Are you participating in any other research studies _____ Yes _____ No

PURPOSE OF RESEARCH

You are invited to participate in a research study of SD-101 (an immuno-stimulatory drug), Ibrutinib (an anti-Lymphoma drug) and radiation therapy to treat your lymphoma.

You were selected as a possible participant in this study because you have been diagnosed with either Follicular Lymphoma, Marginal Zone Lymphoma or Mantle Cell Lymphoma and have either been treated without improvement in your disease *or* your previous treatment worked, but now your Lymphoma is now growing once again.

We hope to learn about the safety and tolerability of different doses of SD-101 when directly injected into your lymphoma when combined with ibrutinib to treat your lymphoma. In addition, this study aims to discover what the outcomes (good or bad) will be in combination with the other treatments mentioned above, (ibrutinib and radiation therapy). SD-101 is a drug currently being studied for the treatment of B-cell lymphomas, and the efficacy of this drug for the treatment of follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma is not yet known. Ibrutinib is a drug which has been approved by the FDA for the treatment of certain subtypes of B-cell lymphoma, including chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinemia. Ibrutinib has not been approved for the treatment of follicular lymphoma.

If you decide to terminate your participation in this study, you should notify **Dr. Ronald Levy** at **(650) 725-6452.**

This research study is looking for a total of up to 30 patients with B cell lymphoma. Up to 15 patients will be enrolled in Phase I of the study; an additional up to 15 patients will be enrolled in Phase II, the expansion of the study. All patients will be enrolled at Stanford University.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 96 weeks with follow up until definite progression of disease or withdrawal by you or at the Protocol Director's discretion.

PROCEDURES

You will be screened at Stanford Cancer Center to see if you are a suitable candidate and meet all research criteria. You will be given this consent to look over and to share with your family and/or health advocates to go over with you. You will be asked if you have any questions regarding the study calendar below and any of the events within that calendar. You are strongly encouraged to take all the time you need to understand all the contents of this consent form. This is a 96-week study which includes injections over a 4 week period in combination with local radiation to a single lymph node region site on days 1 and 2 of the study. In addition, there will be a follow up period every 3-6 months which is standard of care to manage your disease with CTs at intervals per standard practice at Stanford, until disease progression or if you decide to withdraw from the study. This follow up will be ongoing and you will be considered part of this study unless you decide to withdraw or the Principal Investigator, Dr. Ronald Levy, removes you from the study at his discretion.

The experimental part of this study includes the following: monitored maximum tolerated dose of SD-101 in combination with ibrutinib and radiation therapy.
If you withdraw from treatment due to progressive disease, you will be seen within four weeks of the determination of progressive disease for a final visit. If you withdraw due to intolerance of treatment you will be followed weekly until all toxicities have stabilized in the opinion of the Investigator, at which point you will undergo the final visit. If you withdraw for any reason other than progressive disease, you will be seen within 4 weeks of withdrawal for a final visit.
If you choose to participate, Dr. Ronald Levy and his research study staff will follow this schedule of study events.

Pretreatment:

- Complete physical exam including vital signs, weight, and performance status (your ability to perform basic daily activities)
- Collection of medical history
- Monitoring of concomitant medications
- Research blood draw and LDH
- HIV, hepatitis B, and hepatitis C testing
- Urine pregnancy test

- Safety blood labs
- Fine needle aspiration of designated tumor lesion in the treatment site (Lesion A). Fine needle aspiration biopsies of additional lesions may be performed if accessible to needle biopsy
- Meeting with Radiation Oncologist
- Imaging by CT scan or PET/CT scan to assess extent of disease as indicated by study protocol
- A surgical biopsy may be performed, to exclude the possibility of a more aggressive type of lymphoma, if medically necessary. In this case, or potentially in the case that you have lymphoma cells in your blood, we would also collect blood cells by a procedure called apheresis.

