Intratumoral Injection of SD-101, an Immunostimulatory CpG, in combination with Ibrutinib and Local Radiation in Relapsed or Refractory Low-Grade Follicular Lymphoma

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Date: ? 24 January 2020

Document History	Notes
27 April 2016	Initial Approval
25 July 2016	Revision 1, change statistician
4 October 2016	Harmonize versioning and version date Add IRB-number and IND number Re-format title page Duplicate figure deleted
9 January 2017	Language supplied in memo from manufacturer was used to modify drug dilution instructions to align with current available drug formulation from manufacturer. Other corrections and administrative changes: Corrects schedule of events table (adds missing “x”s) Harmonization of fonts and spacing within document Correct misplaced phrase in Synopsis / Sample Size
15 March 2017	Addition of measurement of tumor-specific immune responses as an additional secondary endpoint Multiple revisions of the exclusion criteria Adjustment of the research samples collected: Number of sample tubes adjusted Timepoints of sample collection adjusted Addition of an optional FNA procedure on day 4 Corrects timing of post-treatment FNA to week 6 from week 8 Addition of defined acceptable visit windows for all visits
17 October 2017	Expanded inclusion criteria to include mantle cell lymphoma and marginal zone lymphoma in addition to previous population of low-grade follicular lymphoma Added language supporting efficacy of ibrutinib in mantle cell lymphoma and marginal zone lymphoma Decreased period of monitoring after SD-101 injection from 60 minutes to 30 minutes
24 October 2017	IND version of 17 October 2017 changes

Document History	Notes
7 November 2017	Removed requirement for prior biopsy from inclusion criteria Clarified that SAEs will be tracked until 30 days after last dose of study treatment Consolidated Week 6 and 8 procedures into single Week 6 visit Adjusts distribution of ibrutinib to delete distribution event at Week 4 Study coordinator updated
17 November 2017	IND version of 7 November 2017 changes (version reconciliation)
21 February 2018	Removed Tempus tube blood draw from all visits and deleted visits where that was the only event Distribution of Ibrutinib on Week 2 Day 10 was moved to Week 2 Day 9
18 April 2018	Made explicit that in the case of suspected pseudoprogression, patients may continue on trial until the next response assessment
7 December 2018	Updated study personnel Removed eligibility criteria regarding history of fever Changed phase 2 dose from maximum tolerated dose to recommended phase 2 dose Added that vital signs should be checked 30 minutes after each injection Removed all non-treatment events from Treatment Day 1
24 January 2019	Updated study personnel Updated Treatment “Weeks” to “Days Clarified dose and schedule modifications with SD-101 Clarified re-treatment after hypersensitivity reaction with SD-101 Added APPENDIX E: Contraception Guidelines

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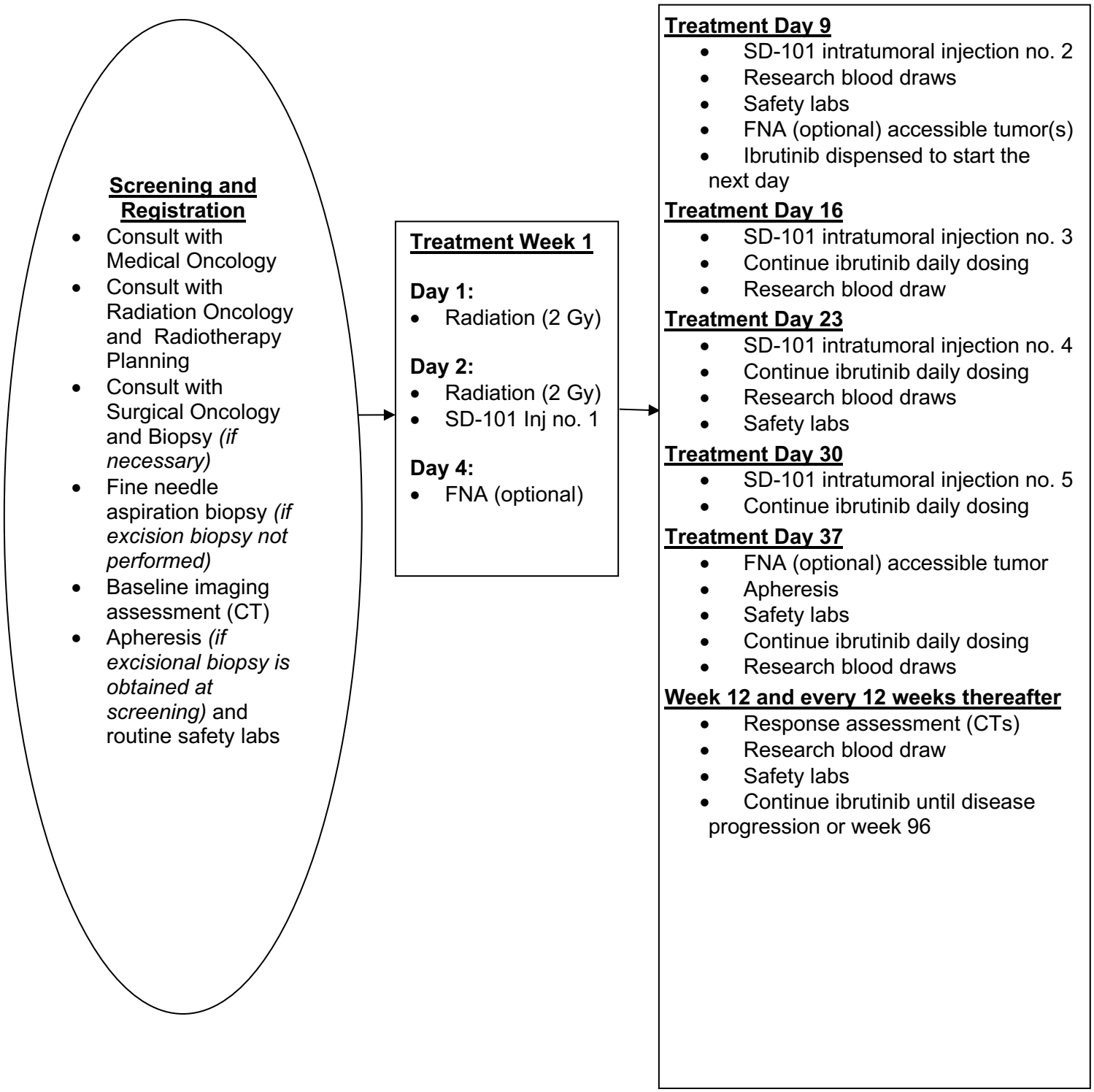
PROTOCOL SYNOPSIS

TITLE	Intratumoral Injection of SD-101, an Immunostimulatory CpG, in combination with Ibrutinib and Local Radiation in Relapsed or Refractory Low-Grade Follicular Lymphoma
STUDY PHASE	Phase 1b/2
INDICATION	Relapsed/Refractory Low grade Follicular Lymphoma, Mantle cell Lymphoma, Marginal Zone Lymphoma
INVESTIGATIONAL PRODUCT OR PROCEDURE	Intratumoral SD-101 plus low-dose local radiotherapy plus oral ibrutinib
PRIMARY OBJECTIVE(S)	**Phase 1b:** 1) To determine the recommended phase 2 dose (RP2D) of intratumoral SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B-cell lymphoma 2) To determine the safety and tolerability of SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B-cell lymphoma **Phase 2:** 1) To evaluate the efficacy of intratumoral SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B-cell lymphoma by assessing overall response rate
SECONDARY OBJECTIVE(S)	**Phase 2:** 1) To evaluate progression-free survival after treatment with intratumoral SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B-cell lymphoma 2) To evaluate the induction of tumor-specific immune responses by treatment with intratumoral SD-101 in combination with ibrutinib and radiation in patients with relapsed or refractory B-cell lymphoma

TREATMENT SUMMARY	Local low-dose radiation therapy to a single site of disease combined with intratumoral injections to the same single site. SD-101 (CpG) – Intratumoral injection on Day 2, then once every week x 4 successive weeks for a total of 5 injections at a dose of 3 mg per dose in cohort 1 or 1 mg per dose in cohort -1. Ibrutinib orally at a dose of 560 mg daily starting on Day 10 until progression of disease or for 96 weeks, whichever comes first. In the safety portion of the study, a starting dose of 3 mg SD-101 and 560 mg ibrutinib will be studied and will follow a 6+3 dose de-escalation design. In the first cohort of 6 subjects, if ≤ 1 subjects experiences a DLT, then that dose level will be chosen as the recommended phase 2 dose. If 2 subjects experience a DLT, then an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6 to 9 subjects experience a DLT, dose de-escalation will occur with a new cohort of 6 subjects at a dose of 1 mg SD-101 and 560 mg ibrutinib. Based on the data from dose de-escalation cohorts, a dose of SD-101 will be chosen and an additional cohort of 15 subjects will be treated at that dose in order to assess the clinical response rate. Immune monitoring and follow-up will occur over the following 24 weeks. Subjects without PD will be followed for immune and clinical response every 12 weeks until Week 96 or progression, whichever comes first.
SAMPLE SIZE	This research study is looking for a total of up to 30 subjects with low-grade follicular lymphoma, marginal zone lymphoma, or mantle cell lymphoma. All subjects will be enrolled at Stanford University. A total of 6 to 15 subjects will be enrolled in the phase 1B 6 x 3 dose de-escalation portion. An additional 15 subjects will be enrolled in the expanded phase 2 cohort. If ≤ 1 of 6 subjects experience a DLT at a dose of intratumoral SD-101 of 3 mg, we will proceed to the expansion phase. If 2 of 6 subjects experience a DLT at 3 mg, then an additional 3 subjects will be enrolled in the same dosing cohort. If ≥ 3 of 6 to 9 subjects

	experience a DLT, then a dose de-escalation cohort -1 of 6 subjects will be opened.
STATISTICAL CONSIDERATIONS	The sample size of 15 subjects in the expanded phase 2 cohort (with resulting total number of 21 to 24 subjects at the RP2D in the combined 1b/2 phases) allows estimation of the response rate +/- 0.21 with 90% confidence. The chance of obtaining three or fewer responses out of 15 is only 2.1% if the true response rate is 49%, with 49% ORR being a historical benchmark for response rate in this population.

SCHEMA


Screening and Registration
Consult with Medical Oncology
Consult with Radiation Oncology and Radiotherapy Planning
Consult with Surgical Oncology and Biopsy (if necessary)
Fine needle aspiration biopsy (if excision biopsy not performed)
Baseline imaging assessment (CT)
Apheresis (if excisional biopsy is obtained at screening) and routine safety labs
Treatment Week 1
Day 1:
Radiation (2 Gy)
Day 2:
Radiation (2 Gy)
SD-101 Inj no. 1
Day 4:
FNA (optional)
Treatment Day 9
SD-101 intratumoral injection no. 2
Research blood draws
Safety labs
FNA (optional) accessible tumor(s)
Ibrutinib dispensed to start the next day
Treatment Day 16
SD-101 intratumoral injection no. 3
Continue ibrutinib daily dosing
Research blood draw
Treatment Day 23
SD-101 intratumoral injection no. 4
Continue ibrutinib daily dosing
Research blood draws
Safety labs
Treatment Day 30
SD-101 intratumoral injection no. 5
Continue ibrutinib daily dosing
Treatment Day 37
FNA (optional) accessible tumor
Apheresis
Safety labs
Continue ibrutinib daily dosing
Research blood draws
Week 12 and every 12 weeks thereafter
Response assessment (CTs)
Research blood draw
Safety labs
Continue ibrutinib until disease progression or week 96

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BID	Twice daily
CBC	Complete blood count
CNS	Central nervous system
CpG	Cytosine-phosphate-Guanine
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertension
IRB	Institutional Review Board
ISS	Immunostimulatory sequence
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MTD	Maximum Tolerated Dose
ODN	Oligonucleotide
OS	Overall survival
PBL	Peripheral blood leukocytes
PLT	Platelet
PD	Progressive disease
PFS	Progression free survival
PQC	Product Quality Complaint
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase 2 dose
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SD-101	Immunostimulant CpG injection (Dynavax)
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objectives

Phase 1b:

1) To determine the recommended phase 2 dose (RP2D) of intratumoral SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B cell lymphoma
2) To determine the safety and tolerability of SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B cell lymphoma

Phase 2:

1) To evaluate the efficacy of intratumoral SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B-cell lymphoma by assessing overall response rate

1.2. Secondary Objectives

Phase 2:

1) To evaluate progression-free survival after treatment with intratumoral SD-101 in combination with ibrutinib and radiation in subjects with relapsed or refractory B-cell lymphoma
2) To evaluate the induction of tumor-specific immune responses by treatment with intratumoral SD-101 in combination with ibrutinib and radiation in patients with relapsed or refractory B-cell lymphoma

2. BACKGROUND

2.1 Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is a group of histologically and biologically distinct lymphoid malignancies. 80 to 90% of NHLs are B-cell lymphomas, and the great majority of the rest are T-cell lymphomas. It is estimated that there will be 71,850 cases of NHL diagnosed in the US in 2015, representing 4% of all cancers diagnosed in the United States.(*1*) An estimated 19,790 deaths will result from NHL in 2015. Reporting from the US Surveillance, Epidemiology, and End Results (SEER) program indicates that the incidence of NHL has increased substantially in recent years, from 10.2 per 100,000 in 1973 to 18.5 in 1990, an increase of 81% overall and about 3.6% per year. The rapid increase in NHL incidence in the 1970s and 1980s has been surpassed only by the increases in lung cancer in women and malignant melanomas in both sexes.(*2*)

Non-Hodgkin's lymphomas encompass many histological types. The Revised European-American Classification of Lymphoid Neoplasms (REAL) developed in 1994 is the currently accepted classification. This was further refined by the World Health Organization (WHO) classification of hematologic malignancies in 1997. Based on this classification, NHLs are grouped into indolent (low-grade), aggressive and highly aggressive lymphomas based on the clinical behavior of each entity. Low-grade lymphomas (indolent lymphomas) can be further subdivided into B-cell and T-cell types. The low-grade B-cell lymphomas include follicular

lymphoma (FL), B-chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma and marginal zone lymphoma (MZL). Mantle cell lymphoma (MCL) is an intermediate grade lymphoma. The T-cell group includes T-CLL and mycosis fungoides.

