyclophosphamide • You will receive Mesna
Day 2-9 (No clinic visit)	• You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim)
Day 10	• You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim) • Collection of approximately 1 tablespoon of blood • You may receive additional mobilizing agent 'plerixafor'
Day 11-completion (Hemapheresis)	• You will take filgrastim at home (if insurance mandates, you may have to come to infusion center to receive filgrastim) • Vital signs • Collection of approximately 1 tablespoon of blood • You may receive additional mobilizing agent 'plerixafor' • Stem cells will be collected by leukapheresis

Stem Cell Transplant: (Arm A and Arm B)
Stem cell transplant will occur approximately two to three weeks after your Cycle 8 of Did therapy. You will be hospitalized for approximately 2 - 3 weeks during your stem cell transplant procedure. This will include the period of time immediately before, during, and while you recover from your stem cell transplant. You will undergo blood tests and additional procedures according to standard hospital practice while you are in the hospital for your stem cell transplant procedure.

Day	What will happen

Pretransplant evaluation during Cycle 8 (Outpatient visits)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • Collection of approximately 4 tablespoons of blood • Pregnancy test, by serum (blood) or urine, if applicable. • EKG • Skeletal survey • Bone marrow aspirate (Collection of approximately 1 tablespoon of bone marrow aspirate for research studies) • MUGA or ECHO • Pulmonary function tests • Chest x-ray • Infectious disease markers per institutional protocol
Day -2 (In hospital)	• You will receive melphalan
Day -1 (In hospital)	• Rest
Day 0 (In hospital)	• Stem cell reinfusion
Day +1- engraftment (In hospital)	• Monitoring and supportive care

Maintenance Therapy (Arm A and Arm B: Cycle 9+)
Each cycle lasts 28 days

Day	What will happen
Day 1 (1-hour clinic and infusion visit)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • You will receive a supply of ixazomib and dexamethasone • Collection of approximately 3 tablespoons of blood • Collection of 24-urine urine sample (collection for 24 hrs prior) • Pregnancy test, by serum (blood) or urine, if applicable. • You will be given daratumumab premedications and daratumumab You will take ixazomib
Day 2-7 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 8 (No clinic visit)	• You will take ixazomib
Day 9-14 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period
Day 15 (No clinic visit)	• You will take ixazomib

Day 16-28 (No clinic visit)	• You will not receive any medication or undergo any tests during this time period

End of Treatment Visit:
(Arm A and Arm B)

Day	What will happen
End of treatment (3-hour clinic visit)	• Physical examination, including weight, height, vital signs and performance status assessment • Neurological assessment • Patient Reported Outcomes (FACT GOG-NTX) • Skeletal survey • Bone marrow aspirate • Collection of approximately 1 tablespoon of bone marrow aspirate for research studies • Collection of approximately 3 tablespoons of blood • Collection of 24-urine urine sample (collection for 24 hrs prior) • Pregnancy test, by serum (blood) or urine, if applicable.

IF YOU ARE A TRANSPLANT-INELIGIBLE PATIENT BUT BECOME ELIGIBLE AFTER INITIATING TREATMENT

If you are initially deemed transplant-ineligible and stratified to the transplant ineligible and you become transplant-eligible after initiation of treatment, you will be able to stop induction at the end of Induction Cycle 8 and proceed to autologous SCT as described earlier.

RESEARCH-ONLY PROCEDURES FOR ALL SUBJECTS IN THIS STUDY:
The following research-only procedures apply to all subjects involved in this research study.

In addition to the blood test a bone marrow aspirate will be obtained prior to the start of treatment. The bone marrow aspirate done at screening will be used for both routine and research purposes and will only be done once at this time point, a sample approximately 15 milliliters or 3 teaspoons will be taken.

After the final dose of the study drug: We would like to keep track of your medical condition after you have taken your final dose of study drug. Your condition will be followed for an additional 4 weeks. If you are removed from the study for unacceptable adverse events, you will be followed until resolution or stabilization of the adverse event occurs. You will then be contacted every 3 months to check on the status of your health and future treatment.

You also must agree to refrain from blood donations during therapy on study and for 8 weeks after therapy is completed.

Who owns my study information and samples?

If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may still be used for this study. Your participation in this research study may contribute to the development of commercial products from which the owners of the investigational drugs used in this study or others may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

What are the possible risks and discomforts?

Drugs for cancer are strong and have side effects. As with any experimental procedure, there may be adverse events or side effects that are currently unknown. Side effects can go away shortly after drug administration is stopped, but some risks could be long-lasting, permanent, serious, life threatening, or even cause death. You should talk to your study doctor about any side effects you have while taking part in the study. The risks involved with this study are listed below. You will be kept fully informed of any events that occur during the course of this clinical study which might affect your safety. If there is new information that might affect your safety, you will be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

If there is any new important safety information or other information that could affect your willingness to participate in this study, the study doctor will let you know.

Are there any risks from taking part in this study?