Day 1:

- First treatment of radiotherapy (2 Gy) to the designated tumor lesion (lesion A)

Day 2:

- Obtain vital signs
- Assessment of adverse events
- Monitoring of concomitant medications (medications currently being taken)
- Second treatment of radiotherapy (2 Gy)
- Intratumoral injection of SD-101 to lesion A (within 12 hours of radiotherapy)

Day 4 (+/- 1 day)

- Fine needle aspiration of accessible tumor may be performed (optional)

Day 9 (+/- 2 days)

- Obtain vital signs
- Assessment of adverse events and toxicity
- Monitoring of concomitant medications (medications currently being taken)
- Routine safety labs
- Fine needle aspiration of accessible tumor for research studies. If additional (untreated) sites of disease are safely accessible by fine needle aspiration, an untreated tumor lesion may be biopsied also (optional). To be performed prior to intratumoral injection #2
- Intratumoral injection of SD101 to lesion A
- Collection of 8 research blood draw tubes
- Distribution of first month supply of ibrutinib

Day 16 (+/- 2 days)

- Obtain vital signs
- Assessment of adverse events and toxicity
- Monitoring of concomitant medications (medications currently being taken)
- Collection of 7 research blood draw tubes
- Intratumoral injection of SD101 to lesion A

Day 23 (+/- 2 days), Day 30 (+/- 2 days)

- Obtain vital signs
- Assessment of adverse events and toxicity
- Monitoring of concomitant medications (medications currently being taken)
- Intratumoral injection of SD101 to lesion A (both week 4 and 5)
- Routine safety labs (week 4 only)
- Collection of 1 research blood draw tube (week 4 only)

Day 37 (+/- 7 days)

- Obtain vital signs
- Assessment of adverse events and toxicity
- Monitoring of concomitant medications (medications currently being taken)
- Routine safety labs
- Fine needle aspiration of the treated site (lesion A) for research studies, if lesion A remains after treatment. In addition, if other untreated sites of disease are safely accessible via fine needle aspiration, these may be biopsied.
- Collect of 8 research blood draw tubes
- Distribution of six week supply of ibrutinib
- *If* a surgical biopsy was performed before treatment, apheresis will be repeated

Week 12 and every 12 weeks thereafter until week 96 (+/- 10 days for each timepoint):

- Physical exam to assess clinical response to treatment
- Obtain vital signs
- Assessment of adverse events and toxicity
- Monitoring of concomitant medications (medications currently being taken)
- Routine safety labs and LDH
- Collect of 1 or 8 research blood draw tubes

- Determination of response to treatment with CT scans of the chest/ abdomen/ pelvis (and neck, if needed); CT scans will be performed weeks 12, 24, 48, 72.
- Distribution of ibrutinib supply
- *If* there is no evidence of disease on the CT scan, a bone marrow biopsy will be obtained to document whether a complete response is achieved.
- If participant has progressive disease, FNA of accessible tumor may be performed (optional).

Final study visit:

- Physical exam to assess clinical response to treatment
- Obtain vital signs
- Assessment of adverse events and toxicity
- Monitoring of concomitant medications (medications currently being taken)
- Routine safety labs and LDH
- Collect of 8 research blood draw tubes
- *If* there has not been a recent CT scan, then response to treatment will be assessed with CT scans of the chest/ abdomen/ pelvis (and neck if needed)
- If progressive disease, FNA will be performed on an accessible tumor site for research studies – (optional).
- *If* there is no evidence of disease on the CT scan, a bone marrow biopsy will be obtained to document whether a complete response is achieved.

Dosing of Ibrutinib:
All participants will take 560mgs of ibrutinib daily, in the form of during the ibrutinib treatment period, which starts at day 10 and ends at week 96 or until progression or treatment is ended for other reasons before week 96.

Dosing of SD101:
Phase I participants: The first 6 participants will receive 3mgs of SD-101. If a less than a third of these first 6 participants experience a serious side effect, then no additional participants will be enrolled in Phase I, and Phase II participants will receive 3mgs of SD 101.

Phase II participants: The dose of this group of 15 participants will receive 3mgs or 1 mg of SD101, based on the best dosage determined from Phase I.

Other procedures:
CT (computerized tomography) scans: create pictures of the inside of your body. CT scans use an x-ray machine together with a special dye injected into a vein in your arm before the scan. CT scans will occur at the Screening visit, and

approximately every 3-6 months after your first study treatment, for the rest of the study or at time if your doctor suspects your Lymphoma is getting worse. CT scans are standard of care for lymphoma.

Bone marrow aspiration and biopsy: First, an area of the hip is numbed, then a needle is inserted into the hip bone to collect the sample. This procedure is done to determine if your lymphoma has spread to the bone marrow. This may be required if your CT scan shows no evidence of residual lymphoma to determine whether there is still lymphoma within the bone marrow.

