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

Protocol No.:

DV3-MEL-01 (SYNERGY-001)

Protocol Version & Date:

Amendment 9.0 dated 20 November 2019

NCT No.:

NCT02521870

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Protocol No.:	DV3-MEL-01 (SYNERGY-001)
Investigational Product:	SD-101
Regulatory Filing Reference Numbers:	US IND: 125878 EudraCT: 2016-004461-47 AUS: CT-2016-CTN-05177-1 NZ: TT50-10123 (2077)
Trial Phase:	Phase 1b/2
Sponsor:	Dynavax Technologies Corporation 2100 Powell Street, Suite 900 Emeryville, CA 94608 United States of America
Study Medical Monitor:	**Global:** Robert Janssen, MD, Senior Vice President and Chief Medical Officer, Clinical Development, Medical and Regulatory Affairs Dynavax Technologies Corporation Tel: (510) 665-0414 Fax: (510) 848-9750 E-mail: rjanssen@dynavax.com **Regional:** Jorge Martinez, MD Medical Director, Hematology/Oncology – Medical Affairs PRA Health Sciences Tel: +49 621-878-2696 E-mail: martinezjorge@prahs.com
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Amendment #9:	20 November 2019	**Amendment #4:**	23 September 2016
Amendment #8:	08 February 2019	**Amendment #3:**	30 March 2016
Amendment #7:	22 June 2018	**Amendment #2:**	18 December 2015
Amendment #6:	02 April 2018	**Amendment #1:**	07 May 2015
Amendment #5:	02 June 2017	**Original Protocol:**	27 March 2015

This trial will be conducted in accordance with the International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines and applicable local legal and regulatory requirements.

PROTOCOL APPROVAL PAGE

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

Regulatory Filing Reference Numbers: US IND: 125878
EudraCT: 2016-004461-47
AUS: CT-2016-CTN-05177-1
NZ: TT50-10123 (2077)

Protocol No.: DV3-MEL-01 (SYNERGY-001)

Amendment #9: 20 November 2019

Amendment #8: 08 February 2019

Amendment #7: 22 June 2018

Amendment #6: 02 April 2018

Amendment #5: 02 June 2017

Amendment #4: 23 September 2016

Amendment #3: 30 March 2016

Amendment #2: 18 December 2015

Amendment #1: 07 May 2015

Original Protocol: 27 March 2015

Sponsor: Dynavax Technologies Corporation
2100 Powell Street, Suite 900
Emeryville, CA 94608
United States of America

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

DocuSigned by:
Robert Janssen
Signer Name: Robert Janssen
Signing Reason: I approve this document
Signing Time: 22-Nov-2019 | 14:01 PST
4A124D96163F453294C9C8C24158BAE1

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

Date

INVESTIGATOR SIGNATURE PAGE

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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United States of America

DECLARATION OF INVESTIGATOR

I confirm that I have read and understood this protocol and agree to conduct the trial as outlined in the protocol and other information supplied to me. I agree to conduct the trial in accordance with ICH E6(R2) GCP guidelines and applicable local legal and regulatory requirements.

Investigator Name (Print)	Investigator Signature	Date

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PROTOCOL SYNOPSIS

Objectives:

NOTE: As of Amendment 9, Phase 1 of the trial is complete. For Phase 2, efficacy and exploratory objectives will not be pursued.

Phase 1 (Dose Escalation: Metastatic Melanoma)

Primary Objectives

- To assess the safety and tolerability of escalating doses of intratumoral SD-101 in combination with intravenous pembrolizumab in patients with metastatic melanoma
- To evaluate the expression of interferon (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
- To determine a recommended Phase 2 dose (RP2D) of SD-101 in combination with pembrolizumab to be evaluated in Phase 2

Exploratory Objectives

- To assess the preliminary response both locally and systemically including:
  - Treatment response of the injected Lesion A (local response)
  - Treatment response of the non-injected lesion(s) (systemic response)
  - Treatment response of all lesions
  - Time to response
- To assess changes in tumor biomarkers

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

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

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 progression-free survival (PFS)

Exploratory Objectives

- To assess changes in tumor biomarkers
- To identify and assess changes in potential tumor neoantigens in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
- 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

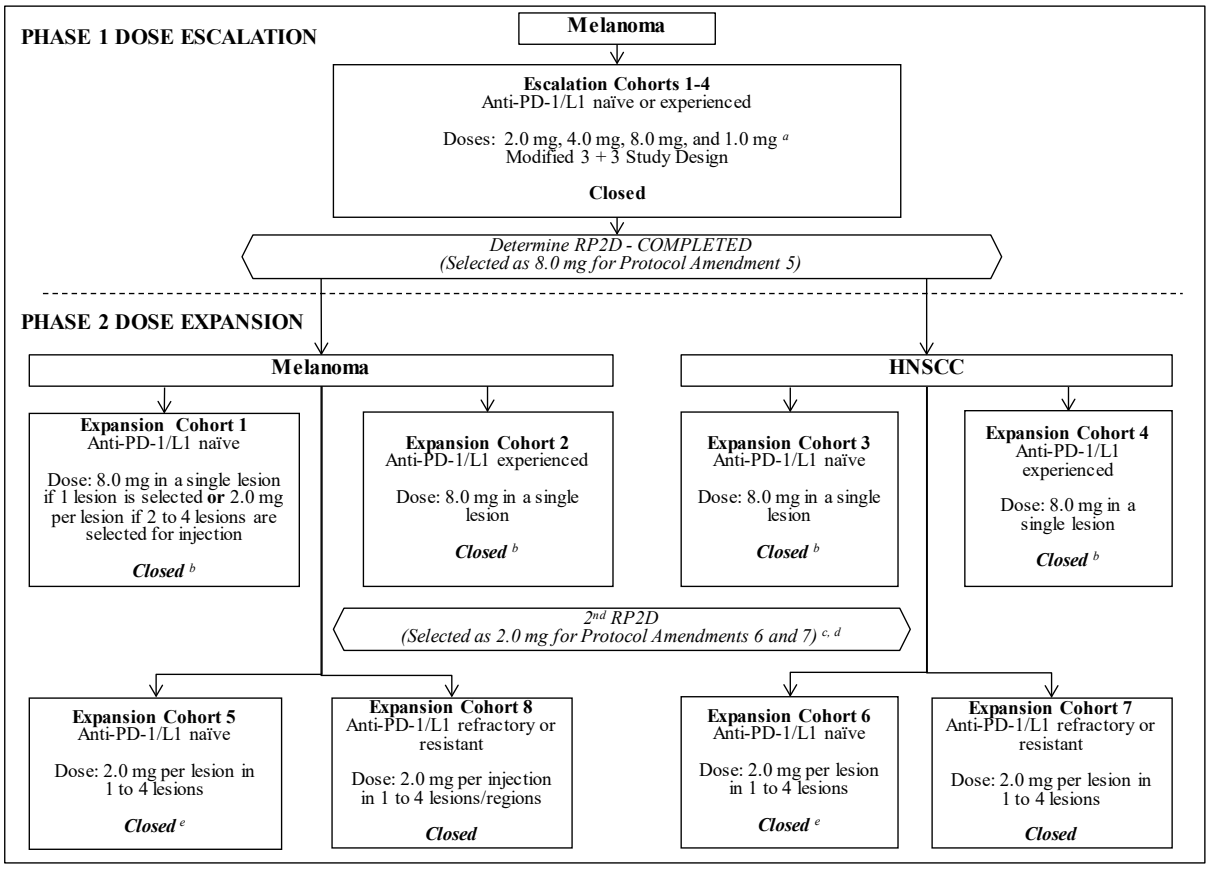
Trial Design: **NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected.**

