**Study Title for Study Participants:**

# Testing two new targeted drug combinations against standard chemotherapy for early relapsing or refractory follicular lymphoma

**Official Study Title for Internet Search on http://www.ClinicalTrials.gov:**
S1608, Randomized Phase II Trial in Early Relapsing or Refractory Follicular Lymphoma

## What is the usual approach to my lymphoma?

You are being asked to take part in this study because you have follicular lymphoma that has either not responded to previous treatment or that has come back after previous treatment. People who are not in a study are usually treated with chemotherapy to try to control the tumor. For patients who receive the usual approach for this cancer, about 20 out of 100 are free of cancer at five years.

## What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

## Why is this study being done?

**The purpose of this study is to compare any good and bad effects of using different drugs in combination with an antibody. An antibody is a protein that can recognize and attack foreign objects (antigens) in the body. Here, the antibody is obinutuzumab. It is looking for CD20, an antigen that is found on tumor cells. Two study drugs will be tested in this study: TGR-1202 and lenalidomide. Each of these study drugs may help the immune system fight cancer. During the study, you will get either obinutuzumab plus TGR-1202, obinutuzumab plus lenalidomide, or obinutuzumab plus the usual approach treatment for your cancer.**

**The addition of TGR-1202 or lenalidomide could shrink your cancer, but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the addition of a study drug should increase the chances of your cancer shrinking by about 45% compared to the usual approach. The antibody (obinutuzumab) and the regular chemotherapy approach are FDA-approved for use in follicular lymphoma, but they aren't usually used together. The immune system drug, TGR-1202, is not FDA approved. The**

**immune system drug lenalidomide is FDA approved, but not for follicular lymphoma (your type of cancer).**

**There will be about 150 people taking part in this study.**

**Another purpose of this study is to test PET/CT scans, which are a way to take pictures of your type of cancer. The researchers want to use PET/CT scans to help diagnose and monitor your cancer. PET/CT scans are a part of regular care for your type of cancer. All of the patients taking part in this study will have PET/CT scans sent to a central PET/CT reviewer.**

**Another purpose of this study is to see whether a set of gene mutations (called m7-FLIPI) can predict whether your lymphoma will respond better or worse to the study treatment. Mutations are permanent changes in your DNA. The researchers will look for the mutations on your tumor tissue and in tumor cells found in your blood. All of the patients taking part in this study will have blood and tissue submitted for these gene mutation tests.**

## What are the study groups?

This study has three study groups.

**Group 1** will receive the following treatment:

| Drug | How Given | Days |
|---|---|---|
| TGR-1202 (study drug 1) | By mouth (pill) with food (within 30 minutes of a meal) | Every day (days 1-28) for 12 cycles |
| Obinutuzumab (antibody) | IV in your vein | Day 1 for 12 cycles |

You will get 12 cycles of treatment. One cycle will be 28 days long. You will not stop taking drug between cycles. After a 28-day cycle ends, the next cycle will begin the following day.

**Group 2** will receive the following treatment:

| Drug | How Given | Days |
|---|---|---|
| Lenalidomide (study drug 2) | By mouth (pill) | Days 1-21 for 12 cycles |
| Obinutuzumab (antibody) | IV in your vein | Day 1 for 12 cycles |

You will get 12 cycles of treatment. One cycle will be 28 days long. You will not get drug every day of each cycle. You will get drug for 21 days, and then have a break for 7 days. After a 28-day cycle ends, the next cycle will begin the following day.

**Group 3**

If you previously received Bendamustine chemotherapy as part of your standard of care, then you will receive the following treatment during this study:

| Drug | How Given | Days |
|---|---|---|
| Obinutuzumab (antibody) | IV in your vein | Day 1 for 12 cycles |
| "CHOP" (usual chemotherapy) | | |
| Cyclophosphamide | IV in your vein | Day 1 for 6 cycles |
| Doxorubicin | IV in your vein | Day 1 for 6 cycles |
| Vincristine | IV in your vein | Day 1 for 6 cycles |
| Prednisone | By mouth (pill) | Days 1-5 for 6 cycles |

You will get 12 cycles of treatment. You will not get drug every day of each cycle. The first 6 cycles will be 21 days long. You will get drug for 5 days, and then have a break for 16 days. After a 21-day cycle ends, the next cycle will begin the following day. The last 6 cycles will be 28 days long. You will get drug on the first day of each cycle, and then have a break for 27 days. After a 28-day cycle ends, the next cycle will begin the following day.