Localized Low-dose Radiation Therapy: is a procedure that uses high energy radiation like x-rays to kill cancer cells. Low dose radiation (locally to the area of one site of one lesion; 2 Gy** x 2) is being given to help SD-101 to increase your immune system to fight your lymphoma. You will receive 2 treatments of low dose radiation at Day 1 and Day 2. In addition, the injection of SD-101 will be given on Day 2 within 12 hours of radiotherapy. As this injection will be in a different location in the Cancer Center from where you receive your radiotherapy at Stanford, we hope at best to have your wait be less than 2 hours.

**2 Gray (Gy) has the equivalent radiation dose of approximately 10000 x-rays. This radiation is localized only to the treatment area.

Apheresis (only for patients with pre-treatment biopsy): This procedure is similar to donating blood but allows certain parts of your blood to be collected while the red blood cells are returned to you. A needle is placed in each arm and you will spend 3-5 hours resting in a chair while the blood is collected from one arm and returned to the other arm. (Patients usually watch a movie or two during the procedure).

Specimens Collection: Blood and Tissue (Lymph Node samples)

- Blood samples (up to 6 tablespoons) will be taken from a vein in your arm at each study visit.
- Fine needle aspirates (FNA) involves the insertion of a needle into the tumor to collect a sample. We will do this from the tumor that we treat and, if possible from a tumor that we do not treat at screening and weeks 2, 8 and at the end of the study if there is residual tumor.
- If you are able to become pregnant, you will be asked to have a pregnancy test done before beginning this research study.

HIV/Hepatitis/HCV You will have a blood tests for HIV, Hepatitis B and Hepatitis C during screening. Positive results will be reported to the local health agency. If you test positive for HIV, counseling will be provided.

Tissue Sampling for Research: The investigators would like to include your tissues in research on lymphoma and they want to save the samples for future research. There are several things you should know before allowing your tissues to be studied.

You have the right to refuse to allow your tissues to be studied now or saved for future study. If you withdraw your permission, the investigators might retain the samples as part of your routine clinical care, but not for additional research.
In order to protect your identity, your study doctor will assign you a unique code, such as a series of numbers and/or letters. Your tissue will be stored under this code. Your study doctor will keep a confidential list linking your name or medical record number to your code number and only authorized persons will have access to this list.

You will be told the results of tests that are part of your clinical care, but you will not be told the results of the research tests, including any future research tests. Any of your samples which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University, Dynavax Technologies Corporation, Janssen Scientific Affairs, LLC and/or others. Donors of samples do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries. Please mark one of the following statements with your initial.

_____ I consent to my samples being saved for future research
Initial

_____ I do not consent to my samples being saved for future research
Initial

Women of Childbearing Potential *(see risks below)*
If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a urine pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite

the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

If you are a man participating in this study and your partner is able to become pregnant, you and your partner must use adequate contraception while you are participating in the study. Your doctor will discuss with you what methods of birth control are considered adequate. You should inform your study doctor if your partner becomes pregnant. Men must agree to not donate sperm during and after the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Ask questions at your visits and/or by contacting the study staff/research coordinator
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Take the study drug as instructed.
- Keep the study drug in a safe place, away from children and for your use only.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

Participation in the study is entirely your choice. If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw from this study, you should notify the study staff at (650) 725-8589. You may also want to speak directly with the **Dr. Ronald Levy at 650-725-6452.**

If you choose to withdraw, or are withdrawn from the study, you will be asked to return to the study clinic for at least one final visit assessment as part of the study's ongoing safety evaluations. All study-related supplies, including unused study drug, must be returned to the study personnel.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director, **Dr. Ronald Levy** if you have any questions.

Drugs may have side effects. The drug used in this study may cause some or all of the side effects listed below. There may also be side effects that we cannot predict at this time.

SD-101

As of July 12th, 2019, SD-101 has been tested in 358 subjects, including healthy volunteers, patients with chronic hepatitis C, and patients with cancer. In most of these patients, the SD-101 was given with other experimental or approved therapies. In all these studies, the SD-101 was injected either under the skin or into a tumor (intratumoral).