This is a phase 1b/2, open-label, multicenter trial designed to evaluate the safety, tolerability, biologic activity, and preliminary efficacy of intratumoral SD-101 injections in combination with intravenous pembrolizumab in patients with metastatic melanoma or recurrent or metastatic HNSCC.

This study will be conducted in 2 phases. Phase 1 evaluates SD-101 given in combination with pembrolizumab in melanoma populations (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease) in up to 4 Dose Escalation cohorts to identify an RP2D to be evaluated in up to 4 Dose Expansion cohorts in Phase 2. Phase 2 also includes up to 4 Dose Expansion cohorts of patients with HNSCC (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease).

The following schema presents the study design for melanoma Phase 1 and Phase 2 and for HNSCC Phase 2.

DV3-MEL-01 Study Design Schema



Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1; HNSCC = head and neck squamous cell carcinoma; RP2D = recommended Phase 2 dose.

[a] 1.0 mg of SD-101 was added at Amendment 4.

[b] At Protocol Amendment 5, enrollment in Dose Escalation Cohorts 1-4 was CLOSED. Based on available data (including efficacy, safety, and pharmacodynamics biomarkers), the sponsor selected 8.0 mg in a single injectable lesion if 1 lesion is selected or 2.0 mg per lesion if 2 to 4 lesions are selected for injection as the RP2D to be evaluated in the Dose Expansion phase.

[c] At Protocol Amendment 6 and based on available data (including efficacy, safety, and pharmacodynamics biomarkers), the sponsor selected a second Phase 2 dose of 2.0 mg per lesion in 1 to 4 injectable lesions to be evaluated in the Dose Expansion phase. Expansion Cohorts 1, 2, 3, and 4 in which patients were treated with 8.0 mg in a single injectable lesion were CLOSED to further enrollment. Cohort 5 (melanoma anti-PD-1/L1 –naïve), Cohort 6 (HNSCC anti-PD-1/L1 –naïve), and Cohort 7 (HNSCC anti-PD-1/L1 –refractory or resistant) were ADDED with patients receiving 2.0 mg per lesion in 1 to 4 injectable lesion(s).

[d] At Protocol Amendment 7 and based on available data (including efficacy, safety, and pharmacodynamics biomarkers), Cohort 8 (melanoma anti-PD-1/L1–refractory or resistant) was ADDED with patients receiving 2.0 mg per injection in 1 to 4 injectable lesions/regions.

[e] For Protocol Amendment 8 and based on available data from the ongoing trial (including efficacy, safety, and pharmacodynamics biomarkers), Cohorts 5 and 6 were CLOSED. Additionally, Cohort 8 (melanoma anti-PD-1/L1-refractory or resistant) was expanded to approximately 50 patients.

Note: For Protocol Amendment 9, enrollment is closed for all cohorts. Enrolled patients should continue to receive their assigned trial treatments as per the protocol.

The status of cohorts for this DV3-MEL-01 protocol at Amendment 9 is as follows:

Cohort	Anti-PD-1 /L1 Treatment Status	Orig	A 1	A 2	A 3	A 4	A 5	A 6	A 7	A 8	A9
Ph 1 Mel – 1	Naïve or experienced	X	X	X	X	X	Closed	Closed	Closed	Closed	Complete
Ph 1 Mel – 2	Naïve or experienced	X	X	X	X	X	Closed	Closed	Closed	Closed	Complete
Ph 1 Mel – 3	Naïve or experienced	X	X	X	X	X	Closed	Closed	Closed	Closed	Complete
Ph 1 Mel – 4	Naïve or experienced	-	-	-	-	X	Closed	Closed	Closed	Closed	Complete
Ph 2 Mel – 1	Naive	-	-	X	X	X	X	Closed	Closed	Closed	Closed
Ph 2 Mel – 2	Experienced	-	-	X	X	X	X	Closed	Closed	Closed	Closed
Ph 2 Mel – 5	Naive	-	-	-	-	-	-	X	X	Closed	Closed
Ph 2 Mel – 8	Refractory or resistant	-	-	-	-	-	-	-	X	X	Closed
Ph 2 HNSCC – 3	Naive	-	-	-	-	X	X	Closed	Closed	Closed	Closed
Ph 2 HNSCC – 4	Experienced	-	-	-	-	X	X	Closed	Closed	Closed	Closed
Ph 2 HNSCC – 6	Naive	-	-	-	-	-	-	X	X	Closed	Closed
Ph 2 HNSCC – 7	Refractory or resistant	-	-	-	-	-	-	X	X	X	Closed

A = Amendment; Closed = Closed to enrollment; Complete = last patient last visit (LPLV) has been reached for all patients; HNSCC = head and neck squamous cell carcinoma; Mel = melanoma; Orig = original; Ph = phase; X = Open for enrollment

Phase 1 Dose Escalation: Melanoma (COMPLETE)

The Phase 1 will consist of up to 4 Dose Escalation cohorts to evaluate the safety and tolerability of SD-101 given in combination with pembrolizumab in melanoma populations (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease) to identify an RP2D to be evaluated in Phase 2.

Phase 1 employs a modified 3 + 3 study design, evaluating escalating dose levels of SD-101 (given with a fixed dose of pembrolizumab) in patients with metastatic melanoma. Cohorts of 3 to 6 patients will be enrolled at each dose level, and each patient will participate in only 1 cohort.

Patients in Escalation Cohorts 1-4 will be administered 2.0 mg, 4.0 mg, 8.0 mg, and 1.0 mg, respectively, of SD-101 in combination with 200 mg pembrolizumab per the Schedule of Trial Events. The melanoma Dose Escalation cohorts, patient populations, and treatment assignments are outlined in the table below.