If you previously received "CHOP" (the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy as part of your standard of care, then you will receive the following treatment during this study:

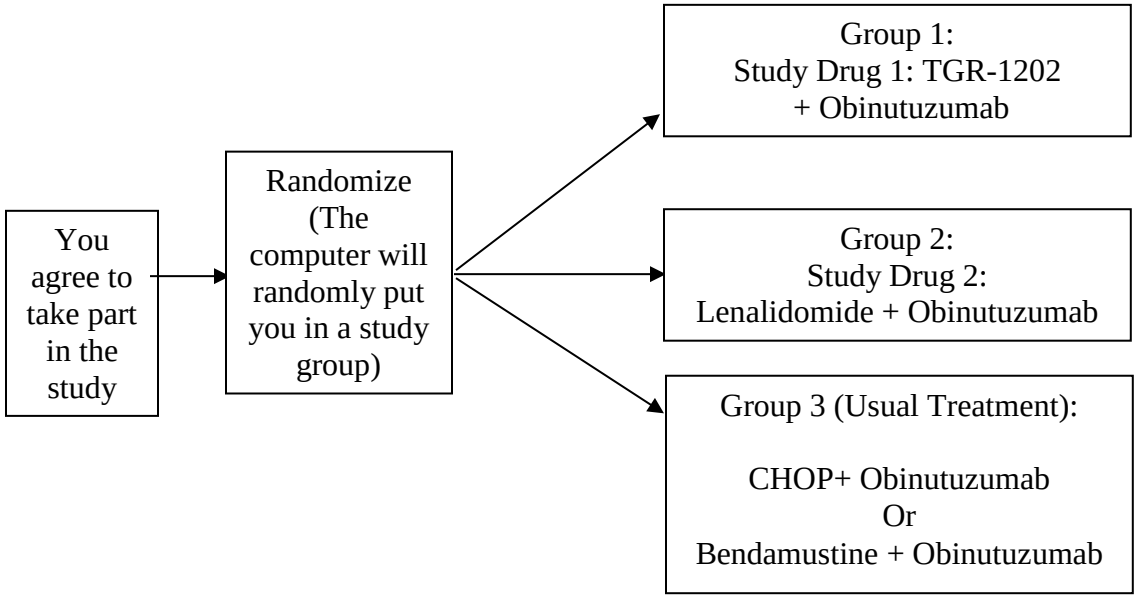
| Drug | How Given | Days |
|---|---|---|
| Obinutuzumab (antibody) | IV in your vein | Day 1 for 12 cycles |
| Bendamustine | IV in your vein | Days 1 and 2 for 6 cycles |

You will get 12 cycles of treatment. You will not get drug every day of each cycle. All 12 cycles will be 28 days long. You will get drug for the first two days of the cycle, and then have a break for 26 days for the first 6 cycles. You will get drug on the first day of each cycle, and then have a break for 27 days for the last 6 cycles. After a 28-day cycle ends, the next cycle will begin the following day.

For all 3 groups, you will keep a medication log of all of the study drugs you take by mouth. You will bring it to your doctor to review each cycle.

A computer will by chance assign you to treatment arms in the study. This is called randomization. This is done by chance because no one knows if one study arm is better or worse than the other. Patient have an equal chance of being randomized to any one of the 3 study groups.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.




## How long will I be in this study?

Groups 1 and 2:
Patients will get treatment on the study for 48 weeks (about 11 months).

Group 3:
Patients who received Bendamustine chemotherapy prior to this study will get treatment (CHOP + Obinutuzumab) on the study for 42 weeks (about 9 ½ months).
Patients who received CHOP chemotherapy prior to this study will get treatment (Bendamustine + Obinutuzumab) on this study for 48 weeks (about 11 months).