Side effects that have been reported in people who have received SD-101 injections include the following:

- Fatigue
- Fever, Chills

- Malaise
- Headache
- Redness, pain, itching or swelling at injection site
- Nausea and/or vomiting
- Diarrhea or constipation
- Muscle aches
- Joint pains, neck pain, back pain
- Rash, itching
- Other flu-like symptoms
- Anemia, low neutrophils, low platelets
- Decreased appetite, dehydration
- Abdominal discomfort
- Cough, nasal congestion
- Mouth pain, throat pain
- Night sweats
- Bruising
- Dizziness
- Shortness of breath
- Ankle/leg swelling
- Infections
- Changes in laboratory values without clinical signs or symptoms

Other side effects, which were uncommon (occurred in one patient each), included hyperthyroidism (overactive thyroid gland), pneumonitis (lung inflammation), pituitary dysfunction, atrial fibrillation (abnormal heart rhythm), septic shock and hypothyroidism (low thyroid function). These all occurred in patients also receiving another treatment at the same time.

There also may be changes in other blood characteristics and components. You will be monitored for any of these changes.

Ibrutinib

The side effects listed below have been reported by patients who have received ibrutinib in clinical trials:

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

Occurrence or increase in frequency of loose or watery stools (Diarrhea)
Muscle and bone pain (Musculoskeletal pain)
Nausea
Low white blood cell count (cells that help fight infection) (Neutropenia)
Bleeding (Haemorrhage)
Rash

Fever (Pyrexia)
Low platelet count (cells that help blood to clot) (Thrombocytopenia)
Common cold (Upper Respiratory Tract Infection)

Side effects that have been seen in at least 1 of every 10 (≥ 10%) patients include:
Pneumonia
Constipation
Swelling of the hands or feet (Oedema peripheral)
Muscle spasms
Vomiting
Joint aches (Arthralgia)
Sores in mouth (Stomatitis)
Headache
High Blood pressure (Hypertension)
Skin infection
Weakness, tingling, numbness, and pain from nerve damage, usually in the hands and feet (Peripheral neuropathy)
Urinary tract infection
Dizziness

Side effects that have been seen in at least 1 of every 100 (≥ 1%) patients include:
Sinus infection (Sinusitis)
Increased level of uric acid in the blood (Hyperuricemia)
Abnormal heart rhythm (Atrial fibrillation)
Non-melanoma skin cancer
Blurry vision (Vision blurred)
Low white blood cell counts with fever (Febrile neutropenia)
Severe infection throughout the body (Sepsis)
Redness of the skin (Erythema)
Increase in specific white blood cell counts (Leukocytosis, Lymphcytosis)
Breaking of the nails (Onychoclasis)
Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
Increased level of "creatinine" in the blood (blood creatinine increased)

Side effects that have been seen in less than 1 of every 100 (<1%) patients include:
Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures. (Tumor lysis syndrome)
Itchy rash (Urticaria)

Inflammation of the fatty tissue underneath the skin (Panniculitis)
Swollen face, lip, mouth, tongue, or throat (Angioedema)
High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome)
Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes, and genitals (Stevens-Johnson syndrome)
Liver failure (Hepatic failure)
Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachyarrhythmias).
Temporary or permanent decrease of brain or nerve function due to reduced blood flow to the brain (mini-stroke or stroke)

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

You should tell your study doctor or medical team about any side effects you are having. Your study doctor may be able to give you medications to help treat the side effects and prevent them from becoming worse. Your study doctor may also choose to stop ibrutinib for a short time or reduce its dose to allow you to recover from any side effects.

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

Effects on the heart
Abnormal heartbeats (atrial fibrillation and/or atrial flutter with some fatal events) have been reported in patients treated with ibrutinib, especially when they also have heart conditions, increased blood pressure, acute infections, or had abnormal heartbeat in the past. Atrial fibrillation/flutter is a common type of abnormal heartbeat. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of

breath. You should tell your study doctor immediately if you develop any of these symptoms while on the study drug.

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

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

Lymphocytosis and leukostasis
You may experience an increase in the number of lymphocytes, which is a specific type of white blood cell, in your blood (lymphocytosis). This may occur in the first few weeks of treatment and you should not assume that this increase in white blood cells means that your disease is worsening. This increase may last for several weeks to months. In rare cases, increased number of white blood cells in your bloodstream may alter blood flow resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in patients treated with ibrutinib. Your study doctor will monitor your blood counts and may administer additional therapy as needed. Talk to your study doctor about what your test results mean.