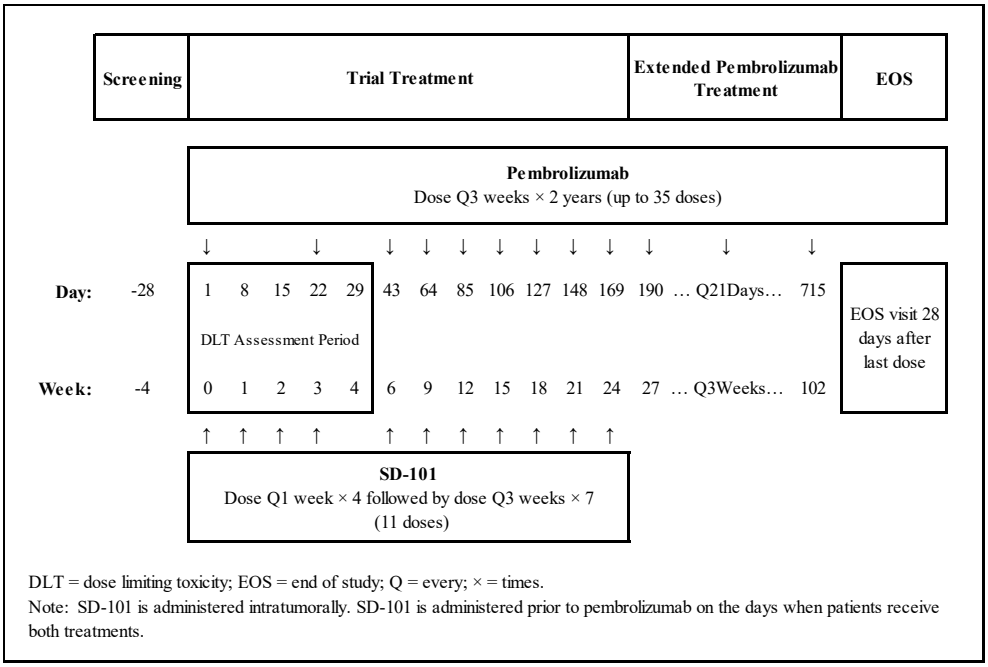
Phase 1 Melanoma Dose Escalation Cohorts (*COMPLETE)*

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	n	Dosing Schema
1	Naïve or experienced	2.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A
2	Naïve or experienced	4.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A
3	Naïve or experienced	8.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A
4	Naïve or experienced	1.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A[a]

[a] Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1.Dosing Schema:
A: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 1 course of SD-101 (4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
[b] 1.0 mg was added in Protocol Amendment 4.

As presented in the Trial Flow Diagram for Dose Escalation Cohorts 1-4, patients with metastatic melanoma will receive 4 weekly doses of SD-101 administered intratumorally on Days 1, 8, 15, 22, and then every 3 weeks on schedule with pembrolizumab for 7 additional doses. Pembrolizumab 200 mg will be administered intravenously every 3 weeks starting on Day 1 for up to 35 treatments (approximately 2 years) or until disease progression. SD-101 will be administered before pembrolizumab on days when both drugs are scheduled to be used.

Trial Flow Diagram for Dose Escalation Cohorts 1 to 4 (*COMPLETE)*



DLT Assessment ***(COMPLETE)***

Phase 1 implements a staggered enrollment for a cohort in addition to enrolling 3 to 6 patients as part of a modified 3 + 3 Dose Escalation design. Patients enrolled under staggered enrollment in Phase 1 are referred to as sentinel patients in the protocol. For sentinel patients in Phase 1, DLTs as defined in the protocol will be assessed during the first 72 hours of dosing prior to dosing of subsequent patients in a cohort as described herein. The DLT assessment period for all Phase 1 patients is 28 days.

The starting dose of SD-101 will be 2.0 mg administered intratumorally and will be given to 1 sentinel patient. If the sentinel patient does not experience a DLT within 72 hours, the second patient in the cohort may be dosed. If no DLT is experienced in the second patient after 72 hours, the third and subsequent patients may be dosed. If a DLT is experienced in the first sentinel patient within 72 hours of injection, a second sentinel patient may be dosed with SD-101 following a safety review and an evaluation of *safe to proceed*. If no DLT is observed after 72 hours in the second sentinel patient, the third and subsequent patients in the cohort may be enrolled.

If there is no DLT observed in the group of 3 or more patients, the next cohort will be enrolled, and escalation will proceed to the next highest dose with a sentinel patient receiving SD-101 at least 72 hours prior to dosing of subsequent patients.

If a DLT is observed in 1 patient in the first 3 patients enrolled in a cohort, enrollment will proceed and the cohort size will be increased up to 6 patients.

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

A minimum of 3 patients will be enrolled in each cohort. The sponsor may also decide to enroll up to 6 patients initially into a cohort. The maximum allowed DLTs per cohort to allow subsequent Dose Escalation is 1 DLT observed in 6 patients. If ≥ 2 of 6 patients experience a DLT in any cohort, Dose Escalation will cease and the previous lower dose of SD-101 may be designated the maximum tolerated dose (MTD).

The planned dose cohorts for SD-101 are 2.0 mg, 4.0 mg, and 8.0 mg. Dose Escalation will continue until an MTD is determined, or a maximum planned dose (ie, a total body dose of 8.0 mg) is reached. A 1.0 mg dose cohort, added in Amendment 4 of this protocol, will not require staggered enrollment with a sentinel patient and may be enrolled concurrently with the higher dose cohorts. Decisions to escalate the dose of SD-101 to the next highest level will be based on review of safety data from the time of the first injection (Day 1) through Day 29 (the DLT assessment period). If 1 DLT in 6 patients or 2 Grade 2 adverse events (AEs) considered drug-related (except for malaise, headache, myalgia, fatigue, or chills) occur in 3 patients in a dose cohort, the Dose Escalation increment for the next dosing cohort will be decreased from 100% to 50%. Intra-patient Dose Escalation is not permitted.

The RP2D of SD-101 given in combination with pembrolizumab will be chosen based on all available data including efficacy, safety, and pharmacodynamic biomarkers (eg, IFN-inducible gene signature and tumor-infiltrating lymphocytes). The sponsor may also choose to investigate lower dose level(s) and enroll 3 or more additional patients prior to Phase 2. A minimum of 6 patients must have been dosed and cleared of DLT either at the identified RP2D or higher before Phase 2 is initiated. If no more than 1 DLT in 6 total patients is observed at a dose level, then the dose will be declared as the RP2D for use in Phase 2 of this trial. Once the RP2D is determined, an additional 6 patients may be enrolled to assess safety at this dose. The RP2D must not exceed the MTD.

