Sponsor: Dynavax Technologies

Protocol Identifier: DV3-LYM-01

Protocol Title: A Phase 1/2, Non-randomized, Open-label, Multicenter, Dose Escalation and Expansion Study of Intratumoral Injections of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma

Document: Protocol Amendment 4.0
Document Date: 21 Mar 2016

NCT #: NCT02266147

Protocol Title:	A Phase 1/2, Non-randomized, Open-label, Multicenter, Dose Escalation and Expansion Study of Intratumoral Injections of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma
Protocol No.:	DV3-LYM-01
Investigational Product:	SD-101
US IND No.:	122809
Study Phase	Phase 1/2
Sponsor:	Dynavax Technologies Corporation 2929 Seventh Street, Suite 100 Berkeley, CA 94710 United States of America
Medical Monitor:	Craig Berman, MD, Medical Monitor Dynavax Technologies Corporation Tel: (510) 665- 0451 Fax: (510) 848-1327 E-mail: cberman@dynavax.com
Clinical Operations:	Marissa Ramirez Associate Director, Clinical Operations Dynavax Technologies Corporation Tel: +1 510 665-4626 Fax: +1 510 848-9750 E-mail: mramirez@dynavax.com
Principal/Coordinating Investigator:	Ronald Levy, MD Professor of Medicine Division of Oncology Stanford Medical Center 269 Campus Drive, CCSR 1105 Stanford, CA 94305 E-mail: levy@stanford.edu
Original Protocol:	08 May 2014
Amendment #1:	24 June 2014
Amendment #2:	10 April 2015
Amendment #3:	05 November 2015
Amendment #4:	21 March 2016

This study will be conducted in accordance with good clinical practice (GCP) as defined in International Conference on Harmonisation (ICH) guidelines and applicable local legal and regulatory requirements.

PROTOCOL APPROVAL PAGE

Protocol Title: A Phase 1/2, Non-randomized, Open-label, Multicenter, Dose Escalation and Expansion Study of Intratumoral Injections of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma

Protocol No.: DV3-LYM-01

Original Protocol: 08 May 2014

Amendment #1: 24 June 2014

Amendment #2: 10 April 2015

Amendment #3: 05 November 2015

Amendment #4: 21 March 2016

Sponsor: Dynavax Technologies Corporation
2929 Seventh Street, Suite 100
Berkeley, CA 94710
United States of America

This protocol has been approved by Dynavax Technologies Corporation. The following signature documents this approval.

21 MAR 2016

Robert Janssen, MD
Chief Medical Officer and Vice President, Clinical Development and Regulatory Affairs

Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 1/2**,** Non-randomized, Open-label, Multicenter, Dose Escalation and Expansion Study of Intratumoral Injections of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma

Protocol No.: DV3-LYM-01

Original Protocol: 08 May 2014

Amendment #1: 24 June 2014

Amendment #2: 10 April 2015

Amendment #3: 05 November 2015

Amendment #4: 21 March 2016

Sponsor: Dynavax Technologies Corporation
2929 Seventh Street, Suite 100
Berkeley, CA 94710
United States of America

DECLARATION OF INVESTIGATOR

I confirm that I have read and understood this protocol, and agree to conduct the study as outlined in the protocol and other information supplied to me. I agree to conduct the study in accordance with good clinical practice (GCP) as defined in International Conference on Harmonisation (ICH) guidelines and applicable local legal and regulatory requirements.

Investigator Signature Date

Investigator Name (Print)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SYNOPSIS

Objectives:

Primary Objectives:

- To assess the safety and tolerability of escalating doses of SD-101 in combination with localized low-dose radiation therapy (XRT) in subjects with untreated low-grade B-cell lymphoma
- To evaluate the pharmacodynamic (PD) profile of interferon (IFN)-inducible genes in whole blood 24 hours after intratumoral injection of SD-101
- To determine the Maximum Tolerated Dose (MTD) or Optimal Dose of intratumoral SD-101 in combination with localized low-dose XRT

Secondary Objectives:

- To evaluate the plasma pharmacokinetics (PK) of SD-101
- To assess the preliminary response both locally and systemically
  - Tumor shrinkage of the treated lesion(s) (Local)
  - Tumor shrinkage outside the treated lesion(s) (Systemic)

Exploratory Objective:

- To estimate the duration of tumor response both locally and systemically

Study Design:

This is a phase 1/2, non-randomized, open-label, multicenter, dose-escalation, and expansion study designed to evaluate the safety and preliminary efficacy of localized low-dose XRT and intratumoral SD-101 injection into a single target lesion (denoted as "Lesion A" in Treatment Cycle 1) in subjects with untreated low-grade B-cell lymphomas who do not require immediate systemic therapy and are appropriate candidates for "watch and wait".

In this protocol, treated lesion(s) is lesion(s) treated with XRT and SD-101; untreated lesion(s) is lesion(s) not treated with XRT and SD-101.

"Lesion A" is the lesion identified to be treated with both XRT and SD-101. Additionally, at least 1 (up to 5) additional lesion(s) that is untreated and outside the field of radiation of "Lesion A" will be recorded and followed per Cheson criteria (1999) in Cycle 1.

This study will be conducted in 2 parts: Part 1 (Dose Escalation) which includes the evaluation of 4 escalating dose levels, and Part 2 (Expansion) which includes enrollment of up to 18 total subjects (9 per cohort) into a 1 mg and 8 mg SD-101 dose cohort. Subjects enrolled in Part 2 with at least stable disease assessed by Cheson criteria for untreated lesions (excluding Lesion A) on Day 180 imaging and who meet all retreatment criteria will be treated with a second cycle of low dose radiation and SD-101. By default, the same lesion (Lesion A) treated in Cycle 1 should be retreated in Cycle 2. If Lesion A has entirely regressed by the time a subject is eligible for retreatment, then another pre-identified lesion (from Cycle 1) may be selected for treatment.

Subjects in Part 2 will be required to complete imaging, laboratory and fine needle aspiration (FNA) of tumors as outlined in the Schedule of Study Assessments. FNA sampling requirement for Part 2 is 2 FNA samples each in both a treated and untreated lesion in Part 2 Cycle 1. FNA sampling requirement for Part 2 Cycle 2 is 1 FNA sample in both a treated and untreated lesion. For Part 2, Cycle 2, if a second untreated lesion is not available or accessible, an

FNA sample collection of this second untreated lesion is not required.

Imaging for the study is at Screening, and Days 90, 180, 360, 540 and 720. Subjects who undergo retreatment at Day 180 will have additional imaging at Day 270.

FNA biopsy samples will be tested for both ribonucleic acid (RNA) expression by NanoString analysis and quantification of immunologic cellular infiltrates by flow cytometry during Cycle 1 and RNA expression by NanoString analysis for Cycle 2.

Safety reporting periods is from initiation of study treatment until Day 90 post initiation of study treatment for both treatment cycles (Day 1-90 in Cycle 1 and Day 180-270 in Cycle 2).

Part 1 - Dose Escalation

Screening		Treatment - Cycle 1							Follow-up	
D -30 …	D -2	D -1	D1		D8	D15	D22	D29	D36 …	D720
Untreated low-grade Lymphoma subjects with at least 2 sites of measurable disease		↑ Low dose radiation to Lesion A[a] (2 doses)	↑	↑ SD-101 Intratumoral injection into Lesion A[a] (5 doses)	↑	↑	↑	↑	Assess response to Lesion A and outside of Lesion A	

D = day.

[a] Lesion A is one site of disease and is the same site throughout the study.

Part 2: Dose Expansion

Patients Undergoing 1 Treatment Cycle:	Screening		Treatment - Cycle 1							Follow-up										
Patients Undergoing 2 Treatment Cycles:	Screening		Treatment - Cycle 1							Follow-up		Treatment - Cycle 2							Follow-up	
	D -30 …	D -2	D -1	D1		D8	D15	D22	D29	D36	D90	D180	D181		D188	D195	D202	D209	D216 …	D720
	Untreated low-grade Lymphoma subjects with at least 2 sites of measurable disease		↑ Low dose radiation to Lesion A[a] (2 doses)	↑	↑ SD-101 Intratumoral injection into Lesion A[a] (5 doses)	↑	↑	↑	↑	Assess response to Lesion A and outside of Lesion A[b]		↑ Low dose radiation to a lesion[c] (2 doses)	↑	↑ SD-101 Intratumoral injection into a lesion[c] (5 doses)	↑	↑	↑	↑	Assess response to treated and non-treated lesions	

D = day.

[a] Lesion A is one site of disease and is the same site throughout the study.

[b] Imaging is Screening, Day 90, Day 180, Day 270, Day 360, Day 540, and Day 720

[c] This lesion may be different than Lesion A from Cycle 1, must meet size requirements per Inclusion #2, and remain the same lesion throughout Treatment-Cycle 2.

Part 1: Dose Escalation

Part 1 is a dose-ranging study using a standard 3 + 3 study design. The starting dose of SD-101 will be 1 mg administered intratumorally and will be given to a cohort of 3 subjects. If no Dose-limiting Toxicity (DLT) is observed in the first

3 subjects, the next cohort will be enrolled and escalation will proceed to the next highest dose. If a DLT is observed in 1 subject in a cohort, enrollment will proceed and the cohort size will be increased up to 6 subjects. If only 1 DLT is observed in 6 subjects in a cohort, escalation will proceed and the next cohort may begin enrollment. However, if ≥ 2 of 6 subjects experience a DLT in any cohort, dose escalation will cease and the previous lower dose of SD-101 will be designated the MTD unless an intermediate dose is chosen to be studied to define the MTD.

The dose cohorts for SD-101 are 1 mg, 2 mg, 4 mg, and 8 mg. If an MTD is not identified, dosing will stop at 8 mg. Decisions to escalate the dose of SD-101 to the next highest level will be based on review of safety data from the time of the first injection (Day 1 [Visit 2]) through 7 days following the last injection (Day 36 [Visit 8]). Intra-subject dose escalation is not permitted.

An Optimal Dose may be selected based on all available data including an assessment of IFN-inducible genes and tolerability data. Based on this evaluation, the Medical Monitor and investigators may choose an intermediate dose instead of the MTD.

Treatment will consist of local radiation given over 2 days (Day -1 [Visit 1] and Day 1 [Visit 2]) (2 Gray [Gy] each day) followed by 5 weekly intratumoral injections with SD-101 on Day 1 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 5), Day 22 (Visit 6), and Day 29 (Visit 7).

Each subject will receive intratumoral injections to Lesion A (same site throughout dose escalation). If at any point during the treatment Lesion A has completely regressed, remaining injections will be given by subcutaneous injection into the site of Lesion A.

Part 2: Expansion

Based on review of safety data in Part 1 (14 September 2015), no DLT or MTD was reported upon completion of dose escalation for the 1 mg, 2 mg, 4 mg, and 8 mg SD-101 dosing cohorts. Subjects will be enrolled in Part 2 at 2 dose cohorts (1 mg and 8 mg) in order to better assess the safety and preliminary efficacy of SD-101. Eighteen subjects (9 per cohort) will be assigned to either a 1 mg or 8 mg SD-101 dose cohort. The dosing schedule for the first cycle of SD-101 treatment will be the same for both Parts 1 and 2 of the study.

In addition, subjects in Part 2 will have the option to undergo a second cycle of localized low-dose radiation and SD-101 treatment (Cycle 2) at the last dose level that they received during Part 2 Cycle 1. Eligible subjects to receive Cycle 2 SD-101 treatment are required to have at least stable disease assessed by Cheson criteria for all Cycle 1 untreated lesions (excluding Lesion A) on Day 180 imaging, have at least one site of measurable and accessible disease (per Cheson criteria 1999) that can be injected, and meet all laboratory and other eligibility criteria (described in Section 10.3). All subjects who undergo retreatment with localized low-dose radiation and SD-101 at Day 180 will complete follow-up procedures as outlined in Appendix 3. If a subject does not consent to be retreated with localized low-dose radiation and SD-101 at Day 180, the subject will continue on study and complete follow-up procedures as outlined in Appendix 2.

If during the enrollment of the expansion cohort, the type and duration of adverse events (AEs) suggests that the MTD has been exceeded, any remaining accrual to that cohort will be temporarily halted and available safety data will be reviewed and discussed with the investigators. A decision will then be made either to stop the study or to restart enrollment at a lower dose level.

Study Population: The study population will include men and women with untreated low-grade B-cell lymphoma with at least 2 measurable sites of disease, 1 of which must be accessible for intratumoral injection and a second tumor lesion that will not be included in the radiation field of the treated lesion. The study population must not be in immediate need for systemic therapy, and must be good candidates for "watch and wait".

Study Period: The total duration of subject participation in this study is up to 748 days. This includes a Screening period beginning up to 28 days prior to the first treatment, a 30-day treatment period, and a follow-up period of up to 690 days. Optional: an optional second 30-day treatment period starting at Day 180 and a follow-up period of up to 510 days for subjects who have consented to receive a second cycle of localized low-dose radiation and SD-101.

Safety Evaluation: A number of measures will be taken to ensure the safety of subjects participating in this trial. These measures will be addressed through the review of Inclusion/Exclusion Criteria and routine safety monitoring, as indicated below.

During active treatment, subjects will undergo targeted physical exams, electrocardiograms (ECGs), and laboratory assessments, which will include a complete blood count (CBC) with differential, platelet assessment, coagulation testing, and serum chemistry (including creatinine [Cr], liver function tests and lactate dehydrogenase [LDH]).

Prior to each study injection, subjects will receive a new Diary Card with instructions to measure and record local injection-site reactions and solicited AEs. The completed Diary Cards will be reviewed with subjects at their next study visit.

During the study follow-up period, safety will be evaluated through the careful monitoring of all clinical and laboratory AEs. Safety assessments will include ECG and specified laboratory parameters (eg, CBC, serum chemistry).

Standard safety monitoring consistent with International Conference on Harmonisation (ICH) guidelines will be employed for DLT assessment and dose-escalation decisions during Part 1 (Dose Escalation). Before dose escalation at each dose level and at any other time that safety data warrant review during Cycle 1 or Cycle 2, as applicable, the coordinating principal investigator will participate in a teleconference with the Dynavax Medical Monitor and Contract Research Organization (CRO) Medical Monitor to review all safety data.

Other Assessments: All subjects will undergo safety assessments, tumor response determinations, and correlative biomarker testing performed at specified study visits, as indicated in Appendix 1, Appendix 2, and Appendix 3.

Disease Assessment Prior to Treatment

Once informed consent is obtained, baseline disease assessments will include:

- Computerized Tomography (CT) scan of neck, chest, abdomen, pelvis, and other areas, as clinically indicated. Positron Emission Tomography (PET) scans will only be permitted if PET/CT is standard of care (SOC) at the participating institution and is performed instead of stand-alone CT.
- Unilateral bone marrow biopsy and aspirate if not previously performed or if performed more than 90 days previously with negative results
- Laboratory assessments
- Copy of pathology report confirming diagnosis

All subjects will be required to have Day 180 imaging and demonstrated stable disease, partial response (PR), or complete response (CR) (per Cheson criteria) and have at least one measurable and accessible target lesion (per palpation or ultrasound guidance) for SD-101 intratumoral injection in order to receive Cycle 2 SD-101 treatment. Eligible subjects must provide consent prior to undergoing treatment in Cycle 2.

Assessment of Disease Response to Treatment

Disease assessment will include CT scans (or PET/CT) at 3 and 6 months after the first SD-101 injection, and then every 6 months for the remainder of the trial. For subjects who receive Cycle 2 XRT and SD-101 treatments, they will have an additional disease assessment (radiographic scans) at 9 months (Day 270) after the first SD-101 injection in Cycle 1.

Response will be assessed by evaluating treated lesion (s) and all sites of untreated disease.

Study Treatments: **Treatments**

- Low-dose radiation (2 Gy × 2 doses)
- SD-101 intratumoral injection

Dosage and Administration

Each subject in Part 1 will receive local XRT administered in 2 fractions of 2 Gy each for a total of 4 Gy over 2 days prior to and followed by 5 weekly intratumoral SD-101 injections to a single target lesion (denoted as “Lesion A”).

The dosing schedule will be the same as Part 1 for Part 2. In addition, subjects in Part 2 will have the option to undergo a second cycle of localized low-dose radiation and SD-101 treatment (Cycle 2) at the last dose level that they received Part 2 Cycle 1.

If at any point during treatment, the treated lesion has completely regressed, remaining injections will be given by subcutaneous injection into the site of the treated lesion. Retreatment at Day 180 (Cycle 2) may only be given to a lesion other than Lesion A if Lesion A has regressed and does not meet minimum size

requirement as described in the retreatment criteria or is otherwise approved by a Dynavax Medical Monitor. Once a lesion is selected, the same lesion must be injected for a given treatment cycle.

The SD-101 doses planned for administration in the Part 1 dose escalation are 1 mg, 2 mg, 4 mg, and 8 mg. SD-101 doses in Part 2 will be 1 mg and 8 mg. Intra-subject dose escalation is not permitted. For Part 2, dose interruptions (allowed for all subjects) may occur and rules for dose reductions (not allowed for subjects in the 1 mg dose cohort) are given in Section 9.0.

Eligibility Criteria:

Inclusion Criteria:

A subject must meet all of the following criteria to be eligible for the study:

1) Biopsy confirmed, untreated, low-grade B-cell lymphoma, including follicular (Grade 1, 2, or 3A) (Harris, Swerdlow et al. 2008), or marginal, or chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with lymph node involvement
2) At least 2 sites of measurable disease per Cheson criteria (must measure at least 1.5 cm in any diameter or 1.0 cm in the shortest diameter if one of the diameters is not ≥ 1.5 cm), 1 of which must be palpable and easily accessible in a low-risk site (eg, inguinal, axillary, cervical, subcutaneous) for intratumoral injection (denoted as "Lesion A" in Treatment Cycle 1) and at least one additional untreated lesion that is located outside the radiation field of the treated lesion (Lesion A) and is accessible for an FNA aspirate.
3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 (Appendix 5)
4) Aged 18 years and older
5) Absolute neutrophil count (ANC) ≥1500/mm^3
6) Platelet count > 100,000/µL
7) Serum Cr ≤ 1.5 × upper limit of normal (ULN)
8) Serum total bilirubin ≤ 1.5 × the (ULN)
9) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN
10) International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy and PT or partial thromboplastin time (PTT) must be within the therapeutic range of intended use of anticoagulants
11) Activated PTT (aPTT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, and the PT or PTT must be within the therapeutic range of intended use of anticoagulants.