There may be risks to being in this study from daratumumab, ixazomib, bortezomib, dexamethasone or from some of the procedures or tests done in this study. Also, your condition may get better but it could stay the same or even get worse.

If you participate in this study, you or your family members should tell the study doctor or the study staff immediately if you have any unusual health problems, injuries, or side effects, even if you do not think these problems are caused by the study or by the study drug(s).

If there is any new important safety information or other information that could affect your willingness to participate in this study, the study doctor will let you know.

When daratumumab is given at the same time with other drugs, some side effects of these drugs may happen more often or may be more severe. There may be other unexpected side effects. The following addresses the side effects seen for these drugs as per reference information for these compounds.

What are the likely risks with daratumumab

Any drug has risks and side effects which may vary from person to person. Side effects may be mild or very severe. Most side effects will go away after treatment is stopped, but some may be long lasting. Side effects seen on research studies can result from a patient's disease, the drug under study, other drugs you are taking, other diseases you have, or a combination of these. This section gives you the

information known so far about side effects seen with daratumumab intravenous infusions and subcutaneous injections.
As of 15 November 2020, approximately 5700 clinical trial patients with multiple myeloma and various other conditions have been treated with daratumumab IV (intravenous, directly into the vein) or SC (subcutaneous, underneath the skin of the abdomen). Of these 5700 patients about 1830 received daratumumab alone, and about 3887 patients received daratumumab in combination with other therapies.

Daratumumab
Daratumumab is commercially approved for the treatment of multiple myeloma and AL amyloidosis. For AL amyloidosis it is currently approved by the FDA (United States) 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 following side effects are observed when daratumumab was given to patients, either alone or in combination with other drugs.

Very common side effects with daratumumab (affects more than 1 in 10 patients).
- Infusion related reaction (see separate section)
- Infection of the upper respiratory tract such as nose, sinuses throat or upper airway
- Infection of the lung (pneumonia)
- Infection of the lower airway (bronchitis)
- Low white blood cells (including neutrophils and lymphocytes); may increase the risk of getting an infection (see also separate section below)
- Low platelets; may increase the risk of bleeding and bruising
- Low red blood cells (anemia)
- Decreased appetite
- Sleeplessness (insomnia)
- Abnormal sensation including numbness/tingling of hands, feet or limbs (sensory neuropathy, paresthesia)
- Headache
- Cough
- Shortness of breath, including wheezing
- Diarrhea
- Constipation
- Nausea
- Vomiting
- Rash, a noticeable change in the texture or color of your skin
- Back pain
- Muscle spasms
- Joint pain
- Swelling of hands, feet or limbs
- Fatigue, or lack of energy

- Weakness, lack of strength
- Fever

Common side effects with daratumumab (affects 1 to 10 in 100 patients).

- 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)
- High blood glucose levels
- Low blood calcium levels
- Loss of body fluids, also known as dehydration
- Dizziness
- Fainting
- Irregular heartbeat
- High blood pressure
- Fluid in lungs (pulmonary edema)
- Inflammation of the pancreas (pancreatitis)
- Itchy skin
- Muscular pain in the chest
- Chills
- 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 patients).

- Cytomegalovirus infection (see separate section on infections below)
- Liver infection (hepatitis) in those patients who are carriers of the hepatitis B virus
- Interference with pre-transfusion blood testing (See **Indirect Antiglobulin Testing** below)

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 side effect to daratumumab that occurs during or shortly after an administration (IV or SC) is called an infusion-related reaction. Infusion–related reactions were reported in approximately half of all patients treated with daratumumab IV. These reactions can be life-threatening and fatal outcomes have been reported when given IV. In patients treated with daratumumab SC, infusion-related reactions were reported in about 9% of the patients. Reactions usually occur with the first administration and during or within the first few hours after the start of the administration.

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. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, low blood pressure or high blood pressure and fluid in the lungs (pulmonary edema). 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 side effect. 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. You may be asked to see a doctor who takes care of patients with airway diseases, and additional medicines for airway problems may be given to you. Your doctor will explain how these additional medicines should be taken. Get emergency medical help if you have any of following: hives, wheezing, difficulty breathing, swelling of your face, lips, tongue, or throat or pain in chest.

Severe reactions have occurred, including narrowing and obstruction of the respiratory airway (bronchospasm), low level of oxygen, shortness of breath, high blood pressure, swelling in the throat and fluid in the lungs (pulmonary edema). 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 anaphylaxis, 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 50,000 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 reaction:

- You will get medications, including steroids, paracetamol/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, 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.

Immunogenicity
In order for daratumumab to be absorbed into the body when injected under the skin, it is combined with a substance called recombinant human hyaluronidase PH20 (rHuPH20). rHuPH20 is an enzyme that improves how quickly and easily medications like daratumumab are absorbed under the skin and into the blood stream.