Follicular lymphoma is the most common type of low-grade B-cell lymphoma, and represents 20% of all non-Hodgkin's lymphomas. It is characterized by an indolent clinical course, but with a potential to transform to a more aggressive form of lymphoma. Follicular lymphoma is most often disseminated at diagnosis, and is rarely cured. Although the disease is sensitive to chemotherapy, radiotherapy and immunotherapy, subjects eventually exhaust all options and succumb to progression of disease. The median survival of all subjects with follicular lymphoma is approximately 10 years. The prognosis of follicular lymphoma subjects can be estimated by a constellation of clinical parameters, described as FLIPI (follicular lymphoma international prognostic index), determined at disease presentation. FLIPI includes one "point" for each of: stage III/IV disease; number of nodal sites involved ≥ 5; LDH > normal; age ≥ 60; and Hb < 12. Subjects with 0 to 1; 2; or ≥ 3 risk factors belong to good, intermediate and poor-risk groups. The 10-year overall survival is 70%, 51% and 36% for the good, intermediate and poor risk groups, respectively (*3*).

Because FL, MZL, and MCL are generally incurable, the principal of treatment is palliation. In advanced-stage low-grade lymphoma subjects, the Stanford group showed no advantage in survival between watchful waiting and early intervention.(*4*) Thus, therapy is instituted only when subjects develop symptoms from their lymphoma. Follicular lymphoma, marginal zone lymphoma and mantle cell lymphoma are sensitive to many treatment modalities, including chemotherapy, radiotherapy and immunotherapy. However, the response is generally not durable and subjects eventually succumb to the disease. Therefore, novel therapies are needed to improve the outcome of subjects with FL, MZL, and MCL.

2.2 Investigational Agents

2.2.1 SD-101

SD-101 is an investigational agent which requires an Investigational New Drug application (IND).

Toll-like receptor 9 (TLR9) ligands have multiple mechanisms of action that modulate the immune system including both direct and indirect anti-tumor effects. The natural ligands for TLR9 are unmethylated CpG oligonucleotide sequences that are rare in vertebrate genomes but prevalent in pathogen genomes including bacteria and viruses. A synthetic CpG product SD-101 is available to us for clinical use from DynaVax Technologies. DynaVax is supplied as a GMP material. SD-101, a Class C CpG, induces an IFN-α signature in both human PBMCs in vitro and non-human primates in vivo. There is considerable experience with SD-101 in normal subjects and in subjects with lymphoma. Based on single-agent studies in healthy volunteers and an ongoing trial of previously untreated low-grade lymphoma subjects, it is safe and well tolerated up to a dose of 5 mg per injection. IND 111985 is held by Stanford Investigator, Robert Lowsky, MD (listed on the title page of this protocol) and will be cross-referenced and used in this study.

Mechanism of Action

CpG-ODN, such as SD-101, are optimized for immune stimulation by substituting sulfur for phosphorus between nucleotide subunits to provide increased resistance to nuclease-mediated degradation. The nucleotide sequences are recognized by TLR-9, a receptor for innate immune recognition of microbial and viral DNA (*5*). Two principal types of human PBMCs express TLR-9 and respond directly to SD-101 *in vitro* or *in vivo*: PDCs (peripheral dendritic cells) and B lymphocytes (*6-10*). Immune activation by CpG results from specific binding to B-cells and plasmacytoid dendritic cells (pDC), with subsequent activation of lymphocyte, macrophage, monocyte, natural killer (NK) and T-cell populations. The intracellular receptor for CpGs is TLR-9. Both innate (non-specific) and adaptive (antigen-specific) immune responses are affected by CpGs. The net result is increased secretion of antibodies from B-cells, cytokines from a variety of cells and increased NK activity as well as improved antigen presentation and T-help that can augment both humoral and cell-mediated immune responses. See Figure 1 below.

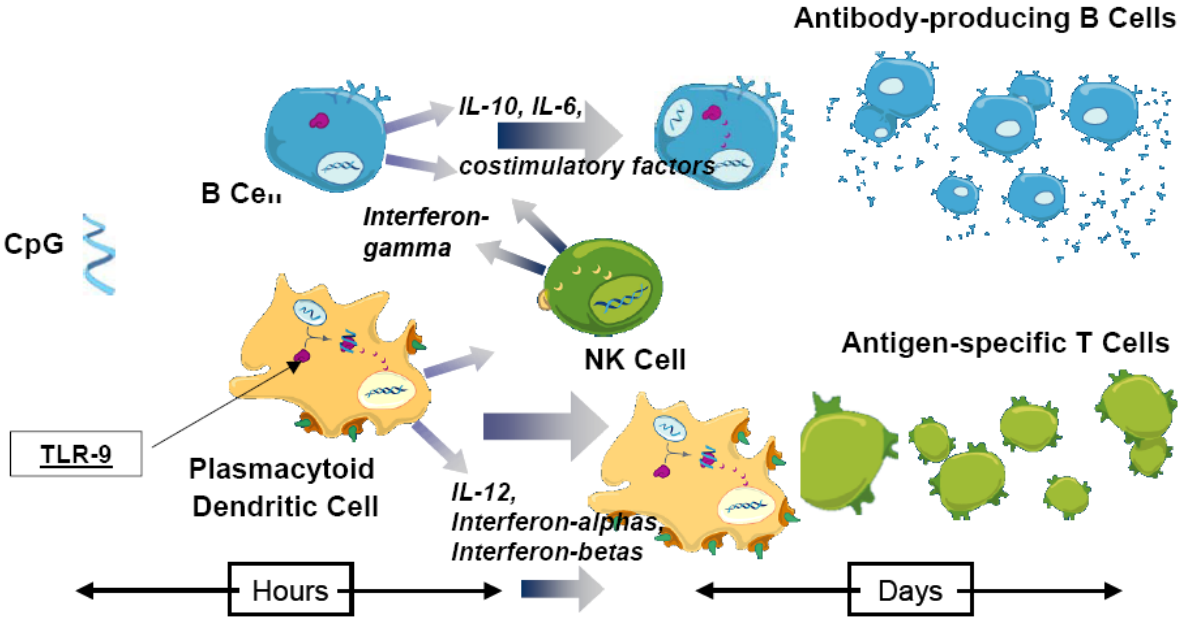


Figure 1. CpG Cellular Mechanism of Action

Metabolism of SD-101

As with other phosphorothioate oligodeoxyribonucleotides, SD-101 is metabolized by exonucleases present in plasma and tissues.

Human Experience with SD-101

Two phase 1 trials of a total of 60 subjects have been completed with SD-101 demonstrating safety up to a dose of 5 mg. Additionally there are 2 ongoing trials of SD-101 in combination with local radiation in low-grade non-Hodgkin's lymphomas.

Dosing rationale

SD-101 will be dosed intratumoral at a starting dose of 3 mg. This dose has been shown to be safe in prior phase 1 trials and PD studies in these trial have shown activity at this dose.

2.2.2 Ibrutinib

Ibrutinib has been approved by the FDA for the treatment of relapse/refractory mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom's Macroglobulinemia, but not for the treatment of relapsed/refractory follicular lymphoma as proposed here.

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (Imbruvica) is approved by the US Food and Drug Administration (FDA) for the treatment of subjects with chronic lymphocytic leukemia or mantle cell lymphoma who have received at least one prior therapy, subjects with CLL with 17p deletion regardless of prior treatment, and subjects with Waldenstrom's macroglobulinemia. Ibrutinib is currently being studied in various additional indications including multiple subtypes of non-Hodgkins lymphoma.

Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

Pharmacokinetics

Absorption: Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in subjects at 560 mg is 953 ± 705 ng·h/mL and in subjects at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib Cmax and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting. Distribution: Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution at steady state (Vd,ss) was 683 L, and the apparent volume of distribution at steady state (Vd,ss/F) was approximately 10000 L.

Metabolism: Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Elimination: Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [14C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Renal Impairment: Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to ibrutinib. There are no data in subjects with severe renal impairment (CLcr < 25 mL/min) or in subjects on dialysis.

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment trial, a single dose of 140 mg of ibrutinib was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n = 6), moderate (n = 10) and severe (n = 8) hepatic impairment relative to subjects with normal liver function. Ibrutinib Cmax increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function.

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors: In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of ibrutinib was administered alone on Day 1 and a single dose of 40 mg of ibrutinib was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 to 9). Ketoconazole increased ibrutinib dose-normalized Cmax and AUC 29-fold and 24-fold, respectively. Simulations using fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

Coadministration of Ibrutinib with CYP3A Inducers: PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib Cmax and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

Efficacy of Ibrutinib in Follicular Lymphoma

Ibrutinib has been studied in the treatment of subjects with low-grade follicular lymphoma. In a phase 1 study of subjects with relapsed or refractory B-cell malignancies, 13 subjects with follicular lymphoma were evaluated for response to ibrutinib, with 7/13 subjects showing a >50% decrease in sum of the largest diameter of each target lesion (*11*). The MTD in this study was 560 mg daily and this dose showed full-target occupancy. Preliminary results from a phase 2 trial of ibrutinib monotherapy in relapsed/refractory follicular lymphoma showed an overall response rate of 30% in 40 subjects on the intention-to-treat analysis. An additional 14 subjects had reduction of tumor size not meeting response criteria (*12*).

Efficacy of Ibrutinib in Marginal Zone Lymphoma

In the PCYC-1121-CA study of 63 patients with marginal zone lymphoma(*13*), ibrutinib was shown to be active, with an overall response rate of 48% with a median duration of response not reached. Response rates were similar across all marginal zone subtypes (MALT, nodal, splenic). On the basis of this trial, ibrutinib received accelerated approval for adult patients with marginal zone lymphoma after at least one prior anti-CD20-based therapy.

Efficacy of Ibrutinib in Mantle Cell Lymphoma

Ibrutinib is FDA-approved for the treatment of relapsed/refractory treatment of mantle cell lymphoma. This is based on an overall response rate of 65.8% with median duration of response of 17.5 months seen in the PCYC-1104-CA trial of 111 patients (*14*). Ibrutinib is now frequently used in the treatment of relapsed mantle cell lymphoma and is being study as a front-line therapy for MCL.

Dosing rationale

Dosing of ibrutinib will be 560 mg daily, based on the proven safety at this level and efficacy in follicular lymphoma as discussed above. This is also the FDA-approved dose for treatment of mantle cell lymphoma and marginal zone lymphoma.

2.2.3 Radiotherapy

Pre-clinical and Clinical Studies

Animal studies of subcutaneous tumors have demonstrated that tumor cells undergo apoptosis upon irradiation. Furthermore, it has been shown that dendritic cells migrate towards irradiated tumor (*15*).

The purpose of using low-dose radiation to a single tumor site in our study is to induce tumor necrosis and/or apoptosis, which in turn releases tumor antigens locally. These tumor antigens will be processed by antigen presenting cells to mount a tumor- specific immune response. This immune response will be augmented by intratumoral injection of SD-101, which is a potent immunostimulant.

Low-dose (2 Gy x 2) radiotherapy has been studied in recurrent follicular lymphoma (*16*). The overall local tumor response rate is estimated at 80 to 90%. The reason for choosing a low-dose radiation is that the low-dose therapy is sufficient to induce tumor cell death and will not jeopardize subjects' opportunity to receive standard radiotherapy at the same anatomic site in the future. Another potential advantage of using a low-dose radiation regimen is to minimize the possibility that the radiation will inhibit tumor-infiltrating dendritic cell functions.

Radiotherapy: Dosage

All subjects will receive 2 Gy radiation to a single tumor site on each of two consecutive days (Day 1 and Day 2).

2.3 Rationale

Research Hypothesis: *Ibrutinib can be safely and feasibly combined with intratumoral injections of SD-101 and local radiation therapy.*

The combination of low-dose local external beam radiotherapy and intratumoral injection of SD-101 to a single site of disease can induce an immune response leading to systemic objective responses in lymphoma subjects. The addition of ibrutinib may have an additive or synergistic effect, prolonging anti-tumor response.

Product Development Rationale

Ibrutinib

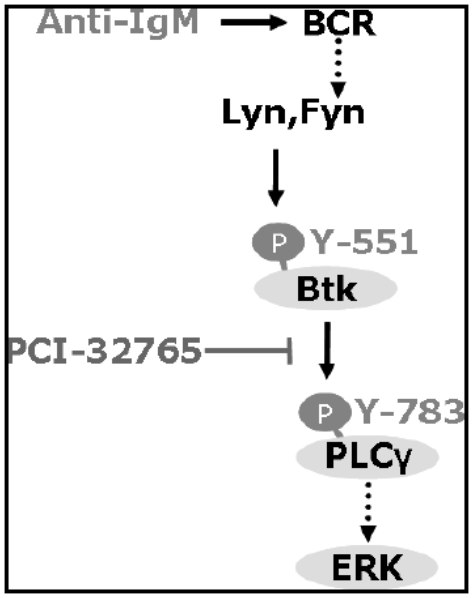


Figure 2. Bruton's Tyrosine Kinase and the B-cell receptor pathway.

Bruton's Tyrosine Kinase (BTK) is part of the B-cell receptor (BCR) signaling pathway. There is strong evidence that lymphoma survival requires BCR signaling. In lymphoma cells, a functional B-cell receptor is conserved, even as the non-expressed immunoglobulin heavy chain (IgH) is typically involved in oncogenic translocations(*17*). In trials of anti-idiotype directed therapies, subjects whose tumor cells developed resistance to treatment did not produce BCR-negative tumor populations as a resistance strategy, indicating that the BCR provides important survival signals for lymphoma cells(*18*). Selective knockdown of BCR components by siRNA causes apoptosis in B-cell lymphoma cell lines(*19*). Some large cell lymphomas have low-level tonic activation of the kinases downstream of the BCR; inhibition of this signaling also results in apoptosis(*20*). Primary follicular lymphoma cells have enhanced BCR pathway signaling when compared with normal B-cells(*21*). Because of cellular dependency on BCR signaling and the restricted expression of the BCR components in B-cell lineages, the BCR pathway has become an attractive target for lymphoma therapies.