12) Female subjects must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication if of childbearing potential as defined in this protocol. Women of childbearing potential (WOCBP) must be willing to use 2 medically acceptable methods of contraception from Day 1 through 120 days after the last dose of trial treatment. The 2 medically acceptable birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

13) Ability to understand and sign informed consent form (ICF) and comply with treatment protocol

Exclusion Criteria:

A subject with any one of the following criteria is not eligible for the study:

1) Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy (including immune modulators or systemic corticosteroids) within 7 days prior to study enrollment

2) Positive for hepatitis B (HBsAg reactive), hepatitis C (HCV RNA qualitative), or human immunodeficiency virus (HIV) (HIV 1/2 antibodies)

3) Diagnosis of mantle or diffuse large-cell lymphoma, Grade 3B follicular lymphoma (Harris, Swerdlow et al. 2008), or gastric mucosa-associated lymphoid tissue (MALT) lymphoma

4) Clinically significant pleural effusion

5) Active infection including cytomegalovirus

6) Pregnant or breast feeding within the projected duration of trial participation through 4 months after the last dose of study treatment

7) Autoimmune disease including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, autoimmune thrombocytopenia, history of uveitis, or other if clinically significant

8) Lymphoma involvement of the central nervous system

9) Received any prior therapy for lymphoma

10) Use of any investigational agent within the last 28 days

11) Serious, non-healing wound, ulcer, or bone fracture

12) If a subject received major surgery, must have recovered adequately from the toxicity and/or complications from the intervention prior to enrollment

13) Clinically significant cardiovascular disease (eg, uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication within 1 year prior to Day -1 (Visit 1); Grade II or greater peripheral vascular disease at study entry

14) Any other significant medical or psychiatric condition, laboratory abnormality, or difficulty complying with protocol requirements that may increase the risk associated with study participation or study drug administration that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for this study

15) History of sensitivity to any component of SD-101

16) A diagnosis of cancer within the last 3 years prior to enrollment or any known additional malignancy that is progressing or requires active treatment. Exceptions are B-cell lymphoma, basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer.

17) Is taking systemic corticosteroids (more than 3 consecutive days) or other immunomodulators or immune suppressive medication

Study Endpoints

Primary Endpoints

- DLTs
- Incidence of injection-site reactions, AEs and serious adverse events (SAEs)
- Changes in IFN-inducible genes

Secondary Endpoints

- Plasma concentrations of SD-101 (Part 1 only)
- Response rate of the treated lesion(s) according to Cheson criteria
- Time to response of treated lesion(s) according to Cheson criteria
- Response rate of untreated lesion(s) according to Cheson criteria
- Time to response of untreated lesion(s) according to Cheson criteria

Exploratory Endpoints

- Duration of response of the treated lesion (s) according to Cheson criteria
- Duration of response of untreated lesions according to Cheson criteria
- Time to next treatment (TTNT)
- Time to progression (TTP)

- Characterization of tumor infiltrating lymphocytes, co-stimulatory molecules, and other immune activated cells following SD-101 treatment

Statistical Methods

This trial is designed to allow preliminary assessments of safety and biological activity in approximately 25-31 subjects. No pre-specified hypothesis testing will be performed. All analyses of demographics, biological activity, and safety will be descriptive.

A total of 13 subjects were enrolled in the Dose Escalation (Part 1) of the trial and approximately 18 subjects will be enrolled in Part 2. If the true response rate is 30%, a sample size of 12 subjects (per dose cohort) will have 74% chance to obtain 3 or more responders and 50% chance to obtain 4 or more responders. A 90% exact binomial confidence interval will be constructed as preliminary efficacy information for further investigation.

Table 12-1 details the probabilities of detecting the number of responses. AEs, SAEs, and abnormal laboratory values will be summarized by the proportion of subjects who experience them.

PK and PD evaluations will assess changes in PK and PD parameters from before to after the second dose of SD-101.

Response rate will be presented as the proportion of subjects who achieved CR or PR. Summary statistics will be provided for time to response, duration of response, TTP, and TTNT.

1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	adverse event
ALT	alanine aminotransferase
Anti-dsDNA	antibodies to double-stranded deoxyribonucleic acid
AST	aspartate aminotransferase
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CpG	cytosine phosphoguanosine
Cr	creatinine
CFR	Code of Federal Regulations
CR	complete response, complete remission
CRF	case report form
CRO	Contract Research Organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
FDA	United States Food and Drug Administration
FLIPI	follicular lymphoma international prognostic index
FNA	fine needle aspiration
GCP	good clinical practice
Gy	Gray, unit of radiation
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation or Term	Definition
IFN	interferon
IMP	investigational medicinal product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDH	lactate dehydrogenase
MALT	mucosa-associated lymphoid tissue
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's lymphoma
ODN	oligodeoxynucleotide
PD	pharmacodynamics
pDC	plasmacytoid dendritic cell
PET	Positron Emission Tomography
PK	pharmacokinetics
PR	partial response, partial remission
PS	Performance Status
RNA	ribonucleic acid
SAE	serious adverse event
SAR	suspected adverse reaction
SLL	small lymphocytic lymphoma
SOC	standard of care
SPD	sum of the products of greatest diameters
SUSAR	suspected unexpected serious adverse reaction
TLR-9	Toll-like receptor-9
TTP	time to progression
TTNT	time to next treatment
WHO	World Health Organization
WOCBP	women of childbearing potential
XRT	radiation therapy

2.0 INTRODUCTION AND RATIONALE

2.1 Background

Non-Hodgkin's lymphoma (NHL) is a group of histologically and perhaps biologically distinct lymphoid malignancies. Eighty to 90% of NHLs are B-cell lymphomas, and the great majority of the rest are T-cell lymphomas. Currently, NHL accounts for approximately 69,740 new cases per year, representing 4.2% of all cancers diagnosed in the United States, and 19,200 cancer deaths per year (National Cancer Institute 2014). Reporting from the US Surveillance, Epidemiology, and End Results (SEER) program indicates that the incidence of NHL has increased 0.5% per year for the past 10 years.

NHLs encompass many histological types. The Revised European-American Classification of Lymphoid Neoplasms (REAL) developed in 1994 is the currently accepted classification of lymphoid neoplasms (Harris, Jaffe et al. 1994). This was further refined by the World Health Organization (WHO) classification of hematologic malignancies in 1997. Based on the WHO classification, NHLs are grouped into low-grade, aggressive, and highly aggressive lymphomas based on the clinical behavior of each entity.

Low-grade lymphomas are subdivided into B-cell and T-cell types. The low-grade B-cell lymphomas include follicular lymphoma, B-chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma and marginal zone lymphoma. The T-cell group includes T-CLL and mycosis fungoides.

All low-grade lymphomas share several common characteristics, including a relatively low-grade and prolonged clinical course, and a potential to transform to a more aggressive form of lymphoma. The tumor is often disseminated at diagnosis, and is rarely cured. Although the disease is sensitive to chemotherapy, radiotherapy, and immunotherapy, patients eventually exhaust all options and succumb to progression of disease. All low-grade B-cell lymphomas will be included in this trial. Follicular lymphoma is the major type of low-grade B-cell lymphoma, representing 13% of all NHLs. It has a prolonged clinical course and is not curable. The median survival of all patients with follicular lymphoma is at least 10 years. The prognosis of follicular lymphoma patients is largely determined by a constellation of clinical parameters, described as follicular lymphoma international prognostic index (FLIPI), determined at disease presentation (Solal-Celigny, Roy et al. 2004). FLIPI includes 1 "point" each for stage III/IV disease, number of nodal sites involved > 4, lactate dehydrogenase (LDH) > normal, age > 60 years, and hemoglobin (Hgb) < 12 gm/dL. Patients with 0 to 1, 2, or ≥ 3 risk factors belong to low-risk, intermediate, and poor risk groups, respectively. Follicular lymphoma is sensitive to many treatment modalities but 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 follicular lymphoma and other low-grade B-cell lymphomas.

2.2 Oligodeoxynucleotides With Cytosine Phosphoguanosine (CpG) Motifs

Bacterial deoxyribonucleic acid (DNA) has long been recognized as having potent stimulatory effects on the immune system, including stimulating rejection of transplantable tumors in mice (Yamamoto, Kuramoto et al. 1988). This activity is mediated preferentially by specific DNA motifs containing a cytosine phosphoguanosine (CpG) dinucleotide and can be replicated by short synthetic oligodeoxynucleotides (CpG-ODN) (Kuramoto, Yano et al. 1992, Tokunaga, Yano et al. 1992, Roman, Martin-Orozco et al. 1997). CpG-ODNs stimulate specific immune cell types by activation of the innate recognition receptor, Toll-like receptor-9 (TLR-9) (Krieg 2006), and have no activity in mice with a homozygous deletion of the TLR-9 gene (Campbell, Cho et al. 2009).

Based on studies with cultured human peripheral blood mononuclear cells, CpG-ODNs can stimulate interferon (IFN)-alpha and interleukin-12 production as well as functional maturation in plasmacytoid dendritic cells (pDCs) (Duramad, Fearon et al. 2005) and can induce proliferation and immunoglobulin production in human B-cells (Krieg, Yi et al. 1995). Signaling by CpG-ODNs through TLR-9 requires active uptake of the ODN as TLR-9 is present only in specific intracellular compartments (Krieg 2002). TLR-9 signaling occurs in 2 distinct intracellular structures, early and late endosomes (Honda, Ohba et al. 2005, Guiducci, Ott et al. 2006), leading to different outcomes. In pDCs, TLR-9 signaling in the early endosome leads to induction of type 1 IFNs, especially IFN-alpha, whereas signaling in late endosomes results in differentiation of pDCs to potent antigen-presenting cells. Differences in sequence and structure lead to different localization to these 2 intracellular compartments, allowing selection of CpG-ODNs that stimulate low or high levels of type 1 IFNs (termed CpG-B and CpG-C class ODN, respectively). SD-101 belongs to the CpG-C class of CpG-ODN and was selected to stimulate very high levels on IFN-alpha as well as inducing maturation of pDC to antigen-presenting cells.

Please refer to the Investigator's Brochure for additional information on nonclinical testing.

2.3 Combined Radiotherapy and Intratumoral CpG-ODN Treatment of Lymphoma

Radiation therapy (XRT) is being employed in this trial because tumor cells undergo cell death upon irradiation (Mirzaie-Joniani, Eriksson et al. 2002) causing the release of tumor antigens locally. These tumor antigens can be processed by antigen presenting cells to initiate a tumor-specific immune response. Combination of XRT with intratumoral SD-101 may thus be able to boost the immunogenicity of the released antigens, promoting generation of a systemic, tumor-specific immune response.

In a number of different animal models, intratumoral injection of CpG-ODN has proven significantly more effective for tumor killing and generation of anti-tumor immunity than systemic administration (Kawarada, Ganss et al. 2001, Lou, Liu et al. 2011). Studies combining XRT and intratumoral CpG-ODN administration have shown efficacy in patients with indolent B-cell lymphomas (Brody, Ai et al. 2010) or cutaneous T-cell lymphoma (Kim, Gratzinger et al. 2012). Regression of untreated tumor sites in a subset of patients provided evidence for

generation of anti-tumor immunity in each of these studies. These 2 studies, as well as virtually all other published studies of CpG-ODN treatment in cancer patients, were done with CpG-ODNs belonging to the CpG-B class, which induces significantly lower levels of type 1 IFNs in humans than CpG-C class ODNs, such as SD-101.

2.4 Clinical Experience With SD-101

In the phase 1, single-blind, dose-escalation study of SD-101 in 26 healthy normal male volunteers, aged 18 years and over (Study DV3-HNV-01), adverse events (AEs) included flu-like symptoms such as headache, chills, fatigue, and pyrexia, as well as injection site reactions such as erythema, induration and pain. Dose-limiting toxicities (DLTs) of severe headache, injection site induration, and neck pain were observed in 1 subject given 5.0 mg of SD-101, resulting in a halt in dose escalation and accrual. Transient lymphopenia was the most common laboratory abnormality observed. There was no evidence of complement activation, coagulation abnormalities, auto-antibody development, or acute AE syndrome.

In the phase 1 single-blind, dose-escalation study of SD-101 in 34 men and women, aged 18 to 55 years, with chronic hepatitis C virus (HCV) infection, SD-101 was administered alone or in combination with ribavirin (Study DV3-HCV-01). Including doses up to 5 mg of SD-101, the majority of AEs were injection site reactions (erythema, swelling, pain, and pruritus), influenza-like illness, pyrexia, and myalgia. Most AEs were mild or moderate in reported severity. One subject in the SD-101 0.1 mg/ribavirin group experienced a serious adverse event (SAE) of hyperthyroidism that was considered probably related to SD-101 and unrelated to ribavirin. No deaths occurred during the study.

In the phase 1b/2, open-label, multicenter, dose-escalation and expansion study, intratumoral SD-101 is being administered in combination with pembrolizumab in subjects with metastatic melanoma (Study DV3-MEL-01). As of 25 February 2016, 5 subjects have been enrolled and treated in Part 1 in the 2 mg SD-101 dose cohort. One subject permanently discontinued from the study at Day 22 due to disease progression. Further dose escalation and enrollment into the 4 mg and 8 mg SD-101 dose cohorts has not been initiated. No DLTs have been reported to date. The study is ongoing.

A summary of the clinical studies conducted to date with SD-101 is provided in the Investigator's Brochure.

At the time of Protocol Amendment 4, for the current study (DV3-LYM-01), the DLT assessment period for all subjects in Part 1 has been completed and the study is ongoing with long term follow-up for subjects in Part 1 and planned enrollment of 18 subjects into Part 2, split evenly between 2 SD-101 dosing cohorts (1 mg and 8 mg). As of 25 February 2016, a total of 10 subjects have been enrolled into Part 2 (6 at 1 mg and 4 at 8 mg). The decision for Part 2 SD-101 dosing is described below. Of note, the data is preliminary and has not been fully monitored.

In Part 1 of this study, 13 subjects were enrolled and treated in 4 dose cohorts (1 mg, 2 mg, 4 mg, and 8 mg) with no DLTs reported. No determination of a Maximum Tolerated Dose (MTD) or optimal dose (for Part 2) was made. Three subjects were enrolled and treated in each of the 1 mg, 2 mg, and 4 mg dose cohorts. Four subjects were enrolled and treated in the 8 mg cohort (1 subject discontinued study treatment after one dose of SD-101 per subject decision for a Grade 2 confusion that occurred secondary to fever and flu-like symptoms). Per preliminary data (study is ongoing), the primary toxicity observed from SD-101 was Grade 1 or 2 flu-like symptoms with onset 4 to 8 hours after SD-101 injection and resolved with symptomatic treatment. The most common laboratory abnormalities were transient decrease in neutrophils that occurred in some subjects and was more common in the 4 mg and 8 mg dose cohorts. One subject in the 8 mg dose cohort with a baseline Day 1 neutrophil count of 1390 cells/mm^3 (etiology unknown) had 2 dose delays due to Grade 3 neutropenia which resolved in 10 to 11 days. There were no Grade 4 or higher AEs reported. Efficacy and pharmacodynamic/correlative translational data demonstrated a decrease in treated and overall tumor burden at the 1 mg, 2 mg, and 4 mg dose cohorts (8 mg efficacy data has not yet been obtained per protocol schedule and limited follow-up to date). The induction of IFN-alpha inducible genes was observed at all 4 dose levels without a substantial difference observed between the dose cohorts. The decision for dosing in Part 2 was to investigate both a low and higher SD-101 dose cohort (1 mg and 8 mg). Two subjects required a dose delay due to Grade 2 and Grade 3 neutropenia, respectively (both treated in the 1 mg dose cohort). There have been no reported Grade 4 or 5 events or SAEs reported for the Part 2 subjects. The study is ongoing.

The preliminary efficacy data from Part 1 (Cheson Criteria 1999) revealed a decrease in both treated and untreated disease. A reduction of the product of diameters in treated tumors occurred in 12 subjects (median -45.3%; range [-87, +100]) and in untreated tumors occurred in 11 subjects (median -8.1%; range [-48, +45]). Induction of alpha-interferon genes, a surrogate for SD-101 activity, occurred at all dose levels with similar level of induction. At the treated site, regulatory T-cells (T Regs) were reduced in 8 of 10 subjects (average decrease 22.3 $\pm$ 9.5%) at Day 8. There was an average reduction of 83.3 $\pm$ 9.9% in follicular T helper cells (Tfh) at Day 8 (n=9 with baseline Tfh).

Five subjects in Part 1 discontinued due to disease progression (3 due to radiographic progression [1 each at 1, 2, and 4 mg], 1 due to increasing symptoms [abdominal pain] attributed to disease progression [2 mg], and 1 subject with CLL who had an increase in peripheral lymphocytes [4 mg]). One subject in Part 2 discontinued due to disease progression (1 mg dose cohort). All other subjects are ongoing.

2.5 Study Rationale and Doses to be Evaluated

This open-label, dose-ranging, multicenter study was designed to evaluate the safety and preliminary efficacy of localized low-dose XRT and intratumoral injection of SD-101 for the treatment of untreated low-grade B-cell lymphoma. The hypothesis to be tested in this study is that SD-101, by virtue of its potency and its ability to induce high levels of IFN, will have

meaningful efficacy in generating antitumor immune responses when combined with XRT. IFNs have multiple effects on both the tumor cells and the tumor infiltrating leukocytes. IFNs can directly inhibit the proliferation of tumor cells and increase major histocompatibility complex class I expression, enhancing antigen recognition. Additionally IFNs have potent effects on tumor infiltrating leukocytes, including enhancing antigen presenting function of dendritic cells, increasing the effector function of T-cells, and activating cytotoxic activity of natural killer cells (Hervas-Stubbs, Perez-Gracia et al. 2011).

The population to be studied will be subjects with untreated low-grade B-cell lymphomas who do not require immediate systemic therapy and are appropriate candidates for "watch and wait". Treatment in Part 1 consists of 1 cycle of local radiation over 2 days (2 Gray [Gy] each day) followed by 5 weekly intratumoral injections of SD-101; doses of 1 mg, 2 mg, 4 mg, and 8 mg will be tested sequentially in a standard 3+3 study design. The dosing schedule is the same in Part 2, and in addition, subjects in Part 2 will have the option to undergo a second cycle of localized low-dose radiation and SD-101 treatment (Cycle 2) at the last dose level that they received in Part 2 Cycle 1. Subjects will be followed until next treatment or until approximately 2 years after the first injection of SD-101. A key feature of this design is that the assessment of tumor regression will be done on one or more evaluable lesions that are neither irradiated nor injected with SD-101. The assumption is made that an effect on sites distal to the treated site provides evidence for generation of an effective systemic anti-tumor immune response.

The SD-101 doses selected are based on previous clinical studies conducted with SD-101 (DV3-HNV-01, DV3-HCV-01), the mechanism of action, and nonclinical studies with SD-101. Based on data from a study in healthy male volunteers (DV3-HNV-01), elevation of biomarkers was seen after a single 0.1 mg subcutaneous dose and increased with doses up to 5 mg. AEs were limited to flu-like symptoms and administration-site pain and induration. For further information, see the Investigator's Brochure.

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.

The rationale for choosing two doses to be explored in dose expansion (Part 2) is to obtain further safety and efficacy data to select a recommended Phase 2 dose. In Part 1, an MTD was not determined, activity was observed but not clearly different between dose cohorts, and induction of alpha-interferon gene expression was observed at all doses and did not differ significantly between dose cohorts.

The rationale for adding a second cycle of localized low-dose XRT and SD-101 (Cycle 2 for subjects with at least stable disease assessed by Cheson criteria for untreated lesions [excluding Lesion A] on Day 180 imaging) is to allow further SD-101 treatment for those subjects who have demonstrated evidence of anti-tumor activity, have tolerated the initial study treatment cycle (Cycle 1) without having experienced a DLT, and are candidates for retreatment per safety-related eligibility criteria. Re-dosing to further stimulate an immune response is a general

immunologic strategy and will be assessed to potentially improve responses in this patient population. An anecdotal report of a patient further responding to retreatment with a TLR-9 agonist (same target as SD-101) was reported by Brody 2010 (Brody, Ai et al. 2010).