Phase 2 Dose Expansion (CLOSED)

NOTE: As of Amendment 9, enrollment in Phase 2 of the trial is closed. Enrolled patients should continue receiving their assigned treatment per protocol.

Study Cohorts

Melanoma

As described in the table below, melanoma Dose Expansion cohorts in Phase 2 will be treated with 8.0 mg or 2.0 mg of SD-101 in combination with 200 mg pembrolizumab every 3 weeks across 3 cohorts. Phase 2 Expansion Cohort 1 will enroll approximately 60 and Cohort 5 will enroll approximately 25 anti-PD-1/L1 naïve patients with melanoma. Cohort 2 will enroll approximately 25 and Cohort 8 will enroll approximately 50 melanoma patients who have disease progression on anti-PD-1/L1 therapy. In melanoma Dose Expansion Cohort 1, SD-101 dosing starts on Day 22 at the second dose of pembrolizumab; whereas, in Cohorts 2, 5, and 8, SD-101 and

pembrolizumab dosing both start on Day 1 (See flow diagram below for dosing schedule).

Phase 2 Melanoma Dose Expansion Cohorts *(CLOSED)*

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	n	Dosing Schema[a]
1	Naïve	8.0 mg in a single injectable lesion if 1 lesion is selected (Lesion A) **or** 2.0 mg per lesion if 2 to 4 lesions are selected for injection (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 60	B
2	Experienced[b]	8.0 mg in a single injectable lesion (Lesion A)	Approximately 25	A
5	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 25	A1
8	Refractory or resistant[c]	2.0 mg in 1 ml per injection in 1 to 4 separate lesions for lesions measuring up to 5 cm in the longest diameter; or for lesions larger than 5 cm, 2.0 mg in 1 ml per injection in 1 to 4 separate regions where the injections are ≥ 5 cm apart (maximum total dose is 8.0 mg)	Approximately 50	A1

Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1.

[a] Dosing Schema:
A: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
B: SD-101 dosing starts on Day 22 at the second dose of pembrolizumab and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
A1: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 1 course of SD-101 (4 weekly then every 3 weeks on schedule with pembrolizumab up to Week 51)

[b] Received prior treatment regimen containing an anti-PD-1/L1 drug.

[c] Received at least 2 doses of an anti-PD-1/L1 therapy and experienced PD within 3 months after last dose of anti-PD-1/L1 therapy. Anti-PD-1/L1 refractory or resistant patients must have documented PD per RECIST v.1.1, which has been confirmed by a second scan at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.

HNSCC

As described in the table below, HNSCC Dose Expansion cohorts in Phase 2 will be treated with 8.0 mg or 2.0 mg of SD 101 in combination with 200 mg pembrolizumab every 3 weeks across 4 cohorts. Phase 2 Expansion Cohorts 3 and 6 will each enroll approximately 25 anti-PD-1/L1 naïve patients. Cohorts 4 and 7 will each enroll approximately 25 HNSCC patients who have disease progression on anti-PD-1/L1 therapy. In HNSCC Dose Expansion Cohort 3, SD-101 dosing starts on Day 22 at the

second dose of pembrolizumab; whereas, in Cohorts 4, 6 and 7, SD-101 and pembrolizumab dosing both start on Day 1 (See flow diagram below for dosing schedule).

Phase 2 HNSCC Dose Expansion *(CLOSED)*

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	n	Dosing Schema[a]
3	Naïve	8.0 mg in a single injectable lesion (Lesion A)[b]	Approximately 25	B
4	Experienced[c]	8.0 mg in a single injectable lesion (Lesion A)[b]	Approximately 25	A
6	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 25	A1
7	Refractory or resistant[d]	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 25	A1

Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1.

[a] Dosing Schema:
A: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
B: SD-101 dosing starts on Day 22 at the second dose of pembrolizumab and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
A1: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 1 course of SD-101 (4 weekly then every 3 weeks on schedule with pembrolizumab up to Week 51)

[b] Patients receive 8.0 mg per lesion in 1 lesion with the option of injecting into up to 4 regions within the lesion in approximate equally divided volumes of an 8.0 mg dose.

[c] Received prior treatment regimen containing an anti-PD-1/L1 drug.

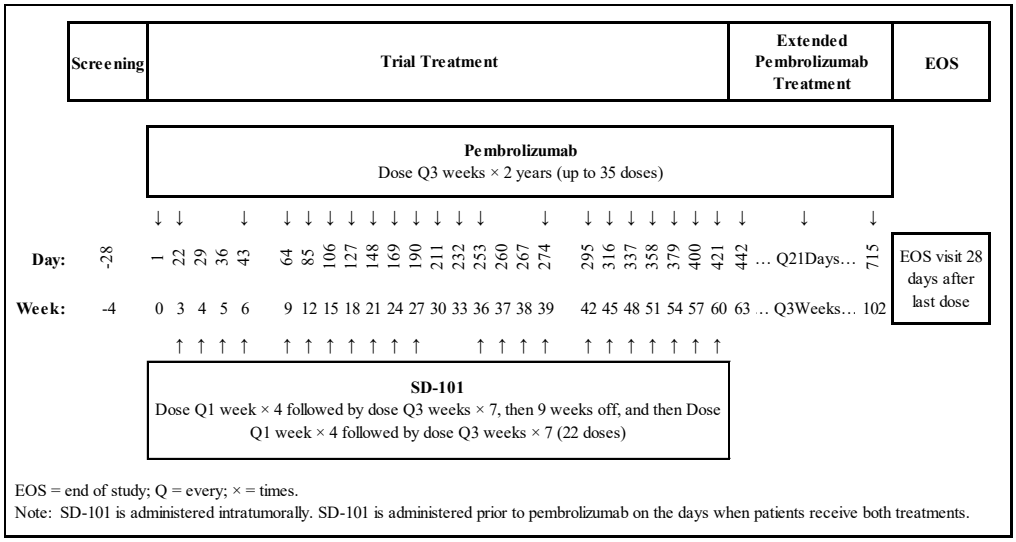
[d] Received at least 2 doses of an anti-PD-1/L1 therapy, where the last dose of anti-PD-1/L1 therapy was within 6 months of study enrollment (Day 1) and have either refractory response (PD occurred within 3 months duration of the start of treatment on anti-PD-1/L1 therapy) OR resistant response (PD occurred beyond 3 months duration of treatment on anti-PD-1/L1 therapy and within 6 months after the last dose of treatment on anti-PD-1/L1 therapy). Anti-PD-1/L1 refractory or resistant patients must have documented PD per RECIST v.1.1, which has been confirmed by a second scan at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.

