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: Statistical Analysis Plan
Document Date: 05 May 2017

NCT #: NCT02266147

Dynavax Technologies Corporation

STATISTICAL ANALYSIS PLAN

Study 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 Identifier:	DV3-LYM-01
Phase	Phase 1/2
Investigational Product:	SD-101
Indication:	Low-grade B-cell Lymphoma
Sponsor:	Dynavax Technologies Corporation 2929 Seventh Street, Suite 100 Berkeley, CA 94710 United States of America
Reference Numbers:	United States IND No.122809

Original Version:	Version 1 (26 June 2015)
Protocol Referenced:	Amendment # 2 (10 April 2015)
Current Version:	Version 2 (05 May 2017)
Protocol Referenced:	Amendment #4 (21 March 2016)

FINAL STATISTICAL ANALYSIS PLAN APPROVAL

Prepared by: Biao Xing — 05 MAY 2017

Biao Xing, PhD
Director, Biometrics
Dynavax Technologies Corporation

Date

Approved by: — 5 MAY 2017

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

Date

08 May 2017.

Abraham Leung, MD
Vice President Clinical Development
Dynavax Technologies Corporation

Date

08 May 2017.

Graeme Currie, PhD
Vice President Clinical Science and Operations
Dynavax Technologies Corporation

Date

TABLE OF CONTENTS

List of Abbreviations and Terms

Abbreviation	Definition
AE	Adverse event
AUC	Area under the curve
C_{max}	Maximum plasma concentration
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
ECG	Electrocardiogram
FNA	Fine needle aspiration
IFN	Interferon
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PK	Pharmacokinetic
PR	Partial response
SAP	Statistical analysis plan
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to maximum plasma concentration
TEAE	Treatment-emergent adverse event
TTNT	Time to next treatment
TTP	Time to progression
WOCBP	Women of child bearing potential
XRT	Radiation therapy

1.0 INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to assess the pharmacokinetics (PK), pharmacodynamics (PD), preliminary efficacy, and safety of SD-101 as described in Protocol DV3-LYM-01 (Amendment #4, 21 March 2016): 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.

2.0 STUDY OVERVIEW

This open-label, dose-ranging, multicenter study was designed to evaluate the safety and preliminary efficacy of localized low-dose radiation therapy (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 interferon-alpha (IFN-α), will generate 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”.

The study has 2 phases: Phase 1 (Dose Escalation) includes the evaluation of 4 levels of doses of SD-101 (1 mg, 2 mg, 4 mg, and 8 mg) that are tested sequentially using a 3+3 dose escalation study design; Phase 2 (Dose Expansion) includes the evaluation of approximately 18 subjects (9 per cohort) into a 1 mg and 8 mg SD-101 dose cohort.

Study treatment consists of local radiation over 2 days (2 Gy each day) followed by 5 weekly intratumoral injections of SD-101. Subjects enrolled in Phase 2 Expansion cohorts who achieve a response of at least stable disease according to Cheson critera for the untreated lesions on Day 180 will have an option to receive a second cycle of low dose radiation and SD-101 injections. Subjects will be followed for safety through Day 720 and for disease assessment per Cheson criteria until next treatment or until approximately 2 years after the first injection of SD-101.

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 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

3.2 Secondary Objectives

- To evaluate the plasma PK of SD-101
- To assess the preliminary response both locally and systemically
  - Tumor shrinkage of the treated lesion(s), which is (are) lesion(s) treated with both XRT and SD-101 (Local)
  - Tumor shrinkage outside the treated lesion(s) (Systemic)

3.3 Exploratory Objective

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

4.0 ANALYSIS VARIABLES

4.1 Primary Endpoints

4.1.1 Dose Limiting Toxicity

Dose limiting toxicity (DLT) is 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]):

1) Any non-hematological toxicity ≥ Grade 3 except for alopecia or nausea controlled by medical management
2) Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
3) Febrile neutropenia of any duration (ANC < 1000/mm^3, temperature ≥ 38.5°C)
4) Grade 4 neutropenia lasting more than 5 days
5) Grade 4 anemia unexplained by underlying disease

6) Any Grade 2 or higher 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

4.1.2 Incidence of Injection-Site Reactions

Injection-site reactions are defined as local AEs that occur following injection of SD-101. The study has specific procedures for collecting injection-site reactions that will be recorded as AEs in the study database. 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 of the local reactions will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (refer to Appendix 6 of protocol).