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

- To assess the safety and tolerability of escalating doses of SD-101 in combination with localized low-dose XRT in subjects with untreated low-grade B-cell lymphoma
- To evaluate the pharmacodynamic (PD) profile of IFN-inducible genes in whole blood 24 hours after intratumoral injection of SD-101
- To determine the MTD or Optimal Dose of intratumoral SD-101 in combination with localized low-dose XRT

3.2 Secondary Objectives

- To evaluate the plasma pharmacokinetics (PK) of SD-101
- To assess the preliminary response both locally and systemically
  - Tumor shrinkage of the treated lesion(s) (Local)
  - Tumor shrinkage outside the treated lesion(s) (Systemic)

3.3 Exploratory Objectives

- To estimate the duration of tumor response both locally and systemically

4.0 INVESTIGATIONAL PLAN

4.1 Study Design

This is a phase 1/2, non-randomized, open-label, multicenter, dose-escalation and expansion study designed to evaluate the safety and preliminary efficacy of localized low-dose XRT and intratumoral SD-101 injection into a single target lesion (denoted as “Lesion A” in Treatment Cycle 1) in subjects with untreated low-grade B-cell lymphomas who do not require systemic therapy and are appropriate candidates for “watch and wait”.

In this protocol, treated lesion(s) is lesion(s) treated with XRT and SD-101; untreated lesion(s) is lesion(s) not treated with XRT and SD-101.

“Lesion A” is the lesion identified to be treated with both XRT and SD-101. Additionally, at least 1 (up to 5) additional lesion(s) that is untreated and outside the field of radiation of “Lesion A” will be recorded and followed per Cheson criteria (1999) in Cycle 1.

This study will be conducted in 2 parts (Study flow diagrams Figure 4-1 and Figure 4-2). Part 1 (Dose Escalation) consists of the evaluation of 4 escalating dose levels, and Part 2 (Expansion),

which includes enrollment of 18 total subjects (9 per cohort) into a 1 mg or 8 mg SD-101 dose cohort.

Subjects in Part 2 will have the option to undergo a second cycle of localized low-dose radiation and SD-101 treatment (Cycle 2) at the last dose level that they received in Part 2 Cycle 1, once they meet eligibility as described in Section 10.3. During Part 2 Cycle 1, all subjects are required to have 2 fine needle aspiration (FNA) samples each from the treated lesion (Lesion A) and untreated lesion (Lesion B) that is located outside the radiation field of the treated lesion (Lesion A). During Part 2 Cycle 2, all subjects will be required to have only 1 FNA from the treated lesion, and an untreated lesion that is located outside the radiation field of the treated lesion. If no accessible untreated lesion is present on Day 180 imaging, then FNA is only required for the treated lesion.

All subjects will undergo safety assessments, PK and PD assessments, tumor response determinations, and correlative biomarker testing performed at specified study visits, as indicated in the Schedule of Study Assessments (Appendix 1, Appendix 2, and Appendix 3).

Once informed consent is obtained, baseline disease assessments will include:

- Computerized tomography (CT) scan of neck, chest, abdomen, pelvis, and other areas, as clinically indicated. Positron Emission Tomography (PET) scans will only be permitted if PET/CT is the standard of care (SOC) at the participating institution.
- Unilateral bone marrow biopsy and aspirate if not previously performed or if performed more than 90 days previously with negative results
- Laboratory assessments
- Copy of pathology report confirming diagnosis

Disease assessment will include CT scans (or PET/CT) at 3 months (Day 90) and 6 months (Day 180) after the first study injection, and then every 6 months for the remainder of the trial. There is an additional CT scan at 9 months (Day 270) for subjects who are retreated at 6 months (Day 180) with a second cycle of localized low-dose radiation and SD-101.

Response will be assessed by evaluating treated lesion(s) and all sites of disease outside of treated lesion(s). All untreated sites followed and recorded in the electronic case report form (eCRF) and used for assessment of disease response per Cheson criteria (1999) should be selected outside of the radiation field of the treated lesion.

Figure 4-1: Study Flow Diagram – Dose Escalation (Part 1)

Part 1 - Dose Escalation										
Screening		**Treatment - Cycle 1**							**Follow-up**	
D -30 …	D -2	D -1	D1		D8	D15	D22	D29	D36 …	D720
Untreated low-grade Lymphoma subjects with at least 2 sites of measurable disease		↑ Low dose radiation to Lesion A[a] (2 doses)	↑	↑	↑ SD-101 Intratumoral injection into Lesion A[a] (5 doses)	↑	↑	↑	Assess response to Lesion A and outside of Lesion A	
D = day.										
[a] Lesion A is one site of disease and is the same site throughout the study.										

Figure 4-2: Study Flow Diagram – Dose Expansion (Part 2)

Part 2: Dose Expansion																				
Patients Undergoing 1 Treatment Cycle:	**Screening**		**Treatment - Cycle 1**							**Follow-up**										
Patients Undergoing 2 Treatment Cycles:	**Screening**		**Treatment - Cycle 1**							**Follow-up**		**Treatment - Cycle 2**							**Follow-up**	
	D -30 …	D -2	D -1	D1		D8	D15	D22	D29	D36	D90	D180	D181		D188	D195	D202	D209	D216 …	D720
	Untreated low-grade Lymphoma subjects with at least 2 sites of measurable disease		↑ Low dose radiation to Lesion A[a] (2 doses)	↑	↑ SD-101 Intratumoral injection into Lesion A[a] (5 doses)	↑	↑	↑	↑	Assess response to Lesion A and outside of Lesion A[b]		↑ Low dose radiation to a lesion[c] (2 doses)	↑	↑ SD-101 Intratumoral injection into a lesion[c] (5 doses)	↑	↑	↑	↑	Assess response to treated and non-treated lesions	
	D = day.																			
	[a] Lesion A is one site of disease and is the same site throughout the study.																			
	[b] Imaging is Screening, Day 90, Day 180, Day 270, Day 360, Day 540, and Day 720																			
	[c] This lesion may be different than Lesion A from Cycle 1, must meet size requirements per Inclusion #2, and remain the same lesion throughout Treatment-Cycle 2.																			

4.2 Parts of Study

4.2.1 Part 1: Dose Escalation

Part 1 is a dose-ranging study using a standard 3 + 3 study design. The starting dose of SD-101 will be 1 mg administered intratumorally and will be given to a cohort of 3 subjects.

If no DLT is observed (Section 9.1) in the first 3 subjects, the next cohort will be enrolled, and escalation will proceed to the next highest dose.

If a DLT is observed in 1 subject in a cohort, enrollment will proceed and the cohort size will be increased up to 6 subjects.

If only 1 DLT is observed in 6 subjects in a cohort, escalation will proceed and the next cohort may begin enrollment.

However, if ≥ 2 of 6 subjects experience a DLT in any cohort, dose escalation will cease and the previous lower dose of SD-101 will be designated the MTD unless an intermediate dose is chosen to be studied to define the MTD.

The dose cohorts for SD-101 are 1 mg, 2 mg, 4 mg, and 8 mg. If an MTD is not identified, dosing will stop at 8 mg. Decisions to escalate the dose of SD-101 to the next highest level will be based on review of safety data from the time of the first injection (Day 1 [Visit 2]) through 7 days following the last injection (Day 36 [Visit 8]). Intra-subject dose escalation is not permitted.

An Optimal Dose may be selected based on all available data including an assessment of IFN-inducible genes and tolerability data. Based on this evaluation, the Medical Monitor and investigators may choose an intermediate dose instead of the MTD.

4.2.2 Part 2: Expansion

As discussed in Section 2.4, on completion of Part 1 dose escalation for all 4 planned cohorts (1, 2, 4, and 8 mg) no DLT, no MTD, nor an Optimal Dose has been determined. As a result, Part 2 dose expansion will be a dose range study with 2 cohorts (SD-101 at 1 mg and 8 mg). This part of the study will enroll 18 subjects (9 in the 1 mg cohort followed by 9 in the 8 mg cohort). The dosing schedule and imaging/tumor assessment will be the same for both parts of the study with the exception of changes described in Section 4.1.

In addition, subjects in Part 2 will have the option to undergo a second cycle of treatment with localized low-dose XRT and SD-101 (Cycle 2) at the last dose level that they received during Part 2 Cycle 1. Part 2 procedures for subjects undergoing 1 treatment cycle and for subjects undergoing 2 treatment cycles are listed in the Schedule of Study Assessments Appendix 2 and Appendix 3, respectively. Localized low-dose radiation and SD-101 will be administered at the last dose level received in Part 2 Cycle 1 for a given subject. Of note, the treated lesions may be different between the first and second dosing cycles (in subjects who undergo repeat dosing at Day 180). The same lesion should be treated for a given Treatment Cycle. In order to receive retreatment at Day 180, subjects must meet all laboratory and eligibility criteria described in Section 10.3.

If during the enrollment of the expansion cohort, the type and duration of AEs suggests that the MTD has been exceeded, any remaining accrual to that cohort will be temporarily halted and available safety data will be reviewed and discussed with the investigators. A decision will then be made either to close a cohort, stop the study, or to restart enrollment at a lower dose level.

4.3 Duration of Study

The total duration of subject participation in this study is up to 748 days for all subjects who enroll in this study. This includes a Screening period beginning up to 28 days prior to the first treatment, a 30-day treatment period, and a follow-up period of up to 690 days for all subjects in dose escalation (Part 1) and all subjects in dose expansion (Part 2) who do not receive retreatment at Day 180. For subjects undergoing Cycle 2 treatment, the second treatment period is 30 days (Day 180-Day 210) followed by a follow-up period of up to 510 days (Day 216-Day 720).

4.4 Study Endpoints

4.4.1 Primary Endpoints

- DLTs
- Incidence of injection-site reactions, AEs, and SAEs
- Changes in IFN-inducible genes

4.4.2 Secondary Endpoints

- Plasma concentrations of SD-101 (Part 1 only)
- Response rate of treated lesion(s) according to Cheson criteria
- Time to response of treated lesion(s) according to Cheson criteria
- Response rate of untreated lesion(s) according to Cheson criteria
- Time to response of untreated lesion(s) according to Cheson criteria

4.4.3 Exploratory Endpoints

- Duration of response treated lesion(s) according to Cheson criteria
- Duration of response outside of treated lesion(s) according to Cheson criteria
- Time to next treatment (TTNT)
- Time to progression (TTP)
- Characterization of tumor infiltrating lymphocytes, co-stimulatory molecules, and other immune activated cells following SD-101 treatment

4.5 Randomization

None of the subjects in this study will be randomized.

4.6 Blinding

Blinding will not be performed as this is an open-label study.

4.7 Appropriateness of Measurements

The measure of response of lesions in this study is based on the Cheson criteria for low-grade B-cell lymphomas (Cheson, Horning et al. 1999, Cheson, Pfistner et al. 2007) (Appendix 4). This is the standard clinical trial assessment of tumor response in NHL clinical studies. The measures of safety in the study are routine clinical and laboratory procedures and assessment of AEs is adapted from the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (National Cancer Institute 2010) (Table 11-1). The measurement of injection site reactions (listed on the Diary Card) is based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Center for Biologics Evaluation and Research 2007) (Appendix 6).

4.8 Study Termination

The final study visit will occur when the last subjects completes the last study visit. The end-of-study date is defined as the date of the last visit of the last participant. However, the sponsor reserves the right to terminate the study at any time. Reasons for discontinuation include but are not limited to:

- Inability to enroll sufficient subjects into the study
- Good Clinical Practices (GCP) compliance issues that compromise the validity of the study

Additional information about stopping the study can be found in Sections 9.1 and 9.2.

Procedures for withdrawal of individual subjects can be found in Section 5.4.

5.0 SELECTION OF SUBJECTS

The study population will include men and women with untreated low-grade B-cell lymphoma with at least 2 measurable sites of disease, 1 of which must be palpable and accessible in a low-risk site (eg, inguinal, axillary, cervical, subcutaneous) for intratumoral injection (denoted as "Lesion A" in Treatment Cycle 1) and a second lesion that will not be included in the radiation field of the treated lesion. Subjects must not be in immediate need of systemic therapy and must be good candidates for "watch and wait". In addition, subjects must meet the Inclusion and Exclusion Criteria as described in detail in Sections 5.1 and 5.2.

A number of measures will be taken to ensure the safety of subjects participating in this trial. These measures will be addressed through inclusion/exclusion criteria and routine monitoring. Many of the exclusion criteria for this study were selected to guard the safety of subjects in this trial.

5.1 Inclusion Criteria

A subject must meet all of the following criteria to be eligible for the study:

1) Biopsy confirmed, untreated low-grade B-cell lymphoma, including follicular (Grade 1, 2, or 3A) (Harris, Swerdlow et al. 2008), or marginal, or CLL/SLL with lymph node involvement
2) At least 2 sites of measurable disease per Cheson criteria (must measure at least 1.5 cm in any diameter or 1.0 cm in the shortest diameter if one of the diameters is not ≥ 1.5 cm), 1 of which must be palpable and easily accessible in a low-risk site (eg, inguinal, axillary, cervical, subcutaneous) for intratumoral injection (denoted as "Lesion A" in Treatment Cycle 1) and at least one additional untreated lesion that is located outside the radiation field of the treated lesion (Lesion A) and is accessible for an FNA aspirate.
3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 (Appendix 5)
4) Aged 18 years and older
5) Absolute neutrophil count (ANC) ≥ 1500/mm^3
6) Platelet count >100,000/μL
7) Serum creatinine (Cr) ≤ 1.5 × upper limit of normal (ULN)
8) Serum total bilirubin ≤ 1.5 × the ULN
9) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN
10) International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, and the PT or partial thromboplastin time (PTT) must be within the therapeutic range of the intended use of anticoagulants
11) Activated PTT (aPTT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, and the PT or PTT is within therapeutic range of intended use of anticoagulants
12) Female subjects must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication if of childbearing potential as defined in this protocol. Women of childbearing potential (WOCBP) must be willing to use 2 medically acceptable methods of contraception from Day 1 through 120 days after the last dose of trial treatment. The 2 medically acceptable birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).
13) Ability to understand and sign informed consent form (ICF) and comply with treatment protocol

5.2 Exclusion Criteria

A subject with any one of the following criteria is not eligible for the study:

1) Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy (including immune modulators or systemic corticosteroids) within 7 days prior to study enrollment
2) Positive for hepatitis B (HBsAg reactive), HCV ribonucleic acid (RNA) qualitative, or human immunodeficiency virus (HIV) (HIV 1/2 antibodies)
3) Diagnosis of mantle or diffuse large-cell lymphoma, Grade 3B follicular lymphoma (Harris, Swerdlow et al. 2008), or gastric mucosa-associated lymphoid tissue (MALT) lymphoma
4) Clinically significant pleural effusion
5) Active infection including cytomegalovirus
6) Pregnant or breast feeding within the projected duration of trial participation through 4 months after the last dose of study treatment
7) Autoimmune disease including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, autoimmune thrombocytopenia, history of uveitis, or other if clinically significant
8) Lymphoma involvement of the central nervous system
9) Received any prior therapy for lymphoma
10) Use of any investigational agent within the last 28 days
11) Serious, non-healing wound, ulcer, or bone fracture
12) If a subject received major surgery, must have recovered adequately from the toxicity and/or complications from the intervention prior to enrollment
13) Clinically significant cardiovascular disease (eg, uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication within 1 year prior to Day -1 (Visit 1); Grade II or greater peripheral vascular disease at study entry
14) Any other significant medical or psychiatric condition, laboratory abnormality, or difficulty complying with protocol requirements that may increase the risk associated with study participation or study drug administration that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for this study
15) History of sensitivity to any component of SD-101

16) A diagnosis of cancer within the last 3 years prior to enrollment or any known additional malignancy that is progressing or requires active treatment. Exceptions are B-cell lymphoma, basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer.

17) Is taking systemic corticosteroids (more than 3 consecutive days) or other immunomodulators or immune suppressive medication

5.3 Definition of Women of Childbearing Potential

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (eg, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. All female subjects are considered to be WOCBP except if they have had a hysterectomy, been postmenopausal for at least 2 years or surgically sterile for at least 1 year. The only exception is that women who have undergone a hysterectomy are considered not to be WOCBP after surgery and are not required to be surgically sterile for a year for study eligibility/treatment.

Postmenopause is defined as:

- Women on hormone replacement therapy
- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL
- Women with irregular menstrual periods and a documented FSH level > 35 mIU/mL

NOTE: FSH level testing is not required for women > 62 years old with amenorrhea for > 1 year. Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

5.4 Removal of Subjects From Study

Subjects may choose to withdraw from the study at any time. The reason for withdrawal will be recorded on the case report form (CRF). Subjects who do not complete at least 4 injections for reasons other than discontinuation for toxicity or who do not have at least one post Screening assessment of tumor response may be replaced. Subjects who permanently discontinue study treatment prior to completion of all 5 planned doses of SD-101 must be followed per protocol according to the Schedule of Assessments for 28 days after the last SD-101 injection (including an early discontinuation [ED] Visit) and do not require any further study procedures. At the discretion of the investigator, these subjects may continue to be followed with SOC imaging and procedures up to a maximum time on study of 720 days (Visit 13) outlined in Appendix 2.

Subjects may also be discontinued from the study by the investigator for any of the following reasons:

- Did not receive the first injection of SD-101
- Is required to permanently discontinue SD-101 injections due to AEs or dose delay due to AEs > 14 days as described in Section 9.2
- Initiation of new treatment for lymphoma
- Noncompliance with study procedures as determined by the investigator or sponsor
- At the discretion of the investigator if it is felt to no longer be in the best interest of the subject to remain on study
- The sponsor decides to terminate the study

The investigator or designee should discuss and consult with Dynavax prior to withdrawing a subject from the study before Day 720 (Visit 13). When a subject discontinues prior to study completion, the procedures detailed for the ED Visit should be performed. When a subject discontinues study prior to completion of all 5 planned SD-101 study treatments, they should undergo an ED Visit at 28 days after the last dose of study drug, if possible.

Additional information about stopping treatment or terminating the study may be found in Sections 4.8, 9.1, and 9.2.

6.0 STUDY MATERIALS AND SUPPLIES

6.1 Low-dose Radiation Therapy

XRT will be administered locally in 2 fractions of 2 Gy over 2 days (Day -1 [Visit 1] and Day 1 [Visit 2]) for a total of 4 Gy prior to the first injection of SD-101 (which begins on Study Day 1 after the XRT is completed). For subjects who have consented to undergo a retreatment of SD-101, a second cycle of localized low-dose XRT will be administered over Day 180 [Visit 10] and Day 181 [Visit 11] prior to the first SD-101 injection during the retreatment period.

6.2 SD-101

6.2.1 Investigational Medicinal Product

SD-101 Drug Product is a clear to slightly opalescent, colorless to pale yellow solution free of visible particles and will be supplied by Dynavax in single use vials. Dilution with sterile 0.9%, preservative free sodium chloride to the appropriate concentration for dosing will be required for all doses; instructions for dilution are provided in the Pharmacy Manual.

