Protocol Title:

A Phase 1b/2, Open-label, Multicenter, Dose-escalation and Expansion Trial of Intratumoral SD-101 in Combination With Pembrolizumab in Patients With Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2, Open-label, Multicenter, Dose escalation and Expansion Trial of Intratumoral SD 101 in Combination with Pembrolizumab in Patients with Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
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Indication:	Metastatic Melanoma
Sponsor:	Dynavax Technologies Corporation 2100 Powell Street Suite 900 Emeryville, CA 94608 United States of America
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FINAL STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Definition
AE	adverse event
anti-PD-1/L1	anti-programmed death receptor-1/ligand 1
ATC	anatomical therapeutic chemical
BORR	best objective response rate
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EOS	End-of-Study (visit)
IFN	interferon
ITT	Intent-To-Treat
HNSCC	head and neck squamous cell carcinom
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
MHC	major histocompatibility complex
NK	natural killer
ORR	objective response rate
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand 1
PFS	progression free survival
PR	partial response
PT	preferred term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities

1.0 INTRODUCTION

This statistical analysis plan contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the safety, tolerability, biologic activity, and preliminary efficacy of SD-101 in combination with pembrolizumab as described in Protocol DV3-MEL-01 (Amendment 8: 08 February 2018): "A Phase 1b/2, Open-label, Multicenter, Dose escalation and Expansion Trial of Intratumoral SD-101 in Combination With Pembrolizumab in Patients With Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)".

Due to strategic changes, only some of the objectives will be evaluated. Those objectives not evaluated will be *italicized* and annotated as *"(not implemented)*", where applicable, throughout this SAP; statistical methods for these objectives are also not described. The main text of this SAP covers only assessment of the objectives by data contained in the clinical database. Pharmacodynamic assessment will be described in an annex to this SAP. Pharmacodynamic objectives will also be annotated.

Groupings of patients to be used in the analyses are also changed from what were described in the protocol, based on the knowledge accumulated through the conduct of the trial.

2.0 STUDY OVERVIEW

This open-label, multicenter, dose-ranging and expansion trial is designed to evaluate the safety and preliminary efficacy of intratumoral SD-101 in combination with pembrolizumab for the treatment of metastatic melanoma and HNSCC. The hypothesis to be tested in the clinical development of SD-101 is that SD-101, by virtue of its potency and its ability to induce high levels of interferons (IFNs), will have meaningful efficacy in generating anti-tumor immune responses when combined with an anti-PD-1 antibody. IFNs have multiple effects on both tumor cells and tumor-infiltrating leukocytes. These IFNs can directly inhibit the proliferation of tumor cells and increase MHC class I expression, enhancing antigen recognition. Additionally, IFNs have potent effects on tumor-infiltrating leukocytes, including enhancing the antigen presenting function of dendritic cells, increasing the effect or function of T cells, and activating cytotoxic activity of NK cells.

The rationale for treating metastatic melanoma and HNSCC with combination anti-PD-1/L1 therapy plus SD-101 is based on the unmet need to improve upon single anti-PD-1/L1 activity in these patient populations and nonclinical data (Protocol Sections 2.4 and 2.5) which suggest improved anti-tumor activity with the combination compared to anti-PD-1/L1 alone.

The study will be performed in 2 phases. The population to be studied in Phase 1 (Dose Escalation) will be patients with metastatic melanoma. The populations to be studied in Phase 2 (Dose Expansion) will be patients with metastatic melanoma and patients with

recurrent or metastatic HNSCC. In phase 1 of the study, doses of 1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg of SD-101 each in a single lesion will be tested in a modified, staggered, 3 + 3 trial design, to identify an optimal dose of SD-101 given in combination with pembrolizumab to be used in Phase 2 (see Protocol section 9.1 for DLT definitions and stopping rules). This optimal dose from Phase 1 is referred to in the protocol as the recommended Phase 2 dose (RP2D) of SD-101. Phase 2 of the study is designed to evaluate the safety and efficacy of SD-101 plus pembrolizumab in both metastatic melanoma and HNSCC patients. Tumor response will be evaluated separately for injected and non-injected lesions as well as all combined lesions in order to assess both a local and systemic response to study treatment.

The trial population includes a total of approximately 284 men and women with at least 1 site of disease that qualifies as a target lesion per RECIST v1.1 and is accessible for intratumoral injection.

Phase 1 Dose Escalation Cohorts 1-4 will include up to 24 patients with metastatic melanoma who are anti-PD-1 naïve or experienced.

Phase 2 Dose Expansion will include approximately 160 patients with metastatic melanoma and approximately 100 patients with recurrent or metastatic HNSCC:

1) Expansion Cohort 1 of approximately 60 melanoma patients who are anti-PD-1/L1 naïve

2) Expansion Cohort 2 of approximately 25 melanoma patients who have disease progression on anti-PD-1/L1 therapy

3) Expansion Cohort 3 of approximately 25 HNSCC patients who are anti-PD-1/L1 naïve

4) Expansion Cohort 4 of approximately 25 HNSCC patients who have disease progression on anti-PD-1/L1 therapy

5) Expansion Cohort 5 of approximately 25 melanoma patients who are anti-PD-1/L1 naïve

6) Expansion Cohort 6 of approximately 25 HNSCC patients who are anti-PD-1/L1 naïve

7) Expansion Cohort 7 of approximately 25 HNSCC patients who are refractory or resistant to anti-PD-1/L1 therapy

8) Expansion Cohort 8 of approximately 50 melanoma patients who are refractory or resistant to anti-PD-1/L1 therapy.

Some of these study groups will be rearranged for final analysis as analysis groups based on tumor indications, anti-PD-1/L1 experience, and dose of SD-101.

Phase 1 results will be presented for each of the 4 dose groups.

Results for Phase 2 objectives, using combined Phases 1 and 2 data, will be presented by 2mg/lesion and 8mg/lesion doses for

- MEL/NAIVE: metastatic melanoma patients who are anti-PD-1/L1 naïve, including
  - subjects in Phase 1 2mg and 8mg groups
  - subjects in Phase 2 Cohort 1 (both 2mg/lesion and 8mg single lesion) and Cohort 5 (2mg/lesion)
- MEL/EXP: metastatic melanoma patients who are anti-PD-1/L1 experienced, including
  - subjects in Phase 1 2mg and 8mg groups
  - subjects in Phase 2 Cohort 2 (both 2mg/lesion and 8mg/lesion) and Cohort 8 (2mg/lesion)
- HNSCC/NAIVE: HNSCC patients who are anti-PD-1/L1 naïve, including
  - subjects in Phase 2 Cohort 3 (both 2mg/lesion and 8mg/lesion) and Cohort 6 (2mg/lesion)
- HNSCC/EXP: HNSCC patients who are anti-PD-1/L1 experienced, including
  - subjects in Phase 2 Cohort 4 (both 2mg/lesion and 8mg/lesion) and Cohort 7 (2mg/lesion)

2.1 Phase 1

Patients in Escalation Cohorts 1-4 will be administered 1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg, respectively, of SD-101 in combination with 200 mg pembrolizumab Q3W per the Schedule of Trial Events (see Protocol Section 4.1.1 for dosing schema).

2.2 Phase 2

Melanoma Dose Expansion cohorts in Phase 2 will be treated with 8.0 mg or 2.0 mg of SD-101 from Phase 1 in combination with 200 mg pembrolizumab Q3W (see Protocol Section 4.1.2 for dosing schema).

HNSCC Dose Expansion cohorts in Phase 2 will be treated with the selected RP2D (8.0 mg or 2.0 mg of SD-101) from Phase 1 in combination with 200 mg pembrolizumab Q3W (see Protocol Section 4.1.2 for dosing schema).