Ibrutinib (PCI-32765) is a selective, small molecule irreversible inhibitor of BTK. In vitro studies showed that ibrutinib binds covalently to a cysteine-481 residue (Cys-481) near the BTK active site and inhibits the enzymatic activity with half maximal inhibitory concentration (IC50) of 0.5 nM (*22, 23*). Preclinical and clinical data indicate that B-cell receptor (BCR) signaling is effectively inhibited by ibrutinib, leading to highly selective cytotoxicity in malignant B-cells.

The inhibitory effect of ibrutinib against other related kinases has been characterized in biochemical assays. Only a small subset of kinases is predicted to contain a modifiable cysteine residue homologous to Cys-481 in BTK, and thus have the potential to be irreversibly modified by ibrutinib. The other Cys-481 containing kinases include EGFR (IC50 = 12 nM); HER2 (IC50 = 22 nM); HER4 (IC50 = 0.6 nM); ITK (IC50 = 12nM); BMX (IC50 = 1nM); JAK3 (IC50 = 22nM); and BLK (IC50 = 1nM).

While the direct cytotoxic function of ibrutinib on lymphoma appears to be driven by inhibition of BTK and therefore interruption of BCR signaling, there is evidence to suggest an independent effect of ibrutinib on non-malignant components of the immune system. BTK is expressed on multiple hematopoietic cells including antigen presenting cells (APCs) such as monocytes, macrophages and dendritic cells (DCs). Dendritic cells derived from *btk-/-* mice appear to have superior T-cell stimulatory function, suggesting that BTK inhibition by ibrutinib may promote T-cell stimulation by APCs(*24*). Additionally, ibrutinib has been shown to promote Th1 immune responses through an off-target effect on ITK(*25*). In mouse models of colon cancer, triple negative breast cancer, and ibrutinib-insensitive lymphoma, ibrutinib enhanced the therapeutic activity of the immune checkpoint blockage with antibodies targeting PD1-L (*26*). These data suggest a potential beneficial role of ibrutinib as an immunomodulatory molecule in the treatment of malignancy.

Dendritic cells and Immunostimulatory Agents

The potential to harness the power and specificity of the immune system is of growing interest in cancer immunotherapy. The main challenge of a successful immunotherapy strategy is to overcome tolerance to tumor antigens and to induce an immune response against the tumor. One such approach uses DCs, and their ability to induce potent T-cell-dependent antigen-specific immune responses to generate tumor- specific immunity. Support for this strategy comes from animal studies that demonstrated that *ex vivo* loading of DCs with tumor lysates, tumor antigen-derived proteins, synthetic major histocompatibility complex (MHC) class I-restricted peptides or whole protein has generated tumor-specific immune responses and anti-tumor activity (*27, 28*). Our group has shown that the injection of DCs into a single tumor site, in combination with systemic chemotherapy, can completely eradicate metastatic lymphoma in an animal model and induce a systemic CD8+ immune response (*29*). Dendritic-cell based vaccination methods have shown some success in clinical trials in subjects with lymphoma, melanoma and prostate cancer (*27-35*). However, these DC-vaccine trials involve expensive and cumbersome *ex vivo* manipulation of dendritic cells.

Radiotherapy combined with CpG

Radiotherapy combined with CpG has been shown to enhance tumor regression. Studies investigating the use of RT in combination with CpG and DC administration demonstrated significant enhancement of tumor regression in murine sarcoma and melanoma models (*36-38*). Our group has identified that the combination of intratumoral injection of CpG and local RT was more efficacious in tumor regression than each modality alone as demonstrated in a murine lymphoma model (*39*). Radiation induces tumor necrosis and apoptosis, which results in the release of tumor antigens. The tumor antigens are processed by antigen presenting cells and generate a tumor-specific immune response that can be augmented by the immunomodulatory effects of CpG injections (*37*).

In order to circumvent the need for collecting and processing dendritic cells *ex vivo*, we developed a novel approach to combine low-dose radiotherapy with intratumoral injection of a CpG-oligodeoxynucleotide (CpG-ODN), a TLR9 agonist, such as CpG-7909, PF-03512676 or SD-101, to elicit an immune response to the tumor. The rationale is that radiotherapy triggers tumor necrosis, apoptosis and inflammatory responses. These events, in turn, act as "danger signals" that recruit dendritic cells to sites of inflammation (*40, 41*). At the site of inflammation, dendritic cells process tumor antigens (provided by necrotic and/ or apoptotic tumor cells), undergo maturation and migrate to draining lymph nodes, where they generate immune response to tumor-antigens. Intratumoral injection of CpG can augment the immune response by recruiting dendritic cells to the tumor site. Furthermore, CpG enhances the antigen presentation property of dendritic cells (*9, 10, 42-46*).

Rationale for combination of intratumoral CpG and systemic ibrutinib

The *in situ* vaccination approach we developed previously uses intratumoral CpG injection to trigger immune responses at a site of disease which can then spread systemically yielding abscopal responses. Effective antigen presentation requires the release of tumor antigens from tumor cells which can then be presented by professional antigen presenting cells such as dendritic cells. Previously we have used low-dose local radiation to induce tumor death at the site of the *in situ* vaccination. As opposed to alternative cytotoxic treatment such as chemotherapy, local radiation minimally affects the systemic immune response. We hypothesized that the use of a targeted anti-lymphoma agent such as ibrutinib could similarly induce cell death at the site of CpG injection. Ibrutinib produces minimal detrimental effect on the immune system, and potentially could augment immune responses. In an animal model of an ibrutinib-sensitive lymphoma, we found striking synergy between ibrutinib and intratumoral CpG (*26*). This effect was seen with doses of ibrutinib and CpG that had minimal single-agent activity. The effect was only produced in immunocompetent animals, and adoptive T-cell transfer from animals treated with this combination could prevent tumor growth in naïve mice without treatment. These data suggest that the antitumor effect of the combination of ibrutinib and CpG is driven by induced immune responses rather than direct effects of these agents on tumor cells. Indeed, in additional mouse models of ibrutinib-insensitive tumors including colon and breast cancer, treatment with ibrutinib and intratumoral CpG produced the same synergistic effect (*47*).

2.4 Study Design

This is a single-arm, single-group, non-randomized, open-label, treatment study of intratumoral SD-101 and local low-dose radiation plus oral ibrutinib. This will be a phase 1b dose de-escalation study followed by a phase 2 expanded cohort at a chosen dose of intratumoral SD-101 designed to evaluate safety (phase 1b) and efficacy (phase 2). The study will be a single-center trial conducted at Stanford University Medical Center.

2.5 Correlative Studies Background

2.5.1 CTL activity against autologous tumor (performed if adequate tumor sample):

The mechanism of immune response to concurrent treatment with CpG and ibrutinib is hypothesized to be mediated at least in part through CTL cells (*26*). We will test the induction of

CTL immune responses in this correlate. PBLs will be collected before and after treatment and co-cultured with autologous tumor to assess for tumor-specific immune responses. Immunophenotyping will identify lymphocyte populations associated with response or resistance.

2.5.2 Immunophenotyping of treated and untreated tumor sites:

Intratumoral injection of CpG has been shown to break tolerance against lymphoma by altering the local tumor microenvironment. Resistance to intratumoral CpG is hypothesized to be mediated via T regulatory cells and potentially other leukocyte populations. This correlative will investigate the cell populations altered at the treatment site and potential abscopal responses by sampling treated and untreated lymph nodes before and after treatment. Multiparameter flow will be performed at the various time points to define immune populations including CD4 and CD8 T-cells, regulatory T-cells, follicular helper T-cells, B-cells (including the malignant B-cells), natural killer cells, dendritic cells and macrophages. The extent of immunophenotyping will depend on the availability of cells from each biopsy.

2.5.3. Anti-tumor antibody response (performed if adequate tumor sample):

Humoral responses against follicular lymphoma have been shown to be associated with clinical benefit in prior idiotype vaccine studies (*48*). The induction of humoral responses by intratumoral injection of CpG and/or treatment with ibrutinib has not been studied but may correlate with clinical benefit. In this correlate, we will test for the development of humoral immunity after treatment.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Biopsy-confirmed Grade 1 or 2, or 3A follicular lymphoma; mantle cell lymphoma; or marginal zone lymphoma. Subjects must have relapsed from or are refractory to prior therapy.

3.1.2 Subjects must have at least one site of disease that is accessible for intratumoral injection of SD-101 *(diameter ≥ 10mm),* percutaneously.

3.1.3 Subjects must have at least one site of measurable disease (see Section 10.2.2 for definition of measurable disease) other than the injection site which is not included in the radiation field.

3.1.4 ECOG Performance Status of 0 or 1

3.1.5 Subjects must be 18 years of age or older.

3.1.6 Required values for initial laboratory tests:

a) Absolute neutrophil count (ANC) ≥ 1000/mm^3 independent of growth factor support

b) Platelets: ≥ 100,000/mm^3 or ≥50,000/mm^3 if bone marrow involvement independent of transfusion support in either situation

c) Hemoglobin: ≥ 8 g/dL (may be transfused)

d) Creatinine: Creatinine clearance > 25 mL/min

e) AST/ALT: ≤ 3 x ULN

f) Bilirubin: ≤ 1.5 x ULN (except for subjects with Gilbert's Syndrome or of non-hepatic origin)

3.1.7 Must be at least 4 weeks since treatment with standard or investigational chemotherapy, biochemotherapy, major surgery, radiation, cytokine therapy, and 8 weeks since any monoclonal antibodies or immunotherapy, and recovered from any clinically significant toxicity experienced during treatment.

3.1.8 Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study (see Appendix E) consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.

3.1.9 Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.

3.1.10 Life expectancy greater than 4 months.

3.1.11 Able to comply with the treatment schedule.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Autoimmune disease requiring treatment within the last 5 years including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, autoimmune thrombocytopenia, uveitis, or other if clinically significant

3.2.2 Major surgery or a wound that has not fully healed within 4 weeks of enrollment.

3.2.3 History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

3.2.4 Requires anticoagulation with warfarin or equivalent vitamin K antagonists.

3.2.5 Requires chronic treatment with strong CYP3A inhibitors.

3.2.6 Vaccinated with live, attenuated vaccines within 4 weeks of enrollment.

3.2.7 Known history of human immunodeficiency virus (HIV) or active Hepatitis C Virus or active Hepatitis B Virus infection or any uncontrolled active systemic infection.

3.2.8 Known CNS lymphoma.

3.2.9 Subjects with a history of prior malignancy with the exception of non-melanoma skin cancer, carcinoma in situ of the cervix, in situ carcinoma of the bladder, stage 1 prostate cancer that does not require treatment, or other malignancy that has undergone potentially curative therapy with no evidence of disease for the last > 2 years and that is deemed by the investigator to be a low risk for recurrence.

3.2.10 History of allergic reactions attributed to compounds of similar composition to SD-101 or ibrutinib

3.2.11 Treatment with an immunosuppressive regimen of corticosteroids or other immunosuppressive medication (eg, methotrexate, rapamycin) within 30 days of study treatment. Note: subjects may take up to 5 mg of prednisone or equivalent daily. Topical and inhaled corticosteroids in standard doses are allowed.

3.2.12 Significant cardiovascular disease (ie, NYHA class 3 congestive heart failure; myocardial infarction with the past 6 months; unstable angina; coronary angioplasty with the past 6 months; uncontrolled atrial or ventricular cardiac arrhythmias).

3.2.13 Pregnant or breast feeding.

3.2.14 Any other medical history, including laboratory results, deemed by the investigator to be likely to interfere with their participation in the study, or to interfere with the interpretation of the results.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study-specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Randomization Procedures

This is a non-randomized trial.

3.5 Study Timeline

Primary Completion:

The study will reach primary completion 60 months from the time the study opens to accrual.

Study Completion:

The study will reach study completion 60 months from the time the study opens to accrual.

4. TREATMENT PLAN

4.1 Dose de-escalation Study Design

The study will use a 6+3 design with a goal of determining the recommended phase 2 dose. We will enroll a cohort of 6 subjects, with a 3 mg dose of intratumoral SD-101 and 560 mg dose of oral ibrutinib. The proposed initial dose of SD-101 is below the maximum tolerated dose as determined in previous trials, and there is extensive data regarding the safety of treatment with ibrutinib at the FDA-approved dose of 560 mg. Because no additional toxicity is anticipated with combination therapy of SD-101 and ibrutinib, the 6+3 dose de-escalation design will be employed, permitting rapid confirmation of the safety of the combination therapy and selection of the recommended phase 2 dose while still allowing detection of any unanticipated toxicity.

If 0 or 1 subjects out of the initial 6 subjects experience a DLT, we will chose this dosing as the recommended phase 2 dose level. If 2 out of 6 subjects experience a DLT, we will expand the

cohort and enroll an additional 3 subjects at the same dose level. If 3 out of 6-9 subjects in the initial dose cohort experience a DLT, then the dose de-escalation cohort -1 will accrue. This dose de-escalation cohort will be treated with 1 mg intratumoral SD-101 and 560 mg ibrutinib. If ≤ 2 out of 6 subjects in the dose de-escalation cohort experience a DLT, then this dose will be considered the RP2D. If 3 or more subjects in the de-escalation cohort experience a DLT, the study will be stopped.

Table 1. Dose Escalation Plan

Cohort	Dose (mg)	Total Enrollment per Cohort	Dose Escalation Rules
-1	1 mg SD-101 560 mg ibrutinib	6	1 of 6 or 2 of 6 DLT, RP2D is established 3 of 6 DLT, trial is stopped
1	3 mg SD-101 560 mg ibrutinib	6-9	0 of 6 or 1 of 6 DLT, RP2D is established at this level 2 of 6 DLT, expand cohort to 9 subjects 2 of 9 DLT, RP2D is established at this level 3 of 6-9 DLT, decrease to dose level -1
Phase 2 Expansion	RP2D	15	If the incidence of study drug-related DLTs as defined previously equals or exceeds 33% of treated subjects at RP2D dose level 1, enrollment will be stopped for dose level 1, and enrollment of 15 subjects will begin at dose level -1. If the incidence of study drug-related DLTs equals or exceeds 33% of treated subjects at RP2D dose level -1, then the trial is stopped

Phase 2 (SD-101 dose Cohort Expansion): Once the safety profile and tolerability of all doses tested has been characterized and the RP2D of SD-101 has been defined during the dose de-escalation phase of this trial, the RP2D dose cohort will be expanded by an additional 15 subjects. This will enable further characterization of the immunoregulatory activity and preliminary antitumor effects of this treatment regimen. The treatment schema for SD-101, RT and ibrutinib will remain the same as previously described.