Some patients who receive rHuPH20 may develop antibodies directed to the PH20 hyaluronidase; approximately 5% of the general population has these antibodies even without ever having been exposed to rHuPH20. In clinical trials, there have not been any links between the development of these antibodies and any negative effects. Antibodies to rHuPH20 could, in theory, interact with human sperm (location of the PH20 hyaluronidase in the body). It is unknown whether these antibodies may interfere with fertilization in humans. Extensive animal studies do not indicate direct or indirect harmful effects of either rHuPH20 or antibodies to rHuPH20 with respect to reproductive function in males or females at doses of rHuPH20 many times greater than those used in this study.**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 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. Signs of an infection may include fatigue, headache, fever, chills, aches and pains, coughing, congestion, chest tightness, or shortness of breath. Majority of the observed infections so far were mild or moderate. Severe infection such as pneumonia and sepsis has 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. Your doctor will tell you about how to prevent the Herpes Zoster Virus infection. Severe liver infection, including cases resulting in death, have occurred in patients who are carriers of hepatitis B virus. 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 *[or if you are already on the study and have been receiving treatment for less than 6 months].* 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.

Indirect Antiglobulin Testing
If you need a blood transfusion, tests are performed on your blood so that suitable donor blood can be given for a transfusion. Daratumumab treatment will affect one of these tests known as an indirect antiglobulin test (IAT; also known as an indirect Coombs test). Therefore, an IAT will be done before you receive daratumumab and the result placed on the patient identification wallet card you will carry for this study. Before a blood transfusion, you should show the wallet card and tell all your health care providers that you are taking daratumumab and that it interferes with pre-transfusion blood testing. You should do this during the entire period that are receiving daratumumab and for at least 6 months after your last daratumumab administration or for as long as your study doctor recommends.

What are the likely risks with Bortezomib

Bortezomib should not be taken if you have ever had a serious allergic reaction to bortezomib, boron, or mannitol. 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 bortezomib works. Tell your doctor about all drugs and supplements you are taking while participating in this study.

Most common bortezomib risks:
The most common risks are those that have occurred in greater than or equal to 30% of patients (3 in 10 patients) who have received bortezomib:

- 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
- Lowered platelets (thrombocytopenia) that may increase the chance of bleeding
- Lowered white blood cells, including neutrophils and lymphocytes (type of white blood cells)
- Lowered red blood cells or anemia which may make you feel tired
- Painful feeling or numbness and tingling in hands and feet, which may not get better after stopping bortezomib. Uncommonly, the nerves that control things like your heart rate, gut movement and urinary bladder may be affected.
- Injection site skin reactions. If the skin reaction is severe, your doctor may no longer give bortezomib under the skin. Instead, bortezomib can be given via a vein.

Progressive multifocal leukoencephalopathy (PML), 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.

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

Very Common bortezomib Risks:
The very common risks are those that have occurred in 10-29% of patients who have received bortezomib:

- 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 build up 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 bortezomib Risks:
Common risks are those that have occurred in 1-9% of patients who have received bortezomib:

- 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 build up 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 bortezomib is injected under the skin

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

- inflammation and fluid build up 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 bortezomib 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.

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

Study Procedures Risks:
In addition to the risks of bortezomib, routine needle sticks for blood samples may cause pain, bruising and rarely, infection at the site where blood is drawn.

What are the likely risks with ixazomib?
There are risks to taking part in any research study. During the study, you may have problems or discomforts and risks from ixazomib, ixazomib and other drug combinations, and/or study procedures. The more commonly occurring discomforts and risks are listed below, as are the rare but serious discomforts and risks. You should discuss these with your study doctor. There is always the possibility that unknown risks may occur, however your doctor will watch closely for problems or discomforts and risks. Many discomforts and risks go away shortly after treatment is stopped or with treatment for the discomforts and risks, but in some cases discomforts and risks may be serious, long- lasting or permanent and may even result in hospitalization or death.

If any discomforts and risks occur, you must tell your study doctor or study staff, even if you do not think they are related to the study drug.

POTENTIAL DISCOMFORTS AND RISKS OF IXAZOMIB
Based on studies of ixazomib it is possible to predict some of the discomforts and risks. However, it is possible that ixazomib may cause risks that have not yet been observed in patients. The following risks might be seen:

- Low platelet count which may increase the chance of bleeding
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
- Nausea
- Vomiting
- Diarrhea
- Numbness or tingling or pain feelings in hands and feet
- Swelling or fluid buildup in the arms or legs
- Flu-like symptoms and other upper respiratory tract infections
- Arthralgia or joint pain
- Lung infections including pneumonia or pneumonitis
- Herpes Zoster that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time

Other discomforts and risks reported in studies with ixazomib, which may have been due to the patient's disease, ixazomib, other medications, or some combination of these include:

- Not feeling like eating
- Electrolyte imbalance (blood chemical imbalance)
- Loss of water from the body (dehydration) because of vomiting and/or loose stools