3.0 STUDY OBJECTIVES

3.1 Phase 1 (Dose Escalation: Metastatic Melanoma)

3.1.1 Primary Objectives

- To assess the safety and tolerability of escalating intratumoral doses of SD-101 in combination with intravenous pembrolizumab in patients with metastatic melanoma
- To evaluate the expression of IFN-inducible genes in whole blood 24 hours after intratumoral injection of SD-101 given with pembrolizumab in patients with metastatic melanoma as a pharmacodynamic marker of SD-101 activity (pharmacodynamic)
- To determine a RP2D of SD-101 in combination with pembrolizumab to be evaluated in Phase 2

3.1.2 Exploratory Objectives

- To assess the preliminary response both locally and systemically including:
  - *Treatment response of the injected Lesion A (local response) (not implemented)*
  - *Treatment response of the non-injected lesion(s) (systemic response) (not implemented)*
  - Treatment response of all lesions
  - *Time to response (not implemented)*
  - To assess changes in tumor biomarkers (pharmacodynamic)

3.2 Phase 2 (Dose Expansion: Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma)

3.2.1 Primary Objectives

- To assess the tumor response both locally and systemically including:
  - Treatment response of the injected lesion(s) (local response)
  - Treatment response of the non-injected lesion(s) (systemic response)
  - Treatment response of all lesions

3.2.2 Secondary Objectives

- To assess the safety and tolerability of SD-101 in combination with pembrolizumab
- To assess the time frame of tumor responses:
  - Time to response
  - Duration of response
- To assess PFS

3.2.3 Exploratory Objectives

- To assess changes in tumor biomarkers

- To identify and assess changes in potential tumor neoantigens in patients with recurrent or metastatic HNSCC (pharmacodynamic)
- To evaluate the expression of IFN inducible genes in whole blood 24 hours after intratumoral injection of SD-101 given with pembrolizumab in patients with recurrent or metastatic HNSCC as a pharmacodynamic marker of SD-101 activity (pharmacodynamic)

4.0 ANALYSIS VARIABLES

Phase 1 – Dose Escalation

Primary Endpoints

- Incidence of DLTs
- Incidence of injection-site reactions, AEs, and SAEs
- Changes in the expression of IFN-inducible genes in whole blood (pharmacodynamic)

Exploratory Endpoints

- ORR per RECIST v1.1
- Changes in tumor-infiltrating lymphocytes, PD-L1 expression, and other gene expression in tumor biopsies (pharmacodynamic)

Phase 2 – Dose Expansion

The primary radiographic endpoints of the study will be based on RECIST v1.1 *and exploratory radiographic endpoints will be based on irRECIST (not implemented)*. All imaging endpoints for the overall response assessment will be based on investigator evaluation. A central imaging laboratory for study image collection and radiographic endpoint determination will be used per sponsor decision.

Primary Endpoints

- ORR per RECIST v1.1

Secondary Endpoints

- Incidence of injection-site reactions, AEs, and SAEs
- Time to response using RECIST v1.1
- Duration of response per RECIST v1.1
- PFS per RECIST v1.1

Exploratory Endpoints

- Changes in correlative biomarkers including tumor-infiltrating lymphocytes and PD-L1 expression at baseline and after SD-101 treatment (pharmacodynamic)
- Changes in potential tumor neoantigens in patients with recurrent or metastatic HNSCC (pharmacodynamic)

- Changes in the expression of IFN-inducible genes in whole blood in patients with metastatic HNSCC (pharmacodynamic)

5.0 SAMPLE SIZE CONSIDERATIONS

The Phase 1 trial is designed to allow preliminary assessments of safety, biological activity, and biomarkers in approximately 24 patients. Phase 2 of this trial is designed to allow preliminary assessments of efficacy, safety, and changes in biomarkers in approximately 210 patients. All analyses will be descriptive.

The Phase 1 trial sample size is based on a modified 3 + 3 dose-escalation trial design.

For the Phase 2 expansion cohorts, the sample sizes were determined based on power analysis of hypothesis tests and/or confidence intervals, although the efficacy analyses will be descriptive.

In Expansion Cohort 1, approximately 60 anti-PD-1/L1 naïve patients with metastatic melanoma will be enrolled. The null hypothesis that the response rate is < 35% will be tested against a 1-sided alternative at a significance level of 0.05. The design will provide greater than 90% power if the true response rate is > 55%. There will be no adjustments for multiplicity.

An exploratory sub-group analysis will be performed for those Expansion Cohort 1 subjects with PD-L1 negative tumors (ie, < 1% positivity) at baseline. It was estimated that this subgroup will have approximately 30 subjects. The analysis will have 80% power to reject the null hypothesis that the response rate is <15% with a one-sided test at a significance level of 0.05 when the true response rate is 35%. There will be no adjustments for multiplicity.

In Expansion Cohort 5, approximately 25 anti-PD-1/L1 naïve melanoma patients will be enrolled. This will allow preliminary estimate of the response rate associated with the dose and dosing schedule chosen for Expansion Cohort 5. If 14 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 37%.

In Expansion Cohort 2, approximately 25 metastatic melanoma patients who have disease progression on anti-PD-1/L1 therapy will be enrolled. The null hypothesis that the true response rate is 10% will be tested against a 1-sided alternative and will be rejected if 6 or more responses are observed. This design yields a type I error rate of 0.05 and 80% power when the true response rate is 30%. There will be no adjustments for multiplicity.

In Expansion Cohort 8, approximately 50 metastatic melanoma patients who are refractory or resistant to anti-PD-1/L1 therapy will be enrolled. If 13 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 15.0%.

In Expansion Cohort 3, approximately 25 anti-PD-1/L1 naïve HNSCC patients will be enrolled. The null hypothesis that the response rate is < 20% will be tested against a 1-sided

alternative at a significance level of 0.05. The design will provide greater than 80% power if the true response rate is > 40%. There will be no adjustments for multiplicity.

In Expansion Cohort 6, approximately 25 anti-PD-1/L1 naïve HNSCC patients will be enrolled. This will allow a preliminary estimate of the response rate associated with the dose and dosing schedule chosen for Expansion Cohort 6. If 9 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 20%.

In Expansion Cohort 4, approximately 25 HNSCC patients who have disease progression on anti-PD-1/L1 therapy will be enrolled. The null hypothesis that the true response rate is 5% will be tested against a 1-sided alternative and will be rejected if 4 or more responses are observed. This design yields a type I error rate of 0.05 and 80% power when the true response rate is 21%. There will be no adjustments for multiplicity.

In Expansion Cohort 7, approximately 25 HNSCC patients who are refractory or resistant to anti-PD-1/L1 therapy will be enrolled. This will allow a preliminary estimate of the response rate associated with the dose and dosing schedule chosen for Expansion Cohort 7. If 4 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 5%.

Although changes to the groupings for the final analysis will be made, there is no impact to the sample size calculation, as all analyses will be descriptive. At some places in above sample size calculation one-sided significance level of 0.05 was referenced, to standardize the analyses, two-sided significance level of 0.05 is used throughout. Power and 95% exact confidence interval descriptions are still applicable if the underlying conditions in various analysis groups hold.

6.0 ANALYSIS POPULATIONS

6.1 Enrolled Population

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

6.2 Safety Population

The safety population will include all enrolled patients who receive at least 1 dose of SD-101 (Protocol section 12.4). The primary analysis population for the study will include the safety population with separate analyses for Phase 1 Dose Escalation and each Phase 2 Dose Expansion analysis group.

6.3 Efficacy Population

The evaluable population will comprise all patients who receive at least 1 dose of both pembrolizumab and SD-101 and who have baseline and at least 1 post-baseline imaging assessment. The ITT population will include all enrolled subjects regardless of having a post-baseline radiographic assessment. Additional subpopulations for an exploratory and

retrospective analysis may include baseline PD-L1 status (positive or negative [ie, < 1% positivity]) and specific prior anti-PD-1/PD-L1 therapy (Protocol section 12.4).