All local reactions that occur will be captured, even if the 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. 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 will solicit 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.

4.1.3 Changes in Interferon-Inducible Genes

IFN-alpha inducible genes will be assayed by quantitative polymerase chain reaction (qPCR) of mRNA isolated from whole blood collected before administration of the first and second doses of SD-101 and after administration of the second dose 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.

4.2 Secondary Endpoints

- Plasma concentrations of SD-101

  PK samples will be collected only in Phase 1 portion of the study at pre-dose and 1,2,4 and 6 hours pose-dose on Day 1, and 24 hours post-dose on Day 9.

- Overall response rate and response rate of treated and untreated lesion(s), respectively

- Time to overall response and time to response of treated and untreated lesion(s), respectively

4.3 Exploratory Endpoints

- Duration of overall response and duration of response of treated and untreated lesion(s), respectively
- 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

4.4 Efficacy Variables

Response to treatment will be evaluated by the investigator at 3 and 6 months after the first study injection and then every 6 months for the remainder of the trial.

Response as assessed by computerized tomography (CT)/positron emission tomography (PET) is in Appendix 1 (Cheson, Horning et al. 1999; Cheson, Pfistner et al. 2007). Response will be assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria.

Response rate is defined as the proportion of subjects who achieved complete response (CR) or partial response (PR). Time to response is defined as time from first dose of SD-101 to time of initial response (CR, PR) for subjects who have response. For subjects who do not have response, time to response will be censored at the last tumor assessment before the end of follow up. For subjects who have a response, duration of response will be measured from the date of initial response (CR, PR) to the date of progression for those who have disease progression. For those who do not have disease progression, duration of response will be censored by the date of last tumor assessment before the end of follow up or before initiation of subsequent therapy.

Time to next treatment is defined as time from last dose of SD-101 to the time of next treatment for those who have next treatment (ie, non-protocol cancer treatment); for subjects who do not have next treatment, time to next treatment will be censored at the end of follow up. Time to progression is defined as the time from first dose of SD-101 to time of disease progression for those who have disease progression; for subjects who do not have disease progression, time to progression will be censored at the date of last tumor assessment before the end of follow up.

4.5 Safety Variables

4.5.1 Adverse Events

Non-serious AE collection will begin at the time of study drug administration and continue through Day 90 and, if treated in Cycle 2, from Day 180 until Day 270 or, for early discontinuation, 7 days or more after the last study injection. Additionally, per protocol section 10.11 - Subjects who are withdrawn due to an AE should have an AE assessment completed 28 days or more after their last study drug injection. Serious adverse event (SAE) collection and reporting will begin at the time the subject signs the informed consent and continue through the duration of trial participation. The severity of AEs will be assessed and confirmed by the investigator and will be graded using the CTCAE Version 4.03 grading scale (Table 11-1 of the protocol). For injection-site reactions, the severity will be assessed using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Protocol Appendix 6).

Screening/Predose Adverse Events

AEs that started or worsened during the time of obtaining informed consent up to the first administration of study drug will be captured on the medical history case report form and in the subject's clinical record.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are AEs that started or worsened after administration of SD-101 and occurred during the protocol specified collection period.

Treatment-Related Adverse Events

Treatment-related TEAEs are defined as TEAEs assessed by investigators as possibly or probably related to study treatment. TEAEs with missing relationship to study treatment will be treated as treatment-related in the summary.

4.5.2 Serious Adverse Events

An AE is considered an SAE if it meets any of the criteria stated in Section 11.4 of the protocol.

4.5.3 Laboratory Assessments

Laboratory assessments are listed below and will be performed according to the Schedule of Study Assessments (Appendix 1-3 of protocol). Sample collections are to be done pre-injection on treatment days.