Clinical safety monitoring of subjects enrolled during this additional Cohort Expansion portion of the study will be the same as conducted during the dose escalation portion of the study (ie, part 1). If the chosen RP2D is dose level 1 (3 mg SD-101) and the combined incidence of study drug-related DLTs of any kind (ie, Grade 3 injection site reaction, hematologic or non-hematologic DLT) is equal to or exceeds 33% of treated subjects at any point during treatment, this will prompt a halt in enrollment at that dose level. Enrollment of 15 subjects will then begin at the lower dose level of 1 mg SD-101. If the incidence of DLTs in the lower dose cohort equals or exceeds 33%, the trial will be stopped.

4.2 Informed Consent and Screening Period

Subjects who may be eligible for the trial will be approached by the Investigator and offered participation in the trial. The Investigator or co-Investigator will explain the study to the potential subject verbally, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.), and will allow the potential subject ample opportunity to ask questions. Following this verbal explanation, the potential subject will be provided with the IRB approved informed consent form and will be afforded sufficient time to consider whether or not to participate in the research. After allowing the potential subject time to read the consent form, the investigator or approved designee (study coordinator) will answer any additional questions the potential subject may have and will obtain the subject's signature on the consent form. The investigator or designee will also sign the consent form. A signed copy of the consent form will be given to the subject, scanned into the medical record and distributed to the pharmacy and CTRU as per Stanford Cancer Clinical Trials Office (CCTO) Standard Operating Procedures. Before any protocol-specified procedures are conducted, each prospective participant must provide informed consent.

The screening period will take place up to 4 weeks prior to first dosing. Studies to evaluate the extent of tumor burden may be performed up to 6 weeks prior to dosing.

Subjects will undergo the following procedures during the screening period:

- Written informed consent
- Medical history and complete physical exam
- Obtain vital signs / ECOG performance status
- Monitoring of concomitant medications
- Hematology: CBC, differential, platelet count
- Chemistry: comprehensive metabolic panel
- LDH
- Urine pregnancy test (for females of childbearing potential)
- Determination of extent of disease with CT scans or PET/CT to evaluate all areas of known or suspected neoplastic disease. Procedures performed prior to subject entry into the trial, but within 6 weeks of first dosing, will fulfill the screening requirements.
- Infectious disease screening- HIV antibody testing, Hepatitis B surface antigen, Hepatitis B core antibody and Hepatitis C antibody testing
- Fine needle aspiration of planned treatment site (if no tissue from excisional biopsy is available for correlative studies). If additional sites of disease are safely accessible via fine needle aspiration, these may be biopsied as well.
- An excisional biopsy may be performed to confirm that the tumor has not transformed to a more aggressive form (optional). Tissue/cells not required for clinical diagnostic assessment may be collected and stored for immune correlative studies.
- Collection of 1 purple top tube for research correlates
- *Only for subjects with sufficient material from an excisional biopsy or, optionally, for patients with circulating lymphoma cells:* Apheresis for collection of peripheral blood

mononuclear cells (PBMC) (approximately 2 hours) to provide adequate sample for immune assays

- *Only for subjects not undergoing apheresis:* 7 additional green top tubes of peripheral blood will be collected for research correlates

4.3 Treatment Period:

The treatment schema and study visit schedule is the same for both the dose de-escalation cohorts and the expanded, phase 2 cohort.

SD-101 will be administered within 12 hours of the completion of radiotherapy during Day 2.

The study agent SD-101 at a dose of either 1 mg or 3 mg will be injected intratumorally on Day 2. Subsequent weekly injections will be administered on days 9, 16, 23 and 30 for a total of 5 intratumoral injections.

Ibrutinib will be taken PO daily starting on Day 10. Dosing will be continuous 560 mg daily throughout the course of the trial. Subjects will continue to take ibrutinib until disease progression or for a total of 96 weeks of therapy, whichever comes first.

All intratumoral SD-101 injections will be carried out at the Clinical Translational Research Unit (CTRU) and/or oncology clinic infusion treatment area (ITA). Vital signs, including weight, will be taken prior to each injection. Subjects will be monitored for at least 30 minutes after each injection with repeat vital signs before being discharged home. Vital signs (blood pressure, heart rate, temperature, respiratory rate and oxygen saturation via pulse oximetry) should be obtained at the end of the monitoring period, within a -5/+15 minute window.

All subjects will be evaluated as described below. The first day of treatment is Day 1, which is the first day of Week 1. Subsequent days or weeks listed are with reference to his landmark.

4.3.1 Day 1:

- First treatment of radiotherapy (2 Gy)

4.3.2 Day 2:

- Obtain vital signs/ ECOG performance status
- Assessment of adverse events and toxicity grading according the CTCAE v4.0
- Monitoring of concomitant medications
- Second treatment of radiotherapy (2 Gy)
- Administration of intratumoral injection no. 1 of SD-101 within 12 hours of radiotherapy

4.3.3 Day 4 (+/- 1 day):

- *Optional* (encouraged but not mandatory) FNA of accessible tumor for research studies. If additional (untreated) sites of disease are safely accessible via fine needle aspiration, these may be biopsied as well.

4.3.4 Day 9 (+/- 2 days)

- Obtain vital signs/ ECOG performance status
- Assessment of adverse events and toxicity grading according the CTCAE v4.0
- Monitoring of concomitant medications
- CBC with Differential and platelet count
- Comprehensive Metabolic panel
- FNA of accessible tumor for research studies. To be performed prior to intratumoral injection no. 2. If additional (untreated) sites of disease are safely accessible via fine needle aspiration, these may be biopsied as well.
- Collection of 1 purple top tube for research correlates. Collection should occur before SD-101 injection no. 2.
- Administration of SD-101 intratumoral injection no. 2 at the same site as previously
- Collection of 7 peripheral blood green top tubes for research correlates
- Distribution of 1 month supply of ibrutinib. Administration of first dose of ibrutinib 560 mg orally will occur the next day. Ibrutinib will be self-administered by the subject daily from this point until progression of disease or for 96 weeks, whichever comes first.

4.3.5 Day 16 (+/- 2 days)

- Obtain vital signs/ ECOG performance status
- Assessment of adverse events and toxicity grading according the CTCAE v4.0
- Monitoring of concomitant medications
- Collection of 7 green top tubes for research correlates
- Administration of SD-101 intratumoral injection no. 3

4.3.6 Day 23 (+/- 2 days); Day 30 (+/- 2 days)

- Obtain vital signs/ ECOG performance status
- Assessment of adverse events and toxicity grading according the CTCAE v4.0
- Monitoring of concomitant medications
- CBC with Differential and platelet count at Day 23 visit
- Comprehensive Metabolic panel at Day 23 visit
- Administration of SD-101 intratumoral injection no. 4 (Day 23), no. 5 (Day 30) at the same injection site as previously
- Collection of 1 purple top tube for research correlates (Day 23 visit only)

4.3.7 Day 37 (+/-7 days)

- Obtain vital signs/ ECOG performance status
- Monitoring of concomitant medications
- Assessment of adverse events and toxicity grading according the CTCAE v4.0
- CBC with Differential, and platelet count
- Comprehensive metabolic panel
- Distribution of a 6-week supply of ibrutinib. Ibrutinib will be self-administered by subject daily.
- FNA of accessible tumor, if available, for research studies. If additional sites of disease are safely accessible via fine needle aspiration, these may be biopsied as well.
- Collection of 1 purple top tube for research correlates

- *Only for subjects with sufficient material from an excisional biopsy:* Apheresis for collection of peripheral blood mononuclear cells (PBMC) (approximately 2 hours) to provide adequate sample for research studies (+/- 10 days).
- *Only for subjects not undergoing apheresis:* Collection of 7 additional green top tubes of peripheral blood for research correlates (+/- 10 days).

4.3.8 Weeks 12, 24, 36, 48, 60, 72, 84 (+/- 10 days):

- History and physical examination
- Obtain vital signs/ ECOG performance status
- Monitoring of concomitant medications
- Assessment of adverse events and toxicity grading according the CTCAE v4.0
- Routine CBC, differential, and platelet count
- Routine Comprehensive metabolic panel
- LDH
- Distribution of ibrutinib. Ibrutinib will be self-administered by subject daily.
- Weeks 12, 24, 48, 72 only - Determination of response to treatment with CT scans of the chest/ abdomen/ pelvis or other medically appropriate imaging modality to evaluate all areas of disease followed by calculation of response by the Cheson Criteria (*49*) for lymphoma subjects (draining lymph nodes of the injected region will be excluded from this assessment, since SD-101 injections may cause transient enlargement of the draining lymph nodes). CT scan is the preferred mode of imaging, however, if a CT scan is contraindicated or if it is felt by the Sponsor Investigator that a PET/CT will be a better modality to assess a particular subject, a PET/CT may be used for evaluation.
- Collection of 1 purple top tube for research correlates
- *Optional:* If there is no evidence of disease on CT scan, a bone marrow biopsy will be obtained to document whether a complete response is achieved.
- At Week 12 only, 7 additional green top tubes of peripheral blood will be collected

4.3.9 Final Study Visit

Subjects who withdraw from treatment due to progressive disease will be seen within 4 weeks of the determination of progressive disease for a final visit. Subjects who withdraw due to intolerance of treatment should be followed weekly until all toxicities have reverted to Grade ≤ 2 or have stabilized in the opinion of the Investigator, at which point they will undergo the final visit. All subjects who withdraw for any reason other than progressive disease will be seen within 4 weeks of withdrawal for a final visit.

At the Final Study Visit, the following procedures will be performed:

- History and physical examination
- Obtain vital signs/ ECOG performance status
- Monitoring of concomitant medications
- Hematology: CBC with differential and platelet count
- Chemistry: comprehensive metabolic panel
- LDH
- Collection of 1 purple top tube for research correlates

- If not already radiologically documented within 4 weeks, determination of extent of disease with CT scans, or any other radiographic procedures determined appropriate by the investigator, followed by calculation of response by the Cheson criteria (*49*).
- If progressive disease, obtain an FNA of accessible tumor(s), if available, for research studies (optional).
- Collection of 7 green top tubes of peripheral blood for research correlates

4.4 Follow-Up Period

After Week 96, subjects will be evaluated every 3 to 6 months with CTs at intervals per standard practice at our institution, until disease progression or subject withdrawal.

4.5 Duration of Therapy

The planned duration of study for each subject is approximately 96 weeks, after which time the primary evaluation of safety, efficacy and immune response will be performed. Subjects will remain on study until development of disease progression, intolerable toxicity or any of the conditions outlined in Section 4.10 (Criteria for removal from study). Treatment toxicity will be evaluated at each study visit during the treatment period and at the final visit in Week 96. After Week 96, low-grade B-cell lymphoma subjects will be followed every 3 to 6 months as part of routine care until disease progression or subject withdrawal from the study.

4.6 Duration of Follow Up

After Week 96, subjects will be followed every 3 to 6 months as part of routine care until disease progression or subject withdrawal from the study. Subjects who withdraw from treatment due to progressive disease will be seen within 4 weeks of the determination of progressive disease for a final visit. Subjects who withdraw due to intolerance of treatment should be followed weekly until all toxicities have reverted to Grade ≤ 2 or have stabilized in the opinion of the Investigator, at which point they will undergo the final visit. All subjects who withdraw for any reason other than progressive disease will be seen within 4 weeks of withdrawal for a final visit.

4.7 Radiotherapy Administration

All subjects will receive 2 Gy radiation to a single tumor site on each of 2 consecutive days (Day 1 and Day 2).

4.8 Investigational Agent Administration: SD-101

The first injection of SD-101 will be performed on Day 2, within 12 hours of the radiation treatment. Subsequent injections of SD-101 will begin approximately one week later (Day 9), to be administered once per week for 3 weeks, for a total of five injections over a 4-week period.

SD-101 is supplied in individual vials at a concentration of 5 mg/mL or 16 mg/mL. Per instruction from Dynavax Pharmacy Manual (Dynavax Study DV3-MEL-01) below, SD-101 at 16 mg/mL will be diluted to a concentration of 5 mg/mL in normal saline prior to pharmacy dispensation.

SD-101 drug product should be removed from storage at 2° to 8°C and placed at ambient temperature prior to preparation for administration per the equilibration protocol below. Each vial of SD-101 drug product and prepared dose are for single-use only.

NOTE: SD-101 drug product or diluted SD-101 drug product is stable at room temperature for 8 hours. The SD-101 drug product or corresponding diluted SD-101 drug product must be used within 8 hours of removal of the SD-101 drug product vial from refrigerated storage. Prior to any drug preparation, prepare a clean working surface. Use aseptic technique to reduce the possibility of contamination, eg, wear gloves, use isopropyl alcohol to wipe down all vials (including rubber stopper area), etc. All syringes and sterile empty vials are for single-use; use only unopened syringes, needles, and/or vials for each step.

4.8.1. SD-101 DRUG PRODUCT EQUILIBRATION PROTOCOL:

Remove SD-101 drug product vial(s) from refrigerated storage. Allow SD-101 drug product to come to ambient temperature for 20 minutes. Gently mix SD-101 drug product by completely inverting vial(s) by hand and repeating 10 times.

NOTE: If diluent has been stored under refrigerated conditions, it must be allowed to come to ambient temperature for 20 minutes prior to preparation of the dosing solution.

4.8.2. PREPARATION OF SD-101 DOSING SOLUTION

All vials (SD-101 drug product, diluted SD-101 drug product, and diluent) are for single-use only. Prepare the appropriate dosing solution as specified below.