Prior anti-PD-1/PD-L1 therapy subpopulations are reflected in the study groups. Analyses will be performed according to the dose groups in Phase 1 and study groups in Phase 2 for evaluable and ITT population.

6.4 Pharmacodynamic Population

The pharmacodynamic population will include all enrolled patients who receive at least 1 dose of SD-101 and who have screening and at least 1 post-baseline assessment of INF-alpha inducible gene expression.

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 patient receives the first dose of the study drug. The date of the last dose of study drug is the date a patient receives the last dose of the study drug.

Treatment-Emergent Period

Treatment-emergent periods are updated from what were described in the protocol (sections 10.3.9 and 10.3.10) to cover the maximum possible reporting periods.

Treatment-emergent period for AEs is defined the date and time of the first dose of study drug administration through 90 days after last dose of study drug administration.

Treatment-emergent period for SAEs is defined as the date and time of the first dose of study drug administration through EOS.

Baseline Value and Post-baseline Value

Unless otherwise specified, the baseline value is defined as the last measurement before the first dose (date and time) of study drug. Post-baseline value is defined as a measurement taken after the first dose 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 patients in the analysis population.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator unless otherwise specified.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (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 17 or higher.
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version 201506.

7.3 Rules for Missing Data

Missing data will not be imputed, except for missing date information for AEs and concomitant medications. The imputed dates will be used to determine the treatment-emergent period. 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 first dose date, then set to first dose date.
  - If both month and day are missing and year ≠ year of first dose date, then set to January 1.
  - If day is missing and month and year = month and year of first dose date, then set to first dose date.
  - If day is missing and month and year ≠ month and year of first dose date, then set to first of the month.
  - If start date is completely missing and AE end date is on or after the first dose date, set to first dose date.
  - If start date is completely missing and AE end date is prior to the first dose 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.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to January 1.
  - If only day is missing, then set to the first of the month.
- If end date of a medication 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 start date or end date of a medication is completely missing, do not impute.

Listings will show the original date information without imputation, but derived parameters (TEAE indicator and duration of AE) will be flagged to indicate the type of imputation performed.

8.0 TIMING OF ANALYSES

Final analyses will be carried out after the last participant has completed their last trial visit, the trial database has been authorized by Dynavax as complete and final, and major protocol deviations have been identified. No interim analysis is planned for this study.

9.0 STATISTICAL METHODS

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

Efficacy and safety data will be analyzed and reported separately by Phase 1 dose group or Phase 2 analysis group.

Descriptive statistics, including the number of patients (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 (or proportions) of patients in each category. All data processing, summarization, and analyses will be performed using SAS Version 9.3 or higher. Specifications for tables, graphs, and data listings will be provided in the tables, figures, listings (TFL) specifications document.

9.1 Patient Disposition

Patient disposition will be summarized for all enrolled patients by dose or analysis group including patients in the safety, evaluable and ITT populations and patients discontinuing the study along with the reasons for discontinuation (as documented on the case report form study exit status).

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

9.2 Protocol Deviations

Patient data will be reviewed for major protocol deviations by the Medical Monitor prior to database lock. A listing of patients with major protocol deviations will be provided, sorted by treatment and describing their deviations. Any exclusions from analysis populations due to protocol deviations will be highlighted.

9.3 Demographics and Baseline Characteristics

Summary statistics for age, weight, height, body mass index at baseline, sex, race, and ethnicity will be presented by dose or analysis group for the safety, evaluable and ITT populations.

Listings will be provided for these parameters for all patients.

9.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version 201506). 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 patients with concomitant medications will be presented alphabetically by anatomical therapeutic chemical (ATC) class and by decreasing order of frequency of preferred terms within each ATC class for the safety population. Patients 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 V17.0 or higher). All medical history data will be provided in a listing.

9.6 Efficacy Analyses

Response of lesions and disease status will be assessed using standard RECIST v1.1 for the primary evaluation of response *and a study specific modified RECIST v1.1 referred to as immune related-RECIST v1.1 (irRECIST v1.1) for an exploratory evaluation (not implemented)*. Therefore, RECIST v1.1 will be used with the following adaptations (Appendix 1):

- Determination of progressive disease (PD) requires a confirmation of PD by imaging ≥ 4 weeks later. In order to confirm PD, both the initial lesion assessment and lesion assessment on the confirmatory scan must meet PD criteria (≥ 20% increase in sum of diameters).
- Continued treatment while awaiting radiologic confirmation of progression is encouraged if the patient is stable.

Patients that are deemed clinically unstable are not required to have repeat imaging for the confirmation of PD.

Objective response rate (ORR) and disease control rate (DCR) will be evaluated for injected and non-injected lesions as well as for all target lesions. The ORR will include patients with complete response (CR) or partial response (PR). The DCR will include patients with CR, PR, or stable disease. The ORR and DCR will be determined by Investigator using RECIST v1.1.

Unless otherwise specified, all efficacy analyses will be performed by:

- Lesion type – injected, non-injected lesions, all target lesions

- Evaluation criteria – RECIST v1.1
- Study Phase – Phase 1 by dose groups, Phase 2 by analysis groups

9.6.1 Objective Response Rate

The ORR is the proportion of patients who achieve a response of either CR or PR. ORR will be summarized and 95% Clopper Pearson confidence interval will be reported for each dose or analysis group.

9.6.2 Best Overall Response

The best overall response rate (BORR) is the proportion of patients who achieve a best response recorded at any post-baseline assessment. BORR will be summarized and 95% Clopper Pearson confidence interval will be reported for each dose or analysis group.

9.6.3 Disease Control Rate

The disease control rate (DCR) is the proportion of patient who had CR, PR, or stable disease. DCR will be summarized and 95% Clopper Pearson confidence interval will be reported for each dose or analysis group.

9.6.4 Time to Objective Response

The time to response (TOR) will be defined as the time from the first dose of SD-101 until the onset of CR or PR. TOR will be summarized descriptively for patients who achieved CR or PR.

9.6.5 Duration of Response

The duration of response is defined as the period of time from the date of initial confirmed PR or CR until the date of PD or death, whichever is earlier. For those patients who achieved response, duration of response will be summarized descriptively. Kaplan-Meier estimate of median duration and 95% confidence interval will be provided.

9.6.6 Progression-Free Survival

The progressive-free survival (PFS) is defined as the period of time from baseline to confirmed PD or death. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS. The proportion of patients who had PFS at the end of the study will be summarized and PFS will be analyzed by Kaplan-Meier method; 95% confidence interval for the median will be provided. Overall survival (OS) is defined as the period of time from baseline to death, and analysis of OS will also be provided similarly as PFS.

9.7 Safety Analyses

Injection related reactions, AEs, SAEs, and abnormal laboratory values will be summarized by the proportion of patients who experience them.

All patients in the safety population will be used in the safety analyses. Safety analyses will be summarized by dose or analysis group.

The treatment-emergent period is defined in Section 7.1.

9.7.1 Dose Limiting Toxicities

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) through Study Day 29 of any of the following:

Non-hematologic adverse event

• Grade ≥ 3 non-hematologic AE 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, with the exclusion of fatigue

• Grade 3 non-hematologic AE (not laboratory, specifically nausea, vomiting, and diarrhea) lasting > 3 days despite optimal supportive care, with the following exceptions:

  • Grade 3 fatigue will NOT be classified as a DLT, regardless of duration.

  • A Grade 3 non-hematologic laboratory AE will only be considered a DLT if it is clinically significant, such as:

    • Medical intervention is required to treat the patient

    • The abnormality leads to hospitalization

    • The abnormality persists for > 1 week

• Grade 4 or 5 non-hematologic AE (not laboratory)

Hematologic toxicity

• Grade 4 or 5 hematologic AE

• Any Grade 3 hematologic laboratory AE, with the exception of lymphopenia, which lasts > 7 days

• Febrile neutropenia Grade 3 or Grade 4:

  • Grade 3 is defined as ANC < 1000/mL with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.