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

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

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

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

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

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

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

Hypertension
Hypertension is also called high blood pressure, and has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your study doctor know if you have any of the symptoms of high blood pressure which may mean that you have developed hypertension or that your hypertension is getting worse. Your study doctor may

adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

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

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

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

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

Drug interruption for any surgical procedures

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

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

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

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

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

<u>Reproductive effects</u>
The effects of ibrutinib on a developing baby are unknown; therefore women who are pregnant or nursing are not allowed to be in this study. Nobody knows what these risks are right now. Some drugs cause women to have their babies prematurely (early) or to have babies with birth defects.

Women: If you are able to have children, you must use a highly effective method of birth control and a barrier method while taking study treatment, as well as for 1 month after you stop taking study treatment, to prevent pregnancy in either you or your partner. A "highly effective method of birth control" is defined as a method that has a low failure rate (ie, less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with 2 hormones, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner. If you are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used.

Men: You must use a barrier method while on treatment with ibrutinib and for 3 months after the last dose of treatment to prevent pregnancy of your partner.

Note: Some birth control pills may not work when you are taking certain drugs. If you have any questions about this, please discuss this with the study doctor.

Be aware that you can still become pregnant even if you use a highly effective method of birth control.

Men: If your partner becomes pregnant while you are on study treatment, or within 3 months of your last dose of ibrutinib, you must notify the study staff. The study staff will discuss this with you further. You should not donate sperm while you are taking the study drug and for 3 months after you stop taking the study drug.

Women: If you become pregnant while you are on study treatment or within 1 month of your last dose of ibrutinib you must notify the study staff. If you become pregnant on the study, you must immediately stop taking the study treatment. The protocol director will continue to collect information about your pregnancy and the birth of your baby even after study treatment is stopped.

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

As with any drug, you may experience an allergic reaction or may have other reactions that are not expected or have not been seen before. Symptoms of an allergic reaction include a rash, hives, itching, and/or difficulty breathing, closing of the throat, swelling of the lips, tongue or face, and rarely, death. You will be monitored carefully at the study site for signs of an allergic reaction after all study injections. Trained medical personnel and emergency equipment are available at the study site to treat you in the event of an allergic reaction. If you have a significant allergic to the drug, the drug may be discontinued permanently for your safety. If the doctors feel the reaction was not significant enough to require discontinuation, they will discuss this with you and obtain your explicit consent again prior to re-starting treatment. **If you think you are having a severe allergic reaction after you leave the study center, call 9-1-1 and seek medical attention immediately.**

Blood Sample Collection

We will collect up to 6 tablespoons of blood for testing at each study visit over the course of the trial. Blood collection may cause pain and bruising at the site of vein puncture, inflammation of the vein, and infection; care will be taken to avoid these complications. Collection can also cause redness, temporary pain and sometimes bruising. Fainting or infection may also occur, however these side effects from blood collections are rare.

Fine Needle Aspirate (FNA) Lymph node aspirate may cause pain, bruising and/or bleeding at site of biopsy, infection, inflammation and swelling; care will be taken to avoid these complications.

Standard radiological test (CT)

For a CT scan, a dye is injected into your vein before the scan. Most patients feel a sensation of warmth, a funny metallic taste in their throat, nausea and a feeling of warmth. Some patients develop hives and itching, but this rarely needs to be treated with antihistamines. 1 in 500 patients may develop a severe reaction which may have to be treated with medications. These reactions may involve tightness in the throat, facial swelling, difficulty breathing, drop in blood pressure, or even a seizure. Medical personnel who perform the scans are trained to treat you if any bad reaction occurs.

Localized radiation therapy (RT): Radiation therapy is painless. Side effects from radiation are usually limited to the area of the patient's body that is under treatment. The main side effects are fatigue and skin irritation, like a mild to moderate sun burn. The fatigue can last for weeks after treatment ends. The irritated skin will heal, but may not be as elastic as it was before. With the low dose of radiation used in this study we do not expect any of these side effects.

Bone marrow aspiration and biopsy: This biopsy may cause pain and bruising at the site of puncture, inflammation, pain, and infection; care will be taken to avoid these complications. Other side effects may include bleeding at the biopsy site. If you have bleeding problems, pressure will be put on the biopsy site to stop the bleeding.