- Hepatitis and human immunodeficiency virus (HIV)- testing at Screening: hepatitis B surface antigen, anti-HBc, 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: hemoglobin (Hgb), hematocrit, white blood cell count with differential, and platelet count
- Coagulation: prothrombin time (PT) and activated partial thromboplastin time (APTT)
- For women of child bearing potential (WOCBP), serum pregnancy testing will be conducted at Screening and serum or urine pregnancy testing at subsequent visits as outlined in Appendix 1 of the protocol. Serum or urine pregnancy must be negative prior to study treatment. Dipstick can be used. All female subjects are considered to be WOCBP except if they have been post-menopausal for at least 2 years or surgically sterile for at least 1 year.
- Reserve serum aliquot specimens will be collected and stored frozen for possible future testing.
- Blood for antibodies to double-stranded DNA (anti-dsDNA) will be collected according to the Schedule of Study Assessments (Appendix 1-3 of protocol).
- Additional details for specific tests are provided in the Laboratory Manual.

4.5.4 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.

4.5.5 Physical Examinations

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

4.5.6 Electrocardiograms

An electrocardiogram (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).

4.6 Pharmacokinetic/Pharmacodynamic Variables

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

PD variables consist of IFN-alpha inducible genes, which will be assayed by quantitative polymerase chain reaction (qPCR) of mRNA isolated from whole blood collected before administration of the first and second doses of SD-101 and after administration of the second dose 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.

5.0 SAMPLE SIZE CONSIDERATIONS

This trial is designed to allow preliminary assessments of safety and biological activity in approximately 25 to 31 subjects. Approximately 13 subjects may be enrolled in the dose escalation part of the trial and approximately 12 to 18 subjects in the second part of the trial. The sample size of the dose escalation is based on a standard 3+3 design and 4 planned dosing cohorts (3 subjects for the first 3 cohorts and a potential of 6 subjects for the last cohort). The sample size for evaluation of response rate is based on the plan to pool all subjects treated at the MTD or optimal dose level which would include 3 escalation subjects and the expansion subjects (approximately 9 to 12 per dose level). For dose expansion, 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 as below:

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

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

6.0 ANALYSIS POPULATIONS

6.1 Enrolled Population

The enrolled population is defined as all subjects who enrolled in the study.

6.2 Safety Population

The safety population is defined as all subjects who receive at least one injection of study drug. The safety population will be used for all analyses of safety data.

6.3 Efficacy Population

The efficacy population is defined as all subjects who receive at least one injection of study drug and have at least one post-treatment tumor assessment. The efficacy population will be used for all analyses of efficacy data. In addition, efficacy analyses will be performed for the Enrolled Population, in which subjects who do not have post-baseline tumor assessment will be treated as non-responders.

6.4 Pharmacokinetic and Pharmacodynamic Population

The PK population will consist of all enrolled subjects who receive the second dose of SD-101 and have measurable assessments at pre-dose through 24 hours post-dose for the second dose of SD-101 (Visit Days 8 and 9).

The PD population will consist of all enrolled subjects who receive at least 1 dose of study drug and both screening and at least 1 post-enrollment assessment of the PD marker of analysis interest.

7.0 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

7.1 Definitions and Computations

Study Day

Study day will be calculated in reference to the date of first dose (Day 1). For assessments conducted on or after the first dose date, study day is calculated as (assessment date – first dose date + 1). For assessments conducted before the first dose date, study day is calculated as (assessment date – first dose date). There will be no Day 0.

Date of First Dose and Date of Last Dose of Study Drug

The date of the first dose of study drug is defined as the date a subject receives the first dose of the study drug. The date of the last dose of study drug is the date a subject receives the last dose of the study drug.

Treatment-Emergent Period

For AEs, the treatment-emergent period is defined as the duration of time from the date and time of the first dose of study drug administration through Day 90 and, if treated in Cycle 2, from Day 180 until Day 270 or, for early discontinuation, within 30 days after their last study injection.

For SAEs, the treatment-emergent period is defined as the duration of time from the date and time of the first dose of study drug administration through the duration of trial participation.