For all Groups:
After you finish treatment on the study, your doctor will continue to watch you for side effects and follow your condition. At a minimum, you will go to the doctor's office every 3 months for the first 2 years, then every six months until 5 years from the time you started the study

## What extra tests and procedures will I have if I take part in this study?

Some of your tumor tissue will be taken prior to the study to make treatment decisions. At the same time, extra tumor tissue will be taken for this study. The results of this bone marrow biopsy will also be shared with the study doctors. No extra bone marrow will be taken for this study.

Blood will be taken for this study (at the same time that you have blood taken for treatment decisions) at the following times:

- Before you receive drug on the first day of treatment,
- After 3 cycles of treatment,
- After 6 cycles of treatment,
- After 12 cycles of treatment (or when you stop protocol treatment), and
- 30 months after you start the study

The tumor tissue and blood samples are required in order for you to take part in this study because the research on the sample is an important part of the study. These samples will be used to look at how your body is reacting to treatment on the study.

Common side effects of the tumor tissue and blood collection are pain, soreness, swelling, bruising, and bleeding at the site of the incision. Rarely, an infection can occur at the site of the incision for the tumor tissue collection or bone marrow collection.

If there is any tissue or blood left after tests are completed for this study, the researchers would like to ask your permission to store it for use in future research. This is called biobanking. It will be discussed more later in the section for optional studies.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. The results of the tests performed will not be given to you or your doctor.

All patients must have a PET/CT scan at the beginning of the study. PET/CT scan is one of the standard of care procedures you have to help diagnose your cancer. If you have had one recently enough (within the last 6 weeks before you register) then you likely will not need to have it repeated. If you have not had one recently enough, you will have to have it repeated in order to take part in the study.

If you are in Group 1, you will need the following extra test during treatment. It is not part of the usual approach for your type of cancer. It is being done because of the treatment drugs that you will get.

Before the study:

- Cytomegalovirus (CMV) test prior to beginning the study. This is a test that your doctor will perform using the blood that you will have collected as part of regular cancer care. CMV is a virus that can cause serious health problems for people with weakened immune systems.

If you are in Group 2, you will need the following extra test during treatment and follow up. It is not part of the usual approach for your type of cancer. It is being done because of the treatment drugs that you will get.

During the study:

- For females of child-bearing potential (FCBP)**: Pregnancy test within 10 – 14 days before starting treatment, then 24 hours before starting treatment. Females with regular or no menstruation must have a pregnancy test weekly for the first 28 days of treatment, every 28 days during treatment, at the time you stop getting treatment, and 28 days after your last dose of treatment. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days of treatment, every 14 days during treatment, at the time you stop getting treatment, 14 days after your last dose of treatment, and 28 days after your last dose of treatment.

**A female of childbearing potential (FCBP) is a female who: 1) has menstruated at some point, 2) has not had her uterus or both ovaries removed; or 3) has not been naturally postmenopausal (stopping menstruation after cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The costs of these additional tests are discussed below in the section, "What are the costs of taking part in this study?."

## What possible risks can I expect from taking part in this study?

**If you choose to take part in this study, there is a risk that the drug combination (obinutuzumab plus TGR-1202, obinutuzumab plus lenalidomide, or obinutuzumab plus the usual approach treatment for your cancer) may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.**

**You also may have the following discomforts:**

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**
- **You may not be able to take part in future studies.**
- **There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job.**
- **There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.**

**The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.**

**There is also a risk that you could have side effects from any of the drugs used in this study.**

**Here are important things to know about side effects:**

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may make it hard for you to have children.**
- **Some side effects may be mild. Other side effects may be very serious and may even result in death.**

**You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:**

- **If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.**
- **Your study doctor will work with you to treat your side effects.**
- **Your study doctor may adjust the study drugs to try to reduce side effects.**
- **The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drugs.**