  • Grade 4 is defined as ANC < 1000/mL with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

Prolonged delay (> 3 weeks) of SD-101 or pembrolizumab dosing due to treatment-related toxicity qualifies as a DLT.

Incidence of DLTs will be tabulated by dose groups in Phase 1, and bar chart of incidence rates of DLTs by dose groups will be generated, if DLTs were observed.

9.7.2 Injection Related Reactions

Incidence of injection-site reactions from the diary card will be tabulated by maximum severity and injection and by analysis group.

Injection related general body symptoms, defined as those symptoms, as determined by the Medical Monitor, with onset with 7 days of and related to the study injection, will be tabulated by maximum severity and injection and by analysis group.

9.7.3 Adverse Events

All AEs will be coded to preferred term and system organ class using MedDRA 17.0 or higher. An AE that started or increased in severity during the treatment-emergent period (refer to Section 7.1) will be considered a 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 drug-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.

Patients 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. AEs that are continuous but change in grade, relationship, or seriousness will be counted as 1 event. TEAEs of unknown severity will be categorized separately. A TEAE of unknown relationship will be considered to be probably related to study drug.

Tabular summaries including numbers and percentages of the following adverse events will be provided:

- Overview of TEAEs;
- TEAEs by SOC and PT;
- TEAEs by SOC, PT, and severity;
- TEAEs by SOC, PT, and relationship to study drug;
- TEAEs leading to study drug discontinuation;
- Serious TEAEs by SOC, PT, and severity;
- Serious TEAEs by SOC, PT, and relationship to study drug;
- Immune Related TEAEs by SOC and PT;
- TEAEs leading to death by SOC and PT.

Listings will be provided for all TEAEs.

9.7.4 Laboratory Assessments

Laboratory test results for neutrophils, lymphocytes, and platelets and their change from baseline will be summarized by tumor type and scheduled visit.

Laboratory data listings will not be produced as clinically significant abnormal laboratory findings are included in AE data.

Anti-dsDNA antibodies (not implemented) and anti-SD-101 antibodies results will be provided as part of the Annex 1 analysis.

9.7.5 Vital Signs

Vital sign data will be provided in a data listing.

9.7.6 Physical Examinations

Individual physical examination data with abnormal findings flagged will be provided in data lists.

9.7.7 Electrocardiograms

ECG data with abnormal findings flagged will be provided in a data listing.

9.8 Pharmacodynamic Analyses

Plan for pharmacodynamic analyses is included in Annex 1 of this SAP.

9.9 Other Analyses

No other analyses are planned.

9.10 Interim Analysis

No interim analysis is planned for this protocol. Safety will be monitored on a regular basis.

9.11 Reporting Output

All outputs will be produced using SAS® version 9.3 or later. The REPORT procedure will be used to produce all tables and listings whenever possible. The SGPLOT procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

Post-text tables, listings, and statistical appendices will be produced as RTF files using output delivery system (ODS) and Times New Roman or a similar font size 8 or larger. Data

will be presented in RTF tables with data in individual cells. Figures will be produced as RTF files using ODS and simplex font. For all outputs, the page numbering will be applied to ensure that when the RTF files are combined, the page numbering remains fixed.

All tables, listings and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2010 or later document (margins: top 1.5", left, right and bottom 1") using 8pt font or larger.

Dose and analysis groups for tables and figures will be as follows:

- for Phase 1: Dose Escalation Phase objectives
  - 1 mg, 2 mg, 4 mg, 8 mg
- for Phase 2: Expansion Phase objectives
  - MEL/Naive (metastatic melanoma patients anti-PD-1/L1 therapy naïve)
    - 2mg, 8mg
  - MEL/Experienced (metastatic melanoma patients progressed on anti-PD-1/L1 therapy)
    - 2mg, 8mg
  - HNSCC/Naive (HNSCC patients anti-PD-1/L1 therapy naïve)
    - 2mg, 8mg
  - HNSCC/Experienced (HNSCC patients progressed on anti-PD-1/L1 therapy)
    - 2mg, 8mg

10.0 REVISION HISTORY

Version	Date	Author	Comments/Rationale for Revision
1.0	04NOV2019	Fang Xie	New Document

11.0 REFERENCES

12.0 LIST OF TABLES

List of tables will be provided in a separate Table of Contents of Tables, Figures and Listings document.

13.0 LIST OF FIGURES

List of figures will be provided in a separate Table of Contents of Tables, Figures and Listings document.

14.0 LIST OF PATIENT DATA LISTINGS

List of listings will be provided in a separate Table of Contents of Tables, Figures and Listings document.

APPENDIX 1 RECIST V1.1

Response Definition

Assessments will use RECIST 1.1 guidelines, which are included in the Study Reference Manual, and study specific modification of the RECIST 1.1 guidelines referred to as immune related RECIST 1.1 (irRECIST 1.1).

RECIST 1.1

Baseline selection of lesions

All lesions are measured by long axis and short axis (perpendicular to the long axis). At baseline, all tumor lesions are identified as either target lesions or non-target lesions and will be evaluated at baseline and every post baseline imaging timepoint.

Target lesions: Minimal size of 1.0 cm by long axis unless a lymph node which must be a minimal size of 1.5 cm by short axis. Superficial lesions must measure at least 10 mm in long diameter and be measurable by calipers to qualify as target lesions. Maximum target lesions are 5 with a maximum of 2 lesions per organ representative of all involved organs.

Non-target lesions: Radiographically visible but do not meet size qualification of target lesions. Lymph nodes must measure at least 1.0 cm by short diameter to qualify as non-target lesions (if smaller considered non-pathologic). Excess target lesions (> 5 overall or 2 per organ) are followed as non-target lesions.

Baseline measurement of lesions

At baseline, the sum of the long diameters of all target lesions (5 lesions total with maximum of 2 lesions per organ representative of all involved organs), is calculated. The sum is referred to as the sum of diameters (SOD) for the baseline timepoint. All other lesions should be identified as non-target lesions and be recorded at baseline.

Postbaseline radiographic response assessment

At each post baseline imaging timepoint, the long axis diameter of all target lesions are measured and recorded. A response of the target lesions is assessed by determination of the overall SOD of the lesions (SOD for that imaging timepoint). A response for each baseline non-target lesion is determined and recorded. The presence of any new lesions are recorded (of note a lymph node must measure at least 1.0 cm by short axis diameter to qualify as a pathologic lesion).

Target lesion response

Complete response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive disease (PD): At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest prior sum of diameters in the trial (this includes the baseline sum if that is the smallest in the trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of least 5 mm.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while in the trial.

Non-target lesion response assessment

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non–target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

New lesion assessment

At each post baseline imaging timepoint, an evaluation of the presence of new lesions (yes/no) is made. The lesions are recorded as new lesions and not target or non-target lesions.

Lymph nodes must be a new lesion and measure at least 10 cm by short diameter to qualify as a new lesion overall response assessment.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion.

Overall response assessment

Overall response assessment is based on target lesion response, non-target lesion response and new lesions and is listed in Figure 1 below.

Figure 1: Overall Response Definitions Using RECIST 1.1

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR

PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

ANNEX 1 PLAN FOR PHARMACODYMAMIC ANALYSIS

Biomarker, anti-SD101 antibodies and pharmacodynamic analysis report including the methods will be provided as part of the final clinical study report.