- High blood creatinine and renal failure which means your kidneys are having trouble working well; Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
- Feeling short of breath or difficulty breathing
- Feeling tired or weak
- Chills
- Cough
- Fever
- Headache
- Pain in the abdomen or back
- Muscle weakness
- Feeling dizzy or dizziness
- Lowered blood pressure that can commonly cause you to feel light headed, faint or pass out when you stand up
- Lowered white blood cells called lymphocytes
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Constipation
- Pain (muscular) in extremities
- Distortion of the sense of taste i.e. an abnormal or impaired sense of taste
- Trouble falling asleep, staying asleep or both

Some discomforts and risks occur with lesser frequency (<1%) than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience and because these events occurred while patients were receiving other drugs as well, we do not know if ixazomib causes such problems. Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute febrile neutrophilic dermatosis (Sweet's syndrome) and pemphigus vulgaris, have been reported in ixazomib studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.

In addition, posterior reversible encephalopathy syndrome has also been reported with ixazomib with lesser frequency (<1%). This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible. Transverse myelitis, also a rare condition (<1%), is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving ixazomib. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether ixazomib causes transverse myelitis, however, as it happened to a patient receiving ixazomib, we are not able to exclude the possibility that ixazomib may have contributed to transverse myelitis.

PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1 %) in patients taking ixazomib. It is not known whether ixazomib may contribute to the development of PML.

During the reporting period, thrombotic microangiopathy (TMA) was identified as an adverse drug reaction. TMA, including thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells and result in blood clots in small blood vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders can occasionally be fatal. TTP, and HUS have been seen rarely (<0.1%) in patients treated with ixazomib.

Overdose has been reported in patients taking ixazomib. Reports of accidental overdose have been associated with risks such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. It is important to take only one dose of ixazomib at a time, and only at the prescribed intervals.

Ixazomib should not be taken if you have ever had an allergic reaction to the active substance or any of the inactive ingredients used in its formulation.

The following side effects may also be a risk with ixazomib because they have been reported with another proteasome inhibitor, bortezomib, in patients with diseases requiring this type of treatment, or in patients who receive ixazomib in combination with other drugs for cancer treatment:

- Reactivation of the herpes virus infection such as herpes zoster (shingles) that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time;
- Rapid death of cancer cells that may let large amounts of the cells into the blood that injure organs, such as kidneys (this is referred to as tumor lysis syndrome);
- Worsening of your heart function (congestive heart failure) that may require additional drugs for treatment or hospitalization;
- Disorders of your lung that could be serious enough to result in death
- Other drugs and supplements may affect the way ixazomib works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

What are the likely risks with dexamethasone?

Glucocorticoids are a class of drugs (including dexamethasone, prednisone, prednisolone, betamethasone, and others depending on local availability) and may cause the following side effects:

- Infection
- Stomach ulcers with bleeding
- Nausea
- Formation of a hole in the small and/or large bowel particularly in people with preexisting bowel problems. This risk is substantial and may be life-threatening
- Irritation and bleeding of the esophagus (tube from mouth to stomach)
- Increased appetite
- Weight gain
- Weight loss due to inability of the body to breakdown and use protein
- Decreased tolerance for starchy foods

- Heart failure in people who have previous heart conditions. This risk is substantial and may be life-threatening.
- Allergic reaction (this may include facial redness, shortness of breath, profuse perspiration, abdominal cramps, fast heartbeat and low blood pressure)
- Acne
- Convulsions
- Brain swelling
- Dizziness
- Headache
- Mood swings
- Eye problems including cataracts, glaucoma and increased blood pressure within the eye
- Development of diabetes and increased requirements for insulin
- Inflammation of the pancreas
- Abdominal swelling
- Retention of fluid and salt
- Loss of potassium
- High blood pressure
- Blood clots in the legs and lungs. This risk is substantial and may be life-threatening.
- Malaise (general feeling of illness)
- Slow wound healing
- Thin, fragile skin, black and blue marks
- Swelling and/or redness of the skin
- Increased sweating
- Abnormal readings of different skin tests
- Allergic skin problems
- Itching
- Increase in body hair
- Muscle weakness or loss of muscle mass
- Bone thinning
- Spinal fracture
- Destruction or fracture of the long bones (thigh/hip and upper arm/shoulder)
- Rupture of tendons
- Disturbances with menstrual cycles
- Development of puffiness in the face that gives the appearance of a “moon face”
- Hormonal disturbances during times of stress or illness
- Hiccups

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

Risks Associated with Autologous Peripheral Blood Stem Cell Collection:

You may experience the side effects listed below while undergoing the collection of lymphocytes (lymphopheresis). These reactions or side effects are usually reversible when the procedure is stopped or with the correct medical care.