Study Dosing Schedule

As presented in the Trial Flow Diagrams for the Dose Expansion Cohorts 1 to 4, patients with metastatic melanoma or HNSCC will receive 2 courses of the SD-101 dose regimen, with 9 weeks off between the 2 courses. In Cohorts 1 and 3, patients will have a lead-in dose of pembrolizumab at Day 1 and start the treatment course on Day 22; whereas, in Cohorts 2 and 4, SD-101 and pembrolizumab treatments will both start on Day 1.

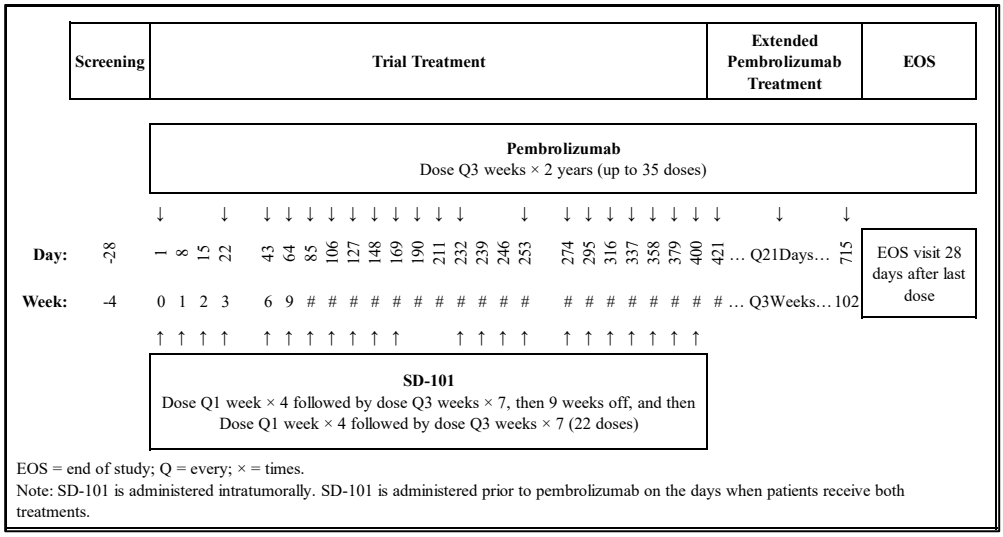
Metastatic melanoma or HNSCC patients in Cohorts 5, 6, 7, and 8 will receive 1 course of SD-101 (4 weekly then every 3 weeks on schedule with pembrolizumab up to Week 51) and dosing with SD-101 and pembrolizumab will both start on Day 1. Pembrolizumab 200 mg will be administered intravenously every 3 weeks until disease progression or up to 2 years. SD-101 will be administered before pembrolizumab on days when both drugs are scheduled to be used.

Trial Flow Diagram for Dose Expansion Cohorts 1 and 3 (*CLOSED)*



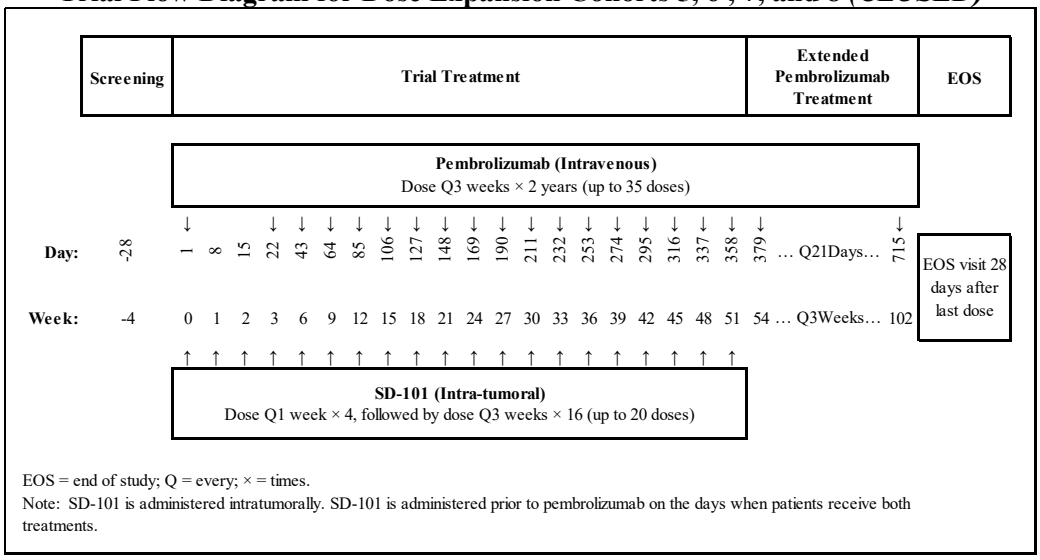
EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

Trial Flow Diagram for Dose Expansion Cohorts 2 and 4 (*CLOSED*)



EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

Trial Flow Diagram for Dose Expansion Cohorts 5, 6 , 7, and 8 *(CLOSED)*



EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

Phase 1 and Phase 2 - Disease Assessment

NOTE: As of Amendment 9, the trial will stop collecting all efficacy endpoints. Assessments of disease response to treatment should be made per Investigator based on local standard of care. This section has been modified accordingly.

Disease response and progression will be assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. If imaging

performed per local standard of care indicates disease progression (PD), it is at the discretion of the investigator whether to repeat imaging for confirmation of PD as per local assessment guidelines.

The protocol also allows patients who are clinically stable and have unconfirmed PD to continue on pembrolizumab and SD-101 per investigator decision. Patients must discontinue all study treatment for confirmed PD.

Patients who discontinue pembrolizumab must discontinue SD-101. Pembrolizumab may be continued as a single agent if SD-101 is discontinued per investigator decision.

Specific procedures to be performed during the trial are described in the Schedule of Trial Events. The statistical methods section of the protocol describes the analysis of data collected in the trial.

Trial Population: 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 naïve
4) Expansion Cohort 4 of approximately 25 HNSCC anti-PD-1/L1 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 on 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

Trial Period: The total duration of patient participation in this trial is up to approximately 110 weeks. This includes a Screening period beginning up to 28 days prior to the first trial treatment, and a trial completion visit approximately 28 days after the last dose of trial treatment.

Safety Evaluation:

NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to simplify collection of safety endpoints. This section has been updated accordingly.

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through inclusion/exclusion criteria and routine safety monitoring. In addition, safety data monitoring during Phase 1 will be reviewed by a Safety Review Team comprised of the Dynavax Medical Monitor, Phase 1 coordinating investigator, and other key safety Dynavax personnel as described in the Cohort Safety Review Plan.