Dynavax Technologies Corporation

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2, Open-label, Multicenter, Dose escalation and Expansion Trial of Intratumoral SD 101 in Combination with Pembrolizumab in Patients with Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
Protocol Identifier:	DV3-MEL-01
Phase	Phase 1b/2
Investigational Product:	SD-101
Indication:	Metastatic Melanoma
Sponsor:	Dynavax Technologies Corporation 2100 Powell Street Suite 900 Emeryville, CA 94608 United States of America
Reference Numbers:	United States IND No. 125878
Original Version:	Version 1: 04 November 2019
Based on Protocol Version:	Amendment # 8: 08 February 2018

FINAL STATISTICAL ANALYSIS PLAN APPROVAL

Prepared by: _____ _____

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Consulting Biostatistician
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Date

Reviewed by: _____ _____

Fang Xie
For Head of Biometrics
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Date

Approved by: _____ _____

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

Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Definition
AE	adverse event
anti-PD-1/L1	anti-programmed death receptor-1/ligand 1
ATC	anatomical therapeutic chemical
BORR	best objective response rate
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EOS	End-of-Study (visit)
IFN	interferon
ITT	Intent-To-Treat
HNSCC	head and neck squamous cell carcinom
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
MHC	major histocompatibility complex
NK	natural killer
ORR	objective response rate
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand 1
PFS	progression free survival
PR	partial response
PT	preferred term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities

1.0 INTRODUCTION

This statistical analysis plan contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the safety, tolerability, biologic activity, and preliminary efficacy of SD-101 in combination with pembrolizumab as described in Protocol DV3-MEL-01 (Amendment 8: 08 February 2018): "A Phase 1b/2, Open-label, Multicenter, Dose escalation and Expansion Trial of Intratumoral SD-101 in Combination With Pembrolizumab in Patients With Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)".

Due to strategic changes, only some of the objectives will be evaluated. Those objectives not evaluated will be *italicized* and annotated as *"(not implemented)*", where applicable, throughout this SAP; statistical methods for these objectives are also not described. The main text of this SAP covers only assessment of the objectives by data contained in the clinical database. Pharmacodynamic assessment will be described in an annex to this SAP. Pharmacodynamic objectives will also be annotated.

Groupings of patients to be used in the analyses are also changed from what were described in the protocol, based on the knowledge accumulated through the conduct of the trial.

2.0 STUDY OVERVIEW

This open-label, multicenter, dose-ranging and expansion trial is designed to evaluate the safety and preliminary efficacy of intratumoral SD-101 in combination with pembrolizumab for the treatment of metastatic melanoma and HNSCC. The hypothesis to be tested in the clinical development of SD-101 is that SD-101, by virtue of its potency and its ability to induce high levels of interferons (IFNs), will have meaningful efficacy in generating anti-tumor immune responses when combined with an anti-PD-1 antibody. IFNs have multiple effects on both tumor cells and tumor-infiltrating leukocytes. These IFNs can directly inhibit the proliferation of tumor cells and increase MHC class I expression, enhancing antigen recognition. Additionally, IFNs have potent effects on tumor-infiltrating leukocytes, including enhancing the antigen presenting function of dendritic cells, increasing the effect or function of T cells, and activating cytotoxic activity of NK cells.

The rationale for treating metastatic melanoma and HNSCC with combination anti-PD-1/L1 therapy plus SD-101 is based on the unmet need to improve upon single anti-PD-1/L1 activity in these patient populations and nonclinical data (Protocol Sections 2.4 and 2.5) which suggest improved anti-tumor activity with the combination compared to anti-PD-1/L1 alone.

The study will be performed in 2 phases. The population to be studied in Phase 1 (Dose Escalation) will be patients with metastatic melanoma. The populations to be studied in Phase 2 (Dose Expansion) will be patients with metastatic melanoma and patients with

recurrent or metastatic HNSCC. In phase 1 of the study, doses of 1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg of SD-101 each in a single lesion will be tested in a modified, staggered, 3 + 3 trial design, to identify an optimal dose of SD-101 given in combination with pembrolizumab to be used in Phase 2 (see Protocol section 9.1 for DLT definitions and stopping rules). This optimal dose from Phase 1 is referred to in the protocol as the recommended Phase 2 dose (RP2D) of SD-101. Phase 2 of the study is designed to evaluate the safety and efficacy of SD-101 plus pembrolizumab in both metastatic melanoma and HNSCC patients. Tumor response will be evaluated separately for injected and non-injected lesions as well as all combined lesions in order to assess both a local and systemic response to study treatment.

The trial population includes a total of approximately 284 men and women with at least 1 site of disease that qualifies as a target lesion per RECIST v1.1 and is accessible for intratumoral injection.

Phase 1 Dose Escalation Cohorts 1-4 will include up to 24 patients with metastatic melanoma who are anti-PD-1 naïve or experienced.

Phase 2 Dose Expansion will include approximately 160 patients with metastatic melanoma and approximately 100 patients with recurrent or metastatic HNSCC:

1) Expansion Cohort 1 of approximately 60 melanoma patients who are anti-PD-1/L1 naïve

2) Expansion Cohort 2 of approximately 25 melanoma patients who have disease progression on anti-PD-1/L1 therapy

3) Expansion Cohort 3 of approximately 25 HNSCC patients who are anti-PD-1/L1 naïve

4) Expansion Cohort 4 of approximately 25 HNSCC patients who have disease progression on anti-PD-1/L1 therapy

5) Expansion Cohort 5 of approximately 25 melanoma patients who are anti-PD-1/L1 naïve

6) Expansion Cohort 6 of approximately 25 HNSCC patients who are anti-PD-1/L1 naïve

7) Expansion Cohort 7 of approximately 25 HNSCC patients who are refractory or resistant to anti-PD-1/L1 therapy

8) Expansion Cohort 8 of approximately 50 melanoma patients who are refractory or resistant to anti-PD-1/L1 therapy.

Some of these study groups will be rearranged for final analysis as analysis groups based on tumor indications, anti-PD-1/L1 experience, and dose of SD-101.

Phase 1 results will be presented for each of the 4 dose groups.

Results for Phase 2 objectives, using combined Phases 1 and 2 data, will be presented by 2mg/lesion and 8mg/lesion doses for

- MEL/NAIVE: metastatic melanoma patients who are anti-PD-1/L1 naïve, including
  - subjects in Phase 1 2mg and 8mg groups
  - subjects in Phase 2 Cohort 1 (both 2mg/lesion and 8mg single lesion) and Cohort 5 (2mg/lesion)
- MEL/EXP: metastatic melanoma patients who are anti-PD-1/L1 experienced, including
  - subjects in Phase 1 2mg and 8mg groups
  - subjects in Phase 2 Cohort 2 (both 2mg/lesion and 8mg/lesion) and Cohort 8 (2mg/lesion)
- HNSCC/NAIVE: HNSCC patients who are anti-PD-1/L1 naïve, including
  - subjects in Phase 2 Cohort 3 (both 2mg/lesion and 8mg/lesion) and Cohort 6 (2mg/lesion)
- HNSCC/EXP: HNSCC patients who are anti-PD-1/L1 experienced, including
  - subjects in Phase 2 Cohort 4 (both 2mg/lesion and 8mg/lesion) and Cohort 7 (2mg/lesion)

2.1 Phase 1

Patients in Escalation Cohorts 1-4 will be administered 1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg, respectively, of SD-101 in combination with 200 mg pembrolizumab Q3W per the Schedule of Trial Events (see Protocol Section 4.1.1 for dosing schema).

2.2 Phase 2

Melanoma Dose Expansion cohorts in Phase 2 will be treated with 8.0 mg or 2.0 mg of SD-101 from Phase 1 in combination with 200 mg pembrolizumab Q3W (see Protocol Section 4.1.2 for dosing schema).

HNSCC Dose Expansion cohorts in Phase 2 will be treated with the selected RP2D (8.0 mg or 2.0 mg of SD-101) from Phase 1 in combination with 200 mg pembrolizumab Q3W (see Protocol Section 4.1.2 for dosing schema).