Baseline Value and Post-baseline Value

Unless otherwise specified, the baseline value is defined as the last measurement before the first administration (date and time) of study drug. Post-baseline value is defined as any measurement taken after the first administration of study drug. Change from baseline is defined as (post-baseline value – baseline value). Both date and time of study drug administration and measurement will be considered when calculating baseline value. If time is not available, then date only will be used.

7.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated by the following SAS code: `age = floor(yrdif(birth_date, consent_date, 'AGE'))`
- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- Missing safety data will not be imputed unless otherwise specified.
- For laboratory results collected as < or > a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For safety analyses, percentages will be calculated based on the number of subjects in the analysis population.
- For by-visit observed data analyses, percentages will be calculated based on the number of subjects with non-missing data as the denominator unless otherwise specified.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and minimum and maximum.
- For categorical endpoints, the summary statistics will include counts and percentages.
- AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced Format B2 (June 2015).

7.3 Rules for Missing Data

In general, missing data will not be imputed.

However, imputation may be performed on partially or completely missing dates of the start and/or end dates of an AE in order to flag whether an AE was treatment-emergent or not. For AEs with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the AE will be considered treatment emergent by default. The following rules will be applied to impute partial dates for AEs:

- If start date of an AE is completely or partially missing, impute as follows:
  - If both month and day are missing and year = year of treatment start date, then set to treatment start date.
  - If both month and day are missing and year ≠ year of treatment start date, then set to January 1.
  - If day is missing and month and year = month and year of treatment start date, then set to treatment start date.
  - If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month.
  - If start date is completely missing and AE end date is on or after the treatment start date, set to treatment start date.
  - If start date is completely missing and AE end date is prior to the treatment start date, do not impute an AE start date.
- If end date of an AE is partially missing, impute as follows:
  - If both month and day are missing, then set to December 31.
  - If only day is missing, then set to last day of the month.
  - If end date is completely missing, do not impute.

Listings will show the original date information without imputation.

8.0 TIMING OF ANALYSES

Final Statistical analysis will be performed at the end of the study. No interim analysis is planned for this study.

9.0 STATISTICAL METHODS

Descriptive statistics, including the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum, will be used to summarize continuous variables. Categorical variables will be summarized by number (n) and percentage (%) of subjects in each category. All data processing, summarization, and analyses will be performed using

SAS Version 9.4 or higher. Specifications for tables, graphs, and data listings will be provided in the tables, figures, listings (TFL) specifications document.

9.1 Subject Disposition

Subject disposition will be summarized by dose group for all subjects as follows: Subjects screened, subjects treated, subjects who completed treatment as well as subject who discontinue treatment and the reasons for discontinuation (as documented on the case report form, including death, loss to follow-up, protocol violation, consent withdrawn to continue treatment, disease progression, AE, or other).

A listing of subjects discontinuing the study after enrollment will be produced.

9.2 Protocol Deviations

Subjects with major protocol deviations will be listed by dose group. Categories of major deviations include at least the following:

- Eligibility criteria not met
- Excluded concomitant medication taken
- Incorrect dose received
- Informed consent not signed before study-specific procedures were performed
- Failing to complete at least 4 injections for reasons other than discontinuation for toxicity or subject withdrawal
- Missing baseline disease assessment or do not have a post-baseline assessment of tumor response.

A detailed list of all major protocol deviations will be determined before database lock and a listing of all major deviations will be provided.

9.3 Demographics and Baseline Characteristics

Summary statistics for age, weight, height, and body mass index at baseline will be presented. Frequency tabulations for sex, race and ethnicity will be presented. Disease history will include disease type, stage, grade and prognostic scores if collected. These summaries will be presented by dose group for the all enrolled, safety, and efficacy populations if they are different.

Listings will be provided for these parameters for all subjects.

9.4 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (B2 format, June 2015). Prior medications are drugs and therapies used before the first dose date. Medications or therapies are considered concomitant if exposure occurs after the first dose date. The number and percentage of subjects with concomitant medications will be presented alphabetically by anatomical therapeutic chemical (ATC) class Level 2 and by decreasing order of frequency of preferred terms within each ATC class for the safety population. Subjects taking the same medication multiple times will be counted once per medication.