In Phase 1, during the DLT assessment period, patients will undergo targeted physical examinations and laboratory assessments, which will include a complete blood count (CBC) with differential, platelet assessment, coagulation testing, thyroid function tests, and serum chemistry (including creatinine, liver function tests, and lactate dehydrogenase [LDH]).

In Phase 1, after the DLT assessment period, safety will be evaluated through the monitoring of the results of all clinical and laboratory assessments. Safety assessments will include specified laboratory parameters (eg, CBC, thyroid function, serum chemistry).

In Phase 1, standard safety monitoring will be employed for DLT assessment and dose-escalation decisions. Before Dose Escalation at each dose level of SD-101 and at any other time during Phase 1 or Phase 2 that warrants additional review due to emerging safety data, the investigators will discuss and review the safety data with the Dynavax Medical Monitor.

Prior to the first 4 initial weekly injections of SD-101 in Phase 1, patients will receive a new Diary Card with instructions to measure and record local injection-site reactions and solicited AEs. The completed Diary Cards will be reviewed with patients at their next study visit.

In Phase 2, safety assessments prior to dosing will be performed according to the local standard of care. The investigator will follow all related AEs observed during the trial until the AEs are considered resolved or until 28 days after the last dose of trial treatment and/or the patient begins new anti-cancer therapy (whichever is earlier).

Serious adverse events (SAEs) will be evaluated from the time of consent through 90 days following cessation of trial treatment or End of Study (EOS) (whichever is

later), or 28 days following cessation of trial treatment if the patient initiates new anti-cancer therapy.

New cancers (not the cancer being investigated under the study), whether AEs or SAEs, will be collected.

Events of clinical interest (eg, overdoses), whether AEs or SAEs, will be collected and followed per the AE and SAE reporting processes.

Overdose of SD-101 or pembrolizumab is considered an Event of Clinical Interest (ECI) and will be collected and reported irrespective of the presence of an associated AE or SAE.

Progression of the cancer under study is not considered an AE or an SAE and should not be reported as an AE or SAE.

Other Assessments:

NOTE: As of Amendment 9, Phase 1 of the trial is complete and enrollment in Phase 2 is closed. Phase 2 of the trial has been modified to continue dosing per protocol. The trial will stop collecting all efficacy endpoints. Assessments of disease response should be made per Investigator based on local standard of care and assessment guidelines. This section has been modified accordingly

All patients will undergo safety assessments, pharmacodynamic testing, tumor response assessments, and tumor biopsies at specified trial visits, as indicated in the Schedule of Trial Events (Appendix 1 through Appendix 4).

Disease Assessment Prior to Treatment

After informed consent is obtained, disease assessments prior to treatment will include:

- Complete physical examination including assessment of superficial lesions with photographic documentation
- Radiographic imaging including computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) scans of the brain, chest, abdomen, pelvis, and other areas, as clinically indicated. In addition, screening imaging for HNSCC patients requires imaging of the neck.
- Laboratory assessments
- Baseline confirmation of PD-L1 expression from a biopsy of the target lesion (Lesion A) that will be injected with SD-101 in Phase 2 Expansion patients. A baseline biopsy should be collected within 28 days prior to the initiation of study treatment. Archival tissue within 3 months of screening is acceptable.
- Copy of pathology report confirming diagnosis

Assessment of Disease Response to Treatment

Disease assessment may include physical examination and CT scans (or MRI) as per local standard of care.

Trial Treatments:

Treatments

- Pembrolizumab
- SD-101

Dosage and Administration

In both Phase 1 and Phase 2, patients will receive 200 mg pembrolizumab intravenously for up to 35 doses. Intra-patient Dose Escalation or reduction is not permitted. Up to 11 doses of SD 101 in Phase 1 and 22 doses in Phase 2 will be administered in combination with pembrolizumab.

The table below presents the dosage and dose administration for each study cohort.

Phase 1 Metastatic Melanoma

In Phase 1 Escalation Cohorts 1-4, SD-101 is injected intratumorally into a target lesion (Lesion A), the same site used throughout the trial. If at any point during treatment, the lesion for injection has completely regressed and there is no other replacement lesion, SD-101 will be injected peritumorally for up to the next 3 doses of SD-101 within the dosing cycle.

Phase 2

In all Phase 2 cohorts, a lesion designated as Lesion A must be selected and must meet the requirement of being a target lesion as defined per RECIST v1.1 and amenable to multiple intratumoral injections of SD-101. If a selected lesion regresses and/or becomes inaccessible for injection, then a replacement lesion, which could be either a target, non-target, or new lesion per RECIST v1.1, may be chosen for injection at subsequent dosing time points. Injection into a new lesion may occur only after consultation with the Dynavax MM.

If at any point during treatment, the lesion for injection has completely regressed and there is no other replacement lesion, SD-101 will be injected peritumorally for up to the next 3 doses of SD-101.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.

Dosage and Dose Administration for Phase 1 and Phase 2 Cohorts

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	Maximum Total Per-patient SD-101 Dose
Phase 1 Melanoma Dose Escalation Cohorts			
1	Naïve or experienced	2.0 mg per lesion in 1 injectable lesion (Lesion A)	2.0 mg
2	Naïve or experienced	4.0 mg per lesion in 1 injectable lesion (Lesion A)	4.0 mg
3	Naïve or experienced	8.0 mg per lesion in 1 injectable lesion (Lesion A)	8.0 mg
4	Naïve or experienced	1.0 mg per lesion in 1 injectable lesion (Lesion A)	1.0 mg
Phase 2 Melanoma Dose Expansion Cohorts			
1	Naïve	8.0 mg in a single injectable lesion if 1 lesion is selected (Lesion A) **or** 2.0 mg per lesion if 2 to 4 lesions are selected for injection (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
2	Experienced	8.0 mg in a single injectable lesion (Lesion A)	8.0 mg
5	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
8	Refractory or resistant	2.0 mg in 1 ml per injection in 1 to 4 separate lesions for lesions measuring up to 5 cm in the longest diameter; or for lesions larger than 5 cm, 2.0 mg in 1 ml per injection in 1 to 4 separate regions where the injections are ≥ 5 cm apart (maximum total dose is 8.0 mg)	8.0 mg
Phase 2 HNSCC Dose Expansion Cohorts			
3	Naïve	8.0 mg per lesion in 1 lesion with the option of injecting into up to 4 regions within the lesion in approximate equally divided volumes of an 8.0 mg dose	8.0 mg
4	Experienced	8.0 mg per lesion in 1 lesion with the option of injecting into up to 4 regions within the lesion in approximate equally divided volumes of an 8.0 mg dose	8.0 mg
6	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
7	Refractory or resistant	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
Please refer to the Pharmacy Manual for additional details on dose administration.			