3.0 STUDY OBJECTIVES

3.1 Phase 1 (Dose Escalation: Metastatic Melanoma)

3.1.1 Primary Objectives

- To assess the safety and tolerability of escalating intratumoral doses of SD-101 in combination with intravenous pembrolizumab in patients with metastatic melanoma
- To evaluate the expression of IFN-inducible genes in whole blood 24 hours after intratumoral injection of SD-101 given with pembrolizumab in patients with metastatic melanoma as a pharmacodynamic marker of SD-101 activity (pharmacodynamic)
- To determine a RP2D of SD-101 in combination with pembrolizumab to be evaluated in Phase 2

3.1.2 Exploratory Objectives

- To assess the preliminary response both locally and systemically including:
  - *Treatment response of the injected Lesion A (local response) (not implemented)*
  - *Treatment response of the non-injected lesion(s) (systemic response) (not implemented)*
  - Treatment response of all lesions
  - *Time to response (not implemented)*
  - To assess changes in tumor biomarkers (pharmacodynamic)

3.2 Phase 2 (Dose Expansion: Metastatic Melanoma or Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma)

3.2.1 Primary Objectives

- To assess the tumor response both locally and systemically including:
  - Treatment response of the injected lesion(s) (local response)
  - Treatment response of the non-injected lesion(s) (systemic response)
  - Treatment response of all lesions

3.2.2 Secondary Objectives

- To assess the safety and tolerability of SD-101 in combination with pembrolizumab
- To assess the time frame of tumor responses:
  - Time to response
  - Duration of response
- To assess PFS

3.2.3 Exploratory Objectives

- To assess changes in tumor biomarkers

- To identify and assess changes in potential tumor neoantigens in patients with recurrent or metastatic HNSCC (pharmacodynamic)
- To evaluate the expression of IFN inducible genes in whole blood 24 hours after intratumoral injection of SD-101 given with pembrolizumab in patients with recurrent or metastatic HNSCC as a pharmacodynamic marker of SD-101 activity (pharmacodynamic)

4.0 ANALYSIS VARIABLES

Phase 1 – Dose Escalation

Primary Endpoints

- Incidence of DLTs
- Incidence of injection-site reactions, AEs, and SAEs
- Changes in the expression of IFN-inducible genes in whole blood (pharmacodynamic)

Exploratory Endpoints

- ORR per RECIST v1.1
- Changes in tumor-infiltrating lymphocytes, PD-L1 expression, and other gene expression in tumor biopsies (pharmacodynamic)

Phase 2 – Dose Expansion

The primary radiographic endpoints of the study will be based on RECIST v1.1 *and exploratory radiographic endpoints will be based on irRECIST (not implemented)*. All imaging endpoints for the overall response assessment will be based on investigator evaluation. A central imaging laboratory for study image collection and radiographic endpoint determination will be used per sponsor decision.

Primary Endpoints

- ORR per RECIST v1.1

Secondary Endpoints

- Incidence of injection-site reactions, AEs, and SAEs
- Time to response using RECIST v1.1
- Duration of response per RECIST v1.1
- PFS per RECIST v1.1

Exploratory Endpoints

- Changes in correlative biomarkers including tumor-infiltrating lymphocytes and PD-L1 expression at baseline and after SD-101 treatment (pharmacodynamic)
- Changes in potential tumor neoantigens in patients with recurrent or metastatic HNSCC (pharmacodynamic)

- Changes in the expression of IFN-inducible genes in whole blood in patients with metastatic HNSCC (pharmacodynamic)

5.0 SAMPLE SIZE CONSIDERATIONS

The Phase 1 trial is designed to allow preliminary assessments of safety, biological activity, and biomarkers in approximately 24 patients. Phase 2 of this trial is designed to allow preliminary assessments of efficacy, safety, and changes in biomarkers in approximately 210 patients. All analyses will be descriptive.

The Phase 1 trial sample size is based on a modified 3 + 3 dose-escalation trial design.

For the Phase 2 expansion cohorts, the sample sizes were determined based on power analysis of hypothesis tests and/or confidence intervals, although the efficacy analyses will be descriptive.

In Expansion Cohort 1, approximately 60 anti-PD-1/L1 naïve patients with metastatic melanoma will be enrolled. The null hypothesis that the response rate is < 35% will be tested against a 1-sided alternative at a significance level of 0.05. The design will provide greater than 90% power if the true response rate is > 55%. There will be no adjustments for multiplicity.

An exploratory sub-group analysis will be performed for those Expansion Cohort 1 subjects with PD-L1 negative tumors (ie, < 1% positivity) at baseline. It was estimated that this subgroup will have approximately 30 subjects. The analysis will have 80% power to reject the null hypothesis that the response rate is <15% with a one-sided test at a significance level of 0.05 when the true response rate is 35%. There will be no adjustments for multiplicity.

In Expansion Cohort 5, approximately 25 anti-PD-1/L1 naïve melanoma patients will be enrolled. This will allow preliminary estimate of the response rate associated with the dose and dosing schedule chosen for Expansion Cohort 5. If 14 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 37%.

In Expansion Cohort 2, approximately 25 metastatic melanoma patients who have disease progression on anti-PD-1/L1 therapy will be enrolled. The null hypothesis that the true response rate is 10% will be tested against a 1-sided alternative and will be rejected if 6 or more responses are observed. This design yields a type I error rate of 0.05 and 80% power when the true response rate is 30%. There will be no adjustments for multiplicity.

In Expansion Cohort 8, approximately 50 metastatic melanoma patients who are refractory or resistant to anti-PD-1/L1 therapy will be enrolled. If 13 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 15.0%.

In Expansion Cohort 3, approximately 25 anti-PD-1/L1 naïve HNSCC patients will be enrolled. The null hypothesis that the response rate is < 20% will be tested against a 1-sided

alternative at a significance level of 0.05. The design will provide greater than 80% power if the true response rate is > 40%. There will be no adjustments for multiplicity.

In Expansion Cohort 6, approximately 25 anti-PD-1/L1 naïve HNSCC patients will be enrolled. This will allow a preliminary estimate of the response rate associated with the dose and dosing schedule chosen for Expansion Cohort 6. If 9 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 20%.

In Expansion Cohort 4, approximately 25 HNSCC patients who have disease progression on anti-PD-1/L1 therapy will be enrolled. The null hypothesis that the true response rate is 5% will be tested against a 1-sided alternative and will be rejected if 4 or more responses are observed. This design yields a type I error rate of 0.05 and 80% power when the true response rate is 21%. There will be no adjustments for multiplicity.

In Expansion Cohort 7, approximately 25 HNSCC patients who are refractory or resistant to anti-PD-1/L1 therapy will be enrolled. This will allow a preliminary estimate of the response rate associated with the dose and dosing schedule chosen for Expansion Cohort 7. If 4 or more responses are observed, the 95% exact confidence interval will yield a lower bound of no less than 5%.

Although changes to the groupings for the final analysis will be made, there is no impact to the sample size calculation, as all analyses will be descriptive. At some places in above sample size calculation one-sided significance level of 0.05 was referenced, to standardize the analyses, two-sided significance level of 0.05 is used throughout. Power and 95% exact confidence interval descriptions are still applicable if the underlying conditions in various analysis groups hold.

6.0 ANALYSIS POPULATIONS

6.1 Enrolled Population

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

6.2 Safety Population

The safety population will include all enrolled patients who receive at least 1 dose of SD-101 (Protocol section 12.4). The primary analysis population for the study will include the safety population with separate analyses for Phase 1 Dose Escalation and each Phase 2 Dose Expansion analysis group.