6.2.2 Instructions for Administration

SD-101 Drug Product will be administered by intratumoral injection into a single target lesion weekly for 5 injections. The doses to be administered are 1 mg, 2 mg, 4 mg, and 8 mg in Part 1

(Dose Escalation). In Part 2 (Expansion), the doses to be administered are 1 mg and 8 mg. In addition, subjects in Part 2 will have the option to undergo a second cycle of localized low-dose radiation and SD-101 treatment (Cycle 2) at the last dose level that they received in Part 2 Cycle 1, once they meet eligibility as described in Section 10.3. For all subjects, dose delay for up to 2 weeks (14 days) is allowed for AEs as described in Section 9.2. For subjects in the 8 mg dose cohort, a maximum of 2 dose reductions is allowed (from 8 mg to 6 mg and then to 4 mg, respectively) for AEs assessed as possibly related or probably related to SD-101 by the investigator (definitions provided in Section 11.3). If the sponsor chooses to close enrollment in the 8 mg dose cohort and enroll at a lower intermediate dose cohort, then allowed dose reduction levels will be provided by the Dynavax Medical Monitor. No dose reduction is allowed for subjects enrolled in the 1 mg cohort. **Note: Dose reductions at the 8 mg dose cohort in Part 2 require the approval of the Dynavax Medical Monitor by phone or e-mail prior to implementing.**

The target lesion, "Lesion A", will be the tumor site selected to receive XRT and SD-101 injections in Treatment Cycle 1. The investigator shall endeavor to choose the largest and most easily accessible tumor site as Lesion A. Lesion A must be easily palpable and in a low-risk site (eg, inguinal, axillary, cervical, subcutaneous). For subjects undergoing retreatment at Day 180, the investigator should follow the same guidance as used to select Lesion A for Treatment Cycle 1. The preference is to select the same treated lesion for Treatment Cycle 2, unless it has completely regressed, then the investigator should choose a different lesion to inject for Treatment Cycle 2. The same lesion should be injected for a given cycle. The same lesion that is irradiated for a given treatment cycle should also be injected. SD-101 injection for a given treatment cycle should not be initiated until the subject has received the planned 2 days of XRT for that cycle.

Ultrasound may be used to assess and provide guidance for injection into the injected lesion. Notation in the source documents should specify location and size (in 2 dimensions) in as much detail as possible.

Designated study-site personnel will be responsible for preparing and administering the study injection. At minimum, syringes will be labeled with the protocol number, subject initials, and subject number.

Prior to injection, the tumor site should be thoroughly cleansed and then wiped with alcohol. Ultrasound may be used to assist injection. Injection should be made as close to the center of the tumor as possible. All of the drug should be injected. If in subsequent injections, the tumor has disappeared, the injection should be made in the same area of the tumor using a subcutaneous injection. Details are provided in the Pharmacy Manual.

6.2.3 Labeling

At a minimum, SD-101 Drug Product will be labeled with the following information: product name, contents, volume, concentration, sponsor name, and a statement indicating that the drug is for investigational use only.

6.2.4 Storage and Handling Instructions

SD-101 Drug Product contains no preservatives and must be stored under refrigerated conditions (2°C to 8°C). SD-101 Drug Product is not to be frozen. Vials of SD-101 Drug Product are for single use only.

A detailed description of the storage and handling instructions for SD-101 Drug Product is provided in the Pharmacy Manual.

The clinical supplies storage area at the site must be monitored closely by the designated site staff for temperature consistency and documentation of temperature monitoring should be maintained. Temperature excursions outside of the recommended storage range may impact product quality and must be reported to Dynavax or designee per the detailed instructions in the Pharmacy Manual.

6.2.5 Control and Accountability of Investigational Medicinal Product

SD-101, the investigational medicinal product (IMP), must be received by a trained designated person at the study site, handled and stored safely and properly, and kept in a secured location with limited access.

The investigator (or responsible designee) must maintain current and accurate records of the receipt (documentation from shipments of IMP received), administration (subject-by-subject and overall accounting), and return of IMP to a Dynavax-specified facility for destruction. All IMP must be stored in a secure location under appropriate conditions with access restricted to authorized personnel.

A study monitor will be responsible for monitoring the drug accountability at the site. The monitor should be contacted with any questions concerning administration of IMP.

Records of IMP accountability, storage, and handling must be made available to the study monitor for the purposes of IMP accountability. Any discrepancy and/or deficiency must be recorded with an explanation.

The investigator must retain all used vials and expired, damaged, and unused IMP until accountability has been confirmed by the study monitor. Any exceptions to this policy must be specifically granted by Dynavax.

At the end of the study, or upon request by Dynavax, all unused IMP must be returned to a Dynavax specified facility for adequate disposition.

Refer to the Pharmacy Manual for detailed instructions on IMP accountability, storage, handling, and return.

IMP may not be used for any purpose other than that described in the protocol.

6.2.6 Treatment Compliance

All study injections and XRT will be administered by designated study personnel only.

7.0 TREATMENT OF SUBJECTS

7.1 Treatment Administered

Each subject in Part 1 will receive localized low-dose XRT administered in 2 fractions of 2 Gy each for a total of 4 Gy over 2 days (Day-1 [Visit 1], Day 1 [Visit 2]) prior to and followed by 5 weekly intratumoral SD-101 injections to a single target lesion, Lesion A (same tumor site treated throughout the study).

The dosing schedule will be the same as Part 1 for Part 2 Treatment Cycle 1. In addition, subjects in Part 2 will have the option to undergo a second cycle of localized low-dose XRT over Day 180 [Visit 10] and Day 181 [Visit 11] followed by 5 weekly intratumoral SD-101 injections (Treatment Cycle 2).

By default, the same lesion (Lesion A) treated in Treatment Cycle 1 should be retreated in Treatment Cycle 2. If at any point during treatment the treated Lesion A has completely regressed, remaining injections will be given by subcutaneous injection into the site of the treated Lesion A. Retreatment at Day 180 (Treatment Cycle 2) may only be applied to a lesion other than Lesion A if Lesion A has regressed and does not meet minimum size requirement as described in the retreatment criteria unless otherwise approved by a Dynavax Medical Monitor. Once a lesion is selected, the same lesion must be injected for a given treatment cycle.

The SD-101 doses planned for administration in the Part 1 dose escalation are 1 mg, 2 mg, 4 mg, and 8 mg. Subjects enrolled in Part 1 will be assigned to the current dose being evaluated, and subjects enrolled in Part 2 will be assigned to the 1 mg or 8 mg dose cohorts in the order of subject enrollment and a dose level which is open and available at the time of enrollment. Subjects who have consented to Cycle 2 treatment will receive SD-101 at the last dose level they received for Part 2 Cycle 1. Intra-subject dose escalation is not permitted. Dose reduction for AEs are only allowed for the 8 mg cohort in Part 2 or other lower dose Part 2 cohort per the Dynavax Medical Monitor. No dose reductions for AEs are allowed for the 1 mg cohort in Part 2 or any Part 1 subjects. For Part 2, dose interruptions (allowed for all subjects) may occur (Section 6.2.2) and rules for dose reductions (not allowed for subjects in the 1 mg dose cohort) are given in Section 9.0.

7.2 Treatment Period

The treatment period is 30 days for each cycle. For Treatment Cycle 1, localized low-dose XRT will be administered on Day-1 (Visit 1) and Day 1 (Visit 2) prior to the first SD-101 injection. SD-101 injections are to be administered at Day 1 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 5), Day 22 (Visit 6), and Day 29 (Visit 7). For the optional Treatment Cycle 2, localized low-dose XRT will be administered on Day 180 (Visit 10) and Day 181 (Visit 11) prior to the first SD-101 injection during the retreatment period. SD-101 injections are to be administered at Day 181 (Visit 11), Day 188 (Visit 12), Day 195 (Visit 14), Day 202 (Visit 15), and Day 209 (Visit 16). Subjects will be followed until TTNT or until approximately 2 years after the first injection of SD-101 (Day 720 [Visit 13 for single-cycle treatment and Visit 21 for retreatment]), whichever occurs earlier.

7.3 Treatment Precaution

IFN-alpha has been shown to inhibit cytochrome P450 (CYP) enzyme 1A2 (Brennan 2012). Since SD-101induces IFN-alpha, SD-101 may inhibit metabolism of drugs by CYP 1A2. The following drugs should be used with caution from Day 1 through Day 36 (and optional Day 180 through Day 216 if consent is provided for SD-101 retreatment): caffeine, theophylline, warfarin, tricyclic antidepressants, clozapine, fluvoxamine, ciprofloxacin, propranolol, and verapamil.

7.4 Prohibited Treatments or Therapies

Subjects may receive other medications that the investigator deems to be medically necessary, with the exception of the medications listed below, which are prohibited during the trial. Subjects who, in the assessment by the investigator, require the use of any of the following treatments for clinical management should be removed from study treatment (see Section 5.4):

- Antineoplastic systemic chemotherapy or biologic therapy
- Any investigational therapy
- Immunosuppressive agents not specified in this protocol (except when used for treating AEs). If used for AEs, the agents must be discontinued prior to resumption of SD-101.
- Systemic steroids and topical steroids whose absorption is expected to result in systemically immunosuppressive steroid levels (that exceeds 10 mg per day of prednisone or equivalent) is prohibited during study treatment and until 30 days after the last dose of SD-101 and is only allowed when used for the acute treatment of AEs.
- Additional XRT after the initiation of SD-101 with the exception that XRT to a symptomatic solitary lesion or to the brain may be considered on an individual case by case basis with Dynavax Medical Monitor approval

- **Prophylactic** use of colony-stimulating factors including granulocyte colony-stimulating factor (G-CSF), pegylated G-CSF, or granulocyte macrophage colony-stimulating factor (GM-CSF)
- Surgery, unless approved by the Dynavax Medical Monitor

7.5 Permitted Therapy

Topical or inhaled or intranasal corticosteroids (with minimal systemic absorption) and non-absorbed intra-articular steroid injections are permitted to treat AEs and may be continued with approval of the Dynavax Medical Monitor. A brief (< 24 hours) course of steroids for prophylaxis against contrast dye allergy is permitted for subjects undergoing tumor assessments per institutional standard.

For flu-like symptoms, prophylactic treatment is recommended pre and post-treatment for the 8 mg cohort and is recommended pre- and post-SD-101 dosing for all subsequent dosing for 1 mg cohort subjects who experience post-treatment flu-like symptoms.

For All Subjects in the 8 mg Dose cohort <u>Pre-Treatment Prophylaxis</u>:

- Subjects should be treated prophylactically with 1 gm acetaminophen approximately 2 hours before and 4 to 6 hours after injection with SD-101.
- Subjects should continue dosing with acetaminophen for 48 hours per acetaminophen dosing guidelines (not to exceed a dose of 3 gm in 24 hours).
- Ibuprofen may also be given pre- and post-treatment for prophylaxis and is recommended for subsequent dosing if subjects have flu-like symptoms that are not adequately treated by acetaminophen.

For All Part 2 Subjects in the 1 mg Dose cohort <u>Pre-Treatment Prophylaxis</u>:

- Subjects are required to be treated prophylactically at the 1 mg dose with 1 gm acetaminophen approximately 2 hours before each injection of SD-101.
- If a subject has significant flu-like symptoms at any dose level, then follow the pre-treatment prophylaxis listed for the 8 mg cohort above.

For All Subjects <u>Post-Treatment</u> in Part 2:

- If a subject experiences any flu-like symptoms up to 48 hours following SD-101 injection, then the subject may take acetaminophen (maximum 3 gm per day), odansetron, or prochlorperazine as needed for 24 to 48 hours post-injection. If symptoms are severe and unresponsive to standard therapy, codeine may be used.

If the flu-like symptoms that are not adequately treated with acetaminophen, ibuprofen may also be used pre- and/or post treatment. Efforts should be made to keep all other concurrent

medications at stable doses during the trial and to refrain from starting any new medications, unless clinically indicated. Therapy to prevent or treat local and/or systemic reactions following administration of study drug may include analgesics, antipyretics, and antihistamines.

8.0 ASSESSMENT OF RESPONSE

Response assessments will be performed at specified time points as listed in the Schedule of Study Assessments (Appendix 1 and Appendix 2). Disease response (radiographic and biomarker [FNA] samples) will be assessed for treated and untreated disease. Treated disease is the injected and irradiated lesion (denoted as "Lesion A" in Cycle 1) and untreated disease is all other target lesions identified at Screening (up to 5 lesions; denoted as "Lesion B through F" in Cycle 1). All untreated disease that is used for assessment of response and recorded in the eCRF must be located outside the radiation field of the treated lesion (Lesion A).

8.1 Interferon-inducible Genes

IFN-inducible gene expression will be measured to determine the induction of IFN-alpha by different doses of SD-101. The levels of IFN-inducible gene expression, along with all available data, will be used to determine the Optimal Dose of SD-101 for Part 2.

8.2 RNA Analysis

Blood for RNA analysis to explore changes in gene expression in response to treatment will be collected.

8.3 Biomarker Analysis

When collected, FNA samples of the treated lesion (denoted as "Lesion A" in Cycle 1), and 1 or more other accessible untreated lesions which are located outside the radiation field of the treated lesion (denoted as "Lesions B through F" in Cycle 1), will be analyzed for changes in correlative biomarkers (changes over time relative to baseline). In Part 2, this biopsy requirement will include 2 FNA samples collected at each required timepoint for biomarker analysis of both FNA samples for cellular phenotyping and NanoString RNA gene expression analysis. For subjects who undergo a second cycle of localized low-dose XRT and SD-101 injections starting at Day 180 in Part 2, they will have additional tumor biopsies collected at Day 180 (Visit 10), Day 188 (Visit 12), and Day 216 (Visit 17) from the treated lesion. A biopsy from an untreated lesion selected outside the field of radiation of the treated lesion may be collected at Day 180 (Visit 10), Day 216 (Visit 17), and Day 270 (Visit 18) as outlined in Section 10.9 and Appendix 3. The biopsies obtained following treatment Cycle 2 are only to be obtained for subjects undergoing Cycle 2 retreatment and only requires a single FNA of each lesion biopsied at a given timepoint. The biomarker analysis will only include NanoString RNA gene expression analysis (not cellular phenotyping). **Note:** If an untreated lesion is not available or accessible, an FNA sample collection of an untreated lesion is not required for Cycle 2.

8.4 Response Evaluation and Criteria

Response to treatment will be evaluated by the investigator at 3 and 6 months (and 9 months for subjects who undergo Cycle 2 treatment [Day 180]) after the first study injection and then every 6 months for the remainder of the trial.

Response of lesions will be assessed by CT or CT/PET and bone marrow biopsy using the Cheson criteria for lymphomas (Cheson, Horning et al. 1999). Response will be assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria:

1) At a minimum, thoracic, abdominal, and pelvic CT scans will be performed even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. CT/PET may be used if they are the standard tools for assessing disease status at a participating institution.
2) Unilateral bone marrow biopsy and aspirates will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a complete response (CR) if the subject was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Response of lesions will be recorded on the CRF based on the definitions in Table 8-1 or Appendix 4 as appropriate. Suspected relapse or disease progression must be confirmed by physical exam, laboratory assessments, repeat bone marrow biopsy (Cheson, Horning et al. 1999) and CT scan. If confirmed, progressive disease should be reported to the sponsor within 7 days. Subjects with suspected relapse or disease progression should continue to follow study procedures until they need another therapy. If a subject requires another therapy, date of treatment and type of treatment will be recorded and they will then be removed from the trial.

Tumor progression is defined as ≥ 50% increase from nadir in the sum of the products of the greatest diameters (SPD), as defined in the Cheson response criteria for NHL (Cheson, Horning et al. 1999) (Table 8-1). The response criteria per Cheson (1999) should be recorded in the database. However, if the subject is evaluated by CT/PET scan then tumor response criteria should be evaluated using updated Cheson criteria (Cheson, Pfistner et al. 2007), which includes CT and PET scans.

Table 8-1: Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
Complete Response	Normal	Normal	Normal	Normal
Complete Response/ Unconfirmed	Normal	Normal	Normal	Indeterminate
	Normal	Normal	≥ 75% decrease	Normal or indeterminate
Partial Response	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/ spleen; new sites	New or increased	New or increased	Reappearance

Source: (Cheson, Horning et al. 1999). Stable disease is defined as less than a partial response but is not progressive disease.

9.0 MANAGEMENT OF STUDY TREATMENT TOXICITIES

During the study follow-up period, safety will be evaluated through the careful monitoring of all clinical and laboratory AEs. Safety assessments will include specified laboratory parameters (eg, complete blood count [CBC], serum chemistry). See Section 10.4.5 for additional details of laboratory testing.

9.1 Dose-limiting Toxicity and Stopping Rules

Standard safety monitoring consistent with International Conference on Harmonisation (ICH) guidelines will be employed for DLT assessment and dose-escalation decisions during the Part 1 (Dose Escalation) of the study. All AEs will be considered in DLT assessment unless an event is clearly unrelated to SD-101. Before dose escalation at each dose level and at any other time that safety data warrant review during Cycle 1 or Cycle 2, as applicable, the coordinating principal investigator will participate in a teleconference with the Dynavax Medical Monitor and Contract Research Organization (CRO) Medical Monitor to review all safety data.

All AEs, including DLTs, are to be reported according to instructions in the Study Reference Manual and graded using the National Cancer Institute CTCAE, Version 4.03 (National Cancer Institute 2010). If a subject experiences a DLT, he or she will be treated according to clinical practice and will be monitored for resolution of the toxicity. For dose escalation purposes, a DLT will be defined as any of the following AEs occurring from the time of the first injection (Day 1 [Visit 2]) through 7 days following the last injection (Day 36 [Visit 8]):

- Any non-hematological toxicity ≥ Grade 3 except for alopecia or nausea uncontrolled by medical management

- Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
- Febrile neutropenia of any duration (ANC < 1000/mm^3, temperature ≥ 38.5°C)
- Grade 4 neutropenia lasting more than 5 days
- Grade 4 anemia, unexplained by underlying disease
- Any Grade ≥ 2 toxicity related to SD-101 (eg, post-injection reaction or influenza-like illness) that does not resolve to Grade ≤ 1 with standard treatment by the time of the next treatment

If a subject has a DLT they should not receive further injections and should be encouraged to complete trial participation and followed for safety through Day 720 (Visit 13).

If a subject is prevented from receiving additional injections per Section 9.2, a review of related safety information will be completed by the Dynavax Medical Monitor, or designee, to determine if the subject should continue in the study.

The protocol may be discontinued by the sponsor at any time (Section 4.8). In the absence of unacceptable treatment-related toxicity or disease progression, subjects may be considered to receive SD-101 treatment for up to 1 year at the discretion of the investigator and beyond 1 year with the agreement of the investigator and the sponsor, under a compassionate use protocol.

9.2 Dose Modification for Adverse Events

Withhold SD-101 for any of the following that are assessed as possibly related or probably related to SD-101 as defined in Section 11.5.

- Grade 3 drug-related AEs of any duration or Grade 3 injection-site reaction (that persists for greater than 7 days). SD-101 treatment may be resumed once the AE has resolved to Grade 1 or baseline with standard treatment. Subjects in the 8 mg cohort may undergo up to 2 dose reductions per investigator decision and Dynavax Medical Monitor approval as described in Section 9.2. If SD-101 is held for Grade 3 neutropenia, the neutrophil count must recover to ≥ 1500 cells/mm^3 prior to resuming SD-101 treatment.
- If a subject requires > 10 mg per day of prednisone or equivalent to treat an AE, SD-101 may be resumed when the corticosteroid is discontinued or the dose is decreased to ≤ 10 mg per day of prednisone (or equivalent).

A minimum of 5 days must also elapse between injections. If the 5-day interval cannot be adhered to, then the next injection should be delayed and administered at the time of the next scheduled injection. If SD-101 is delayed for > 14 days due to an AE, then SD-101 should not be resumed.