**The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.**

**Study Group 1 and Group 2 and Group 3- Possible side effects of the antibody obinutuzumab:**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving obinutuzumab, more than 20 and up to 100 may have: |
|---|
| • **Nausea**<br>• **Tiredness, fever**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**<br>• **Low blood pressure which may cause feeling faint** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving obinutuzumab, from 4 to 20 may have: |
|---|
| • **Anemia which may require blood transfusion**<br>• **Pain**<br>• **Diarrhea, vomiting**<br>• **A tear or hole in internal organs that may require surgery which may cause difficulty swallowing**<br>• **Chills** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving obinutuzumab, from 4 to 20 may have: |
|---|
| • **Infection, especially when white blood cell count is low**<br>• **Bruising, bleeding**<br>• **Dizziness, headache**<br>• **Painful urination**<br>• **Inability to control urine**<br>• **Cough, shortness of breath**<br>• **Runny nose**<br>• **Hair loss, itching, rash, hives**<br>• **Flushing**<br>• **High blood pressure which may cause blurred vision** |

| **RARE, AND SERIOUS**<br>In 100 people receiving obinutuzumab, 3 or fewer may have: |
|---|
| • **Chest pain**<br>• **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness**<br>• **Abnormal heartbeat**<br>• **Prior liver infection that returns which may cause yellow eyes and skin, tiredness**<br>• **Kidney damage which may require dialysis**<br>• **A new skin cancer resulting from treatment of earlier cancers** |

**Study Group 1 - In addition to side effects outlined for obinutuzumab, people who are in Group 1 may also experience the possible side effects of the study drug TGR-1202 listed below. Some of these side effects may be more common or worse because of the drug combination.**

**Possible side effects of TGR-1202:**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving TGR-1202, more than 20 and up to 100 may have: |
|---|
| • **Diarrhea, nausea**<br>• **Tiredness** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving TGR-1202, from 4 to 20 may have: |
|---|
| • **Anemia which may require blood transfusion**<br>• **Bloating, constipation, heartburn, vomiting**<br>• **Pain**<br>• **Sores in the mouth which may cause difficulty swallowing**<br>• **Swelling of arms, legs**<br>• **Fever**<br>• **Infection, especially when white blood cell count is low** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving TGR-1202, from 4 to 20 may have: |
|---|
| • **Cold symptoms such as stuffy nose, sneezing, sore throat**<br>• **Bruising, bleeding**<br>• **Loss of appetite**<br>• **Dizziness, headache**<br>• **Changes in taste**<br>• **Abnormal body movement**<br>• **Cough, shortness of breath**<br>• **Itching, rash** |

| **RARE AND SERIOUS**<br>In 100 people receiving TGR-1202, 3 or fewer may have: |
|---|
| • **Liver damage which may cause yellowing of eyes and skin, swelling**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**<br>• **Severe blood infection**<br>• **Kidney damage which may require dialysis**<br>• **A new skin cancer unrelated to an earlier cancer**<br>• **Damage to the brain which may cause changes in thinking and may be life-threatening**<br>• **Damage to the lungs which may cause shortness of breath**<br>• **Fluid around lungs**<br>• **Swelling and redness of the skin**<br>• **Dry skin** |

**Study Group 2 - In addition to side effects outlined for obinutuzumab, people who are in Group 2 may also experience the possible side effects of the study drug lenalidomide listed below. Some of these side effects may be more common or worse because of the drug combination.**

**Risk Profile for Lenalidomide (CC-5013))**

**Possible side effects of lenalidomide:**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving lenalidomide (CC-5013), more than 20 and up to 100 may have: |
|---|
| • **Anemia which may require blood transfusion**<br>• **Constipation, diarrhea**<br>• **Tiredness**<br>• **Bruising, bleeding** |

**OCCASIONAL, SOME MAY BE SERIOUS**

In 100 people receiving lenalidomide (CC-5013), from 4 to 20 may have:

- **Infection, especially when white blood cell count is low**
- **Dizziness, fainting**
- **Blurred vision**
- **Cloudiness of the eye, visual disturbances**
- **Pain**
- **Dry mouth, skin**
- **Heartburn, nausea, vomiting**
- **Chills, fever**
- **Swelling of the body**
- **Fall**
- **Weight loss, loss of appetite**
- **Dehydration**
- **Muscle weakness**
- **Abnormal unpleasant sensation, body movement**
- **Changes in taste**
- **Headache**
- **Feeling of "pins and needles" in arms and legs**
- **Numbness, tingling or pain of the arms and legs**
- **Depression**
- **Difficulty sleeping**
- **Change in mood**
- **Cough, shortness of breath**
- **Nose bleed**
- **Increased sweating**
- **Itching, rash**
- **Sores on the skin**
- **High blood pressure which may cause headaches, dizziness, blurred vision**
- **Low blood pressure which may cause feeling faint**
- **Blood clot which may cause swelling, pain, shortness of breath**