6.3 Efficacy Population

The evaluable population will comprise all patients who receive at least 1 dose of both pembrolizumab and SD-101 and who have baseline and at least 1 post-baseline imaging assessment. The ITT population will include all enrolled subjects regardless of having a post-baseline radiographic assessment. Additional subpopulations for an exploratory and

retrospective analysis may include baseline PD-L1 status (positive or negative [ie, < 1% positivity]) and specific prior anti-PD-1/PD-L1 therapy (Protocol section 12.4).

Prior anti-PD-1/PD-L1 therapy subpopulations are reflected in the study groups. Analyses will be performed according to the dose groups in Phase 1 and study groups in Phase 2 for evaluable and ITT population.

6.4 Pharmacodynamic Population

The pharmacodynamic population will include all enrolled patients who receive at least 1 dose of SD-101 and who have screening and at least 1 post-baseline assessment of INF-alpha inducible gene expression.

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 patient receives the first dose of the study drug. The date of the last dose of study drug is the date a patient receives the last dose of the study drug.

Treatment-Emergent Period

Treatment-emergent periods are updated from what were described in the protocol (sections 10.3.9 and 10.3.10) to cover the maximum possible reporting periods.

Treatment-emergent period for AEs is defined the date and time of the first dose of study drug administration through 90 days after last dose of study drug administration.

Treatment-emergent period for SAEs is defined as the date and time of the first dose of study drug administration through EOS.

Baseline Value and Post-baseline Value

Unless otherwise specified, the baseline value is defined as the last measurement before the first dose (date and time) of study drug. Post-baseline value is defined as a measurement taken after the first dose 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 patients in the analysis population.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator unless otherwise specified.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (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 17 or higher.
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version 201506.

7.3 Rules for Missing Data

Missing data will not be imputed, except for missing date information for AEs and concomitant medications. The imputed dates will be used to determine the treatment-emergent period. 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 first dose date, then set to first dose date.
  - If both month and day are missing and year ≠ year of first dose date, then set to January 1.
  - If day is missing and month and year = month and year of first dose date, then set to first dose date.
  - If day is missing and month and year ≠ month and year of first dose date, then set to first of the month.
  - If start date is completely missing and AE end date is on or after the first dose date, set to first dose date.
  - If start date is completely missing and AE end date is prior to the first dose 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.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to January 1.
  - If only day is missing, then set to the first of the month.
- If end date of a medication 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 start date or end date of a medication is completely missing, do not impute.

Listings will show the original date information without imputation, but derived parameters (TEAE indicator and duration of AE) will be flagged to indicate the type of imputation performed.

8.0 TIMING OF ANALYSES

Final analyses will be carried out after the last participant has completed their last trial visit, the trial database has been authorized by Dynavax as complete and final, and major protocol deviations have been identified. No interim analysis is planned for this study.

9.0 STATISTICAL METHODS

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

Efficacy and safety data will be analyzed and reported separately by Phase 1 dose group or Phase 2 analysis group.

Descriptive statistics, including the number of patients (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 (or proportions) of patients in each category. All data processing, summarization, and analyses will be performed using SAS Version 9.3 or higher. Specifications for tables, graphs, and data listings will be provided in the tables, figures, listings (TFL) specifications document.

9.1 Patient Disposition

Patient disposition will be summarized for all enrolled patients by dose or analysis group including patients in the safety, evaluable and ITT populations and patients discontinuing the study along with the reasons for discontinuation (as documented on the case report form study exit status).

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

9.2 Protocol Deviations

Patient data will be reviewed for major protocol deviations by the Medical Monitor prior to database lock. A listing of patients with major protocol deviations will be provided, sorted by treatment and describing their deviations. Any exclusions from analysis populations due to protocol deviations will be highlighted.

9.3 Demographics and Baseline Characteristics

Summary statistics for age, weight, height, body mass index at baseline, sex, race, and ethnicity will be presented by dose or analysis group for the safety, evaluable and ITT populations.

Listings will be provided for these parameters for all patients.

9.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version 201506). 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 patients with concomitant medications will be presented alphabetically by anatomical therapeutic chemical (ATC) class and by decreasing order of frequency of preferred terms within each ATC class for the safety population. Patients 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 V17.0 or higher). All medical history data will be provided in a listing.

9.6 Efficacy Analyses

Response of lesions and disease status will be assessed using standard RECIST v1.1 for the primary evaluation of response *and a study specific modified RECIST v1.1 referred to as immune related-RECIST v1.1 (irRECIST v1.1) for an exploratory evaluation (not implemented)*. Therefore, RECIST v1.1 will be used with the following adaptations (Appendix 1):

- Determination of progressive disease (PD) requires a confirmation of PD by imaging ≥ 4 weeks later. In order to confirm PD, both the initial lesion assessment and lesion assessment on the confirmatory scan must meet PD criteria (≥ 20% increase in sum of diameters).
- Continued treatment while awaiting radiologic confirmation of progression is encouraged if the patient is stable.

Patients that are deemed clinically unstable are not required to have repeat imaging for the confirmation of PD.

Objective response rate (ORR) and disease control rate (DCR) will be evaluated for injected and non-injected lesions as well as for all target lesions. The ORR will include patients with complete response (CR) or partial response (PR). The DCR will include patients with CR, PR, or stable disease. The ORR and DCR will be determined by Investigator using RECIST v1.1.

Unless otherwise specified, all efficacy analyses will be performed by:

- Lesion type – injected, non-injected lesions, all target lesions

- Evaluation criteria – RECIST v1.1
- Study Phase – Phase 1 by dose groups, Phase 2 by analysis groups

9.6.1 Objective Response Rate

The ORR is the proportion of patients who achieve a response of either CR or PR. ORR will be summarized and 95% Clopper Pearson confidence interval will be reported for each dose or analysis group.

9.6.2 Best Overall Response

The best overall response rate (BORR) is the proportion of patients who achieve a best response recorded at any post-baseline assessment. BORR will be summarized and 95% Clopper Pearson confidence interval will be reported for each dose or analysis group.

9.6.3 Disease Control Rate

The disease control rate (DCR) is the proportion of patient who had CR, PR, or stable disease. DCR will be summarized and 95% Clopper Pearson confidence interval will be reported for each dose or analysis group.

9.6.4 Time to Objective Response

The time to response (TOR) will be defined as the time from the first dose of SD-101 until the onset of CR or PR. TOR will be summarized descriptively for patients who achieved CR or PR.

9.6.5 Duration of Response

The duration of response is defined as the period of time from the date of initial confirmed PR or CR until the date of PD or death, whichever is earlier. For those patients who achieved response, duration of response will be summarized descriptively. Kaplan-Meier estimate of median duration and 95% confidence interval will be provided.

9.6.6 Progression-Free Survival

The progressive-free survival (PFS) is defined as the period of time from baseline to confirmed PD or death. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS. The proportion of patients who had PFS at the end of the study will be summarized and PFS will be analyzed by Kaplan-Meier method; 95% confidence interval for the median will be provided. Overall survival (OS) is defined as the period of time from baseline to death, and analysis of OS will also be provided similarly as PFS.

9.7 Safety Analyses

Injection related reactions, AEs, SAEs, and abnormal laboratory values will be summarized by the proportion of patients who experience them.

All patients in the safety population will be used in the safety analyses. Safety analyses will be summarized by dose or analysis group.

The treatment-emergent period is defined in Section 7.1.

9.7.1 Dose Limiting Toxicities

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) through Study Day 29 of any of the following:

Non-hematologic adverse event

• Grade ≥ 3 non-hematologic AE 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, with the exclusion of fatigue

• Grade 3 non-hematologic AE (not laboratory, specifically nausea, vomiting, and diarrhea) lasting > 3 days despite optimal supportive care, with the following exceptions:

  • Grade 3 fatigue will NOT be classified as a DLT, regardless of duration.