All medications recorded on the case report form will be listed.

9.5 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 18.1).

All medical history data will be provided in a listing.

9.6 Analyses of Sepcified Endpoints

9.6.1 Primary Endpoints

9.6.1.1 Dose Limiting Toxicities

Incidence of DLTs will be tabulated by dose groups, and bar chart of incidence rates of DLT by dose groups will be generated.

9.6.1.2 Incidence of Injection-Site Reactions

Incidence of local site reactions, AEs, and SAEs will be tabulated by maximum severity and dose for all dose groups.

9.6.1.3 Changes in IFN-Inducible Genes

For each IFN-inducible gene, the fold increase from baseline will be summarized by dose groups. A line graph of the fold increase from baseline by dose groups will be generated. A composite score for IFN-inducible genes may be generated by calculating the geometric mean of subsets of gene scores relative to baseline for each subject followed by calculating the arithmetic mean of the geometric means within each cohort. The analyses will be performed by the Preclinical Research Group at Dynavax. The outputs as well as the summary report will be attached to the Clinical Study Report (CSR) as an appendix.

9.6.2 Secondary Endpoints

9.6.2.1 Plasma Concentrations of SD-101

For PK concentrations, changes from pre-second dose to 24 hours post-second dose of SD-101 will be summarized by dose groups. C_{max}, T_{max}, half-life, and area under the concentration-time curve (AUC), if possible, will also be summarized by dose groups.

Summaries of PK concentration by dose groups will also be presented graphically where possible.

The analyses will be performed by the Preclinical Research Group at Dynavax. The outputs as well as the summary report will be attached to the CSR as an appendix.

9.6.2.2 Overall Response Rate and Response Rate of Treated Lesion(s) and Untreated Lesion(s) Respectively

Overall response rate and response rate of treated lesion(s), untreated lesion(s) respectively will be analyzed descriptively and 90% exact binomial confidence interval will be calculated for each dose group.

In addition, percent change from baseline over time as well as best percent change from baseline in treated lesion(s), untreated lesion(s) and all target lesions, respectively, will be plotted.

9.6.2.3 Time to Overall Response and Time to Response of Treated Lesion(s) and Untreated Lesion(s) Respectively

Time to overall response and time to response of treated lesion(s) and untreated lesion(s) respectively will be summarized descriptively by dose groups.

9.6.3 Exploratory Endpoints

9.6.3.1 Duration of Overall Response and Duration of Response of Treated Lesion(s), and Untreated Lesion(s) Respectively

For those subjects who achieved overall response or response on treated lesion(s) and untreated lesion(s), repectively, duration of response for each of these will be summarized by dose groups, and individual duration of response will be plotted.

9.6.3.2 Time to Next Treatment

TTNT will be summarized by dose groups and Kaplan-Meier methods will be used to summarize time to next treatment; the 95% CI for the median will be provided.

9.6.3.3 Time to Progression

TTP will be summarized by dose groups and Kaplan-Meier methods will be used to summarize time to progression; the 95% CI for the median will be provided.

9.6.3.4 Other Exploratory Analyses

Tumor infiltrating lymphocytes, co-stimulatory molecules, and other immune activated cells following SD-101 treatment may be summarized descriptively by dose group.

9.7 Safety Analyses

All subjects in the safety population will be used in the safety analyses. Safety analyses will be summarized by dose group as treated. No formal statistical testing will be performed.

The treatment-emergent period is defined in Section 7.1.

9.7.1 Adverse Events

All AEs will be coded to preferred term and system organ class using MedDRA Version 18.1.