Pregnancy Risks: There is no information about the risks of SD-101 on pregnancy or to the developing baby; therefore it is important that during the study, you do not get pregnant. If you are pregnant or currently breast-feeding, you may not participate in this study. In addition to pregnancy tests you will be asked to take before beginning the study and during the study, you must agree to avoid sexual intercourse or use birth control methods judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth

control. You agree to notify the investigator as soon as possible if you do not use your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study. By agreeing to participate in this study, you are also allowing the study staff to ask follow-up questions and request medical records about your pregnancy and its outcome (for example, type of birth, number of babies and health of baby[ies])

POTENTIAL BENEFITS

This research study is being conducted to understand the safety, and potential good effect of SD-101 in combination with Ibrutinib and Radiation therapy for low-grade B-cell lymphoma. Knowledge gained from this study may also help to develop this therapy for other people with Lymphoma.

The investigational drug SD-101 in combination with Ibrutinib may stimulate your immune system to fight your lymphoma. However, there is no assurance that this will happen. There is a chance that your health could get worse or stay the same while you are participating in the study.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You do not have to participate in this study to receive treatment for your lymphoma. If you choose not to participate in this study, there may be other treatments available to you. You may discuss alternative treatments and their risks and benefits with your study doctor.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

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.

CONFIDENTIALITY

The purpose of this research study is to obtain data or information on the safety and effectiveness of CpG SD-101 in combination with ibrutinib and local radiation therapy; the results will be provided to the trial supporters Janssen Scientific Affairs, LLC, Dynavax Technologies Corporation, the NIH, the Food and Drug Administration and other federal and regulatory agencies as required.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to the trial supporters, Dynavax Technologies Corporation and Janssen Scientific Affairs, LLC, Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

We hope to learn about the safety and tolerability of dose levels of intratumoral injections (into your tumor site) of SD-101 in combination with Ibrutinib and local radiation to treat your low-grade, B-cell lymphoma. In addition, this study has been designed to discover what the outcomes (good or bad) will be in combination with the other treatments mentioned above, (ibrutinib and radiation therapy). Your information will be kept in a secure location at Stanford University Medical Center, accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study patients will be assigned an ID code that will consist of a three digit number. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. Your personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including

receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:
Dr. Ronald Levy at 269 Campus Drive, CCSR 1105, Stanford, CA 94305

What Personal Information Will Be Obtained, Used or Disclosed?
PHI that may be used and disclosed in connection with this research study will include but not be limited to, information on the past treatment of your disease and any future, tests, examinations, and treatment that you receive as part of this study. This may include blood and urine tests, physical examinations, measurements of your tumor, results of analysis of your tumor samples, study drugs that are administered and side effects. This health information may include identifiers such as name, date of birth, geographical location, medical record number, and participant number.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director **Ronald Levy, MD**
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary

- Research Staff which may include lab staff, study coordinators, research nurses, data mangers, pharmacists, and the radiology department.

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institutes of Health (NIH)
- The U.S. Food and Drug Administration (FDA)
- Dynavax Technologies Corporation
- Janssen Scientific Affairs, LLC

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on December 31, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____

Printed Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment
You can receive partial or full reimbursement for your time and expenses (car travel and hotel stays only) as a result of taking part in this study. Receipts for your hotel stay must be provided to the Study Coordinator to receive this reimbursement at each visit.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.

Supporters
Dynavax Technologies Corporation and Janssen Scientific Affairs, LLC are providing the 2 drugs for this study. Dynavax Technologies Corporation will be providing the **SD-101** and Janssen Scientific Affairs LLC will provide the **Ibrutinib** and funding.

The **National Institutes of Health** is providing financial support and material for this study and some financial support for the facility and staff where part or all of the study is taking place.

Leukemia & Lymphoma Foundation and **Rising Tide Foundation For Clinical Cancer Research** also provide funding for the study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in

obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director**, Dr. Ronald Levy.** You may contact him now or later at **650-725-6452**

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, **Dr. Ronald Levy** at **650-725-6452.**

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at **650-723-5244** or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact **the research coordinator at 650-498-6000**

Alternate Contact: If you cannot reach the Protocol Director, please contact **the research coordinator at 650-498-6000**

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ☐ Yes ☐ No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Printed name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of witness Date

_____
Printed name of witness

(e.g., staff, translator/interpreter, family member)

- Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.
- The English consent form (referred to as the "Summary Form" in the regulations):
  - Must be signed by the witness AND the Person Obtaining Consent (POC).
  - The non-English speaking participant/LAR does not sign the English consent.
  - The non-English speaking participant/LAR should not sign the HIPAA participant line
  - If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.