Eligibility Criteria:

CLOSED

Inclusion Criteria (Phase 1)

A patient must meet all of the following criteria to be eligible for enrollment (defined as receiving the first trial treatment [ie, pembrolizumab or SD-101]) in the trial:

1) Willing and able to provide written informed consent for the trial
2) Aged 18 years and older
3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1
4) Patient must have adequate organ function as indicated by the following laboratory values:

Hematological

- Absolute neutrophil count (ANC) ≥ 1,500 /mcL
- Platelet count ≥ 100,000 /mcL
- Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L

Renal

- Serum creatinine ≤ 1.5 × upper limit of normal (ULN) OR
- Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl) ≥ 60 mL/min for subject with creatinine levels > 1.5 × institutional ULN

Hepatic

- Serum total bilirubin:
  - ≤ 1.5 × ULN **OR**
  - < 3 × ULN for persons with Gilbert's syndrome **OR**
  - Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 × ULN
- Aspartate transaminase (AST) and alanine transaminase (ALT) (also known as serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase)
  - ≤ 2.5 × ULN **OR**
  - ≤ 5 × ULN for patients with liver metastases

Coagulation

- International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless patient is receiving anticoagulant therapy, and as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants

- Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless patient is receiving anticoagulant therapy, and as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5) Have provided 2 tissue biopsy samples taken of the target lesion (Lesion A) as a single biopsy split into 2 samples or 2 separate biopsies that meet the minimal sample size requirement per the study laboratory manual. One sample is for determining PD-L1 expression level by immunohistochemistry and can be an archival sample of the anticipated target lesion that has been collected within 3 months of screening. The other sample is for RNA expression profiling and must be a fresh biopsy.
6) Life expectancy of at least 6 months
7) Female patients of childbearing potential, as defined in this protocol, must have a negative urine or serum pregnancy test within 72 hours prior to taking the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative then a serum test is required which must be negative for the patient to enroll. Women of childbearing potential (WOCBP) must be willing to use 2 medically acceptable methods of contraceptive from Day 1 through 120 days after the last dose of trial treatment. The 2 medically acceptable birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

   Male patients of childbearing potential, as described in this protocol, must agree to use an adequate method of contraception from Day 1 through 120 days after the last dose of trial treatment.

   Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

Inclusion Criteria (Phase 1 only: Melanoma)

A patient must meet the following to be eligible for Phase 1:

8) Histologically or cytologically confirmed unresectable or metastatic (stage IV) melanoma
9) For Phase 1 Escalation Cohorts 1-4, must have at least 1 lesion that qualifies as a target lesion per RECIST v1.1 except for the minimum measurement of 10 mm in diameter for superficial lesions, is easily accessible (palpable or can be visualized by ultrasound), and is amenable to multiple intratumoral injections. If superficial, the target lesion must be documented photographically.

Inclusion Criteria (Phase 2 only: Melanoma)

A patient must meet the following to be eligible for Phase 2 (as applicable to the expansion cohorts):

10) Histologically or cytologically confirmed recurrent or unresectable or metastatic (stage IV) melanoma

11) Must have at least 2 lesions that qualify as a target lesion per RECIST v1.1, and 1 of the qualifying lesions must be easily accessible (palpable or can be visualized by ultrasound) and amenable to multiple intratumoral injections. The target lesion should be of sufficient size such that the required tumor biopsies do not significantly affect tumor assessment per RECIST v1.1. If superficial, the target lesion must measure at least 10 mm in diameter, be measured by calipers, and be documented photographically. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.

12) Expansion Cohort 2: Must have documented PD per RECIST v1.1 on a prior treatment regimen containing an anti-PD-1/L1 drug (see Appendix 6 for definition of PD per RECIST v1.1)

13) Expansion Cohort 8: Must have all of the following:

    a) Received at least 2 doses of an anti-PD-1/L1 therapy

    b) PD occurred within 3 months after last dose of anti-PD-1/L1 therapy

    c) Documented PD per RECIST v.1.1, which has been confirmed by a second assessment at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression

Inclusion Criteria (Phase 2 only: HNSCC)

A patient must meet the following to be eligible for Phase 2 (as applicable to the expansion cohorts):

14) Histologically or cytologically confirmed recurrent or metastatic HNSCC that could not be treated with curative intent.

15) Must have at least 1 lesion that qualifies as a target lesion per RECIST v1.1, and which must be easily accessible (palpable or can be visualized by ultrasound) and amenable to multiple intratumoral injections. The target lesion should be of sufficient size such that the required tumor biopsies do not significantly affect tumor assessment per RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.

16) Expansion Cohort 4: Must have documented PD per RECIST v1.1 on a prior treatment regimen containing an anti-PD-1/L1 drug (see Appendix 6 for definition of PD per RECIST v1.1)

17) Expansion Cohort 7: Must have all of the following:

    a) Received at least 2 doses of an anti-PD-1/L1 therapy, where the last dose of anti-PD-1/L1 therapy was within 6 months of study enrollment (Day 1)

    b) Refractory response, ie, PD occurred within 3 months duration of the start of treatment on anti-PD-1/L1 therapy; **OR** resistant response, ie, PD occurred beyond 3 months duration of treatment on anti-PD-1/L1 therapy and within 6 months after the last dose of treatment on anti-PD-1/L1 therapy

    c) Documented PD per RECIST v.1.1, which has been confirmed by a second assessment at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression

Exclusion Criteria (Phase 1 and Phase 2)

A patient with any 1 of the following criteria is not eligible for enrollment in the trial:

1) Received systemic chemotherapy or biological cancer therapy (except anti-PD-1/L1 therapy) within 3 weeks prior to study enrollment

2) Received prior radiotherapy within 2 weeks of start of study therapy. A shorter washout period may be permitted after approval by the Medical Monitor.

3) Received small molecule inhibitor targeted therapy, such as tyrosine kinase inhibitors, within 2 weeks prior to study enrollment

4) Has not recovered to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or better from the AEs due to cancer therapeutics prior to study enrollment

   NOTE: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia or Grade 2 AEs that qualify as Grade 2 due to replacement hormonal or steroid therapy are exceptions to this criterion and may qualify for the study with approval by a Dynavax Medical Monitor.

   If a patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to enrollment.