Withdraw SD-101 for any of the following that are assessed as possibly related or probably related to SD-101 as defined in Section 11.5:

- Grade 3 AE (except for alopecia or nausea) which is not controlled by medical management
- Grade 4 AE
- SD-101 dosing is delayed for more than 14 days
- SAE that is assessed as a suspected adverse reaction (SAR) (Section 11.3.2) or an adverse reaction (Section 11.3.1)

9.3 Reasons for Stopping a Subject From Receiving Additional Injections

Subjects may be discontinued from study treatment by the investigator for any of the following reasons:

- Noncompliance with study procedures as determined by the investigator or sponsor
- Pregnancy or begins breastfeeding
- Use of or need for prohibited medications
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AEs as defined in Section 9.2
- Adverse drug reaction that requires study drug discontinuation per protocol (see Section 9.2)
- Need for > 2 dose delays due to toxicity as per the dose modification guidelines described in Section 9.2

If in the opinion of the investigator, a change or discontinuation of therapy would be in the best interest of the subject.

The investigator or designee must notify Dynavax when a subject has been discontinued from treatment. Any subject who is discontinued from treatment prior to the completion of planned 5 doses of SD-101 should be followed up with an ED visit scheduled 28 days after the last dose of SD-101. The subject then should be permanently discontinued from the study or may continue to be followed on study with SOC laboratory, x-ray, and safety evaluation until Day 720 (Visit 13).

9.4 Management of Subject Safety

During active treatment, subjects undergo targeted physical exams and laboratory assessments, which will include a CBC with differential, coagulation testing, platelet assessment, chemistry, liver function tests, and LDH.

Subjects who have consented to receive a second cycle of study treatment will have to meet eligibility as described in Section 10.3.

Subjects should receive full supportive care to treat injection site reactions and other toxicities. Management of adverse effects will be at the discretion of the treating investigator. An unscheduled visit (Section 10.10) should be performed if there is suspected disease progression or subject safety concerns. All supportive therapies will be recorded in the subject's CRF.

Injection-site reactions are expected to spontaneously subside. Local reactions are to be treated at the discretion of the treating physician. The site is not to be injected if local pain, tenderness, or swelling persists from a previous injection or other cause; the injection may be postponed until the symptoms have resolved or the injection may be skipped, following discussion with the Medical Monitor.

Subjects who are stopped from receiving additional study injections will be followed for safety through Day 720 (Visit 13).

Please refer to Section 10.11 for procedures regarding ED.

9.5 Pre-Treatment Prophylaxis and Post-Treatment

Based on the safety review of these AEs in Part 1, prophylaxis and treatment of SD-101 related flu-like symptoms are recommended. Details are provided in Section 7.5.

10.0 TRIAL ASSESSMENTS

All tests and evaluations required at specified time points are listed in the Schedule of Study Assessments (Appendix 1, Appendix 2, and Appendix 3). The results of these tests and evaluations must be entered in the subject's source document and also recorded on the subject's electronic data capture (EDC) CRF. Additional evaluations may be done at the discretion of the investigator and with sponsor approval.

Procedures to be performed for each study visit are described in Appendix 1, Appendix 2, and Appendix 3.

For subjects who have not consented to receive Cycle 2 treatment of localized low-dose XRT and SD-101, these subjects will continue on study at Day 180 (Visit 10) and complete follow-up procedures as outlined in Appendix 2. These subjects include all Part 1 and Part 2 subjects who do not qualify for SD-101 retreatment as outlined in Section 10.3 or have withdrawn consent prior to receiving additional SD-101 injections in this study.

10.1 Informed Consent and Screening Log

The investigator or designee must review the ICF with each prospective subject to be certain that the prospective subject understands the procedures and risks of the trial. Prospective subjects who wish to participate in the trial must provide written informed consent by signing the ICF before undergoing any Screening procedures (Appendix 1, Appendix 2, and Appendix 3). Informed consent must be obtained for subjects who choose to receive retreatment prior to

undergoing Cycle 2 treatment of localized low-dose XRT and SD-101 injections. A subject may withdraw consent to be treated with SD-101 at any time prior to or during the retreatment period.

The investigator or designee will maintain a log of all subjects who sign the ICF. At a minimum, the log will include a subject identifier, the dates of informed consent and screening procedures, the outcome of the screening, and the reason the subject did not enroll in the trial.

Additional requirements for informed consent are presented in Section 15.3.

10.2 Screening Assessments

Assessments to be completed during the Screening period are listed in Appendix 1, Appendix 2, and Appendix 3.

If a subject has results from SOC visits for any of the following assessments completed within 30 days prior to signing the ICF for this trial, those results may be used in lieu of repeating the study procedures during the 28-day Screening period:

- Vital signs
- Physical exam
- Electrocardiogram (ECG)
- Hepatitis and HIV testing
- Chemistry
- Hematology
- Coagulation

Please note that SOC CT or PET/CT imaging conducted prior to the 28-day Screening period will not be permitted. This assessment must be completed at Screening to ensure current baseline measurements are captured. In addition, add a copy of a record of lesion size at a timepoint at least 3 months prior to baseline should be added to the subject's CRF.

10.3 Cycle 2 Treatment

Subjects in Part 2 must provide consent to receive a second cycle of study treatment (2 days of localized low-dose radiation over Day 180 and Day 181 followed by 5 weekly SD-101 injections starting on Day 181 at the last dose level that the subjects were previously treated with in Part 2 Treatment Cycle 1).

- Understand and consent to receive SD-101 retreatment, including all additional imaging and safety laboratory procedures and assessments
- Have at least stable disease assessed by Cheson criteria for all Cycle 1 untreated lesions (excluding Lesion A) on Day 180 imaging

- Have at least 1 measurable and accessible lesion on Day 180 imaging which is injectable and meets the size criteria as a target lesion per Cheson criteria
- Have an absolute neutrophil count (ANC) $\geq 1500/mm^3$ and platelet count >100,000/µL
- Female subjects must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication if of childbearing potential as defined in this protocol. WOCBP (Section 5.3) must be willing to use 2 medically acceptable methods of contraception from Day 1 through 120 days after the last dose of Cycle 2 treatment. Pregnant or breastfeeding subjects are not eligible to receive further study treatment.

Subjects are INELIGIBLE to receive a second cycle of study treatment if one or more criteria are met below:

- Prior DLT on this study during Treatment Cycle 1
- History of sensitivity to any component of SD-101

10.4 Safety Assessments

The safety assessments listed below will be the same for Part 1 and Part 2. The Schedule of Study Assessments is provided in Appendix 1, Appendix 2, and Appendix 3.

10.4.1 Medical and Medication History

Medical history includes clinically significant diseases, surgeries, cancer history, and all medications (eg, prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the subject within 28 days prior to the Screening visit (Appendix 1, Appendix 2, and Appendix 3).

10.4.2 Vital Signs

Vital signs will be recorded and will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure. Vital signs taken at injection visits will include oral temperature. See Appendix 1, Appendix 2, and Appendix 3 for Schedule of Study Assessments.

10.4.3 Physical Examinations

The investigator or qualified designee will conduct physical examinations. A complete physical examination will be conducted at Screening and ED visits, and a targeted physical examination (based on interval history and/or AEs) will be conducted at all other visits (Appendix 1, Appendix 2, and Appendix 3).

Assessment of the Liver and Spleen must be done during the physical exams that are completed at Screening, Day 90, Day 180, Day 360, Day 540, Day 720, Unscheduled Visit, and ED Visit, where lesions are evaluated and the Cheson criteria are used to assess overall response.

10.4.4 Electrocardiogram

An ECG (12-lead with standard parameters of heart rate, shape, size and duration of P wave, P-R interval, QRS, and T wave configuration) will be performed at Screening, after treatment on Day 15 (Visit 5), and on Day 36 (Visit 8) (Appendix 1, Appendix 2, and Appendix 3).

10.4.5 Safety Laboratory Assessments

Laboratory assessments are listed below and will be performed according to the Schedule of Study Assessments (Appendix 1, Appendix 2, and Appendix 3). All safety laboratory tests are to be performed at the trial site's local laboratory. Sample collections are to be done pre-injection on treatment days.

- Hepatitis and HIV testing at Screening: hepatitis B surface antigen, hepatitis B core antigen, anti-HCV, and anti-HIV
- Chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), Cr, glucose, calcium, AST, ALT, gamma glutamyl transpeptidase (GGT), LDH, bilirubin, alkaline phosphatase, and C-reactive protein (CRP)
- Hematology: Hgb, hematocrit, white blood cell count with differential, and platelet count
- Coagulation: prothrombin time (PT) and activated partial thromboplastin time (APTT)
- For WOCBP, serum pregnancy testing will be conducted at Screening. Serum or urine pregnancy must be negative prior to initiation of study treatment as outlined in Appendix 1, Appendix 2, and Appendix 3. Serum or urine pregnancy must be negative prior to study treatment. Dipstick can be used. All female subjects are considered to be WOCBP except as defined in Section 5.3.
- Reserve serum aliquot specimens will be collected and stored frozen for possible future testing.
- Blood for antibodies to double-stranded deoxyribonucleic acid (anti-dsDNA) will be collected as outlined in Appendix 1, Appendix 2, and Appendix 3. Quantitative results for anti-dsDNA are required.
- Additional details for specific tests are provided in the Laboratory Manual.

10.4.6 Injection-site Reaction Assessments

Assessments of local injection-site reactions to intratumoral injections will be collected for 7 days following each injection.

Prior to study injection on Day 1 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 5), Day 22 (Visit 6), and Day 29 (Visit 7), subjects will receive a new Diary Card with instructions to measure and record local injection-site reactions and solicited AEs. The completed Diary Cards will be reviewed with the subjects at their next study visit.

Subjects are to be observed for a minimum of 30 minutes post-injection for the collection of any local injection-site reactions during the SD-101 Treatment Cycle 1 and optional Treatment Cycle 2.

See Appendix 1, Appendix 2, and Appendix 3 for Schedule of Study Assessments.

10.4.7 Adverse Events

AEs, as defined in Section 11.3, will be evaluated from immediately after the first study treatment from Day -1 (Visit 1) through Day 90 (Visit 9) and, if dosing in Cycle 2, from Day 180 [Visit 10] until Day 270 [Visit 18] (Appendix 1, Appendix 2, and Appendix 3). AE assessments at the ED Visit should occur 7 days or more after their last study injection. Subjects who are withdrawn due to an AE should have an AE assessment completed 28 days or more after their last study drug injection. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

10.4.8 Serious Adverse Events

SAEs, as defined in Section 11.4.1, will be evaluated from the time the consent is signed through the duration of trial participation (Appendix 1, Appendix 2, and Appendix 3). Any SAE occurring from the time the consent is signed through completion, whether or not related to IMP, must be reported within 24 hours to Dynavax or its designee within 24 hours of the knowledge of the event.

10.4.9 Concomitant Medications

Any prescription medication and over-the-counter drug or natural/herbal preparations, including vitamins and dietary supplements, including those for the treatment of any AEs, taken by the subject from Screening through the end of the treatment period (Day 90 [Visit 9] for 1 cycle of treatment or Day 270 [Visit 18] for 2 cycles of treatment) will be reported (Appendix 1, Appendix 2, and Appendix 3). Concomitant medications used to treat an SAE or immunomodulator drugs taken after Day 90 (Visit 9) for 1 cycle of treatment or after Day 270 (Visit 18) for 2 cycles of treatment through Day 720 (Visit 13) or ED are also to be reported.

10.5 Disease Assessments

Disease assessments will be the same for Part 1 and Part 2 (Appendix 1, Appendix 2, and Appendix 3).

- Disease assessment will consist of CT scan of neck, chest, abdomen and pelvis, and other areas as clinically indicated. PET scans will only be permitted if PET/CT is SOC at the participating institution.
- Unilateral bone marrow biopsy and aspirate will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

10.6 Pharmacokinetic Assessments

PK assessments will be done for Part 1 only. PK samples will be collected for Part 1 before and after the second dose of SD-101 in Part 1 only. Collections are to be performed pre-dose; 1, 2, 4, and 6 hours (± 10 minutes) post-dose on Day 1; and 24 (± 3) hours post-dose on Day 9 in Part 1 only (Appendix 1).

10.7 Pharmacodynamic Assessments

Details of testing for PD assessments (blood draws and FNA sampling) are provided in the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) and the Laboratory Manual. Blood will be collected for RNA analysis. Collections are to be done pre-XRT or pre-injection on treatment days.

- Blood for IFN-alpha inducible gene expression. Collections are to be done pre-XRT or pre-injection on treatment days. On Day 9, the sample is to be collected 24 (± 3) hours after the Day 8 injection. These IFN samples will also be collected in Part 2 for subjects who have consented to receive Cycle 2 treatment of SD-101 injections; on Day 189, the sample is to be collected 24 (± 3) hours after the Day 188 injection.
- Blood for RNA expression assessment is collected in both Part 1 and Part 2 as listed in the Schedule of Assessments. Samples will be retained for possible gene expression studies to be performed using other techniques.
- RNA gene expression analysis and profiling will be conducted on one of the 2 FNA samples of tumor lesions in Part 2 Treatment Cycle 1 (target treated lesion [denoted as “Lesion A”] and an untreated lesion [denoted as “Lesion B”]). In Part 2 Treatment Cycle 2, a single FNA sample of the target treated and the untreated lesions will be collected. **Note:** If an untreated lesion is not available or accessible for subjects at Day 180 who are undergoing Cycle 2, an FNA sample collection of an untreated lesion is not required Details are provided in the Laboratory Manual.

- Assessment of tumor infiltrating lymphocytes will be conducted on the second FNA sample of tumor lesions (treated and untreated) in Part 2 Treatment Cycle 1. **Note:** If an untreated lesion is not available or accessible, an FNA sample collection of an untreated lesion is not required. There will be no FNA samples collected in Part 2 Treatment Cycle 2 that will involve the analysis of tumor infiltrating lymphocytes with flow cytometry. Details are provided in the Laboratory Manual.

10.8 Immunogenicity Assessment

Blood for antibodies to SD-101 will be collected at Days -1 (Visit 1), 36 (Visit 8), and 360 (Visit 11) in Part 1 and Part 2 (Appendix 1, Appendix 2), and optional Days 181 (Visit 11), 216 (Visit 17), 270 (Visit 18) and 360 (Visit 19) for SD-101 retreatment in Part 2 (Appendix 3).

10.9 Fine Needle Aspirate of Tumor Lesions

Exploratory assessments for Part 1 and Part 2 are described separately in the Schedule of Study Assessments (Appendix 1, Appendix 2, and Appendix 3).

- In Part 1, a single FNA sampling is obtained from the treated lesion (Lesion A) on Day-1 and Day 8 with optional sampling on Day 36 and following disease progression. FNA sampling of an additional untreated (Lesion B) is optional but recommended.
- In Part 2 Treatment Cycle 1, 2 FNA samples each from each lesion biopsied is required. FNA sampling is required from both the treated lesion (Lesion A) and a second untreated lesion (Lesion B) selected outside the field of radiation of the treated lesion (Lesion A). Two FNA samples will be collected each from Lesion A at Day 1, Day 8, and Day 36. Two FNA samples will be collected each from Lesion B at Day 1, Day 36, and Day 90.
- In Part 2 Treatment Cycle 2, one single FNA sample collected from the treated lesion is required, and one single FNA sample collected from the untreated lesion that is located outside the field of radiation of the treated lesion is recommended. The FNA sample collected from the untreated lesion must be selected outside the field of radiation of the treated lesion. FNA sampling is required at Day 180, Day 188 and Day 216 from the treated lesion. FNA sampling from the untreated lesion is recommended but optional at Day 180, Day 216 and Day 270. **Note:** If a second untreated lesion is not available or accessible, an FNA sample collection of a second untreated lesion is not required.

10.10 Unscheduled Visit

An unscheduled visit (Appendix 1, Appendix 2, and Appendix 3) should be performed if there is suspected disease progression or subject safety concerns. If disease progression is suspected, it must be reported to the sponsor within 24 hours (Section 8.4) and confirmation of disease progression should be documented by completing a targeted physical examination (including assessment of the Liver and Spleen [Section 10.4.3]) based on subject-reported symptoms including vital signs (heart rate, blood pressure, respiratory rate), serum chemistry, hematology, CT scan, and unilateral bone marrow biopsy and aspirate if clinically indicated by new

abnormalities in the peripheral blood counts or blood smear (Section 8.4). Fine needle aspirate samples may be collected at an unscheduled visit, if the ± 21 days visit window at Visit 8 is used, or at a visit to assess disease progression. If an unscheduled visit is performed because of a safety concern related to IMP, at a minimum, the following should be performed: a targeted physical examination based on subject-reported symptoms including vital signs (heart rate, blood pressure, and respiratory rate), serum chemistry, and hematology.

10.11 Early Discontinuation Visit

Subjects should be encouraged to complete the entire study; however, if a subject decides to withdraw, every effort should be made to complete the ED visit (Appendix 1, Appendix 2, and Appendix 3) within a window no later than the next scheduled study visit (and at least 7 days following the last injection). Subjects who are withdrawn due to an AE should have an AE assessment completed 28 days or more after their last study drug injection. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

11.0 REPORTING AND DOCUMENTATION OF ADVERSE EVENTS

11.1 Investigator's Responsibilities

This trial will be conducted in accordance with the protocol; GCP as defined in ICH guidelines and applicable local legal and regulatory requirements. Investigators are responsible for monitoring the safety of subjects throughout the course of the study and for providing appropriate medical care. The investigator will perform all tasks directly or is responsible for overseeing and training qualified site personnel as delegated to perform trial tasks. In addition, investigators are responsible for alerting Dynavax to any event that seems unusual and for reporting all AEs, SAEs, and deaths in the appropriate CRFs.

11.2 Injection-site Reactions

Local reactions (eg, redness, swelling, pain at or near the injection site) to intratumoral injections will be collected for 7 days following each injection. Local injection site reactions are considered AEs if they persist longer than 7 days. The severity for all local reactions (including those which persist longer than 7 days) will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 6).

Dynavax will capture all local reactions that occur, even if their diameter of the largest dimension does not meet a Grade 1 on the severity scale. As such, any reaction smaller than this size cannot be graded, but will still be recorded in the clinical database and the severity will be marked as "not applicable" ("N/A").

The subject will be provided with a Diary Card at timepoints outlined in the Schedule of Study Assessments. Instructions will be provided to the subject on measuring and recording local injection-site reaction data (eg, redness, swelling, pain at or near injection site). Further, the Diary Card solicits certain pre-defined AEs (eg, malaise, headache, chills, myalgia, fatigue,

fever) and other health changes. All data documented by the subject on Diary Cards will be collected, reviewed by the study nurse/coordinator with the subject, and recorded on the appropriate CRF. The severity of predefined AEs and other health changes will be assessed and confirmed by the investigator and will be graded using the CTCAE Version 4.03 grading scale by system organ class (National Cancer Institute 2010). If the appropriate grading or description cannot be applied, then the investigator may elect to use the adapted CTCAE Version 4.03 grading scale (Table 11-1) to assess the AE.

Further information will be provided in the Study Reference Manual.

11.3 Adverse Events

An AE is any untoward medical occurrence in a subject who receives a pharmaceutical product, whether or not there is a causal relationship with the investigational treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Medical conditions present at Screening (ie, before informed consent is obtained) or present before the first study treatment (Day -1 [Visit 1]) are not AEs and are not recorded on the AE CRF. These medical conditions should be adequately documented on the Medical History CRFs. Any increase in severity or frequency of a medical condition documented as medical history after first study treatment will be recorded as an AE and will be captured on the AE CRF.

An uncomplicated pregnancy is not an AE or SAE and should not be reported as an AE/SAE. Subjects should be followed as described in Section 11.6.