- A sterile anticoagulant solution is used to prevent your blood from clotting in the machine. The anticoagulant works by binding to calcium in your blood. You may experience tingling of your lips or fingers, a "vibrating" sensation, or more rarely, nausea, vomiting or muscle tightness. To counteract these possible symptoms, we give replacement calcium to you by vein during the procedure. If these symptoms occur despite replacement calcium, more calcium will be given until symptoms resolve.
- You will receive about 1 to 2 quarts of anticoagulant solution by vein during each collection procedure. If you have a history of heart failure or kidney disease, you may retain some of this fluid, causing increased weight or swelling in your hands or feet. A large volume of extra fluid may cause shortness of breath. These symptoms can be treated with diuretics such as Lasix.
- The anticoagulant solution contains dextrose (sugar). If you have diabetes, you may require extra insulin to keep your blood sugar level within the desired range.
- Low blood pressure, high blood pressure, or slow pulse may occur as a result of blood being moved through the machine. If these occur, the procedure will be slowed or stopped until symptoms resolve.
- Blood pressure medicines called Angiotensin Converting Enzyme (ACE) inhibitors should not be taken before your collection procedure. These medications may cause low blood pressure during your collection procedure. If you are on an ACE inhibitor, your physician may prescribe an alternate blood pressure medication.
- Some blood platelets (cells in the blood involved in clotting) are removed during stem cell collection. If your platelet counts drop very low, you may need to receive a platelet transfusion to prevent bleeding. Your red cells and plasma may not be returned to you if there are any problems with needle placement in your veins or with the apheresis equipment. A decreased red blood cell count may occur as a result. However your counts should return to normal within 8 weeks. If your blood counts are extremely low, you may need to receive a red cell transfusion to prevent symptoms.
- Some patients with a history of migraine can have return of their migraine headaches with therapy. If you have a migraine history, notify your physician and you will be treated with magnesium by vein to help prevent migraines.
- Although extremely rare, serious or life-threatening reactions are possible and include allergic reactions, infections, seizures, air embolism or arrhythmias (abnormal heart rhythms). We will carefully monitor you for these and if they begin, we will immediately stop the procedure and treat you accordingly.

Risks Associated with Autologous Peripheral Blood Stem Cell Transplant:

Likely (greater than 50% chance that this will happen)

- Condition in which the number of white blood cells circulating in the blood is abnormally low. This increases the risk of infection, which may be serious or life-threatening.
- Low number of platelets, which may cause bleeding or bruising (thrombocytopenia). Bleeding may be serious or life-threatening and may require a blood transfusion.
- Low number of red blood cells that can cause tiredness or shortness of breath (anemia). This may require a blood transfusion.
- Decrease in platelets and/or red blood cells and/or white blood cells at the same time. This may lead to an increase in infection, an increase in bruising or bleeding and/or may cause you to feel tired.
- Fever and/or chills
- Flu-like symptoms

- Fatigue
- Loss of appetite
- Weight loss
- Diarrhea
- Nausea
- Vomiting
- Partial hair loss or thinning of hair
- Skin rash, or hives (swollen, pale red patches or bumps on the skin)

Less Likely (between 1 - 50% chance that this will happen)

- Bone pain
- Wheezing
- Shortness of breath
- Lightheadedness
- Back or chest pain
- Inflammation of the throat and tongue
- Decreased levels of sodium in the blood, which can cause confusion, seizures, fatigue and low levels of consciousness (hyponatremia)
- Painful or difficult urination
- Bladder irritation which may cause blood in the urine
- Abnormal kidney function which, rarely, could lead to kidney damage
- Abnormal thyroid function which may cause changes in your body's rate of metabolism

Rare but Serious (less than 1% chance that this will happen)

- Severe allergic reaction, symptoms of which may include a fast heart rate, shortness of breath, low blood pressure, sweating, swelling of the throat, and face rash within a few minutes of treatment.
- Heart damage, symptoms of which may include shortness of breath or difficulty catching your breath, rapid or irregular heartbeat (palpitations), weakness, dizziness, fatigue, fainting, nausea, vomiting, sweating, swelling of your ankles, feet or abdomen, rapid weight gain, or chest pain, discomfort or pressure.
- Bladder damage, which could lead to bladder pain or pain when urinating, urinary incontinence, bladder infection, inflammation or distension, frequent urination, weak urination, or nocturia (excessive urination at night).
- Lung inflammation or scarring of the lung, which could lead to fever, cough, chills, shortness of breath, weight loss, poor appetite, sharp chest pain when breathing, rapid shallow breath, or inability to take a deep breath due to chest pain.
- Abnormal liver function which, rarely, could lead to liver inflammation or liver damage (jaundice or liver failure).
- Failure to resume production of blood cells which can be fatal.
- Serious disturbances of the immune system which can result in lifethreatening infections.
- Red blood cell destruction by the immune system.
- Mouth and throat sores that may be painful and cause difficulty eating.
- Bleeding of stomach and intestines (gastrointestinal) that may cause blood when vomiting or black, tarry stools.
- Infection due to contamination of the stem cell products during their storage or drawing.