**RARE, AND SERIOUS**

In 100 people receiving lenalidomide (CC-5013), 3 or fewer may have:

- **Abnormal heartbeat**
- **Heart attack, heart failure which may cause shortness of breath, swelling of ankles, and tiredness**
- **Liver damage which may cause yellowing of eyes and skin, swelling**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Damage to organs in the body when donor cells attack host organs**

| **RARE, AND SERIOUS**<br>In 100 people receiving lenalidomide (CC-5013), 3 or fewer may have: |
|---|
| • **Kidney damage which may require dialysis**<br>• **Damage to muscle which may cause muscle pain, dark red urine**<br>• **Cancer of bone marrow caused by chemotherapy**<br>• **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions**<br>• **Increased tumor size**<br>• **A new cancer unrelated to an earlier cancer**<br>• **A new cancer resulting from treatment of earlier cancer**<br>• **Stroke which may cause paralysis, weakness**<br>• **Damage to the lungs which may cause shortness of breath**<br>• **Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure**<br>• **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **Difficulty stimulating enough stem cells in the bloodstream for future transplant** |

**Study Group 3**

**In addition to side effects outlined for obinutuzumab, patients who are in Group 3 and who received bendamustine prior to the study may also experience the possible side effects of CHOP listed below. Some of these side effects may be more common or worse because of the drug combination.**

**Possible side effects of CHOP:**

| **COMMON, SOME MAY BE SERIOUS**<br>**In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),**<br>**more than 20 and up to 100 may have:** |
|---|
| • **Hair loss**<br>• **Constipation, nausea, vomiting, loss of appetite**<br>• **Sores in mouth**<br>• **Infection, especially when white blood cell count is low**<br>• **Absence of menstrual period which may decrease the ability to have children**<br>• **Blood in urine**<br>• **Red colored urine, saliva, or sweat**<br>• **Pain or redness at the site of injection or area of previous radiation**<br>• **Numbness and tingling of fingers or toes**<br>• **Headache, jaw pain and/or muscle pain**<br>• **Weakness and difficulty walking**<br>• **In children and adolescents: decreased height**<br>• **Loss of bone tissue** |

| **COMMON, SOME MAY BE SERIOUS**<br>**In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),**<br>**more than 20 and up to 100 may have:** |
|---|
| • **Mood swings**<br>• **Skin changes, acne**<br>• **Swelling of the body, tiredness, bruising**<br>• **Swelling of lower legs**<br>• **High blood pressure which may cause headaches, dizziness, blurred vision**<br>• **Pain in belly**<br>• **Increased appetite and weight gain**<br>• **Weight gain in the belly, face, back and shoulders** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>**In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),**<br>**from 4 to 20 may have:** |
|---|
| • **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions**<br>• **Damage to the bone which may cause joint pain and loss of motion**<br>• **Loss or absence of sperm which may lead to an inability to father children**<br>• **Stuffy nose**<br>• **Fluid around the heart**<br>• **Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose**<br>• **Swelling of the body which may cause shortness of breath**<br>• **Swelling and redness at the site of the medication injection or area of previous radiation**<br>• **Sores in the throat or stomach**<br>• **Diarrhea**<br>• **Hepatitis which may cause yellow eyes and skin**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**<br>• **Cancer of the bone marrow (leukemia) caused by chemotherapy**<br>• **Damage to organs which may cause infection, bleeding, may require transfusions**<br>• **Darkening of the nail beds or skin or hands and feet**<br>• **Loss of nails**<br>• **Anemia which may cause tiredness, or may require transfusion**<br>• **Drooping eyelids**<br>• **Hoarseness**<br>• **Cloudiness of the eye, visual disturbances**<br>• **Glaucoma** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>**In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),**<br>**from 4 to 20 may have:** |
|---|
| • **Non-healing wound**<br>• **Diabetes**<br>• **Kidney stones**<br>• **Heartburn** |

| **RARE, AND SERIOUS**<br>**In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),**<br>**3 or fewer may have:** |
|---|
| • **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy**<br>• **Swelling of the brain which may cause dizziness and confusion**<br>• **Scarring of the lungs**<br>• **Infection, especially when white blood cell count is low**<br>• **Bruising, bleeding**<br>• **Severe blood infection**<br>• **Seizure**<br>• **Bleeding from sores in the stomach**<br>• **Broken bones** |