An AE that started or increased in severity during the treatment-emergent period (refer to Section 7.1of this document) will be considered a TEAE. A summary table will be provided for the overview of TEAEs. The number and percentage of subjects with TEAEs as classified by system organ class and preferred term, as well as the number and percentage of subjects with at least 1 TEAE, will be summarized by severity and dose group. Similar summaries will also be provided for TEAEs related to the study drug, TEAEs leading to study discontinuation, and serious TEAEs. Severity of TEAEs will be graded according to the National Cancer Institute Cancer Therapy and Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE). A study treatment-related TEAE is defined as any TEAE with at least a possible relationship to the study drug as assessed by the investigator or that is missing the assessment of causal relationship whose relationship to the study drug could not be ruled out.

Incidence of local site reactions, injection-site reaction AEs and SAEs will be tabulated by maximum severity and dose for all dose groups

Subjects with multiple occurrences of events for a given preferred term, system organ class, or overall will only be counted once at the worst severity and strongest relationship to study drug for each preferred term, system organ class, and overall, respectively. TEAEs of unknown severity will be categorized separately. A TEAE of unknown relationship will be considered to be related to study drug.

Separate listings will be provided for all AEs, AEs leading to study drug discontinuation, serious SAEs, and fatal AEs.

9.7.2 Laboratory Assessments

Laboratory data in this study consist of hematology, serum chemistry, coagulation, anti-dsDNA antibodies, and anti-SD-101 antibodies. Quantitative laboratory test results and their change from baseline will be summarized by scheduled visit. The last value before the first dose of study drug will be used as baseline.

For anti-dsDNA and anti SD-101 antibody results, fold change from baseline will be summarized by dose group and scheduled visit. The analyses will be performed by the Preclinical Research Group at Dynavax. The outputs as well as the summary report will be attached to the CSR as an appendix.

Laboratory data and shift analysis tables for hematology and serum chemistry tests will also be presented by CTCAE grade. Each laboratory result will be flagged as low (L), normal, or high (H) at each visit according to the laboratory reference ranges.

All laboratory data will be provided in data listings.

9.7.3 Vital Signs

Temperature, blood pressure (systolic and diastolic), and heart rate will be summarized at baseline and each subsequent scheduled assessment by dose groups as treated. Baseline results are defined as the last vital sign results taken before the date and time of the first dose of study drug. Change from baseline will be calculated and presented for each parameter at all scheduled post-baseline assessment time points.

Vital sign data will be provided in a data listing.

9.7.4 Physical Examinations

Individual physical examination data with abnormal findings flagged will be listed.

9.7.5 Electrocardiograms

The numbers and percentages of subjects with categories of normal, not clinically significant abnormal, and clinically significant abnormal will be tabulated for the 12-lead ECG at scheduled visits. Shift tables showing changes from baseline to each scheduled visit and from baseline to the worst post-baseline measurement in overall ECG interpretation will be presented. The last value recorded before the first dose of study drug will be used as baseline. A summary table of 12-lead ECG parameters will be provided.

ECG data will be provided in a data listing.

9.8 Analysis of Pharmacokinetics/Pharmacodynamics

For PK concentrations, changes from pre-second dose to 24 hours post-second dose of SD-101 will be summarized by dose groups where possible. Cmax, Tmax, half-life, and area under the concentration-time curve will also be summarized. A graphical summary of PK concentrations will be generated where possible.

PD parameters are part of the primary endpoints, and their analyses are described in the primary endpoints section of this analysis plan.

These analyses will be performed by the Preclinical Research Group at Dynavax. The outputs as well as the summary report will be attached to the CSR as appendices.

9.9 Other Analyses

No other analyses are planned.

9.10 Interim Analysis

This is a Phase 1/2 dose-escalation trial. No interim analysis is planned for this protocol.

9.11 Reporting Output

All outputs will be produced using SAS® version 9.4 or later.

Post-text tables, listings, and statistical appendices will be produced as PDF and RTF files using output delivery system (ODS) and Times New Roman or a similar font size 9 or larger. Data will be presented in PDF and RTF tables with data in individual cells. Figures will be produced as PDF and RTF files using ODS and Times New Roman font.

All tables, listings and statistical appendices will be produced to landscape.

Tables and listings will be presented by dose group, if appropriate.