Risks Associated with Melphalan:
The following side effects are most common side effects of melphalan:

- Bone marrow suppression (lower blood cell counts including white blood cells, red blood cells, and platelets). This is usually reversible if melphalan is withdrawn early enough. However, irreversible bone marrow failure has been reported. Your study doctor will monitor your blood cell counts very carefully throughout this study
- Nausea
- Vomiting
- Diarrhea
- Oral ulceration

The following side effects are rare:

- Liver disorders
- Lung damage (leading to shortness of breath and coughing)
- Skin effects (rash, itching, and hair loss)
- Allergic reactions. Rare occurrences of anaphylaxis have been reported after multiple courses of treatment.

Please ask your study doctor for information regarding these side effects.

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

Risks Associated with Radiological Scans and X-Rays:
You will be exposed to radiation from nuclear medicine and x-rays. These procedures are necessary for your medical care and will occur even if you do not participate in this study. The estimated radiation dose that you will receive is equal to or less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for example, x-ray technologist, radiologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study is minimal.

MUGA:
For your MUGA scan, a small amount of radioactive material will be injected by either a hand-held needle or a machine. Such injections are generally quite safe, but any injection involves some risks. The injection could harm a nerve, artery or vein, or cause infection. The radioactive material could also leak from your veins a little, causing swelling and discomfort. After injection and a waiting period for the drug to circulate within your body, you will be asked to lie very still for several minutes while the scan takes place.

Study Procedure Risks:
Needle sticks for blood samples and/or bone marrow procedures may cause pain, bruising, and rarely, infection at the site of the needle puncture

What are the reproductive risks of daratumumab, ixazomib or bortezomib: Female Participants

The effects of daratumumab on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. If you are a woman, taking part in the 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. If you are a man, the effect of daratumumab on your sperm is unknown.
If you are a woman and becoming pregnant is a possibility, you will be required to undergo a pregnancy test prior to taking daratumumab. Both male and female patients must use effective methods of birth control during the course of the study, and for 3 months after stopping daratumumab.
The type of birth control you use must be discussed with, and approved by, the study doctor before you begin the study. If you are female and become pregnant during the study, you must tell the study doctor immediately.
If you are a woman:

- You must not donate eggs during the study and for 3 months after your last dose of study drug.

If you are a man:

- The effect of the study drug on your sperm is unknown.
- You must not donate sperm during the study and for 3 months after your last dose of study drug.

There are additional side effects that have been seen in patients that have taken daratumumab. Please ask your study doctor for information regarding these side effects
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We do not know if the study drugs ixazomib, or bortezomib will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study.

You must have a negative pregnancy test prior to enrolling in the study.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see examples below):

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex or non latex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time is recommended.	

You must use birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male Participants

We do not know if using ixazomib will affect sperm. Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period (including interruptions in treatment). Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non latex condom with or without a spermicidal agent) during the entire study drug treatment period, and for 90 days after completing study drug treatment. Or, you should completely avoid having heterosexual intercourse.

Vasectomy	Latex or non latex condom with or without a spermicidal agent
	Diaphragm with spermicide; Cervical cap with spermicide; Sponge with spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

If your female partner is unable to become pregnant for one of the following reasons, the use of birth control measures is not required during this study:

- Her healthcare provider confirmed that she is postmenopausal.
- She has had her uterus, or both ovaries, or both fallopian tubes removed.

Otherwise, if your female partner could become pregnant, you:

- Should let her know you are in this study.
- Must practice abstinence (not have sex) or you must always use a condom with spermicide during treatment and for an additional 90 days after the last dose of daratumumab, ixazomib or bortezomib.
- You should be aware that no one birth control method is 100% effective.
- Your female partner should also consider using an acceptable method of effective contraception such as:
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Hormonal birth control method: pill, shots/injections, implants (placed under the skin by a healthcare provider), skin patches
- Female barrier method: diaphragm, cervical cap, contraceptive sponge (a female condom is not an option because there is a risk of tearing when both partners use a condom.)
- You must not donate sperm during treatment and for an additional 90 days after the last dose of daratumumab, ixazomib or bortezomib.

Female and Male Participants

The pregnancy, breastfeeding, and birth control information in this document is specific to daratumumab, ixazomib or bortezomib. There may be additional risks to an unborn child or breastfed baby from other chemotherapy that you may receive during the study. This may require that you change the type and/or length of time that you must use birth control or length of time that you must avoid breastfeeding. Please discuss this with the study doctor.

What if you become pregnant or breastfeed during the study?
If you decide to participate in this study, you must agree to not become pregnant or to breastfeed.

If you become pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

What if your partner is pregnant when you begin this study or becomes pregnant during the study?
If your partner is pregnant when you begin this study or becomes pregnant during treatment and for an additional 90 days after stopping daratumumab, ixazomib or bortezomib, you must tell the study doctor or study staff right away. To prevent exposure of the unborn child to daratumumab, ixazomib or bortezomib through semen, you will be required to practice sexual abstinence (not have sex), or you must wear a condom during vaginal sex.