**In addition to side effects outlined for obinutuzumab, patients who are in Group 3 and who received CHOP prior to the study may also experience the possible side effects of bendamustine listed below. Some of these side effects may be more common or worse because of the drug combination.**

**Possible Side Effects of Bendamustine**

| **COMMON, SOME MAY BE SERIOUS**<br>**In 100 people receiving Bendamustine, more than 20 and up to 100 may have:** |
|---|
| • **Anemia which may cause tiredness, or may require blood transfusions**<br>• **Constipation, diarrhea, nausea, vomiting**<br>• **Fever, tiredness**<br>• **Bruising, bleeding**<br>• **Infection, especially when white blood cell count is low**<br>• **Loss of appetite**<br>• **Headache**<br>• **Cough** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>**In 100 people receiving Bendamustine, from 4 to 20 may have:** |
|---|
| • **Sores in mouth which may cause difficulty swallowing**<br>• **Pain at the site of injection**<br>• **Swelling and redness at the site of the medication injection**<br>• **Weight loss**<br>• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**<br>• **Severe blood infection**<br>• **Dehydration**<br>• **A new cancer resulting from treatment of a prior cancer**<br>• **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions**<br>• **Kidney damage which may cause swelling, may require dialysis**<br>• **Blisters on the skin**<br>• **Itching, rash**<br>• **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**<br>• **High blood pressure which may cause dizziness, blurred vision**<br>• **Shortness of breath** |

| **RARE, AND SERIOUS**<br>**In 100 people receiving Bendamustine, 3 or fewer may have:** |
|---|
| • **None** |

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

**<u>Risks of Developing Second Primary Cancers</u>:**

**Sometimes a second primary cancer arises after patients have undergone cancer therapy, including therapy using chemotherapeutic agents used to treat multiple myeloma. Recently, in clinical trials of patients with newly diagnosed multiple myeloma, a higher number of second cancers has also been reported in patients treated with high doses of chemotherapy (induction therapy) and/or stem cell transplant followed by prolonged (maintenance) lenalidomide therapy compared to those who received induction therapy and/or transplant without maintenance lenalidomide.**

**We do not know at this time whether prolonged lenalidomide therapy in this clinical setting actually increases the risk of second primary cancers. No increase in second primary cancers has been observed in patients receiving lenalidomide therapy who have relapsed multiple myeloma or other types of cancer.**

**We will be carefully monitoring these events (second primary cancers) in on-going studies of lenalidomide therapy and will inform you if there are any changes. We want you to be aware of this possibility and to continue to follow standard medical advice for prevention and early detection of other cancers during and after your treatment.**

**Reproductive risks:**

**You should not get pregnant, breastfeed, or father a baby while in this study. You should also not get pregnant or breastfeed for 18 months following the end of treatment. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. Certain vaccinations may need to be postponed for infants born to mothers who have been exposed to obinutuzumab during pregnancy.**

**Pregnancy information for lenalidomide (Group 2):**

**Note that this information only applies to patients who are randomized to Group 2 to receive lenalidomide.**

**All patients assigned to Group 2 must follow guidelines for prevention of pregnancy. This is because there is a risk of harm to a fetus if pregnancy occurs while taking these agents. These guidelines are outlined below:**

**WOMEN:**

**If you are a woman, you must not be pregnant.**

**You will be considered not of child-bearing potential if you meet the following criteria:**

- **have not achieved menarche**
- **absence of menstrual periods (natural menopause) for the past 24 consecutive months or**
- **have had a hysterectomy (the surgical removal of the uterus) or both ovaries surgically removed**