4.8.2.1 DILUTION & DOSE PREPARATION

Note: This section requires the use of 1 vial of 16 mg/mL SD-101 drug product. Draw **1.1 mL** of 0.9% sodium chloride diluent in a 3 mL syringe and transfer into an empty sterile mixing vial (2 or 5 mL capacity).

Note: While injecting the 0.9% sodium chloride diluent into the empty vial, ensure that pressure does not build up in the vial by equalizing the pressure recurrently. Draw **0.50 mL** from the SD-101 drug product vial (16 mg/mL) in a 1 mL syringe attached with a 20-25G needle, and transfer into the same sterile mixing vial containing the **1.1 mL** diluent. Mix the solution by gently inverting the vial completely 10 times. This mixing vial will contain a 5 mg/mL solution of SD-101.

FOR 3 mg DOSE: Using a 20-25G needle, draw **0.60 mL** of the diluted SD-101 drug product from the mixing vial into a 1 mL syringe for the administration of a 3 mg fixed dose of SD-101. **A 25-30G needle must be used to administer the dose of SD-101.**

FOR 1 mg DOSE: Using a 20-25G needle, draw **0.20 mL** of the diluted SD-101 drug product from the mixing vial into a 1 mL syringe for the administration of a 1 mg fixed dose of SD-101. **A 25-30G needle must be used to administer the dose of SD-101.**

The site of injection will be into an accessible enlarged lymph node or subcutaneous tumor site. Injections will be prepared and administered by a person designated by the principal investigator (eg, sub-investigators, study nurses) in response to written orders from the investigators.

4.9 Investigational Agent Administration: Ibrutinib

Subjects will begin treatment with ibrutinib on Day 10 of study treatment.

Ibrutinib is supplied as white opaque 140 mg capsules marked with "ibr 140" in black ink. Subjects will take 4 capsules daily for a total dose of 560 mg PO. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study.

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Ibrutinib will be dispensed to subjects in bottles at designated visits. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be re-dispensed to anyone.

4.10 General Concomitant Medication and Supportive Care Guidelines

4.10.1 Prohibited Therapies

Subjects may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Immunosuppressive agents
- Chronic systemic corticosteroids above a dose of 5mg prednisone daily
- Any non-oncology live vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).
- Chronic (more than 7 days) therapy with a strong CYP3A inhibitor (see Appendix D).
- Chronic (more than 7 days) therapy with a strong CYP3A inducer (see Appendix D)

4.10.2 Restricted Therapies

<u>CYP3A Inhibitors</u>

Use of a strong CYP3A inhibitor for more than 7 days is prohibited. If a moderate CYP3A inhibitor must be used, the dose of ibrutinib will be reduced by 140 mg daily. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. Subjects taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

<u>Surgeries and Procedures</u>

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

For planned minor procedures (such as a central line placement, lymph node biopsy (not including fine needle biopsy), thoracentesis, or paracentesis) ibrutinib should be held for at least

3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure, or at the discretion of the investigator

4.11 Criteria for Removal from Study

Subjects may withdraw from the study at any time and for any reason. Possible reasons for withdrawal include the following:

- DLT
- Progressive neoplastic disease
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Subject withdraws consent to continue participation
- An adverse event which in the opinion of the Investigator precludes further participation in the trial
- The Investigator removes the subject from the trial in the best interests of the subject
- Study termination
- The Investigator removes the subject from the trial due to non-compliance
- The subject is lost to follow-up.
- Female subjects who become pregnant during this study.

If a subject withdraws from the trial, attempts should be made to contact the subject to determine the reason(s) for discontinuation. All procedures and evaluations required by the Final Study Visit should be completed in the event of early withdrawal. All subjects who discontinue the trial secondary to an adverse event must be followed until resolution or stabilization of the adverse event.

This trial is subject to continuing approval of IRB at Stanford University and drug and funding under a cross-filed IND from the drug companies, DynaVax and Janssen Scientific Affairs, LLC. Reasons for early trial discontinuation may include, but are not limited to, unacceptable toxicity of study drug, a request to discontinue the trial from a regulatory authority, protocol violations, or poor enrollment.

4.12 Alternatives

Alternative therapies for this subject population will be discussed with each subject and would include standard chemotherapy regimens, radiotherapy, monoclonal antibodies, other investigational treatments (if available), or watchful waiting.

5. INVESTIGATIONAL AGENT INFORMATION

5.1 SD-101

Toll-like receptor 9 (TLR9) ligands have multiple mechanisms of action that modulate the immune system including both direct and indirect anti-tumor effects. The natural ligands for TLR9 are unmethylated CpG oligonucleotide sequences that are rare in vertebrate genomes but

prevalent in pathogen genomes including bacteria and viruses. A synthetic CpG product SD-101 is available for clinical use from DynaVax Technologies. DynaVax is supplied as a GMP material. SD-101, a Class C CpG, induces an IFN-α signature in both human PBMCs in vitro and non-human primates in vivo. There is considerable experience with SD-101 in normal subjects and in subjects with lymphoma. Based on single-agent studies in healthy volunteers and an ongoing trial of previously untreated low-grade lymphoma subjects, it is safe and well tolerated up to a dose of 5 mg per injection. IND 111985 is held by Stanford Investigator, Dr. Robert Lowsky (listed on the title page of this protocol) and will be cross referenced and used in this study.

Mechanism of Action

CpG-ODN, such as SD-101, are optimized for immune stimulation and sulfur for phosphorus between nucleotide subunits to provide increased resistance to nuclease-mediated degradation. The nucleotide sequences are recognized by TLR-9, a receptor for innate immune recognition of microbial and viral DNA (*5*). Two principal types of human PBMCs express TLR-9 and respond directly to SD-101 in vitro or in vivo: PDCs (peripheral dendritic cells) and B lymphocytes (*6-10*). Immune activation by CpG results from specific binding to B-cells and plasmacytoid dendritic cells (pDC), with subsequent activation of lymphocyte, macrophage, monocyte, natural killer (NK) and T-cell populations. The intracellular receptor for CpGs is TLR-9. Both innate (non-specific) and adaptive (antigen-specific) immune responses are affected by CpGs. The net result is increased secretion of antibodies from B-cells, cytokines from a variety of cells and increased NK activity as well as improved antigen presentation and T-help that can augment both humoral and cell-mediated immune responses. (see Figure 1).

. Human Experience with SD-101

In a phase 1, randomized single-blind, placebo controlled study of SD-101 in 26 healthy volunteers, 0.1 mg; 1 mg; 3 mg; and 5 mg dose cohorts were analyzed. Secondary outcome pharmacodynamics measures included level of serum cytokines and levels of blood biomarkers (interferon-alpha inducible genes). A dose-dependent induction of IFN-inducible genes was observed, which reached a plateau at the 3 mg level. A trial of SD-101 in 34 subjects with chronic HCV infection tested doses up to 5 mg with or without ribavirin. In both trials, influenza-like symptoms including headache, chills, fatigue, and fever were common as well as local injection site reactions including erythema, induration and pain. In the trial of healthy volunteers, there was one DLT of headache, neck pain, and local induration at the 5 mg dose. In the trial of subjects with chronic HCV, there was one SAE of hyperthyroidism which was considered to probably be related to SD-101.

We are currently participating in a phase 1 clinical trial of SD-101 in lymphoma subjects who have relapsed after allo-transplantation (NCT01745354). In that study, subjects receive low-dose radiation to one site of disease (as in the current proposed trial) followed by intratumoral injection of SD-101 at doses of 0.1 mg, 1 mg and 3 mg in successive cohorts. We have observed no significant toxicity, and we have observed abscopal tumor responses in all subjects. In addition, there is an ongoing trial of intratumoral SD-101 in combination with local radiation in untreated low-grade Hodgkin's lymphomas. This trial has completed enrollment of the first 3 cohorts of 1 mg, 2 mg, and 4 mg and is currently treating subjects on the final dose cohort of 8 mg. No DLT has been observed in the first 3 cohorts.

Stanford CpG 6 mg Protocol (IRB-13956)

Our group reported results from a phase 1-2 study of in situ vaccination with CpG TLR9 agonist PF-3512676 in subjects with relapsed low-grade lymphoma (*50*). 15 subjects were enrolled on study, and received low-dose RT (4 Gy over 2 days) to a solitary tumor site, and 6 mg of PF-3512676 by intratumoral injection to the same tumor site immediately before the first RT dose, after the second RT dose, and weekly for 8 consecutive weeks. This vaccination strategy was well tolerated with no Grade 3 toxicities. One subject had a complete clinical response, 3 subjects had partial responses, and 2 subjects had stable disease. Induction of tumor-reactive memory CD8+ T-cells was demonstrated. Low-dose RT was selected for use in this protocol since the dose was adequate to induce tumor cell death, but did not affect the ability for subjects to receive higher treatment doses to the same sites in the future and potentially minimized radiation-induced inhibition the induced immune response.

A similar in situ vaccination strategy was explored in cutaneous T-cell lymphoma (CTCL), specifically mycosis fungoides (MF) (*50*). Subjects with MF stages IA-IVA who failed standard therapy were eligible. The immunization site was treated with low-dose RT (2 Gy x 2), bracketed by intratumoral injection of PF-3512676 followed by weekly intratumoral PF-3512676 x 8. 15 subjects were included. After the initial 6 subjects, a second immunization site was added at Week 4 to enhance systemic response. A total of 5 partial responses were observed (30% OR); 2 of 6 treated with single immunization and 3 of 9 with dual immunization. Median time to response was 8 weeks, duration of response 7 weeks, and time to progression 20+ weeks. Common toxicities were injection site and flu-like symptoms; mostly Grade 1 to 2 and all transient.

The treated immunization sites had significant reduction of CD25+, Foxp3+ T-cells ($p < 0.01$). Similar reduction in S100+, CD1a+ DCs was observed post immunization ($p < 0.025$). A qualitative analysis suggested more remarkable reduction of CD25+ T-cells and skin DCs in clinical responders vs non-responders ($p = 0.058, 0.121$). PF-3512676 dose-responsive activation of peripheral blood PDCs was observed in vitro. This novel in situ vaccination strategy is feasible in CTCL/MF with acceptable toxicities. Depletion of tissue T-regs may be observed at immunized sites, and reduction of skin DCs may suggest cross-priming and migration of DCs to regional lymph nodes. These Stanford preclinical and clinical studies using CpG intratumorally demonstrated a toxicity profile similar to that obtained using SC injection.

Stanford CpG 18 mg Protocol (IRB 14820)

In our clinical trial using intratumoral injection of CpG (PF-03512676, Pfizer, Inc.) at a dose level of 18 mg combined with 2 x 2 Gy radiation, 15 subjects with previously treated and 15 subjects with previously untreated B-cell lymphoma were evaluated. The treatments were well tolerated, with mild-to-moderate injection site reaction, flu-like symptoms, fever and headache being the most common adverse events. There were no SAEs in this Stanford trial. Clinical regressions were observed in both treatment arms, but the rate was no higher than in our previous trial of 6 mg of CpG.

Adverse Events in Stanford Clinical Studies with CpG

Local injection reactions have consisted of pain, erythema, edema, inflammation and induration. Although these reactions are common, they usually resolve within 2 days. Flu-like symptoms

including fever, myalgia, arthralgia, fatigue, headaches, rigors and/or musculoskeletal pain have often been observed in subjects treated with CpG.

Among the subjects treated on the Stanford study (Protocol 13956), the treatment was well-tolerated as anticipated. There were mild-to-moderate injection site reactions such as erythema, induration, swelling, warmth, pain. Injections were discontinued early at the discretion of the investigator in one MF subject due to Grade 2 injection site reaction. The systemic adverse events included mild-to-moderate flu-like symptoms, fevers, chills, myalgia, arthralgia, headaches and fatigue. One subject also reported cough, decreased appetite, rhinorrhea and sore throat although this was felt to be not-related. There was one report of dizziness. All adverse events were grades 1 and 2.

Out of the 30 subjects treated in the study using 18 mg of CpG (Protocol 14820), the most commonly reported adverse events were injection site reaction, flu-like symptoms, fatigue, and headache. All adverse reactions were Grade 1 or 2 and most resolved within 2 days. 2 subjects required interruption of injections (one subject received 7 of 10 and one subject received 8 of 10) due to Grade 2 injection site reactions. Another subject had Grade 2 pleural effusion that contained reactive T-cells and the fluid did not recur after drainage.

5.2 Ibrutinib

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (Imbruvica) is approved by the US Food and Drug Administration (FDA) for the treatment of subjects with chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, mantle cell lymphoma, and marginal zone lymphoma who have received at least 1 prior therapy, as well as subjects with CLL with 17p deletion regardless of prior treatment. Ibrutinib is currently being studied in various additional indications including multiple subtypes of non-Hodgkins lymphoma. Ibrutinib is not FDA-approved for the treatment of follicular lymphoma as proposed in this trial.

Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

Pharmacokinetics

Absorption: Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in subjects at 560 mg is 953 ± 705 ng·h/mL and in subjects at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib Cmax and AUC by

approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.

Distribution: Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution at steady state (Vd,ss) was 683 L, and the apparent volume of distribution at steady state (Vd,ss/F) was approximately 10000 L.

Metabolism: Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite-to-parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Elimination: Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [14C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Renal Impairment: Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to ibrutinib. There are no data in subjects with severe renal impairment (CLcr < 25 mL/min) or in subjects on dialysis.

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment trial, a single dose of 140 mg of ibrutinib was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n = 6), moderate (n = 10) and severe (n = 8) hepatic impairment relative to subjects with normal liver function. Ibrutinib Cmax increased 5.2-; 8.8-; and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function.