The study doctor will notify Millennium and Janssen of the pregnancy and ask to obtain information on the pregnancy outcome for both the mother and baby.

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

What are the other risks and discomforts associated with this study?
Risks and side effects of venipuncture/intravenous needle insertion:
Infrequent (occurs in 1% to 10% of people - from 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Rare (occurs in less than 1% or people - less than 1 out of 100 people): severe pain, swelling, infection from the actual injection, dizziness and/or and fainting.

Risks and Side Effects of EKG (Electrocardiogram):
Rare – Occurs in less than 1% of people (less than 1 out of 100 people):
Side effects that may be associated with the EKG electrode placement are skin irritation, redness, and chafing of the skin at the placement site.

Risks and Side Effects of Bone Marrow Aspirate and Biopsy
Possible side effects of a bone marrow aspirate and biopsy include bleeding, infection, bruising, pain or discomfort at the biopsy site and possible side effects from the local anesthetic (pain or bruising at the injection site).

The bone marrow test is performed by using a needle to obtain a small sample of bone marrow from the pelvic bone. The main discomfort associated with this test is pain when the bone marrow is being withdrawn. In order to make the procedure more comfortable, you will get a local anesthetic to numb the area. A mild sedative may also be given to you. While you are sedated, you will be able to respond to commands.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?

This study is not designed to benefit you directly. Your myeloma may improve while you are in this study but it may not, and it may even get worse. It is possible that you may not receive any direct benefit from this study. You may receive the information about your health. This study is designed to learn more if the combination of daratumumab, ixazomib or bortezomib will help control the disease. The study results may be used to help others in the future.

Will I be compensated for my time and effort?

Your participation in this study is entirely voluntary and you will not receive any payment for participation. Your participation in the study may result in discoveries or products. The discoveries and products may have commercial value. If there is commercial value, you will not receive any compensation from the discoveries or products.

What are my other options?

Other treatment

If you decide not to enter this study there is care available to you outside of research, such as:

- Standard treatment including:
  - Melphalan and prednisone
  - Dexamethasone alone or in combination with other drugs
  - Bortezomib alone or in combination with other drugs
  - Cyclophosphamide alone or in combination with other drugs
  - Thalidomide alone or in combination with other drugs
  - Lenalidomide and dexamethasone.
  - Bortezomib, lenalidomide and dexamethasone
- Participate in another research study.
- Receive the same drugs, but not as part of a research study.
- No therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

The study doctor will discuss these with you. You do not have to be in this study to be treated for multiple myeloma.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

How will you protect my private information that you collect in this study?

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the

research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

In addition to the investigators listed on the first page of this consent form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study:

Your medical record information (identified by a case number) may also be shared with (or "disclosed to") other persons and organizations involved in this research, including:

- Millennium Pharmaceuticals, Inc., it's collaborators or designees ,
- Janssen Scientific Affairs and its representatives
- the study's Data Safety Monitor
- the Food and Drug Administration (FDA) and any other regulatory authorities to which the results of this study will be submitted to review the study findings
- Emory Office of Research Compliance
- the Emory Institutional Review Board
- the Office for Clinical Research, the Clinical Trials Audit & Compliance Office

Study records can be opened by court order or produced in response to a subpoena or a request for production of documents unless a Certificate of Confidentiality is in place for this study.

The information about your health and treatment during the study may be used by or sent to parties in other countries for clinical research, safety-reporting, and any other study-related uses described in this form. Some of these countries may not have data protection or privacy laws that offer the same level of protection as the data protection and privacy laws in the United State. However, such parties will do everything possible to keep your coded information confidential.

The information collected during this study may also be added to research databases and used in the future by the sponsor and other companies and people working for or with the sponsor to: develop a better understanding of the safety and effectiveness of the study drugs; study other therapies for patients; develop a better understanding of diseases included in this study; and improve the efficacy, design and methods of future studies.

The results of this study may be presented at meetings or in publications, but your name will not appear in any presentations or publications.

Medical Record

If you are or have been an Emory Healthcare patient, you have an Emory Healthcare medical record. If you are not and have never been an Emory Healthcare patient, you do not have one. Please note that an Emory Healthcare medical record **will** be created if you have any services or procedures done by an Emory provider or facility for this study.

If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign **will** be placed in your Emory Healthcare medical record. Emory Healthcare may create study information about you that can help Emory Healthcare take care of you. For example, the results of study tests or procedures. These useful study results will/will not be placed in your Emory Healthcare medical record. Anyone who has access to your medical record will be able to have access to all the study

information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory does not control results from tests and procedures done at other places, so these results would not be placed in your Emory Healthcare medical record. They will not likely be available to Emory Healthcare to help take care of you. Emory also does not have control over any other medical records that you may have with other healthcare providers. Emory will not send any test or procedure results from the study to these providers. If you decide to be in this study, it is up to you to let them know.