**If you do not meet these criteria, you will be considered a female of child-bearing potential. If there is ANY chance that you can become pregnant, you must follow the guidelines below.**

**In addition, with your doctor's knowledge and approval, you agree to use TWO reliable forms of birth control or practice complete abstinence from heterosexual intercourse during the following time periods related to this study:**

- **for at least 28 days before starting lenalidomide**
- **while participating in this study**
- **during dose interruptions**
- **and for 18 months after discontinuation from the study**

**You agree to inform the investigator immediately if:**

- **you have any reason to suspect you are pregnant**
- **you find that circumstances have changed and that there is a risk of becoming pregnant**
- **you have stopped using the approved forms of TWO reliable birth control methods.**
- **you must talk to your doctor before changing any birth control methods.**

**The following methods of birth control are considered acceptable birth control methods:**

| Highly Effective Methods | Additional Effective Methods |
|---|---|
| 1) Intrauterine device (IUD)<br>2) Hormonal (birth control pills, injections, implants, levonorgesterol-releasing, intrauterine system (IUS), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel]<br>3) Tubal ligation<br>4) Partner's vasectomy | 1) Latex condom<br>2) Diaphragm<br>3) Cervical Cap |

**You must use at least one highly effective method and one additional effective method of birth control AT THE SAME TIME. However, your doctor may recommend that you use two barrier methods for medical reasons.**

**Special Note: Certain HIV-protease inhibitors, griseofulvin, modafinil, pencillins, rifampin, rifabutin, phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort may reduce the effectiveness of hormonal contraceptives during and up to one month after discontinuation of these concomitant therapies.**
**Therefore, females of childbearing potential requiring treatment with one or more of these drugs must choose ONE non-hormonal method as the highly effective method of birth control (IUD, tubal ligation, partner's vasectomy) along with ONE of the additional effective methods (latex condom, diaphragm, cervical cap) or abstain from heterosexual contact while taking lenalidomide.**

**If you have sex without using TWO reliable methods of birth control, or if for any reason you think you may be pregnant, you must IMMEDIATELY stop taking lenalidomide and tell your doctor.**

**You will have pregnancy tests before and during treatment, even if you agree not to have reproductive heterosexual intercourse. You will have a pregnancy test done by the doctor every week during the first 28 days of this study. You will then have a pregnancy test every 28 days during your participation in this study if your menstrual cycles are regular or every 14 days if your cycles are irregular. You will also have a pregnancy test if you miss**

**your period or have unusual menstrual bleeding. In addition, you will have pregnancy tests when you are discontinued from the study and at day 28 after discontinuation from the study if your menstrual cycles are regular. If your menstrual cycles are irregular, you will have pregnancy tests when you are discontinued from the study and at days 14 and 28 after discontinuation from the study.**

**You must not breastfeed a baby while you are participating in this study and for 18 months after you have been discontinued from the study.**

**You must NEVER share lenalidomide (or other study drugs) with someone else. You must NEVER donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study. You will be counseled at least every 28 days and at discontinuation from the trial about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, and abstaining from blood and donations.**

**If you have any reason to suspect you are pregnant, you must IMMEDIATELY stop taking lenalidomide and tell your doctor. If you have a positive pregnancy test while participating in this study, you must IMMEDIATELY stop taking lenalidomide and tell your study doctor. If you have a positive pregnancy test within 28 days after you have been discontinued from this study, you must IMMEDIATELY tell your doctor.**

**Study subjects who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).**

**<u>MEN</u>:**

**You have been informed about the risk of birth defects and you agree to use a latex condom every time you have sex with a female of childbearing potential while you are participating in this study and for at least 28 days after you have been discontinued from the study, even if you have had a successful vasectomy. You must tell your doctor if you have sex with a female of childbearing potential without using a latex condom or if you think for any reason your partner may be pregnant.**

**You must NEVER share lenalidomide (or other study drugs) with someone else. You must NEVER donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you have been discontinued from the study. You will be counseled at least every 28 days regarding abstaining from donating blood, sperm, or semen; birth control requirements; not sharing lenalidomide (and other study drugs); and the potential risks of fetal exposure.**