Drug Interactions

Co-administration of Ibrutinib with CYP3A Inhibitors: In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of ibrutinib was administered alone on Day 1 and a single dose of 40 mg of ibrutinib was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 to 9). Ketoconazole increased ibrutinib dose-normalized Cmax and AUC 29-fold and 24-fold, respectively. Simulations using fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

Co-administration of Ibrutinib with CYP3A Inducers: PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib Cmax and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

Clinical Safety with Ibrutinib

Mantle Cell Lymphoma: The data described below reflect exposure to ibrutinib in a clinical trial that included 111 subjects with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months. The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2). The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections. Fatal and serious cases of renal failure have occurred with ibrutinib therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of subjects. Adverse reactions from the MCL trial (N = 111) using single-agent ibrutinib 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 2: Non-Hematologic Adverse Reactions in ≥ 10% of Subjects with MCL (N = 111)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4(%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative site	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	40
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 3: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Subjects with MCL (N = 111)

	Percent of Subjects (N = 111)	
	All Grades (%)	**Grade 3 or 4(%)**
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Chronic Lymphocytic Leukemia:

The data described below reflect exposure to ibrutinib in a randomized clinical trial that included 391 randomized subjects with previously treated CLL or SLL. The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia. Approximately 5% of subjects in the ibrutinib arm discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of subjects.

Efficacy of Ibrutinib in Follicular Lymphoma

Ibrutinib has been studied in the treatment of subjects with low-grade follicular lymphoma. In a phase 1 study of subjects with relapsed or refractory B-cell malignancies, 13 subjects with follicular lymphoma were evaluated for response to ibrutinib, with 7/13 subjects showing a >50% decrease in sum of the largest diameter of each target lesion (*11*). The MTD in this study was 560 mg daily and this dose showed full-target occupancy. Preliminary results from a phase 2 trial of ibrutinib monotherapy in relapsed/refractory follicular lymphoma showed an overall response rate of 30% in 40 subjects on the intention-to-treat analysis. An additional 14 subjects had reduction of tumor size not meeting response criteria (*12*).

Table 4: Non-Hematologic Adverse Reactions ≥ 10% Reported in CLL

System Organ Class ADR Term	IMBRUVICA (N = 195)		Ofatumumab (N = 191)	
	All Grades (%)	Grade 3 or 4(%)	All Grades (%)	Grade 3 or 4(%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and admin site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term. The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Table 5: Treatment-Emergent Decrease of Hemoglobin, Platelets, or Neutrophils in CLL

Sys	IMBRUVICA (N = 195)		Ofatumumab (N = 191)	
	All Grades (%)	Grade 3 or 4(%)	All Grades (%)	Grade 3 or 4(%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

5.3 Radiotherapy

Pre-clinical and Clinical Studies

Animal studies of subcutaneous tumors have demonstrated that tumor cells undergo apoptosis upon irradiation. Furthermore, it has been shown that dendritic cells migrate towards irradiated tumor (*15*).

The purpose of using low-dose radiation to a single tumor site in our study is to induce tumor necrosis and/or apoptosis, which in turn releases tumor antigens locally. These tumor antigens will be processed by antigen presenting cells to mount a tumor- specific immune response. This immune response will be augmented by intratumoral injection of SD-101, which is a potent immunostimulant.

Low-dose (2 Gy x 2) radiotherapy has been studied in recurrent follicular lymphoma (*16*). The overall local tumor response rate is estimated at 80 to 90%. The reason for choosing a low-dose radiation is that the low-dose therapy is sufficient to induce tumor cell death and will not jeopardize subjects' opportunity to receive standard radiotherapy at the same anatomic site in the future. Another potential advantage of using a low-dose radiation regimen is to minimize the possibility that the radiation will inhibit tumor-infiltrating dendritic cell functions.

Radiotherapy: Dosage

All subjects will receive 2 Gy radiation to a single tumor site on each of 2 consecutive days (Day 1 and Day 2).

5.4 Availability

SD-101 will be supplied by DynaVax Technologies Corporation. Ibrutinib will be supplied by Janssen Scientific Affairs, LLC.

5.5 Agent Ordering

Describe how the agent will be requested and provide mailing address and phone number.

SD-101 will be requested and ordered directly from:

Dynavax Technologies
2929 Seventh Street, Suite 100
Berkeley, CA 94710

Ibrutinib will be requested by the study site investigational pharmacy.

5.4 Agent Accountability

Supplies of the SD-101 and ibrutinib will be stored in the Stanford University Medical Center Investigational Pharmacy in a secure location with restricted access. The Investigational Pharmacist will maintain drug accountability records.

6. DOSE MODIFICATIONS

6.1 Dose/ Schedule Modifications of SD-101

The SD-101 dose of will not be reduced except by the rules listed in the study design. In the case of adverse events affecting the feasibility or safety of injection, as judged by the investigator, injections may be delayed or omitted until resolution of the adverse event to Grade ≤1 or baseline and after re-assessment by investigator. When doses are delayed, all five intratumoral injections may still be delivered, provided all five are given within a span of 8 weeks and there is a minimum interval of 3 days between injections. In the case of local injection site reactions that cause dose delays or modifications and are not DLTs, the Investigators are asked to avoid administering subsequent injections near to this site and to document the reaction with a photograph when possible.

6.2 Re-Treatment after Hypersensitivity Reaction (HSR) for SD-101

All subjects must be observed for at least 30 minutes after administration of SD-101 for onset of acute hypersensitivity reactions. All hypersensitivity should be appropriately managed according to standard local practice.

Following treatment-related anaphylaxis (any grade) or grade 3-4 non-anaphylactic hypersensitivity reaction (urticaria, serum sickness, Stevens-Johnson Syndrome, or Toxic Epidermal Necrolysis) occurring after intratumoral treatments, all study agents will be permanently discontinued for that patient. Following a Grade 2 treatment-related non-anaphylactic hypersensitivity reaction, re-treatment may be considered following discussion and with an explicit agreement from the Investigator and the patient. Premedication with antihistamines and acetaminophen with or without a corticosteroid is recommended for subsequent treatments.

6.3 Dose Modifications for Ibrutinib

Ibrutinib dose modifications may occur starting on Day 31. Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, this will be considered a DLT. Doses of ibrutinib may be held for surgeries or procedures as listed below in Section 4.9.2. Dose of ibrutinib will be reduced by 140 mg daily if chronic treatment with a moderate CYP3A inhibitor is required (see Section 4.9.2).

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Overview:

As the sponsor of the Study, the Sponsor Investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. Safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

7.2 Management of Safety Data:

All adverse events regardless of causality and special situations and product quality complaints with or without an adverse event will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be recorded and reported starting from when the subject signs the informed consent form and will continue until 30 days after the last dose of study drug.

Definitions:

Adverse Events (AEs): An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious Adverse Event (SAE): An adverse event which meets one or more the following criteria is considered serious.

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs insubject hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.
- Is medically important

Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject

or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization:

For reports of hospitalization, details of the sign, symptom or diagnosis which led to the hospitalization must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)

Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-threatening Conditions:

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

Adverse Events of Special Interest:

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Major Hemorrhage

  Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

- Intracranial Hemorrhage

  Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

- Other Malignancies

  In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Unanticipated (Unlisted) Problem Involving Risks to Participants or Others (UPs):

Adverse Event that is:

Unexpected: Not in the consent form, investigator brochure, protocol, package insert, or label, or unexpected in its specificity, severity or frequency AND

Related to the research: Caused by, or probably caused by research activity. Events caused by progression of underlying disease are NOT related. If a device is involved; the event was caused by, or associated with the device AND caused harm or increased risk of harm: Involves harm to participants or others, or places participants or others at increased risk of harm.

Unlisted adverse events related to the drug ibrutinib:

An adverse event will be considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.imbruvica.com/

Product Quality Complaint (PQC):

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: eg, altered delivery rate in a controlled release product
- Physical Defect: eg, abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: eg, autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

7.3 Assessing Adverse Events:

Events must be assessed by the investigator as to whether they are unexpected, related to the research procedures, and/or harmful. To qualify as an unanticipated problem involving risks to participants or others (UP), an event must be Unexpected and Related and Harmful.

7.4 Adverse Event Reporting Requirements

7.4.1 Adverse Events

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study-specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious

Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the last dose of the study treatment.

Adverse events, which are not serious, should be captured in the CRF. The research team will meet regularly to discuss AEs being experienced by the participants.

7.4.2 Serious Adverse Events

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study-specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences. Deaths within 30 days of a subject being treated with the study drug will be reported within 5 days, all other SAEs will be reported within 10 days of the SI becoming aware of the event. All SAEs which are possibly or definitely related to the study will be reported to DynaVax using the MedWatch 3500a form within 24 hours of the SI being informed of the event.

7.4.3 Requirements related to reporting to Janssen Scientific Affairs, LLC

In addition to the above reporting, the SI will use the following guidelines in reporting adverse events and product quality complaints to Janssen Scientific, LLC.

Maintenance of Safety Information

All safety data will be maintained in a clinical database in a retrievable format. The Sponsor Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, eg, to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators will record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts

The Sponsor Investigator will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section Transmission Methods, in English within 24-hours of becoming aware of the event(s).

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of subject withdrawal must be reported directly by the Sponsor Investigator, within 24 hours becoming aware, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report .

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

The Sponsor Investigator is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch no. s shall be collected or any reports failure of expected pharmacological action (ie, lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the Sponsor Investigator within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A

sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the Sponsor Investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC

8. CORRELATIVE/SPECIAL STUDIES

8.1 Blood and tissue acquisition

Research blood draws will be processed within the laboratory of Ronald Levy at Stanford University and stored as cryopreserved peripheral blood mononuclear cells (green top tubes) and plasma (purple top tubes).

Excisional lymph node biopsy prior to first dosing, which will be processed and stored as single cell suspensions within the laboratory of Ronald Levy at Stanford University.

FNA biopsies will be processed within the laboratory of Ronald Levy at Stanford University and stored as single cell suspensions.

Leukapheresis to obtain peripheral blood mononuclear cells (PBMC) may be performed during the screening period (prior to Day 1) and at Day 37, if excisional biopsy is obtained at screening.

8.2 Storage of blood and tissue samples

Samples will be stored as viable single cells suspensions in liquid nitrogen and cell-depleted serum at -80°C within the laboratory of Ronald Levy at Stanford University. Remaining unused samples will be stored for potential future correlative studies including flow cytometric studies with additional potential biomarkers, gene expression analysis, and high-throughput sequencing of immunoglobulin and T-cell receptors.

Access to samples will be limited only to research personnel involved in performing the correlative studies. Samples will be labeled with a unique subject identification code and all sample consent, acquisition, handling, storage and processing will be in accordance with

HIPAA and any other state or federal laws or regulations concerning the use or storage of human tissue for research purposes.

8.3 Lymphocyte activity against autologous tumor (performed if adequate tumor sample):

PBL and/or PBMCs will be obtained from all subjects, as described above, cryopreserved, and thawed, then used to for detection of tumor-specific T-cell responses by flow cytometry.

Autologous tumors undergo negative selection with antibody-bound paramagnetic beads and are then activated for 72 hours with CpG. These activated tumor B-cells are irradiated to 50 Gy in a Cesium-137 irradiator then used as stimulator cells in 24 hour co-culture with autologous subject PBMCs collected at the specified time points. Negative controls run in parallel include PBMC incubated with media alone. Positive controls for lymphocyte functional capacity will include anti-CD3 plus anti-CD28 stimulation. After co-culture, PBMC are stained for CD4; CD8; and a panel of T cell activation associated markers. Tumor-specific immune responses are calculated as the increase in percentage of activated T-cell subsets (CD4 or CD8) specifically in response to co-culture with autologous tumor at post-treatment time points compared to pre-treatment time points.

8.4 Immunophenotyping of treated and untreated tumor sites

Cells recovered from fine needle aspiration of treated and any easily accessible untreated sites will be processed for analysis by flow cytometry. Multiparameter flow will be performed at the various time points to define immune populations including CD4 and CD8 T-cells, regulatory T-cells, follicular helper T-cells, B-cells (including the malignant B-cells), natural killer cells, dendritic cells and macrophages. The extent of immunophenotyping will depend on the availability of cells from each biopsy.

8.5 Anti-tumor antibody response (performed if adequate tumor sample):

For IgM expressing lymphomas, pre – and post – treatment serum will be incubated with autologous tumor cells, followed by staining with FITC-labeled anti-human IgG antibodies and detection by flow cytometry. Additionally, Western blotting of tumor cell lysate using sera followed by anti-human IgG detectors may be performed and anti-idiotypic humoral responses may be assayed.

9. STUDY CALENDAR

Procedures	Screen	Day 1 Week 1 **RT**	Day 2 Week 1 **RT** **IT SD-101**	Day 4 Week 1 **FNA** (optional)	Day 9 Week 2 **FNA** **IT SD-101** **Ibrutinib**	Day 16 Week 3 **IT SD-101**	Day 23 and 30 Week 4 and 5 **IT SD-101**	Day 37 Week 6 **Safety Assessment**	Weeks 12, 24, 36, 48, 60, 72, 84 **Safety and Response Evaluation**	Final Study Visit
Visit Windows				+/- 1 day	+/- 2 days	+/- 2 days	+/- 2 days	+/-7 days	+/- 10 days	
Written Informed Consent	X									
Inclusion/Exclusion Criteria	X									
History and Physical Exam	X								X	X
Adverse Event Evaluation			X		X	X	X	X	X	X
Concomitant Medication	X		X		X	X	X	X	X	X
Vital Signs and Performance Status	X		X		X	X	X	X	X	X
Urine Pregnancy Test	X [1]									
Tumor Biopsy [2] (optional)	X [2]									
Fine needle aspiration	X [3]			X [3]	X [3]			X [3]		X [3]
Research Blood Samples [4]	X				X		X [5]	X	X	X
CBC with differential	X				X		X [6]	X	X	X
Comprehensive Metabolic Panel	X				X		X [6]	X	X	X
HIV and hepatitis testing	X [7]									
LDH	X								X	X
Radiation		X(2 Gy)	X (2 Gy)							
SD-101 Injection			X [8]		X [8]	X [8]	X [8]			
Ibrutinib supply dispensed					X			X [9]	X [9]	
Imaging Studies (CT)	X								X [14]	X [10]
Bone Marrow Biopsy (conditional) [11]									X [11] (optional)	X [11] (optional)
Apheresis [12] (conditional)	X [12]							X [12]		
Additional Research Peripheral Blood [13] (conditional)	X [13]				X [13]	X [13]		X [13]	X [13]	X [13]

[1] Pregnancy test - for women of childbearing potential only

[2] Tumor excisional biopsy (optional) to be done during screening if indicated to rule out transformation. Tissue not needed for clinical diagnostics may be collected for use in correlative studies

[3] Fine needle aspiration of the tumor site chosen for treatment at screening, Day 9 (prior to second SD-101 injection) and Day 37. Optional FNA on Day 4. Fine needle aspiration of additional tumor (outside of the radiation field) to be done concurrently if amenable to biopsy.