The researchers will review the results of certain study tests and procedures only for the research. The researchers **will not** be looking at the results of these tests and procedures to make decisions about your personal health or treatment.

How long will my records be kept?

- The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of 5 years and for as long (indefinite) as it may take to complete this research study.
- If you have questions about the keeping of your research records or access to your files, please call Dr. Ajay K. Nooka, the investigator in charge at 404-778-1900.

In Case of Injury

If you get ill or injured from being in the study, Emory will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this research, you should contact Dr. Ajay K. Nooka at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.
If you get ill or injured as the direct result of being in this study, then, depending on what insurance you may have, the study supporter may pay for some or all of the costs for your medical treatment of the illness or injury if it:

(a) is not a medical condition that you had before you started the study;
(b) is not the result of the natural progress of your disease or condition;
(c) is not caused by your failure to follow the study plan; and
(d) is not proven to be directly caused by the negligence of an Emory employee. "Negligence" is the failure to follow a standard duty of care.

If your case meets all four of these requirements and you are uninsured or have Medicare or Medicaid, then the study supporter will pay all of the costs of your medical treatment for the illness or injury. If you have Medicare or Medicaid, the study supporter may need information about your identity and your treatment. They will give this information to the government agencies that run these programs.
If your case meets all four of these requirements and you have private insurance, Emory will look at the claims for these costs to see if they can be sent to your insurer for payment. Your insurer may be told that you are in a research study and given information about your treatment.

You will have to pay for any costs that the study supporter or your insurer does not pay. The study supporter will pay for any of the costs that are not paid by your insurance provider. The study supporter will not pay for costs like co-payments that your insurer says you have to pay.

Emory has not set aside any money to pay you or to pay for your treatment if you get ill or injured from being in the study. The only exception to this policy is if it is proved that your injury or illness is directly caused by the negligence of Emory employee.

Costs

You will not be charged for any tests specifically required for this research study, but you or your insurance company will be billed for tests or procedures that are considered part of your normal cancer care. This includes treatment costs that would be billed if you were not on this study, including but not limited to drugs, routine laboratory tests, x-rays, scans, surgeries, routine medical care, and physician charges.

Payment for drugs and procedures that are considered part of your normal cancer care will be billed to you or your insurance company. Your health insurance company may not pay for these charges because you are in a research study. If your insurance company does not pay for costs associated with this research study that are part of your normal cancer care, then you will be billed for these costs. You are responsible for paying for any insurance co-pays (if applicable to your policy), any deductible indicated by your insurance policy, and any charges your insurance company does not pay. You will not be charged for the study drug (daratumumab, or ixazomib). You and your insurance company will be billed for the costs of bortezomib and dexamethasone.

So that you do not have unexpected expenses from being in this study, ask your study doctor for a list of the tests or procedures that are considered part of your normal cancer care, including the treatment of side effects.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for.

If you do not have insurance, Emory will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Withdrawal from the Study

You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

You can be taken off the study (with or without your consent) for any of these reasons:

- you experience adverse events
- your condition gets worse
- new information becomes available that necessitates removing you from the study
- funding for the study is stopped
- it is in your best medical interest, in the opinion of your study doctor, for you to stop study participation.

You may be removed from this study if your tumor grows, unacceptable side effects occur, you withdraw your consent, or your doctor or the study sponsor thinks you should stop receiving the study drug. If you do not follow the study instructions given to you by the study doctor, you may be taken off of the study. Millennium Pharmaceuticals, Inc., Janssen Pharmaceuticals, the FDA, and/ or the Institutional Review Board may decide to stop the study, and you would then be taken off of the study.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study.

PHI that Will be Used/Disclosed:
The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information. We will use and disclose your PHI for the administration and payment of any costs relating to subject injury from the study.

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:

By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- Millennium Pharmaceuticals, its collaborators or designees.
- The Sponsor may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The research team and the Sponsor may use and disclose your PHI, including disclosure to insurance carriers to administer payment for subject injury.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including: Food and Drug Administration.
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at: [redacted]

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure

that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the main study.

Other Items You Should Know about Your Privacy

Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. The Sponsor, and people and companies working with the Sponsor on this study are not covered by the Privacy Rules. They will only use and disclose your information as described in this Consent and Authorization.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information

Contact Dr. Ajay K. Nooka at [redacted]:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at [redacted]:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

Consent and Authorization

☐ Would you be willing to fill in an optional questionnaire related to SC daratumumab? Please initial in the box if you are interested to fill the survey form

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in the main study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

_____
Name of Subject

_____ _____ ____:____ am / pm
Signature of Subject (18 or older and able to consent) **Date** **Time (please circle)**

TO BE FILLED OUT BY STUDY TEAM ONLY

_____
Name of Person Conducting Informed Consent Discussion

_____ _____ ____:____ am / pm
Signature of Person Conducting Informed Consent Discussion **Date** **Time (please circle)**