**You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (or other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the**

**risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.**

**Genetic Risks**

**Genetic research has the risk of loss of privacy. There is a small risk that if people other than the researchers were given your genetic facts, they could misuse them. If genetic information was given to employers or insurers it could affect your ability to get a job or be insured. Misuse could cause problems for family members. In order to minimize these risks, your genetic information will be kept confidential as noted in this form.**

**Genetic Information Nondiscrimination Act (GINA)**

**A U.S. federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:**

- **Health insurance companies and group health plans may not request your genetic information that we get from this research.**
- **Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.**
- **Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. The GINA protections do not help you if you work for a company with less than 15 employees.**

**Be aware that this U.S. federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. For more information about risks and side effects, ask your study doctor.**

## What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drug(s)/study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

## Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

## What are my rights in this study?

**Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.**

**For questions about your rights while in this study, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.**

## What are the costs of taking part in this study?

The lenalidomide, obinutuzumab, and TGR-1202 will be supplied at no charge while you take part in this study. The cost of getting these drugs ready and giving them to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that any, or all, of these drugs may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

Additionally, the section above titled “What extra tests and procedures will I have if I take part in this study?” discussed requirements for submitting specimens for testing before and during the study, and for having PET/CT before the study.

Specimens: You are required to have tumor tissue, bone marrow, and blood submitted at several time points while you are on this study. These samples are all being taken at the same time as procedures that you will have as standard of care for treating your disease, so the procedures are not paid for by the study. You and/or your health plan/insurance company will still be responsible for the costs of these procedures. The study will pay for the costs of the supplies and

shipment of the specimens, and for the extra tests that will be performed. You and/or your health plan/insurance company will not be charged for these supplies, shipment, or additional tests.

PET/CT scan: You are required to have a PET/CT scan before the study. PET/CT scans are part of the standard of care procedures for diagnosing your disease, so the study will not pay for the PET/CT scan. You and/or your health plan/insurance company will be responsible for the costs of this procedure. However, some patients might need to have the scan repeated if you have not had one recently enough. Some insurance companies will not pay for the second scan. The study does not have funds to pay for the second scan, so you and/or your health plan/insurance company will still be responsible for this cost. If you will need to have the scan repeated before starting the study, you should verify with your health plan/insurance company that this cost will be paid for before having the scan repeated.

You will not be paid for taking part in this study.

## What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

No funds have been set aside to compensate you in the event of injury.

## Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- Montana Cancer Consortium
- The study sponsor and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

## Where can I get more information?

**You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).**

**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.**

## Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact information for your study doctor is listed on the consent cover page.

# ADDITIONAL STUDIES SECTION:

**This section is about optional studies you can choose to take part in**

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say ‘no’ to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of “yes” or “no” for each of the following studies.

**1. Future Contact**

**I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.**

**YES NO**

**2. Optional Sample Collections for Biobanking for Possible Future Studies**

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

As part of the study, you will have blood and tissue taken for genetic studies. It is possible that there will be left over blood and/or tissue after the tests are complete. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

## WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) A sample from the blood and tissue that was collected at the time of your blood draw and biopsy will be sent to the Biobank. The blood and tissue will be used for the tests described above, and the researchers would like to store the leftover blood and tissue for future research. Your samples and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
2) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

## *WHAT ARE THE POSSIBLE RISKS?*

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

## *HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?*

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

## *WHAT ARE THE POSSIBLE BENEFITS?*

You will not benefit from taking part.

Your samples may be helpful to research whether you do or do not have cancer. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

## *ARE THERE ANY COSTS OR PAYMENTS?*

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

*WHAT IF I CHANGE MY MIND?*

If you decide you no longer want your samples to be used, you can call the study doctor, who will let the researchers know. Contact information for your study doctor is listed on the consent cover page. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

*WHAT IF I HAVE MORE QUESTIONS?*

If you have questions about the use of your samples for research, contact the study doctor. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer to show whether or not you would like to take part in each option

**SAMPLES FOR FUTURE RESEARCH STUDIES:**

**My samples and related information may be kept in a Biobank for use in future health research.**

**YES NO**

This is the end of the section about optional studies.

## Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)