[4] Consisting of 1 purple top tube.

[5] The indicated research labs are collected on Day 23 and not Day 30

[6] CBCD and CMP monitoring to be done at Day 23 and not Day 30

[7] Hepatitis and HIV testing to include hepatitis B surface antigen, anti-HBc antibody, anti-HCV antibody, and anti-HIV antibody

[8] Subjects must be monitored at least 30 minutes after all injections of SD-101 before discharge

[9] Ibrutinib to be self-administered by subject starting on Day 10 and continuing daily until Week 96, disease progression, or removal from study. Event indicates dispensing of supply.

[10] Imaging performed at final study visit only if there has not been interval imaging within the last 4 weeks

[11] Bone marrow biopsy (conditional) only if subject achieves a complete response by imaging to confirm complete response

[12] Apheresis (conditional) only if subject had excisional biopsy prior to treatment with sufficient sample to perform immune assay correlative study or, optionally, if patient has circulating lymphoma cells.

[13] 7 green top tubes to be collected: This collection will occur for all patients at Day 9, Day 16, Week 12, and final study visit. Additionally, 7 green top tubes (conditional) will be collected for patients not undergoing apheresis at the following timepoints: screening and Day 37.

[14] CT scans to be performed on Weeks 12; 24; 48; 72

10. MEASUREMENTS

10.1 Phase 1B - Primary Outcome Measure

The primary outcome measure for the phase 1b portion will be the observation of **dose-limiting toxicity**. This outcome measure assesses a safety issue. The outcome will be measured at each visit during the trial.

10.1.1 Dose-Limiting Toxicity Definition

DLTs are defined as:

Days 1-30:

- Any Grade 4 treatment-related toxicity;
- Any Grade ≥ 3 treatment related toxicity persisting despite adequate/maximal medical therapy and/or prophylaxis. [NOTE: Grade 3 or lower treatment related skin rash not requiring systemic steroid therapy or other immunosuppressive therapy or Severe (Grade 3) flu-like symptoms are not considered DLTs. Grade 3 rash may be treated by withholding ibrutinib and/or systemic corticosteroids for up to 7 days. If rash resolves or improves to Grade 1, subjects may be restarted at the same dose of ibrutinib. If Grade 3 rash recurs upon restarting ibrutinib, then this will be considered a DLT];
- Any Grade ≥ 3 non-hematologic study drug-related toxicity will be considered a dose-limiting toxicity
- Any Grade ≥ 3 hematological study drug-related toxicity
- Grade ≥ 3 treatment related clinical autoimmune reaction involving major organs, which are defined as liver, pancreas, lung, heart, kidney, bowel, bone marrow and CNS (including the eye) which does not resolve to baseline or Grade 1 within 6 weeks;
- Grade ≥ 3 Injection Site Reaction;

Days 31-731:

- Any Grade 4 treatment related non-hematologic toxicity;
- Any Grade ≥ 3 treatment related toxicity persisting despite adequate/maximal medical therapy and/or prophylaxis. [NOTE: Grade 3 or lower treatment related skin rash not requiring systemic steroid therapy or other immunosuppressive therapy or Severe (Grade 3) flu-like symptoms are not considered DLTs];
- Grade ≥ 3 treatment related clinical autoimmune reaction involving major organs, which are defined as liver, pancreas, lung, heart, kidney, bowel, bone marrow and CNS (including the eye) which does not resolve to baseline or Grade 1 within 6 weeks
- Any Grade ≥ 3 hematologic toxicity that persists despite protocol-defined dose-modification of ibrutinib. (see Section 4.1)

10.1.2 Measurement Methods

Dose-limiting toxicity will be assessed using CTCAE v4.0.

10.1.3 Measurement Time Points

Dose-limiting toxicity will be assessed continuously throughout the trial. Adverse event information will be collected at each visit. Safety labs will be collected on Days 9; 23; 37; week 12; and every 12 weeks thereafter until the final study visit.

10.2 Phase 2 - Primary Outcome Measure

The primary outcome measure for the phase 2 portion will be to evaluate the response rate of intratumoral SD-101 in combination with ibrutinib and radiation in subjects.

10.2.1 Relevant Subset

This outcome will be measured on any individual who has received at least one intratumoral injection of SD-101 at the recommended phase 2 dose level. This will include any subjects treated during the phase 1B portion who were treated at the recommended phase 2 dose level.

10.2.2 Response Definition

Tumor response rates (CR, PR) will be calculated based on the Lugano classification (*51*) for low-grade B-cell lymphomas.

Definition of Measurable and Non-Measurable Lesions

Measurable Lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.

Non-Measurable (evaluable) Lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:

- Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.
- All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

Definition of Index/Non-Index Lesions

All measurable lesions, up to a maximum of **5 lesions per organ** and **10 lesions in total,** should be identified as *index* lesions to be measured and recorded on the medical record at Screening. The *index* lesions should be representative of all involved organs. In addition, *index* lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a sum of the products of diameters (SPD) for all *index* lesions will be calculated and considered the baseline sum of the products of diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the *index* lesions at tumor assessment (TA).

Measurable lesions, other than *index* lesions, and all sites of non-measurable disease, will be identified as *non-index* lesions. *Non-index* lesions will be recorded on the medical record and should be evaluated at the same assessment time points as the *index* lesions. In subsequent

assessments, *non-index* lesions will be recorded as "stable or decreased disease," "absent," or "progression."

Definition of Response

Response will be based upon the Lugano Classification (Table 6). To better assess systemic responses, an additional response assessment will be reported which will exclude any index lesions which were within the irradiation field. Overall response will include both complete and partial responses.

Table 6. IRB-36750 response based upon the Lugano Classification

Response and Site	CT-Based Response
Complete	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	No extralymphatic sites of disease
Nonmeasured lesion	Absent
Organ enlargement	Regress to normal
New lesions	None
Bone marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	When no longer visible, 0 × 0 mm
	For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Absent/normal, regressed, but no increase
Organ enlargement	Spleen must have regressed by > 50% in length beyond normal
New lesions	None
Bone marrow	Not applicable
No response or stable disease	**Stable disease**
Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	No increase consistent with progression
Organ enlargement	No increase consistent with progression
New lesions	None
Bone marrow	Not applicable
Progressive disease	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	PPD progression:

Table 6. IRB-36750 response based upon the Lugano Classification

Response and Site	CT-Based Response
Extranodal lesions	An individual node/lesion must be abnormal with:
	LDi > 1.5 cm and
	Increase by ≥ 50% from PPD nadir and
	An increase in LDi or SDi from nadir
	0.5 cm for lesions ≤ 2 cm
	1.0 cm for lesions > 2 cm
	In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
	New or recurrent splenomegaly
Nonmeasured lesions	New or clear progression of preexisting nonmeasured lesions
New lesions	Regrowth of previously resolved lesions
	A new node > 1.5 cm in any axis
	A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
	Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent involvement

Table 3. LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions

10.2.3 Measurement Methods

Response assessment will be performed based on CT imaging. CT scan is the preferred mode of imaging, however, if a CT scan is contraindicated or if it is felt by the Sponsor Investigator that a PET/CT will be a better modality to assess a particular subject, a PET/CT may be used for evaluation.

10.2.4 Measurement Time Points

Subjects will undergo imaging studies at screening, and at the 12 Week visit. Imaging will be performed at Week 24 as part of routine follow-up and to assess safety and response. Subsequent imaging as part of routine follow-up will be done every 3 to 6 months.

10.3 Phase 2 - Secondary Outcome Measure – Progression free survival

The secondary outcome measure for the phase 2 portion will be progression-free survival.

10.3.1 Relevant Subset

This outcome will be measured on any individual who has received at least one intratumoral injection of SD-101 at the recommended phase 2 dose level. This will include any subjects treated during the phase 1B portion who were treated at the recommended phase 2 dose level.

10.3.2 Progression-free Survival Definition

Progression-free Survival is defined as the time elapsed between treatment initiation (Day 1) and tumor progression or death from any cause. Progression will be defined using the Lugano Classification (Section 10.2.2, Table 6). It is recommended in difficult cases to confirm PD by serial imaging. If it is felt by the Sponsor Investigator that a participant may be experiencing immune-related pseudoprogression resulting in PD, then at the discretion of the Sponsor Investigator, that participant may continue on study until the next response assessment. Participants who meet the definition for PD on two consecutive response assessments will be assessed as PD and treatment must be discontinued

10.3.3 Measurement Methods

Progression will be assessed based on CT imaging. CT scan is the preferred mode of imaging, however, if a CT scan is contraindicated or if it is felt by the Sponsor Investigator that a PET/CT will be a better modality to assess a particular subject, a PET/CT may be used for evaluation.

10.3.4 Measurement Time Points

Subjects will undergo imaging studies at screening, and at the 12 Week visit. Imaging will be performed at Week 24 as part of routine follow-up and to assess safety and response. Subsequent imaging as part of routine follow-up will be done every 3 to 6 months.

10.4 Phase 2 - Secondary Outcome Measure – Induction of tumor-specific immune responses

An additionally exploratory secondary outcome measure for the phase 2 portion will be the induction of tumor-specific immune responses.

10.4.1 Relevant Subset

This outcome will be measured on any individual who has received at least one intratumoral injection of SD-101 at the recommended phase 2 dose level. This will include any subjects treated during the phase 1B portion who were treated at the recommended phase 2 dose level. This analysis will be limited to individuals with adequate research samples collection to perform the required assays.

10.4.2 Tumor-specific Immune Response Definition

Tumor-specific immune responses will be defined as lymphocyte activity against autologous tumor over the baseline of activity against media only.

10.4.3 Measurement Methods

Tumor-specific immune responses will be assayed as in section 8.3, *Lymphocyte activity against autologous tumor*.

10.4.4 Measurement Time Points

Tumor-specific immune responses are calculated as the increase in percentage of activated T-cell subsets (CD4 or CD8) specifically in response to co-culture with autologous tumor at

post-treatment time points compared to pre-treatment time points. All post-treatment time points will be evaluated, but the primary timepoint for analysis will be from Day 37 samples.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director and Coordinator will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Case Report Forms (CRFs) are printed to record all protocol-related information on each trial participant. CRFs will summarize the clinical findings and observations necessary to ensure safety of participants on the study. CRF design and creation will be completed prior to enrollment of the first participant. The plan is to work with the OnCore Team **CCTO-OnCore@stanford.edu** for CRF design and storage as well as in all subject binders that will include same CRFs to be kept locked in the lymphoma research area.

These study-specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the above mentioned OnCore database system and will be maintained by the OnCore team, Research Coordinator and Protocol Director. CRFs will be kept in a locked office, only accessible to the research team.

11.4 Confidentiality

Subject records will be kept in a secure location at Stanford University Medical Center, accessible only to research authorized personnel. The subject identity will be kept as confidential as possible as required by law. Except as required by law, the subject will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study subjects 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 subject identity will not be disclosed. The subject's personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

The phase 1B portion of this trial is designed to allow preliminary assessments of safety and biological activity. No pre-specified hypothesis testing will be performed.

The phase 2 portion of this trial will be powered to detect an improvement in response equal to the combined overall response rate of each intervention alone (SD-101 and ibrutinib)

12.2 Primary Analysis

12.2.1 Analysis Population

Phase 1B – Safety

The safety population will consist of all enrolled subjects who received at least one dose of any study treatment. The safety population will be used for the analysis of safety data.

Phase 2 – Efficacy

The response-evaluable population is defined as all enrolled subjects who received at least one dose of study treatment (ibrutinib or SD-101) and provided at least one post-baseline response (or disease) assessment. The response-evaluable population will be used as the primary population for analyses based on overall response.

12.2.2 Analysis Plan

The phase 1B portion of this trial is designed to allow preliminary assessments of safety and biological activity. No pre-specified hypothesis testing will be performed.

The phase 2 portion of this trial will be powered to detect an improvement in response equal to the combined overall response rate (ORR) of each intervention alone (SD-101 and ibrutinib).

12.3 Sample Size

12.3.1 Accrual estimates

Sample Size – Dose Escalation Cohorts

6 to 15 subjects may be enrolled in the dose de-escalation cohorts in a 6+3 study design.

Sample Size – Phase 2 Expanded Cohort

15 subjects will be enrolled in the phase 2 expanded cohort.

We estimate accruing an average of 10 subjects per year based on prior experience with this subject population. The Stanford STRIDE database reports 40 subjects with BOTH an ICD9 diagnosis of nodular lymphoma (202.0) AND encounter for antineoplastic chemotherapy and immunotherapy (V58.1) occurring in the year 2015 – indicating the number of subjects with this diagnosis who required treatment in the prior calendar year.

12.3.2 Sample size justification

The reported overall response rate with single-agent ibrutinib in a similar population of relapsed/refractory low-grade follicular lymphoma has been 30% (12 of 40 subjects) (*12*), and

we previously reported an ORR of 27% to intratumoral CpG (4 of 15 subjects) (*50*). We will therefore expect overall response rate of >57% (ie, a 27% improvement over ibrutinib alone).

This trial design will enroll a minimum of 21 subjects at the recommended phase 2 dose (a minimum of 6 subjects in phase 1b and 15 subjects in the phase 2 expansion). For a true response rate of 57%, this sample size will provide 83.6% power to detect a significantly improved (95% confidence interval) response rate as compared to the previously reported ORR of 30% with ibrutinib alone.

A total of 6 to 15 subjects will be enrolled in the phase 1B 6 x 3 dose de-escalation portion. An additional 15 subjects will be enrolled in the expanded phase 2 cohort.