The reporting period for all non-serious AEs begins at the time of first study treatment (Day -1 [Visit 1]) through Day 90 (Visit 9) and, if dosing in Cycle 2, from Day 180 [Visit 10] until Day 270 [Visit 18]. Subjects who are withdrawn due to an AE should have an AE assessment completed 28 days or more after their last study drug injection. All AEs will be captured on the AE CRF.

AEs should be documented in terms of a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the principal investigator or reported by the subject at each trial visit.

If an AE is associated with or resulted from an overdose of IMP (for the purpose of this trial defined as more than twice the protocol-specified dose), it will be documented on the AE CRF and will also be reported to Dynavax or the Dynavax designee within 24 hours. Clinically significant laboratory abnormalities, as determined by the investigator, will be recorded as AEs.

All related AEs observed during the trial are to be followed by the principal investigator until the AEs are resolved, or until the subject has completed the trial. Dynavax may request additional follow-up on specific unresolved events.

11.3.1 Definition of Adverse Reaction

An adverse reaction (AR) is defined as any AE caused by the use of a pharmaceutical product. ARs are a subset of all suspected AEs for which there is reason to conclude that the pharmaceutical product caused the event.

11.3.2 Definition of Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the study treatment caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study treatment and AE. An SAR implies a lesser degree of certainty about causality than AR, which means an AE caused by a study treatment.

11.3.3 Definition of Unexpected Adverse Event or Suspected Adverse Reactions

An AE or SAR is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been previously observed.

11.4 Serious Adverse Events

11.4.1 Definition of Serious Adverse Events

An AE is considered an SAE if it meets any of the following criteria:

- Results in death
- Is life-threatening

  Note: An AE or SAR is considered "life-threatening" if, in the view of the either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability or incapacity

  That is, the event severely or permanently disrupts the subject's ability to perform normal life functions or daily activities.
- Results in a congenital anomaly or birth defect
- Is medically significant (important medical event)

Medical and scientific judgment should be exercised in deciding whether SAE reporting is 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 patient. Examples of such events are allergic bronchospasm requiring treatment in an emergency room, serious blood dyscrasias or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

11.4.2 Serious Adverse Event Reporting Requirements

Any SAE that occurs from the time the consent is signed through completion of the subject's participation in the study, whether or not the SAE is related to the investigational product, **must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event**. The contact information for reporting SAEs is provided in the Study Reference Manual. General SAE reporting instructions are as follows:

- Record all SAEs on the AE CRF
- Submit SAE documents according to instructions in the Study Reference Manual
- For SAEs, record the primary event on the AE CRF; describe events occurring secondary to that primary event on the SAE form in the narrative description of the case
- Death is an outcome, not an event. Record the event that resulted in the death on the AE CRF.
- For hospitalizations for surgical or diagnostic procedures, record the illness leading to the surgical or diagnostic procedure as the SAE, not the procedure itself. Capture the procedure in the narrative as part of the action taken in response to the illness
- Elective hospitalizations will not be considered SAEs and do not need to be reported. However, complications that prolong elective hospitalizations should be recorded as SAEs. Emergency room visits of less than 24 hours do not meet the criterion of hospitalization for SAE reporting purposes.

The report should contain, at a minimum, the following information:

- Subject identifiers (ie, subject number)
- Suspected medicinal product
- AE term (must be listed as serious)
- Contact information for person reporting event

The relationship of the SAE to study treatment will be assessed by the investigator (Section 11.5.2). Follow-up information should be actively sought and submitted as it becomes available.

If the SAE is assessed as possibly or probably related to study treatment, it must be followed until it is considered stable or resolved.

Any SAE assessed as not related to study treatment will be followed as clinically indicated until its resolution or, if non-resolving, until it is considered chronic or stable or until study completion.

The investigator will assess relationship to study treatment. In addition, the sponsor will assess relationship to study treatment and determine expectedness based on the current Investigator Brochure. The sponsor's determination of relatedness will define whether an event is a suspected unexpected serious adverse reaction (SUSAR). The sponsor will report all SUSARs to regulatory authorities as expedited reports in accordance with applicable regulatory requirements (21 Code of Federal Regulations [CFR] 312.32[c] in the US). All other SAEs will be reported as part of regulatory safety updates, as required, such as in annual reports.

11.5 Adverse Event Severity and Relationship to Study Treatment

11.5.1 Severity Grading of Adverse Events

The severity of AEs will be graded based on adapted CTCAE, Version 4.03 (Table 11-1).

Table 11-1: Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03)

AE Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Source: Adapted from CTCAE, Version 4.03 (National Cancer Institute 2010).
ADL = activities of daily living; AE = adverse event.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For all AEs and SAEs, if there is a change in the severity after onset, the event should be reported as a single entry with the maximum severity grading captured.

11.5.2 Relationship of Adverse Events to Study Treatment

The investigator will determine the relationship of the AE to study treatment using the definitions provided in Table 11-2.

Table 11-2: Definitions for Relationship of Adverse Events to Study Treatment

Relationship to Study Treatment	Definition
Not Related	Another cause of the event is most plausible; *or* clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; *or* a causal relationship is considered biologically implausible.
Possibly Related	An event that follows a reasonable temporal sequence from administration of the study treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.
Probably Related	An event that follows a reasonable temporal sequence from administration of the study treatment, *and* there is a biologically plausible mechanism for study treatment causing or contributing to the AE, *and* the event could not be reasonably explained by the known characteristics of the subject's clinical state. In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

AE = adverse event.

The investigator will follow all related AEs observed during the study until the AEs are considered resolved, or until the subject has completed the study.

The investigator will follow all related SAEs observed during the study assessed as possibly or probably related to study treatment until the SAEs are considered stable or resolved.

The sponsor may request additional follow-up on specific unresolved AEs.

11.6 Reporting and Documentation of Pregnancy

Any subject who becomes pregnant during the study will be discontinued from study treatment and followed for pregnancy outcome. Follow-up information should be actively sought by the principal investigator and submitted to Dynavax or designee as soon as it becomes available. The principal investigator will complete the pregnancy reporting form and all other relevant CRFs. Uncomplicated pregnancies are not considered an AE/SAE. A complicated pregnancy or a pregnancy with an adverse outcome may meet criteria for an AE or SAE and would then also be reported according to the appropriate requirements.

A subject who becomes pregnant will be instructed to report the pregnancy to the study site as soon as possible. A report of the pregnancy will be completed by the principal investigator or designee and will document details of the pregnancy, outcome of pregnancy, and details of delivery. The subject should be followed by the principal investigator through the remainder of the pregnancy for safety assessments.

The sponsor or designee must be notified as soon as possible once the study site learns of a pregnancy. Pregnancy report forms provided by the sponsor or designee must be completed and submitted to Dynavax or designee. The contact information for reporting pregnancy is provided in the Study Reference Manual.

12.0 STATISTICAL METHODS

12.1 General

This trial is designed to allow preliminary assessments of safety and biological activity. No pre-specified hypothesis testing will be performed. All analyses of demographics, biological activity, and safety will be descriptive. Details of statistical analyses for this study will be provided in the Statistical Analysis Plan.

AEs, SAEs, and abnormal laboratory values will be summarized by the proportion of subjects who experience them.

Response rate will be presented as the proportion of subjects who achieved CR or partial response (PR). Summary statistics will be provided for time to response, duration of response, TTP, and TTNT.

In general, categorical data will be summarized as counts and percentages (or proportions) and continuous data will be summarized with descriptive statistics such as mean, standard deviation, median, minimum and maximum.

Final analyses will be carried out after the last participant has completed the Final Study Visit, the study database has been authorized by Dynavax as complete and final, and major protocol deviations have been identified. Subject data will be reviewed for major protocol deviations by the Dynavax Medical Monitor prior to database lock. A listing of subjects with major protocol deviations will be provided, sorted by treatment and describing their deviations.

12.2 Sample-size Considerations

This trial is designed to allow preliminary assessments of safety and biological activity in approximately 25 to 31 subjects. Thirteen subjects were enrolled in the dose escalation part of the trial and approximately 12 to 18 subjects are planned in the second part. Table 12-1 summarizes the probabilities of detecting the number of responses if a total of 9 or 12 subjects (including subjects already enrolled in Phase 1) are enrolled in the target Phase 2 cohort. For example, if the true response rate is 30%, a sample size of 12 subjects will have 74% chance to obtain 3 or more responders and 50% chance to obtain 4 or more responders. A 90% exact binomial confidence interval will be constructed as preliminary efficacy information for further investigation. The numbers of responses and probabilities of detecting a response if total population size for a cohort is 9 or 12 subjects is provided in Table 12-1.

Subjects who do not complete at least 4 injections for reasons other than discontinuation for toxicity or who do not have at least one post Screening assessment of tumor response may be replaced.

Table 12-1: Probabilities of Detecting Response

Number of Responses	Probabilities of Detecting Response	
	Subjects Enrolled (N=9)	Subjects Enrolled (N=12)
≥ 1	95%	98%
≥ 2	80%	91%
≥ 3	53%	74%
≥ 4	27%	50%
≥ 5	9%	27%

12.3 Study Analysis Populations

The safety population will include all subjects who receive radiation treatment and at least one dose of SD-101.

The efficacy population will include all subjects in the safety population who receive Screening imaging and bone marrow biopsy and at least one post baseline imaging assessment or who die prior to first post-baseline imaging.

12.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the safety population will be listed by subject and summarized. Descriptive summary statistics (sample size, mean, median, standard deviation, and range, when appropriate) will be provided for the continuous variables such as age, weight, and height. Count and percentage will be reported for categorical variables such as sex, race, and ethnicity.

Age will be calculated between a subject's birth date and the date of his/her consent.

12.5 Pharmacokinetic and Pharmacodynamic Analyses

The PK and PD population will consist of all subjects in the safety population who receive the second dose of SD-101 and have assessments at pre-dose through 24 hours post-dose.

For PK, changes from pre-second dose to 24 hours post-second dose of SD-101 will be summarized by dose level. Maximum observed concentration (C_{max}), time to reach C_{max} (T_{max}), half-life, and area under the concentration-time curve will be evaluated.

IFN-alpha inducible genes will be assayed by quantitative polymerase chain reaction (qPCR) before administration of the first and second doses of SD-101 and after administration of SD-101. These genes will be assessed during Cycle 1 and, as applicable, Cycle 2. The fold increase will be analyzed as a surrogate for the activity of SD-101. The core group of genes measured will be ISG-54, Mx-B, IFN-alpha, TNF-alpha, IP-10, IRF-7, GBP-1, MCP-1, and MCP-2. Other genes may be tested to elucidate the patterns seen in the core genes. The fold increases will be analyzed per individual gene and as the geometric mean of their combination or a subset of the same.

Additional analyses will include analysis of tumor samples (FNA) including analysis for RNA gene expression profiling and the analysis of immunologic related cells. The procedure for FNA collection is described in Section 10.9 and in the Laboratory Manual.

12.6 Safety Analyses

All safety data will be analyzed descriptively for the safety population. The most important safety parameters will be presented for all sites combined. Summary statistics will be used to describe the incidence of all injection-site reactions, AEs, SAEs, and deaths. DLTs occurring in Part 1 will be summarized by dose level received and presented in both tables and listings.

12.7 Response Analyses

Rate of response of Lesion A and rate of response outside Lesion A will be analyzed descriptively and 90% exact binomial confidence interval will be calculated for both lesion response rates and overall response rate. Time to response and duration of response will be summarized for subjects who achieved CR or PR on study. Time to response is measured from first dose of SD-101 to CR or PR. Duration of response is measured from initial response (CR, PR) to progression or end of follow up for those who do not have disease progression.

12.8 Interim Analysis

No formal interim analysis is planned for this study.

13.0 STUDY DOCUMENTATION AND DIRECT ACCESS

13.1 Source Documents

The investigator must maintain detailed records of all study participants who are enrolled in the study or who undergo Screening. Source documents include, but are not limited to, subject medical records and investigator's subject study files, as well as all test results.

The following minimum information should be entered into the enrolled subject's source documents:

- The date the subject entered the study and the subject number
- The study protocol number and the name Dynavax Technologies
- The date that informed consent was signed
- Evidence that the subject meets study eligibility requirements (eg, medical history, study procedures and/or evaluations)
- The dates of all study-related subject visits
- Evidence that study-required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of study medication accountability
- Occurrence and status of any AEs
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued early, including the reason for discontinuation
- Any deviations from the protocol

13.2 Direct Access to Source Data/Documents

Qualified individuals designated by Dynavax or its representative will monitor all aspects of the study at regular intervals throughout the study and following study completion. This monitoring is for the purpose of verifying adherence to the protocol including appropriate storage of IMP, completeness and exactness of the data being entered onto the CRFs, and compliance with United States Food and Drug Administration (FDA) or other regulatory agency regulations. The investigator and investigator's institution agree to allow these monitors access to all study records, CRFs, and corresponding portions of the subject's clinical study files; to allow access to the clinical supplies, dispensing, and storage areas; and if requested, to assist the monitors. The investigator further agrees to permit direct access to source data/documents for trial-related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, and regulatory inspection(s).

In certain circumstances, a secondary audit may be conducted by members of Dynavax's Quality Assurance group or by Dynavax's designated representative. The investigator will be notified if this is to take place, and advised as to the nature of the audit.

14.0 DATA QUALITY ASSURANCE

The study sites will be monitored by Dynavax or its designee according to GCP and standard operating procedures. Prior to initiation of the study, representatives from Dynavax or its designee will review with the site personnel information about the investigational product, proper storage of IMP, protocol requirements, and monitoring requirements. During and after the study, periodic site visits will be made to monitor for compliance, including verification of the accuracy and completeness of data recorded on the CRFs, source documents, and IMP accountability records.

15.0 ETHICS

15.1 Institutional Review Board/Independent Ethics Committee

The protocol and informed consent documents must be reviewed and approved by an appropriately composed IRB. The study will not be initiated at a site until appropriate written IRB approval of the protocol, ICF, and all recruiting materials (if applicable) is obtained by the investigator. Copies should be reviewed and approved by Dynavax prior to submission to the IRB. The investigator will submit periodic reports on the progress of the study as required by the IRB, in accordance with applicable governmental regulations, and in agreement with the policy established by Dynavax. In addition, the investigator will inform the IRB of any protocol amendments and administrative changes, and will obtain appropriate written IRB approval of all protocol amendments.

15.2 Ethical Conduct of the Study

This study will be conducted in accordance with the protocol; GCP as defined in ICH guidelines and applicable local regulatory requirements.

The study will be registered as a Phase 1/2 study on www.clinicaltrials.gov.

15.3 Informed Consent

The investigator is responsible for obtaining informed consent from each subject participating in the study in compliance with US CFR Title 21, Part 50, Title 45 Part 46, and ICH and IRB guidelines. Prior to initiation of the study at the site, the ICF must be reviewed and accepted by Dynavax and approved by the governing IRB. The investigator or authorized designee will discuss the purpose and pertinent details of the study with each subject, and the subject must understand, sign, and date the appropriate IRB-approved ICF before undergoing any study-specific procedures. The ICF must be personally signed and dated by the subject and by the person who conducted the informed consent discussion. Additional signature requirements may exist. The original signed and dated ICF will be retained with the subject's study records, and a

copy of the signed ICF will be given to the subject. The investigator or designee will maintain a log of all subjects who sign the ICF. At a minimum, the log will include a subject identifier, the dates of informed consent and screening procedures, the outcome of the screening, and the reason the subject did not enroll in the trial.

15.4 Subject Confidentiality

The investigator is responsible for maintaining the privacy and confidentiality of the subject's medical or health information collected during the study. The investigator is also responsible for ensuring that all use, review and disclosure of subject's medical or health information is in accordance with HIPAA regulations and the ICF approved by the IRB and signed by the subject. Specifically, all data collected about a subject during the study will be identified only by a number and the subject's initials.

16.0 DATA HANDLING AND RECORD KEEPING

16.1 Case Report Forms

Electronic case report forms (eCRF) will be used at the clinical trial site to collect trial data for enrolled subjects. Information on subjects who fail Screening, including demographic information and reason for screen fail, will be collected. The eCRFs are part of a controlled-access EDC system managed by Dynavax or its authorized representative. Study staff with access to this EDC system will be trained prior to use. When data are available, authorized clinical trial site personnel will carefully and accurately record the data on the eCRF. The EDC system may be used to record original data and changes of data, with all changes tracked by the system in an electronic audit trail. Sites must ensure that all source documents are maintained according to ICH/GCP guidance and support the data that are entered onto the eCRFs.

The eCRF data will be captured in a system validated according to procedures that comply with the applicable local legal and regulatory requirements and the ICH Guidelines for GCP (Topic E6, July 1996, Section 5.5.3). The eCRFs will be reviewed and signed by the investigator listed on FDA Form 1572 or applicable regulatory investigator agreement. After database lock, the investigator will receive a copy of the subject data for archiving at the study site.

16.2 Data Handling

The sponsor will designate a CRO to perform data management. The CRO will write a data management plan outlining the data management systems, procedures, and agreements between the CRO and sponsor. The plan will be reviewed and signed by a representative of the sponsor's data management department.

Validation checks will be conducted to capture data errors, and data clarification queries will be generated at the time of data monitoring. Validation checks and queries will be issued to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

Data verification against the source documents at the site will be performed by the sponsor or its designee prior to any interim analysis and prior to locking of the trial database. Following the completion of source data verification, a thorough review of data will be completed manually by the clinical data managers to ensure data consistency and to identify and request correction of any remaining data errors. All queries will be resolved or closed with written documentation providing reasons for irresolvable queries. Additional manual validation checks will be performed as needed.

16.3 Coding of Adverse Events, Drugs, and Diseases

AEs and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHO Drug).

16.4 Record Retention

The investigator must retain all records relating to the conduct of this study (including subject's study records, receipt and disposition of all investigational materials, subject exclusion logs, signed consent forms, CRFs, all correspondence, and other supporting documentation) for at least 2 years after a marketing application for the drug is approved; or if an application is not filed or not approved for the drug, for at least 2 years after clinical development for the drug has been formally discontinued. However, in certain instances, documents may need to be retained for a longer period if required by regulatory requirements or by an agreement with Dynavax.

The investigator may withdraw from the responsibility of retaining records only after transferring custody of the records to another individual who will accept responsibility for them. A written notice of transfer must be provided to Dynavax prior to or no later than 10 days after transfer.

The investigator must allow representatives of the FDA, the governing IRB, or other regulatory agencies to inspect all study records. If informed of such an inspection, the investigator will notify Dynavax immediately.

The investigator must obtain written approval from Dynavax prior to the destruction of any records relating to the conduct of this study.

17.0 USE OF INFORMATION AND PUBLICATION

It is understood by the investigator that the information generated in this study is the property of Dynavax. It is understood that the investigator is obliged to provide Dynavax with complete test results, all study data, and access to all study records.

All efforts should be made for abstracts and publications to be jointly authored by investigators and Dynavax. No publications based upon any preliminary study data shall occur prior to full completion of the clinical trial. Dynavax will be furnished with a copy of any other proposed

publication. Dynavax's comments shall be given without undue delay, and not later than within 60 days.

Results from the investigation shall not be made available to any third party by the investigators or any of their staff.

It is understood by the investigator that the information generated in this study may be used by Dynavax in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the investigator is obligated to provide Dynavax with complete test results, all study data, and access to all study records.

Dynavax recognizes the importance of communicating medical study data, and therefore encourages their publication in reputable scientific journals and at seminars or conferences.