  • A Grade 3 non-hematologic laboratory AE will only be considered a DLT if it is clinically significant, such as:

    • Medical intervention is required to treat the patient

    • The abnormality leads to hospitalization

    • The abnormality persists for > 1 week

• Grade 4 or 5 non-hematologic AE (not laboratory)

Hematologic toxicity

• Grade 4 or 5 hematologic AE

• Any Grade 3 hematologic laboratory AE, with the exception of lymphopenia, which lasts > 7 days

• Febrile neutropenia Grade 3 or Grade 4:

  • Grade 3 is defined as ANC < 1000/mL with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.

  • Grade 4 is defined as ANC < 1000/mL with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

Prolonged delay (> 3 weeks) of SD-101 or pembrolizumab dosing due to treatment-related toxicity qualifies as a DLT.

Incidence of DLTs will be tabulated by dose groups in Phase 1, and bar chart of incidence rates of DLTs by dose groups will be generated, if DLTs were observed.

9.7.2 Injection Related Reactions

Incidence of injection-site reactions from the diary card will be tabulated by maximum severity and injection and by analysis group.

Injection related general body symptoms, defined as those symptoms, as determined by the Medical Monitor, with onset with 7 days of and related to the study injection, will be tabulated by maximum severity and injection and by analysis group.

9.7.3 Adverse Events

All AEs will be coded to preferred term and system organ class using MedDRA 17.0 or higher. An AE that started or increased in severity during the treatment-emergent period (refer to Section 7.1) will be considered a 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 drug-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.

Patients 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. AEs that are continuous but change in grade, relationship, or seriousness will be counted as 1 event. TEAEs of unknown severity will be categorized separately. A TEAE of unknown relationship will be considered to be probably related to study drug.

Tabular summaries including numbers and percentages of the following adverse events will be provided:

- Overview of TEAEs;
- TEAEs by SOC and PT;
- TEAEs by SOC, PT, and severity;
- TEAEs by SOC, PT, and relationship to study drug;
- TEAEs leading to study drug discontinuation;
- Serious TEAEs by SOC, PT, and severity;
- Serious TEAEs by SOC, PT, and relationship to study drug;
- Immune Related TEAEs by SOC and PT;
- TEAEs leading to death by SOC and PT.

Listings will be provided for all TEAEs.

9.7.4 Laboratory Assessments

Laboratory test results for neutrophils, lymphocytes, and platelets and their change from baseline will be summarized by tumor type and scheduled visit.

Laboratory data listings will not be produced as clinically significant abnormal laboratory findings are included in AE data.

Anti-dsDNA antibodies (not implemented) and anti-SD-101 antibodies results will be provided as part of the Annex 1 analysis.

9.7.5 Vital Signs

Vital sign data will be provided in a data listing.

9.7.6 Physical Examinations

Individual physical examination data with abnormal findings flagged will be provided in data lists.

9.7.7 Electrocardiograms

ECG data with abnormal findings flagged will be provided in a data listing.

9.8 Pharmacodynamic Analyses

Plan for pharmacodynamic analyses is included in Annex 1 of this SAP.

9.9 Other Analyses

No other analyses are planned.

9.10 Interim Analysis

No interim analysis is planned for this protocol. Safety will be monitored on a regular basis.

9.11 Reporting Output

All outputs will be produced using SAS® version 9.3 or later. The REPORT procedure will be used to produce all tables and listings whenever possible. The SGPLOT procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

Post-text tables, listings, and statistical appendices will be produced as RTF files using output delivery system (ODS) and Times New Roman or a similar font size 8 or larger. Data

will be presented in RTF tables with data in individual cells. Figures will be produced as RTF files using ODS and simplex font. For all outputs, the page numbering will be applied to ensure that when the RTF files are combined, the page numbering remains fixed.

All tables, listings and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2010 or later document (margins: top 1.5", left, right and bottom 1") using 8pt font or larger.

Dose and analysis groups for tables and figures will be as follows:

- for Phase 1: Dose Escalation Phase objectives
  - 1 mg, 2 mg, 4 mg, 8 mg
- for Phase 2: Expansion Phase objectives
  - MEL/Naive (metastatic melanoma patients anti-PD-1/L1 therapy naïve)
    - 2mg, 8mg
  - MEL/Experienced (metastatic melanoma patients progressed on anti-PD-1/L1 therapy)
    - 2mg, 8mg
  - HNSCC/Naive (HNSCC patients anti-PD-1/L1 therapy naïve)
    - 2mg, 8mg
  - HNSCC/Experienced (HNSCC patients progressed on anti-PD-1/L1 therapy)
    - 2mg, 8mg

10.0 REVISION HISTORY

Version	Date	Author	Comments/Rationale for Revision
1.0	04NOV2019	Fang Xie	New Document

11.0 REFERENCES

12.0 LIST OF TABLES

List of tables will be provided in a separate Table of Contents of Tables, Figures and Listings document.

13.0 LIST OF FIGURES

List of figures will be provided in a separate Table of Contents of Tables, Figures and Listings document.

14.0 LIST OF PATIENT DATA LISTINGS

List of listings will be provided in a separate Table of Contents of Tables, Figures and Listings document.

APPENDIX 1 RECIST V1.1

Response Definition

Assessments will use RECIST 1.1 guidelines, which are included in the Study Reference Manual, and study specific modification of the RECIST 1.1 guidelines referred to as immune related RECIST 1.1 (irRECIST 1.1).

RECIST 1.1

Baseline selection of lesions

All lesions are measured by long axis and short axis (perpendicular to the long axis). At baseline, all tumor lesions are identified as either target lesions or non-target lesions and will be evaluated at baseline and every post baseline imaging timepoint.

Target lesions: Minimal size of 1.0 cm by long axis unless a lymph node which must be a minimal size of 1.5 cm by short axis. Superficial lesions must measure at least 10 mm in long diameter and be measurable by calipers to qualify as target lesions. Maximum target lesions are 5 with a maximum of 2 lesions per organ representative of all involved organs.

Non-target lesions: Radiographically visible but do not meet size qualification of target lesions. Lymph nodes must measure at least 1.0 cm by short diameter to qualify as non-target lesions (if smaller considered non-pathologic). Excess target lesions (> 5 overall or 2 per organ) are followed as non-target lesions.

Baseline measurement of lesions

At baseline, the sum of the long diameters of all target lesions (5 lesions total with maximum of 2 lesions per organ representative of all involved organs), is calculated. The sum is referred to as the sum of diameters (SOD) for the baseline timepoint. All other lesions should be identified as non-target lesions and be recorded at baseline.

Postbaseline radiographic response assessment

At each post baseline imaging timepoint, the long axis diameter of all target lesions are measured and recorded. A response of the target lesions is assessed by determination of the overall SOD of the lesions (SOD for that imaging timepoint). A response for each baseline non-target lesion is determined and recorded. The presence of any new lesions are recorded (of note a lymph node must measure at least 1.0 cm by short axis diameter to qualify as a pathologic lesion).

Target lesion response

Complete response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive disease (PD): At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest prior sum of diameters in the trial (this includes the baseline sum if that is the smallest in the trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of least 5 mm.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while in the trial.

Non-target lesion response assessment

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non–target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

New lesion assessment

At each post baseline imaging timepoint, an evaluation of the presence of new lesions (yes/no) is made. The lesions are recorded as new lesions and not target or non-target lesions.

Lymph nodes must be a new lesion and measure at least 10 cm by short diameter to qualify as a new lesion overall response assessment.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion.

Overall response assessment

Overall response assessment is based on target lesion response, non-target lesion response and new lesions and is listed in Figure 1 below.

Figure 1: Overall Response Definitions Using RECIST 1.1

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR

PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

ANNEX 1 PLAN FOR PHARMACODYMAMIC ANALYSIS

Biomarker, anti-SD101 antibodies and pharmacodynamic analysis report including the methods will be provided as part of the final clinical study report.