If ≤ 1/6 subjects experience a DLT at a dose of intratumoral SD-101 of 3 mg, we will proceed to the expansion phase. If 2/6 subjects experience a DLT at 3 mg, then an additional 3 subjects will be enrolled in the same dosing cohort. If ≥ 3 of 6 to 9 subjects experience a DLT, then a dose de-escalation cohort -1 of 6 subjects will be opened.

The sample size of 15 subjects in the expanded phase 2 cohort (with resulting total number of 21 to 24 subjects at the RP2D in the combined 1b/2 phases) allows estimation of the response rate +/- 0.21 with 90% confidence. The chance of obtaining three or fewer responses out of 15 is only 2.1% if the true response rate is 49%, with 49% ORR being a historical benchmark for response rate in this population.

12.3.3 Effect size justification

The reported overall response rate with single-agent ibrutinib in a similar population of relapsed/refractory low-grade follicular lymphoma has been 30% (12/40 subjects) (*12*), and we previously reported an ORR of 27% to intratumoral CpG (4/15 subjects) (*50*).

12.4 Criteria for future studies

If the results are promising, we will also consider future trials, broadening the selection criteria to include other types of lymphoma. If we do not detect at least 6 responses in this first trial we will consider designing a new trial with a different dose and/or schedule of SD-101 and ibrutinib, depending on what is learned from the immune response evaluations. We will also consider initiating a different trial testing another immune stimulant, depending on the results of our pre-clinical animal models.

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APPENDICES

APPENDIX A: Participant Eligibility Checklist

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the subject's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	Intratumoral Injection of SD-101, an Immunostimulatory CpG, in combination with Ibrutinib and Local Radiation in Low-Grade Follicular Lymphoma
Protocol Number:	**IRB-36750 / LYMNHL0135**
Principal Investigator:	**Ronald Levy, MD**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Biopsy-confirmed Grade 1 or 2, or 3A follicular lymphoma; mantle cell lymphoma; or marginal zone lymphoma. Subjects must have relapsed from or are refractory to prior therapy.	☐	☐	
2. Subjects must have at least one site of disease that is accessible for intratumoral injection of SD-101 (diameter ≥ 10mm), percutaneously.	☐	☐	
3. Subjects must have at least one site of measurable disease other than the injection site which is not included in the radiation field.	☐	☐	
4. ECOG Performance Status of 0 or 1	☐	☐	
5. Subjects must be 18 years of age or older.	☐	☐	

6. Required values for initial laboratory tests: a) Absolute neutrophil count (ANC) $\geq 1000/mm^3$ independent of growth factor support b) Platelets: $\geq 100,000/mm^3$ or $\geq 50,000/mm^3$ if bone marrow involvement independent of transfusion support in either situation c) Hemoglobin: ≥ 8 g/dL (may be transfused) d) Creatinine: Creatinine clearance > 25 mL/min e) AST/ALT: ≤ 3 x ULN f) Bilirubin: ≤ 1.5 x ULN (except for subjects with Gilbert's Syndrome or of non-hepatic origin)	☐	☐	
7. Must be at least 4 weeks since treatment with standard or investigational chemotherapy, biochemotherapy, major surgery, radiation, cytokine therapy, and 8 weeks since any monoclonal antibodies or immunotherapy, and recovered from any clinically significant toxicity experienced during treatment.	☐	☐	
8. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.	☐	☐	
9. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study	☐	☐	
10. Life expectancy greater than 4 months.	☐	☐	
11. Able to comply with the treatment schedule.	☐	☐	
12. Ability to understand and the willingness to sign a written informed consent document.	☐	☐	

Exclusion Criteria (From IRB approved protocol)			
1. Autoimmune disease requiring treatment within the last 5 years including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, autoimmune thrombocytopenia, uveitis, or other if clinically significant	☐	☐	
2. Major surgery or a wound that has not fully healed within 4 weeks of enrollment.	☐	☐	
3. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.	☐	☐	
4. Requires anticoagulation with warfarin or equivalent vitamin K antagonists.	☐	☐	
5. Requires chronic treatment with strong CYP3A inhibitors.	☐	☐	
6. Vaccinated with live, attenuated vaccines within 4 weeks of enrollment.	☐	☐	
7. Known history of human immunodeficiency virus (HIV) or active Hepatitis C Virus or active Hepatitis B Virus infection or any uncontrolled active systemic infection.	☐	☐	
8. Known CNS lymphoma.	☐	☐	
9. Subjects with a history of prior malignancy with the exception of non-melanoma skin cancer, carcinoma in situ of the cervix, in situ carcinoma of the bladder, stage 1 prostate cancer that does not require treatment, or other malignancy that has undergone potentially curative therapy with no evidence of disease for the last > 2 years and that is deemed by the investigator to be a low risk for recurrence.	☐	☐	
10. History of allergic reactions attributed to compounds of similar composition to SD-101 or ibrutinib	☐	☐	

11. Treatment with an immunosuppressive regimen of corticosteroids or other immunosuppressive medication (eg, methotrexate, rapamycin) within 30 days of study treatment. Note: subjects may take up to 5 mg of prednisone or equivalent daily. Topical and inhaled corticosteroids in standard doses are allowed.	☐	☐	
12. Significant cardiovascular disease (ie, NYHA class 3 congestive heart failure; myocardial infarction with the past 6 months; unstable angina; coronary angioplasty with the past 6 months; uncontrolled atrial or ventricular cardiac arrhythmias).	☐	☐	
13. Pregnant or breast feeding.	☐	☐	
14. Any other medical history, including laboratory results, deemed by the investigator to be likely to interfere with their participation in the study, or to interfere with the interpretation of the results.	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

APPENDIX B: Definition of Tumor Response Using irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* and all new measurable lesions (ie, Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥ 25% when compared to SPD at nadir.
- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- irProgressive Disease (irPD): At least 25% increase Percentage Change in Tumor Burden (ie, taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR) or irStable Disease (irSD): *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- irProgressive Disease (irPD): Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (ie, the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- Immune-Related Complete Response (irCR): Complete disappearance of *all* tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- Immune-Related Partial Response (irPR): The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline.

At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).

- Immune-Related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- Immune-Related Progressive Disease (irPD): It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  - At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.
  - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Table 7: Immune-Related Response Criteria Definitions

Index Lesion Definition	**Non-Index Lesion Definition**	**New Measurable Lesions**	**New Unmeasurable Lesions**	**% change in tumor burden** (including measurable new lesions when present)	**Overall irRC Response**
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
				< -50% to < +25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	< -50% to < +25%	irSD
				> +25%	irPD
Progressive Disease	Any	Any	Any	≥ +25%	irPD

Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

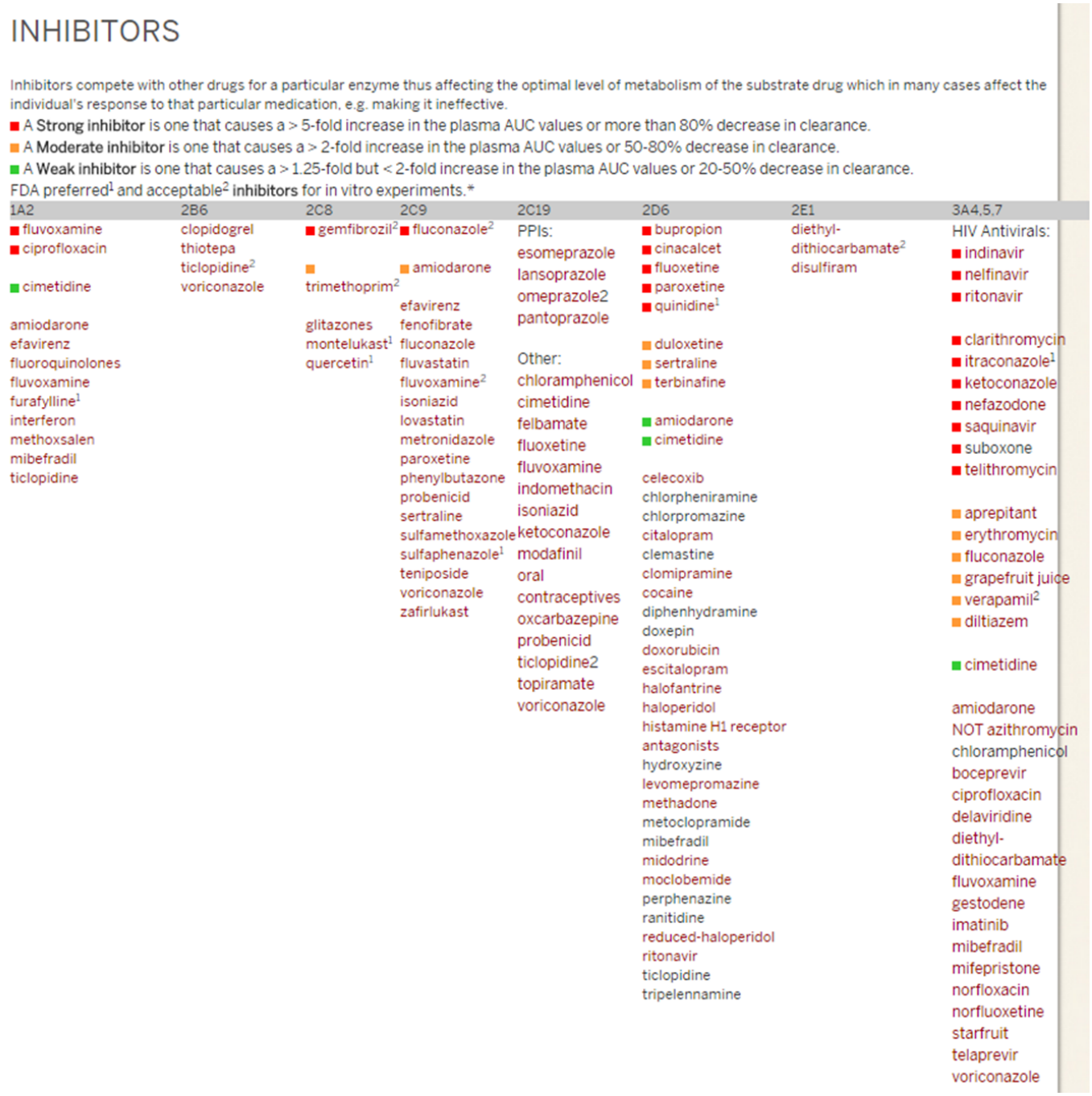
irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

APPENDIX C: ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX D: List of P450 inhibitors and inducers

A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/



INHIBITORS

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g. making it ineffective.

- A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments.*

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
fluvoxamine	clopidogrel	gemfibrozil[2]	fluconazole[2]	PPIs:	bupropion	diethyl-dithiocarbamate[2]	HIV Antivirals:
ciprofloxacin	thiotepa			esomeprazole	cinacalcet	disulfiram	indinavir
	ticlopidine[2]		amiodarone	lansoprazole	fluoxetine		nelfinavir
cimetidine	voriconazole	trimethoprim[2]		omeprazole2	paroxetine		ritonavir
			efavirenz	pantoprazole	quinidine[1]		
amiodarone		glitazones	fenofibrate				clarithromycin
efavirenz		montelukast[1]	fluconazole	Other:	duloxetine		itraconazole[1]
fluoroquinolones		quercetin[1]	fluvastatin	chloramphenicol	sertraline		ketoconazole
fluvoxamine			fluvoxamine[2]	cimetidine	terbinafine		nefazodone
furafylline[1]			isoniazid	felbamate			saquinavir
interferon			lovastatin	fluoxetine	amiodarone		suboxone
methoxsalen			metronidazole	fluvoxamine	cimetidine		telithromycin
mibefradil			paroxetine	indomethacin			
ticlopidine			phenylbutazone	isoniazid	celecoxib		aprepitant
			probenicid	ketoconazole	chlorpheniramine		erythromycin
			sertraline	modafinil	chlorpromazine		fluconazole
			sulfamethoxazole	oral	citalopram		grapefruit juice
			sulfaphenazole[1]	contraceptives	clemastine		verapamil[2]
			teniposide	oxcarbazepine	clomipramine		diltiazem
			voriconazole	probenicid	cocaine		
			zafirlukast	ticlopidine2	diphenhydramine		cimetidine
				topiramate	doxepin		
				voriconazole	doxorubicin		amiodarone
					escitalopram		NOT azithromycin
					halofantrine		chloramphenicol
					haloperidol		boceprevir
					histamine H1 receptor antagonists		ciprofloxacin
					hydroxyzine		delaviridine
					levomepromazine		diethyl-dithiocarbamate
					methadone		fluvoxamine
					metoclopramide		gestodene
					mibefradil		imatinib
					midodrine		mibefradil
					moclobemide		mifepristone
					perphenazine		norfloxacin
					ranitidine		norfluoxetine
					reduced-haloperidol		starfruit
					ritonavir		telaprevir
					ticlopidine		voriconazole
					tripelennamine		

This website is continually revised and should be checked frequently for updates.

APPENDIX E: Contraception Guidelines

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects who are WOCBP are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Male subjects are expected to use a condom, in addition to a highly effective method as noted in the list below:

1. Progestogen only hormonal contraception associated with inhibition of ovulation
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen and progesterone, vaginal ring, injectables, implants, and hormonal intrauterine devices (IUDs), such as Mirena
3. Nonhormonal IUDs, such as ParaGard
4. Bilateral tubal occlusion
5. Vasectomized partner with documented azoospermia 90 days after procedure

- Vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

6. Intrauterine hormone-releasing system
7. Complete abstinence
    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse
    - Complete abstinence is an acceptable form of contraception and must be used throughout the duration of the study treatment plus an additional 160 days
    - No additional method of contraception is required when complete abstinence is elected.
    - Participant WOCBP who choose complete abstinence must continue to have pregnancy tests at screening and within 72 hours prior to each study treatment.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
8. Use a condom in male subjects with female partners.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, and/or post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method
5) Diaphragm with spermicide
6) Cervical cap with spermicide
7) Vaginal sponge with spermicide
8) Male or female condom with or without spermicide*
9) Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

* A male and a female condom must not be used together.