Dose groups will be formatted as follows:

- Phase I
  - 1 mg
  - 2 mg
  - 4 mg
  - 8 mg
  - Overall
- Phase II
  - 1 mg
  - 8 mg

- Both Phases
  - 1 mg
  - 8 mg

10.0 REVISION HISTORY

Version	Date	Author	Comments/Rationale for Revision
1.0	26JUN2015	Jason Chan	New Document per Protocol Version 2
2.0	05MAY2017	Biao Xing	Amendment per Protocol Version 4

11.0 REFERENCES

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.

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.

12.0 LIST OF TABLES

Table 14.4.13	Summary of Injection Site Reactions By Dose Number, Dose Group and by Maximum Severity
Table 14.4.14	Summary of Deaths by Dose Group
Table 14.5.1	Summary of Observed Values and Change from Baseline by Dose Group: Hematology
Table 14.5.2	Shift Table of Hematology Parameters by Dose Group
Table 14.5.3	Summary of Observed Values and Change from Baseline by Dose Group: Chemistry
Table 14.5.4	Shift Table of Chemistry Parameters by Dose Group
Table 14.5.5	Summary of Observed Values and Change from Baseline by Dose Group: Coagulation
Table 14.5.6	Shift Table of Coagulation Parameters by Dose Group
Table 14.6.1	Summary of Vital Signs by Dose Group
Table 14.6.2	Summary of ECG by Dose Group
Sub-Report	Summary of Plasma Concentration of SD-101 by Dose Group
Sub-Report	Summary of Fold Change in Interferon-Inducible Genes Expression by Dose Group
Sub-Report	Summary of Observed Values and Change from Baseline of Antibodies to SD-101 by Dose Group
Sub-Report	Summary of Observed Values and Change from Baseline of Antibodies to Double-Stranded DNA (anti-dsDNA) by Dose Group

13.0 LIST OF FIGURES

14.0 LIST OF SUBJECT DATA LISTINGS

Listing 16.2.1.1	Subject Disposition and Reasons for Discontinuation From Study
Listing 16.2.1.2	Analysis Populations and Reasons for Exclusion
Listing 16.2.1.3	Protocol Deviations
Listing 16.2.2.1	Demographics and Baseline Characteristics
Listing 16.2.2.2	Medical History
Listing 16.2.2.3	Disease History
Listing 16.2.2.4	Concomitant and Prior Medications
Listing 16.2.3	Study Drug Administration
Listing 16.2.4.1	Tumor Assessment
Listing 16.2.4.2	Disease Response Assessment
Listing 16.2.5	Next Treatment for B-cell Lymphoma
Listing 16.2.6.1	Adverse Events
Listing 16.2.6.2	Serious Adverse Events
Listing 16.2.6.3	Dose Limiting Toxicity
Listing 16.2.6.4	Injection-Site Reactions
Listing 16.2.6.4	Adverse Events Leading to Discontinuation of Study Treatment
Listing 16.2.6.5	Adverse Events Resulting in Death
Listing 16.2.6.6	Deaths
Listing 16.2.7.1	Hematology Results
Listing 16.2.7.2	Chemistry Results
Listing 16.2.7.3	Coagulation Results
Listing 16.2.7.4	Pregnancy Test Results
Listing 16.2.8.1	Vital Sign Results
Listing 16.2.8.2	Physical Examination Results
Listing 16.2.8.3	ECG Results
Listing 16.2.9.1	Bone Marrow Biopsy-Aspirate Results
Listing 16.2.9.2	Fine Needle Aspirate (FNA) Results
Sub-Report	Pharmacokinetic Concentration
Sub-Report	Interferon Inducible Genes
Sub-Report	Antibodies to Double-Stranded DNA (anti-dsDNA) Results
Sub-Report	Antibodies to SD-101 Results

APPENDIX 1: 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
SD	Failure to attain CR/PR or PD	(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 PD	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, Horning et al. 1999; Cheson, Pfistner et al. 2007).
CR = complete remission; CT = computed tomography; FDG = [^{18}F] fluorodeoxyglucose; PD = progressive disease; PET = positive emission tomography; PR = partial remission; SD = stable disease; SPD = sum of the product of the diameters.