Any results of medical investigations with Dynavax's products and all publications, lectures, and manuscripts based thereon shall be exchanged and discussed by the investigators and Dynavax's representatives prior to submission for publication or presentation. Due regard shall be given to Dynavax's legitimate interests, eg, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.

Dynavax will be furnished with a copy of any proposed publication and allowed to make comments. In cases of publications or presentations of material arising from multicenter clinical investigations, Dynavax is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent and the prior review of Dynavax. In case of disagreement among the investigators participating in a multicenter investigation, Dynavax will be the final arbiter. If Dynavax's comments are not accepted, the senior author of the manuscript and Dynavax's representatives shall promptly meet and endeavor to agree mutually on the final wording and disposition of the publication. The above procedure also applies to information on prematurely discontinued and other incomplete studies.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. Dynavax will not quote from publications by investigators in its scientific information or promotional material without full acknowledgment of the source (ie, author and reference).

18.0 REFERENCES

Brennan, B. J., Xu, Z.X., Grippo, J.F. (2012). "Effect of peginterferon alfa-2a (40KD) on cytochrome P450 isoenzyme activity."

Brody, J. D., W. Z. Ai, D. K. Czerwinski, J. A. Torchia, M. Levy, R. H. Advani, Y. H. Kim, R. T. Hoppe, S. J. Knox, L. K. Shin, I. Wapnir, R. J. Tibshirani and R. Levy (2010). "In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study." J Clin Oncol **28**(28): 4324-4332.

Campbell, J. D., Y. Cho, M. L. Foster, H. Kanzler, M. A. Kachura, J. A. Lum, M. J. Ratcliffe, A. Sathe, A. J. Leishman, A. Bahl, M. McHale, R. L. Coffman and E. M. Hessel (2009). "CpG-containing immunostimulatory DNA sequences elicit TNF-alpha-dependent toxicity in rodents but not in humans." J Clin Invest **119**(9): 2564-2576.

Center for Biologics Evaluation and Research (2007). Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, Food and Drug Administration.

Cheson, B. D., S. J. Horning, B. Coiffier, M. A. Shipp, R. I. Fisher, J. M. Connors, T. A. Lister, J. Vose, A. Grillo-Lopez, A. Hagenbeek, F. Cabanillas, D. Klippensten, W. Hiddemann, R. Castellino, N. L. Harris, J. O. Armitage, W. Carter, R. Hoppe and G. P. Canellos (1999). "Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group." J Clin Oncol **17**(4): 1244.

Cheson, B. D., B. Pfistner, M. E. Juweid, R. D. Gascoyne, L. Specht, S. J. Horning, B. Coiffier, R. I. Fisher, A. Hagenbeek, E. Zucca, S. T. Rosen, S. Stroobants, T. A. Lister, R. T. Hoppe, M. Dreyling, K. Tobinai, J. M. Vose, J. M. Connors, M. Federico and V. Diehl (2007). "Revised Response Criteria for Malignant Lymphoma." Journal of Clinical Oncology **25**(5): 579-586.

Duramad, O., K. L. Fearon, B. Chang, J. H. Chan, J. Gregorio, R. L. Coffman and F. J. Barrat (2005). "Inhibitors of TLR-9 act on multiple cell subsets in mouse and man in vitro and prevent death in vivo from systemic inflammation." J Immunol **174**(9): 5193-5200.

Guiducci, C., G. Ott, J. H. Chan, E. Damon, C. Calacsan, T. Matray, K. D. Lee, R. L. Coffman and F. J. Barrat (2006). "Properties regulating the nature of the plasmacytoid dendritic cell response to Toll-like receptor 9 activation." J Exp Med **203**(8): 1999-2008.

Harris, N. L., E. S. Jaffe, H. Stein, P. M. Banks, J. K. Chan, M. L. Cleary, G. Delsol, C. De Wolf-Peeters, B. Falini, K. C. Gatter and et al. (1994). "A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group." Blood **84**(5): 1361-1392.

Harris, N. L., S. H. Swerdlow, E. S. Jaffe, G. Ott, B. N. Nathwani, D. de Jong, T. Yoshino and D. Spagnolo (2008). Follicular lymphoma. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. S. H. Swerdlow, E. Campo, N. L. Harris et al. Lyon, France, International Agency for Research on Cancer (IARC)**:** 220-226.

Hervas-Stubbs, S., J. L. Perez-Gracia, A. Rouzaut, M. F. Sanmamed, A. Le Bon and I. Melero (2011). "Direct Effects of Type I Interferons on Cells of the Immune System." Clinical Cancer Research **17**(9): 2619-2627.

Honda, K., Y. Ohba, H. Yanai, H. Negishi, T. Mizutani, A. Takaoka, C. Taya and T. Taniguchi (2005). "Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction." Nature **434**(7036): 1035-1040.

Kawarada, Y., R. Ganss, N. Garbi, T. Sacher, B. Arnold and G. J. Hammerling (2001). "NK- and CD8(+) T cell-mediated eradication of established tumors by peritumoral injection of CpG-containing oligodeoxynucleotides." J Immunol **167**(9): 5247-5253.

Kim, Y. H., D. Gratzinger, C. Harrison, J. D. Brody, D. K. Czerwinski, W. Z. Ai, A. Morales, F. Abdulla, L. Xing, D. Navi, R. J. Tibshirani, R. H. Advani, B. Lingala, S. Shah, R. T. Hoppe and R. Levy (2012). "In situ vaccination against mycosis fungoides by intratumoral injection of a TLR9 agonist combined with radiation: a phase 1/2 study." Blood **119**(2): 355-363.

Krieg, A. M. (2002). "CpG motifs in bacterial DNA and their immune effects." Annu Rev Immunol **20**: 709-760.

Krieg, A. M. (2006). "Therapeutic potential of Toll-like receptor 9 activation." Nat Rev Drug Discov **5**(6): 471-484.

Krieg, A. M., A. K. Yi, S. Matson, T. J. Waldschmidt, G. A. Bishop, R. Teasdale, G. A. Koretzky and D. M. Klinman (1995). "CpG motifs in bacterial DNA trigger direct B-cell activation." Nature **374**(6522): 546-549.

Kuramoto, E., O. Yano, Y. Kimura, M. Baba, T. Makino, S. Yamamoto, T. Yamamoto, T. Kataoka and T. Tokunaga (1992). "Oligonucleotide sequences required for natural killer cell activation." Jpn J Cancer Res **83**(11): 1128-1131.

Lou, Y., C. Liu, G. Lizee, W. Peng, C. Xu, Y. Ye, B. A. Rabinovich, Y. Hailemichael, A. Gelbard, D. Zhou, W. W. Overwijk and P. Hwu (2011). "Antitumor activity mediated by CpG: the route of administration is critical." J Immunother **34**(3): 279-288.

Mirzaie-Joniani, H., D. Eriksson, A. Sheikholvaezin, A. Johansson, P.-O. Löfroth, L. Johansson and T. Stigbrand (2002). "Apoptosis induced by low-dose and low-dose-rate radiation." Cancer **94**(S4): 1210-1214.

National Cancer Institute (2010). Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services.

National Cancer Institute. (2014). "SEER Cancer Statistics Factsheets: Non-Hodgkin Lymphoma." Retrieved 28Mar2014, from http://seer.cancer.gov/statfacts/html/nhl.html

Oken, M. M., R. H. Creech, D. C. Tormey, J. Horton, T. E. Davis, E. T. McFadden and P. P. Carbone (1982). "Toxicity and response criteria of the Eastern Cooperative Oncology Group." Am J Clin Oncol **5**(6): 649-655.

Roman, M., E. Martin-Orozco, J. S. Goodman, M. D. Nguyen, Y. Sato, A. Ronaghy, R. S. Kornbluth, D. D. Richman, D. A. Carson and E. Raz (1997). "Immunostimulatory DNA sequences function as T helper-1-promoting adjuvants." Nat Med **3**(8): 849-854.

Solal-Celigny, P., P. Roy, P. Colombat, J. White, J. O. Armitage, R. Arranz-Saez, W. Y. Au, M. Bellei, P. Brice, D. Caballero, B. Coiffier, E. Conde-Garcia, C. Doyen, M. Federico, R. I. Fisher, J. F. Garcia-Conde, C. Guglielmi, A. Hagenbeek, C. Haioun, M. LeBlanc, A. T. Lister, A. Lopez-Guillermo, P. McLaughlin, N. Milpied, P. Morel, N. Mounier, S. J. Proctor, A. Rohatiner, P. Smith, P. Soubeyran, H. Tilly, U. Vitolo, P. L. Zinzani, E. Zucca and E. Montserrat (2004). "Follicular lymphoma international prognostic index." Blood **104**(5): 1258-1265.

Tokunaga, T., O. Yano, E. Kuramoto, Y. Kimura, T. Yamamoto, T. Kataoka and S. Yamamoto (1992). "Synthetic oligonucleotides with particular base sequences from the cDNA encoding proteins of Mycobacterium bovis BCG induce interferons and activate natural killer cells." Microbiol Immunol **36**(1): 55-66.

Yamamoto, S., E. Kuramoto, S. Shimada and T. Tokunaga (1988). "*In vitro* augmentation of natural killer cell activity and production of interferon-alpha/beta and -gamma with deoxyribonucleic acid fraction from *Mycobacterium bovis* BCG." Jpn J Cancer Res **79**(7): 866-873.

APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS (PART 1 ONLY)

Trial Period:		**Screening**	**Treatment**							**Follow-up**						**ED**[a]	**UNS**[b]
	Visit:	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	ED	UNS
	Day:	- 30 to -2	-1	1	8	9[c]	15	22	29	36	90	180	360	540	720		
Procedure:	**Visit Window (days):**									±3	±14	±14	±14	±14	±14		
				DLT Evaluation Period[d]													
Informed consent		X															
Diary card[e]				X	X		X	X	X	X							
Medical and medication history		X	X														
Vital signs[f,w]		X	X	X	X		X	X	X	X						X	X
Physical examination[g,w]		X	X					X		X	X	X	X	X	X	X	X
Electrocardiogram[w]		X					X[h]			X							
HIV and hepatitis testing[i,w, y]		X															
Chemistry[j,w, y]		X	X					X		X	X	X	X	X	X	X	X
Hematology[k,w, y]		X	X		X		X	X		X	X	X	X	X	X	X	X
Coagulation[l,w, y]		X	X					X		X						X	
Pregnancy testing[m, y]		X	X		X		X	X	X							X	
Unilateral bone marrow biopsy and aspirate[n]		X															X
Localized XRT			X	X													
SD-101 intratumoral injection[z]				X	X		X	X	X								
Post-treatment observation (minimum 30 minutes)				X	X		X	X	X								
Injection-site reaction assessment				X	X		X	X	X	X							
Blood for IFN-alpha inducible gene expression (PD)[o]			X	X	X	X											
Blood for RNA to study gene expression changes[p]		X	X	X	X	X	X	X	X	X	X	X	X				
Fine needle aspirate[q]			X		X					X							X

APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS (PART 1 ONLY) (CONT'D)

Trial Period:		**Screening**	**Treatment**							**Follow-up**						**ED**[a]	**UNS**[b]
	Visit:	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	ED	UNS
	Day:	- 30 to -2	-1	1	8	9[c]	15	22	29	36	90	180	360	540	720		
Procedure:	**Visit Window (days):**									±3	±14	±14	±14	±14	±14		
				DLT Evaluation Period[d]													
Serum for anti-dsDNA[x, y]			X							X			X				
Serum for anti-SD-101			X							X			X				
Plasma for pharmacokinetics[r]					X	X											
Reserve serum aliquot[s]			X		X	X		X		X						X	
CT Scan (Neck/Chest/Abdomen/Pelvis)[t]		X									X	X	X	X	X	X	X
Adverse Events[u]			X	X	X		X	X	X	X	X					X	
Serious Adverse Events			X	X	X		X	X	X	X	X	X	X	X	X	X	
Concomitant Medications[v]			X	X	X		X	X	X	X	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	

APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS (PART 1 ONLY) (CONT'D)

FOOTNOTES

AE = adverse event; ALT = alanine aminotransferase; anti-dsDNA = antibodies to double-stranded deoxyribonucleic acid; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CR = complete response; CRP = C-reactive protein; CT = computed tomography; D = Day; DLT = dose-limiting toxicity; ED = early discontinuation; FNA = fine needle aspiration; GGT = gamma-glutamyl transpeptidase; HBc = hepatitis B core antigen; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; IFN = interferon; IMP = investigational medicinal product; LDH = lactate dehydrogenase; PD = pharmacodynamics; PET/CT = Positron Emission Tomography/computed tomography; PK = pharmacokinetics; PT = prothrombin time; RNA = ribonucleic acid; SAE = serious adverse event; SOC = standard of care; UNS = unscheduled visit; WBC = white blood cell; WOCBP = women of childbearing potential; XRT = radiation therapy.

[a] Every effort should be made to complete the ED visit within a window no later than the next scheduled study visit (and at least 7 days following the last injection). Subjects who are withdrawn due to an AE should be followed for up to 28 days or more after their last dose of study drug. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

[b] An unscheduled visit should be performed if there is suspected disease progression or subject safety concerns. If disease progression is suspected, it must be reported to the sponsor within 24 hours (Section 8.4) and confirmation of disease progression should be documented by completing a targeted physical examination (including assessment of the liver and Spleen) based on subject-reported symptoms including vital signs (heart rate, blood pressure, respiratory rate), serum chemistry, hematology, CT scan, and unilateral bone marrow biopsy and aspirate if clinically indicated by new abnormalities in the peripheral blood counts or blood smear (Section 8.4). Fine needle aspirate samples are only to be collected at an unscheduled visit if the ±21 days visit window at Visit 8 is used or at a visit to assess disease progression. If an unscheduled visit is performed because of a safety concern related to IMP, at a minimum, the following should be performed: a targeted physical examination based on subject-reported symptoms including vital signs (heart rate, blood pressure, and respiratory rate), serum chemistry, and hematology.

[c] The Day 9 visit (Visit 4) must occur 1 day (24 ± 3 hours) after the Day 8 (Visit 3) visit.

[d] DLT evaluation will be based on review of safety data through 7 days following the end of treatment (Day 36 [Visit 8] or ED).

[e] A new diary card should be issued at Visits 2, 3, 5, 6 and 7 prior to study injection. Diary cards should be reviewed for injection site reactions and solicited AEs at Visits 3, 5, 6, 7, and 8.

[f] Includes oral temperature (only at study injection visits), heart rate, respiratory rate, and systolic and diastolic blood pressure.

[g] The investigator or qualified designee will conduct physical examinations. A complete physical examination is conducted at Screening and ED, and a targeted physical examination (based on interval history and/or AEs) is conducted at all other visits. Assessment of the liver and spleen must be done during the physical exams that are completed at Screening, Day 90, Day 180, Day 360, Day 540, Day 720, Unscheduled Visit and ED Visit, where lesions are evaluated and the Cheson criteria are used to assess overall response.

[h] Electrocardiogram on Day 15 to be performed after SD-101 dosing.

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

[j] Chemistry (includes sodium, potassium, chloride, bicarbonate, BUN, Cr, glucose, calcium, AST, ALT, GGT, LDH, bilirubin, alkaline phosphatase) and CRP.

[k] Includes Hgb, hematocrit, WBC count with differential, and platelet count.

[l] Includes PT and APTT.

APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS (PART 1 ONLY) (CONT'D)

FOOTNOTES (CONT'D)

[m] For WOCBP, serum pregnancy testing will be conducted at Screening and serum or urine pregnancy test at subsequent visits. Serum or urine pregnancy must be negative prior to study treatment. Dipstick can be used. All female subjects are considered to be WOCBP except as defined in Section 5.3.

[n] Unilateral bone marrow biopsy and aspirates will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a CR if the subject was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear (Section 8.4).

[o] IFN-inducible gene expression measured at Day -1 (Visit 1, baseline) prior to radiation, at Day 1 (Visit 2) prior to injection, at Day 8 (Visit 3) prior to injection, and at Day 9 (Visit 4) which is 24 (± 3) hours after injection.

[p] Blood for RNA analysis is to be collected pre-injection on treatment days.

[q] FNA samples will be collected from Lesion A at Visit 1 and 3. Collection of FNA samples from 1 or more additional lesions, if accessible, is encouraged but is optional. Collection of FNA samples at Visit 8 and a visit to assess disease progression is optional. Collections are to be done pre-XRT or pre-injection on treatment days. The Day 36 sample can be collected ±21 days from Visit 8.

[r] Plasma PK samples will be obtained pre-dose; 1, 2, 4, and 6 hours (± 10 minutes) post-dose (Visit 3); and 24 (± 3) hours post-dose (Visit 4) in Part 1 only.

[s] An extra aliquot of serum will be collected and stored frozen for possible future testing.

[t] PET scans will only be permitted if PET/CT is the SOC at the participating institution. Perform a CT scan of neck, chest, abdomen, pelvis and other areas as clinically indicated at all imaging timepoints.

[u] The AE assessment at the ED Visit should occur 7 days or more after the subject's last study injection. Subjects who are withdrawn due to a AE should have an AE assessment completed 28 days or more after the last study drug injection. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

[v] All concomitant medications taken by the subject from Screening through Day 90 (Visit 9) will be reported. Concomitant medications used to treat an SAE or immunomodulator drugs taken after Day 90 (Visit 9) through Day 720 (Visit 13) or ED are also to be reported.

[w] Results from SOC assessments completed within 30 days prior to a subject signing informed consent, may be used in lieu of repeating those study procedures during the 28 day Screening window: vital signs, physical exam, electrocardiogram, hepatitis and HIV testing, chemistry, hematology, coagulation. In addition, a copy of a record of lesion size at a timepoint at least 3 months prior to baseline should be added to the subject's CRF.

[x] Quantitative results for anti-dsDNA are required.

[y] All safety laboratory tests are to be performed at the local laboratory.

[z] The treated lesion should be labeled as Lesion A. The same lesion should be injected throughout Cycle 1, and if the lesion regresses, SD-101 should be injected into a peritumoral area.

APPENDIX 2: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 1 TREATMENT CYCLE)

Trial Period:		**Screening**	**Treatment - Cycle 1**							**Follow-up**						**ED**[a]	**UNS**[b]
	Visit:	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	ED	UNS
	Day:	- 30 to -2	-1	1	8	9[c]	15	22	29	36	90	180	360	540	720		
Procedure:	**Visit Window (days):**				±1		±1	±1	±1	±3	±14	±14	±14	±14	±14		
Informed consent		X															
Diary card[d]				X	X		X	X	X	X							
Medical and medication history		X	X														
Vital signs[e, f]		X	X	X	X		X	X	X	X						X	X
Physical examination[f,g]		X	X					X		X	X	X	X	X	X	X	X
Electrocardiogram[f]		X					X[h]			X							
HIV and hepatitis testing[f,i,t]		X															
Chemistry[f,j,t]		X	X					X		X	X	X	X	X	X	X	X
Hematology[f,k,t]		X	X		X		X	X	X	X	X	X	X	X	X	X	X
Coagulation[f,l,t]		X	X					X		X						X	
Pregnancy testing[m, t]		X															
Unilateral bone marrow biopsy and aspirate[n]		X															X
Localized XRT			X	X													
SD-101 intratumoral injection[y]				X	X		X	X	X								
Post-treatment observation (minimum 30 minutes)				X	X		X	X	X								
Injection-site reaction assessment				X	X		X	X	X	X							
Blood for IFN-alpha inducible gene expression (PD)[o]			X	X	X	X											
Blood for RNA to study gene expression changes[p]		X	X	X	X	X	X	X	X	X	X	X	X				
Fine needle aspirate of treated lesion (Lesion A)[q]			X		X					X							
Fine needle aspirate of untreated lesion (Lesion B)[r]			X							X	X						

APPENDIX 2: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 1 TREATMENT CYCLE) (CONT'D)

Trial Period:		**Screening**	**Treatment - Cycle 1**							**Follow-up**						**ED**[a]	**UNS**[b]
	Visit:	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	ED	UNS
	Day:	- 30 to -2	-1	1	8	9[c]	15	22	29	36	90	180	360	540	720		
Procedure:	**Visit Window (days):**				±1		±1	±1	±1	±3	±14	±14	±14	±14	±14		
Serum for anti-dsDNA[s,t]			X							X			X				
Serum for anti-SD-101			X							X			X				
Reserve serum aliquot[u]			X		X			X		X						X	
CT Scan (Neck/Chest/Abdomen/Pelvis)[v]		X									X	X	X	X	X	X	X
Adverse Events[w]			X	X	X		X	X	X	X	X					X	
Serious Adverse Events			X	X	X		X	X	X	X	X	X	X	X	X	X	
Concomitant Medications[x]			X	X	X		X	X	X	X	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	

APPENDIX 2: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 1 TREATMENT CYCLE) (CONT'D)

FOOTNOTES

AE = adverse event; ALT = alanine aminotransferase; anti-dsDNA = antibodies to double-stranded deoxyribonucleic acid; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CR = complete response; CRP = C-reactive protein; CT = computed tomography; D = Day; DLT = dose-limiting toxicity; ED = early discontinuation; FNA = fine needle aspiration; GGT = gamma-glutamyl transpeptidase; HBc = hepatitis B core antigen; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; IFN = interferon; IMP = investigational medicinal product; LDH = lactate dehydrogenase; PD = pharmacodynamics; PET/CT = Positron Emission Tomography/computed tomography; PT = prothrombin time; RNA = ribonucleic acid; SAE = serious adverse event; SOC = standard of care; UNS = unscheduled visit;; WBC = white blood cell; WOCBP = women of childbearing potential; XRT = radiation therapy.

[a] Every effort should be made to complete the ED visit within a window no later than the next scheduled study visit (and at least 7 days following the last injection). Subjects who are withdrawn due to an AE should be followed for up to 28 days or more after their last dose of study drug. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

[b] An unscheduled visit should be performed if there is suspected disease progression or subject safety concerns. If disease progression is suspected, it must be reported to the sponsor within 24 hours (Section 8.4) and confirmation of disease progression should be documented by completing a targeted physical examination (including assessment of the Liver and Spleen) based on subject-reported symptoms including vital signs (heart rate, blood pressure, respiratory rate), serum chemistry, hematology, CT scan, and unilateral bone marrow biopsy and aspirate if clinically indicated by new abnormalities in the peripheral blood counts or blood smear (Section 8.4). Fine needle aspirate samples are only to be collected at an unscheduled visit if the ±21 days visit window at Visit 8 is used or at a visit to assess disease progression. If an unscheduled visit is performed because of a safety concern related to IMP, at a minimum, the following should be performed: a targeted physical examination based on subject-reported symptoms including vital signs (heart rate, blood pressure, and respiratory rate), serum chemistry, and hematology.

[c] The Day 9 visit (Visit 4) must occur 1 day (24 ± 3 hours) after the Day 8 (Visit 3) visit.

[d] A new diary card should be issued at Visits 2, 3, 5, 6 and 7 prior to study injection. Diary cards should be reviewed for injection site reactions and solicited AEs at Visits 3, 5, 6, 7, and 8.

[e] Includes oral temperature (only at study injection visits), heart rate, respiratory rate, and systolic and diastolic blood pressure.

[f] Results from SOC assessments completed within 30 days prior to a subject signing informed consent, may be used in lieu of repeating those study procedures during the 28-day Screening window: vital signs, physical exam, electrocardiogram, hepatitis and HIV testing, chemistry, hematology, coagulation. In addition, a copy of a record of lesion size at a timepoint at least 3 months prior to baseline should be added to the subject's CRF.

[g] The investigator or qualified designee will conduct physical examinations. A complete physical examination is conducted at Screening and ED, and a targeted physical examination (based on interval history and/or AEs) is conducted at all other visits. Assessment of the liver and spleen must be done during the physical exams that are completed at Screening, Day 90, Day 180, Day 360, Day 540, Day 720, Unscheduled Visit and ED Visit, where lesions are evaluated and the Cheson criteria are used to assess overall response.

[h] Electrocardiogram on Day 15 to be performed after SD-101 dosing.

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

[j] Chemistry (includes sodium, potassium, chloride, bicarbonate, BUN, Cr, glucose, calcium, AST, ALT, GGT, LDH, bilirubin, alkaline phosphatase) and CRP.

[k] Includes Hgb, hematocrit, WBC count with differential, and platelet count.

[l] Includes PT and APTT.

APPENDIX 2: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 1 TREATMENT CYCLE) (CONT'D)

FOOTNOTES (CONT'D)

[m] For WOCBP, serum pregnancy testing will be conducted at Screening. Serum or urine pregnancy must be negative prior to initiation of study treatment. All female subjects are considered to be WOCBP except as defined in Section 5.3.

[n] Unilateral bone marrow biopsy and aspirates will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a CR if the subject was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear (Section 8.4).

[o] IFN-inducible gene expression measured at Day -1 (Visit 1, baseline) prior to radiation, at Day 1 (Visit 2) prior to injection, at Day 8 (Visit 3) prior to injection, and at Day 9 (Visit 4) which is 24 (± 3) hours after injection.

[p] Blood for RNA analysis is to be collected pre-injection on treatment days.

[q] Two FNA samples will be collected from Lesion A on Day -1, Day 8 (Visit 3), and Day 36 (Visit 8). Collections are to be done pre-XRT or pre-injection on treatment days. There is a ± 21 day window for the FNA sample collection at Day 36.

[r] Collection of 2 FNA samples from Lesion B, on Day -1, Day 36 (Visit 8), and Day 90 (Visit 9). Collections are to be done pre-XRT or pre-injection on treatment days. There is a ± 21 day window for the FNA sample collection at Day 90.

[s] Quantitative results for anti-dsDNA are required.

[t] All safety laboratory tests are to be performed at the local laboratory.

[u] An extra aliquot of serum will be collected and stored frozen for possible future testing.

[v] PET scans will only be permitted if PET/CT is the SOC at the participating institution. Perform a CT scan of neck, chest, abdomen, pelvis and other areas as clinically indicated at all imaging timepoints.

[w] The AE assessment at the ED Visit should occur 7 days or more after the subject's last study injection. Subjects who are withdrawn due to a AE should have an AE assessment completed 28 days or more after the last study drug injection. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

[x] All concomitant medications taken by the subject from Screening through Day 90 (Visit 9) will be reported. Concomitant medications used to treat an SAE or immunomodulator drugs taken after Day 90 (Visit 9) through Day 720 (Visit 13) or ED are also to be reported.

[y] The treated lesion should be labeled as Lesion A. The same lesion should be injected throughout Cycle 1, and if the lesion regresses, SD-101 should be injected into a peritumoral area.

APPENDIX 3: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 2 TREATMENT CYCLES)

Trial Period:		**Screening**	**Treatment - Cycle 1**							**Follow-up**		**Treatment - Cycle 2**							**Follow-up**					**ED**[a]	**UNS**[b]
	Visit:	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	UNS
	Day:	- 30 to -2	-1	1	8	9[c]	15	22	29	36	90	180[y]	181[y]	188	189	195	202	209	216	270	360	540	720		
Procedure:	**Visit Window (days):**				±1		±1	±1	±1	±3	±14	±14		±1		±1	±1	±1	±3	±14	±14	±14	±14		
Informed consent[y]		X										X													
Diary card[d]				X	X		X	X	X	X															
Medical and medication history		X	X																						
Vital signs[e, f]		X	X	X	X		X	X	X	X			X	X		X	X	X	X					X	X
Physical examination[f,g]		X	X					X		X	X	X	X				X		X	X	X	X	X	X	X
Electrocardiogram[f]		X					X[h]			X															
HIV and hepatitis testing[f,i,t]		X																							
Chemistry[f,j,t,z]		X	X					X		X	X	X					X		X	X	X	X	X	X	X
Hematology[f,k,t,z]		X	X		X		X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Coagulation[f,l,t,z]		X	X					X		X		X					X		X					X	
Pregnancy testing[m, t]		X										X[m]													
Unilateral bone marrow biopsy and aspirate[n]		X																							X
Localized XRT[y]			X	X								X	X												
SD-101 intratumoral injection[y]				X	X		X	X	X				X	X		X	X	X							
Post-treatment observation (minimum 30 minutes)				X	X		X	X	X				X	X		X	X	X							
Injection-site reaction assessment				X	X		X	X	X	X			X	X		X	X	X	X						
Blood for IFN-alpha inducible gene expression (PD)[o]			X	X	X	X						X	X	X	X										
Blood for RNA to study gene expression changes[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Fine needle aspirate of treated Lesion[q]			X		X					X		X		X					X						
Fine needle aspirate of untreated Lesion[r]			X							X	X	X							X	X					

APPENDIX 3: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 2 TREATMENT CYCLES) (CONT'D)

Trial Period:		**Screening**	**Treatment - Cycle 1**							**Follow-up**		**Treatment - Cycle 2**							**Follow-up**					**ED**[a]	**UNS**[b]
	Visit:	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	UNS
	Day:	- 30 to -2	-1	1	8	9[c]	15	22	29	36	90	180[y]	181[y]	188	189	195	202	209	216	270	360	540	720		
Procedure:	**Visit Window (days):**				±1		±1	±1	±1	±3	±14	±14		±1		±1	±1	±1	±3	±14	±14	±14	±14		
Serum for anti-dsDNA[s,t]			X							X		X							X		X				
Serum for anti-SD-101			X							X		X							X	X	X				
Reserve serum aliquot[u]			X		X			X		X		X		X			X		X					X	
CT Scan (Neck/Chest/Abdomen/Pelvis)[v]		X									X	X								X	X	X	X	X	X
Adverse Events[w]			X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X				X	
Serious Adverse Events			X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Concomitant Medications[x]			X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

APPENDIX 3: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 2 TREATMENT CYCLES) (CONT'D)

FOOTNOTES

AE = adverse event; ALT = alanine aminotransferase; anti-dsDNA = antibodies to double-stranded deoxyribonucleic acid; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CR = complete response; CRP = C-reactive protein; CT = computed tomography; D = Day; DLT = dose-limiting toxicity; ED = early discontinuation; FNA = fine needle aspiration; GGT = gamma-glutamyl transpeptidase; HBc = hepatitis B core antigen; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; IFN = interferon; IMP = investigational medicinal product; LDH = lactate dehydrogenase; PD = pharmacodynamics PET/CT = Positron Emission Tomography/computed tomography; PT = prothrombin time; RNA = ribonucleic acid; SAE = serious adverse event; SOC = standard of care; UNS = unscheduled visit;; WBC = white blood cell; WOCBP = women of childbearing potential; XRT = radiation therapy.

[a] Every effort should be made to complete the ED visit within a window no later than the next scheduled study visit (and at least 7 days following the last injection). Subjects who are withdrawn due to an AE should be followed for up to 28 days or more after their last dose of study drug. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

[b] An unscheduled visit should be performed if there is suspected disease progression or subject safety concerns. If disease progression is suspected, it must be reported to the sponsor within 24 hours (Section 8.4) and confirmation of disease progression should be documented by completing a targeted physical examination (including assessment of the Liver and Spleen) based on subject-reported symptoms including vital signs (heart rate, blood pressure, respiratory rate), serum chemistry, hematology, CT scan, and unilateral bone marrow biopsy and aspirate if clinically indicated by new abnormalities in the peripheral blood counts or blood smear (Section 8.4). Fine needle aspirate samples are only to be collected at an unscheduled visit if the ±21 days visit window at Visit 8 is used or at a visit to assess disease progression. If an unscheduled visit is performed because of a safety concern related to IMP, at a minimum, the following should be performed: a targeted physical examination based on subject-reported symptoms including vital signs (heart rate, blood pressure, and respiratory rate), serum chemistry, and hematology.

[c] The Day 9 visit (Visit 4) must occur 1 day (24 ± 3 hours) after the Day 8 (Visit 3) visit.

[d] A new diary card should be issued at Visits 2, 3, 5, 6 and 7 prior to study injection. Diary cards should be reviewed for injection site reactions and solicited AEs at Visits 3, 5, 6, 7, and 8.

[e] Includes oral temperature (only at study injection visits), heart rate, respiratory rate, and systolic and diastolic blood pressure.

[f] Results from SOC assessments completed within 30 days prior to a subject signing informed consent, may be used in lieu of repeating those study procedures during the 28-day Screening window: vital signs, physical exam, electrocardiogram, hepatitis and HIV testing, chemistry, hematology, coagulation. In addition, a copy of a record of lesion size at a timepoint at least 3 months prior to baseline should be added to the subject's CRF.

[g] The investigator or qualified designee will conduct physical examinations. A complete physical examination is conducted at Screening and ED, and a targeted physical examination (based on interval history and/or AEs) is conducted at all other visits. Assessment of the liver and spleen must be done during the physical exams that are completed at Screening, Day 90, Day 180, Day 360, Day 540, Day 720, Unscheduled Visit and ED Visit, where lesions are evaluated and the Cheson criteria are used to assess overall response.

[h] Electrocardiogram on Day 15 to be performed after SD-101 dosing.

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

[j] Chemistry (includes sodium, potassium, chloride, bicarbonate, BUN, Cr, glucose, calcium, AST, ALT, GGT, LDH, bilirubin, alkaline phosphatase) and CRP.

[k] Includes Hgb, hematocrit, WBC count with differential, and platelet count.

[l] Includes PT and APTT.

APPENDIX 3: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 2 TREATMENT CYCLES) (CONT'D)

FOOTNOTES (CONT'D)

[m] For WOCBP, serum pregnancy testing will be conducted at Screening. Serum or urine pregnancy must be negative prior to initiation of Cycle 1 study treatment and within 3 days prior to initiation of Cycle 2 study treatment. Study treatment consists of localized low-dose radiation and SD-101 injections. All female subjects are considered to be WOCBP except as defined in Section 5.3.

[n] Unilateral bone marrow biopsy and aspirates will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. UNS bone marrow biopsy will be performed only if indicated per SOC. The bone marrow biopsy will be performed to confirm a CR if the subject was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear (Section 8.4).

[o] IFN-inducible gene expression measured at Day -1 (Visit 1, baseline) prior to radiation, at Day 1 (Visit 2) prior to injection, at Day 8 (Visit 3) prior to injection, and at Day 9 (Visit 4) which is 24 (± 3) hours after injection.

[p] Blood for RNA analysis is to be collected pre-injection on treatment days.

[q] In Part 2, Treatment Cycle 1, the collection of 2 FNA samples are required from an treated lesion (Lesion A) on Day -1 (Visit 1), Day 8 (Visit 3), and Day 36 (Visit 8). In Part 2 Treatment Cycle 2, a single FNA sample will be collected from the Treatment Cycle 2 treated lesion on Day 180 (Visit 10), Day 188 (Visit 12), and Day 216 (Visit 17). Collections are to be done pre-XRT or pre-injection on treatment days. There is a ± 21 day window for the FNA sample collection at Day 36 and Day 216.

[r] In Part 2, Treatment Cycle 1, the collection of 2 FNA samples each are required from an untreated lesion (Lesion B) on Day -1 (Visit 1), Day 36 (Visit 8), and Day 90 (Visit 9).
For Part 2, Treatment Cycle 2, a single FNA of an untreated lesion may be collected on Day 180 (Visit 10), Day 216 (Visit 17) and Day 270 (Visit 18). The untreated lesion must be selected outside the field of radiation of the treated lesion. There is a ± 21 day window for the FNA sample collection at Day 90 and Day 270. If there is no accessible untreated lesion(s), then FNA untreated lesion is not required.

[s] Quantitative results for anti-dsDNA are required.

[t] All safety laboratory tests are to be performed at the local laboratory.

[u] An extra aliquot of serum will be collected and stored frozen for possible future testing.

[v] PET scans will only be permitted if PET/CT is the SOC at the participating institution. Perform a CT scan of neck, chest, abdomen, pelvis and other areas as clinically indicated at all imaging timepoints. The Day 180 CT scan can be done within 2 weeks prior to the subject receiving the first dose of localized radiation at the Day 180 visit only if the subject has consented to be treated with a second treatment cycle of localized low-dose radiation and SD-101.

[w] The AE assessment at the ED Visit should occur 7 days or more after the subject's last study injection. Subjects who are withdrawn due to a AE should have an AE assessment completed 28 days or more after the last study drug injection. If the subject is discontinuing study, the ED can be performed at the same visit as the AE assessment.

[x] All concomitant medications taken by the subject from Screening through the end of the treatment period (Day 90 [Visit 9] for 1 cycle of SD-101 treatment or Day 270 [Visit18] for 2 cycles of SD-101 treatment) will be reported. Concomitant medications used to treat an SAE or immunomodulator drugs taken after Day 90 (Visit 9) for 1 cycle of treatment or after Day 270 (Visit 18) for 2 cycles of treatment through Day 720 (Visit 13) or ED are also to be reported.

APPENDIX 3: SCHEDULE OF STUDY ASSESSMENTS (PART 2 – SUBJECTS UNDERGOING 2 TREATMENT CYCLES) (CONT'D)

FOOTNOTES (CONT'D)

[y] Day 180 is the first day of localized low-dose XRT and Day 181 is the second day of localized low-dose XRT for subjects who have consented to receive Cycle 2 treatment of SD-101. Day 180 and Day 181 XRT procedures should be completed before a subject receives Cycle 2 treatment of SD-101. The dose of SD-101 is the last dose level received in Part 2 Cycle 1. If a subject does not consent to be treated with localized low-dose radiation and SD-101 at Day 180, the subject will continue on the study and complete follow-up procedures outlined in Appendix 2. A lesion injected for Cycle 2 may be different than Cycle 1 but must meet size requirements per Inclusion Criterion #2. Do not change the label of lesions from Cycle 1 (ie, the lesion injected in Cycle 2 may be Lesion A-G). The same lesion should be injected throughout a cycle. If the lesion regresses, then SD-101 should be injected in a peritumoral area.

[z] Subject must meet eligibility criteria for laboratory assessments to receive Cycle 2 SD-101 treatment.

APPENDIX 4: RESPONSE DEFINITIONS FOR CLINICAL TRIALS

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; 1 or more PET-positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
Stable Disease	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or progressive disease	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of > 1 node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET-positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Source: (Cheson, Pfistner et al. 2007).
CR = complete response; CT = computed tomography; FDG = [^{18}F] fluorodeoxyglucose; PET = Positive Emission Tomography; PR = partial response; SPD = sum of the products of the diameters.

APPENDIX 5: ECOG PERFORMANCE STATUS INDEX

The ECOG Performance Status is credited to the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status
0	Fully active, able to carry on all predisease 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 housework, 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.

Source: (Oken, Creech et al. 1982).
Available at: http://www.ecog.org/general/perf_stat.html. Accessed 09 October 2015.

APPENDIX 6: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Source: (Center for Biologics Evaluation and Research 2007).

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.