5) Received a transfusion of blood products (including platelets or red blood cells) or colony-stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study enrollment

6) Is expected to require any other form of anti-cancer therapy while in the trial

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

8) Positive for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection as determined by laboratory tests for HBsAg, anti-HBc, and anti-HBs; anti-HCV; and anti-HIV -1/2, respectively
9) History of or current uveal or ocular or mucosal melanoma
10) Active infection including cytomegalovirus
11) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 120 days after the last dose of trial treatment
12) Active autoimmune disease requiring systemic treatment in the past 2 years or a disease that requires immunosuppressive medication including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome, or autoimmune thrombocytopenia. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
13) Current pneumonitis or history of (non-infectious) pneumonitis that required steroids
14) An immune-related AE from a previous immunotherapeutic agent that has not resolved to Grade 1 or less prior to study enrollment. The exception is a Grade 2 AE which qualifies as Grade 2 due to replacement steroid therapy which may be allowed with approval by a Dynavax Medical Monitor.
15) Known active central nervous system metastases or carcinomatous meningitis

    NOTE: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of trial treatment and with any neurologic symptoms returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
16) Use of any investigational agent within the last 28 days prior to study enrollment
17) Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
18) Any other significant medical or psychiatric condition, laboratory abnormality, or difficulty complying with protocol requirements that may increase the risk associated with trial participation or trial drug administration that may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for this trial
19) History of sensitivity to any component of SD-101 or hypersensitivity reaction to treatment with a monoclonal antibody and/or any of its excipients
20) Any known additional malignancy that is progressing or requires active treatment. Exceptions are cutaneous melanoma or HNSCC under study per protocol, or basal

cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy.

Exclusion Criteria (Phase 2, Melanoma Expansion Cohorts 1 and 5 only)

21) Melanoma considered resectable with curative intent

22) Prior therapy with an anti-PD-1/L1 agent

23) Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients

Exclusion Criteria (Phase 2, Melanoma Expansion Cohorts 2 and 8 only)

24) Melanoma considered resectable with curative intent

25) Any prior combination therapy involving agents given by intratumoral injection that target the innate immune pathway or system such as oncolytic viral or microbial therapy (eg, T-VEC [talimogene laherparepvec]), toll-like receptors (TLR) agonists, STING or RIG-1 and an anti-PD-1/L1 inhibitor

Exclusion Criteria (Phase 2, HNSCC Expansion Cohorts 3 and 6 only)

26) HNSCC considered resectable with curative intent

27) Prior therapy with an anti-PD-1/L1 agent

28) Require anticoagulation therapy

Exclusion Criteria (Phase 2, HNSCC Expansion Cohorts 4 and 7 only)

29) HNSCC considered resectable with curative intent

30) Any prior combination therapy involving agents given by intratumoral injection that target the innate immune pathway or system such as oncolytic viral or microbial therapy (eg, T-VEC), TLR agonists, STING or RIG-1 and an anti-PD-1/L1 inhibitor

31) Require treatment on anticoagulation therapy

Trial Endpoints:

NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected. The collection of safety endpoints has been simplified. This section has been modified accordingly.

Phase 1

Primary Endpoints

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

Exploratory Endpoints

- Objective response rate (ORR) per RECIST v1.1
- Disease control rate (DCR) per RECIST v1.1
- Time to response per RECIST v1.1
- Changes in tumor-infiltrating lymphocytes, PD-L1 expression, and other gene expression in tumor biopsies

Phase 2

Primary Endpoints - No longer collected as of Amendment 9

- ORR per RECIST v1.1

Secondary Endpoints

- Incidence of injection-site reactions, AEs, and SAEs

The following Secondary Endpoints (Phase 2) will not be collected as of Amendment 9:

- Time to response per RECIST v1.1
- Duration of response per RECIST v1.1
- Radiographic PFS per RECIST v1.1
- **Exploratory Endpoints - No longer collected as of Amendment 9**Radiographic primary and secondary endpoints evaluated using irRECIST
- Changes in correlative biomarkers including tumor-infiltrating lymphocytes and PD-L1 expression at baseline and after SD-101 treatment
- Changes in potential tumor neoantigens in patients with recurrent or metastatic HNSCC
- Changes in the expression of IFN-inducible genes in whole blood in patients with metastatic head and neck squamous cell carcinoma

Statistical Methods

Note: As of Amendment 9, Phase 1 of the trial is complete. Analyses of data collected from Phase 1 will be performed as specified below. For Phase 2, the trial will stop collecting efficacy and exploratory endpoints, and the collection of safety endpoints has been simplified. Thus, after study completion, only selected analyses as detailed in this section will be performed and exploratory objectives will not be pursued.

Phase 1 portion of this trial is designed to allow preliminary assessments of safety and biological activity in approximately 24 patients. All analyses of demographics, safety, biological activity, and biomarkers will be descriptive.

Injection-site reactions, AEs, SAEs, and abnormal laboratory values will be summarized by the proportion of patients in the all-treated population who experience them.

Phase 2 of this trial is designed to allow preliminary assessments of efficacy, safety, and changes in biomarkers in approximately 160 melanoma patients and approximately 100 HNSCC patients. All analyses of demographics, efficacy, safety, and changes in biomarkers will be descriptive.

Sample size estimates for metastatic melanoma expansion cohorts: Although the analyses will be descriptive, the sample sizes for the expansion cohorts were determined based on power analyses of hypothesis tests and/or confidence intervals.

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 > 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 patients 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 1-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 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 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 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%.

Sample size estimates for HNSCC expansion cohorts: In Expansion Cohort 3, approximately 25 anti-PD-1/L1 naïve 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 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 6, approximately 25 anti-PD-1/L1 naïve HNSCC patients will be enrolled. This will allow 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 7, approximately 25 patients who are refractory or resistant to anti-PD-1/L1 therapy will be enrolled. This will allow 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%.

Analyses

Based on measurements per RECIST v1.1, ORR will be presented as the proportion of patients who achieved complete response (CR) or partial response (PR). DCR will be presented as the proportion of patients with CR, PR, or stable disease. Summary statistics will be provided for time to response and duration of response.

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

Summary statistics will be provided for changes in number of tumor-infiltrating lymphocytes and in PD-L1 and other gene expression in tumors from baseline to protocol-specified time points during treatment.

1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-PD-1/L1	anti-programmed death receptor-1/ligand 1
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate transaminase
BUN	blood urea nitrogen
CBC	complete blood count
CpG	cytidine phosphoguanosine
CFR	Code of Federal Regulations
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EOS	End-of-Study (visit)
FDA	United States Food and Drug Administration

Abbreviation or Term	Definition
FSH	follicle stimulating hormone
GCP	good clinical practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	Interferon
IRB/IEC	Institutional Review Board/Independent Ethics Committee
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
LDH	lactate dehydrogenase
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NSCLC	non-small cell lung cancer
ODN	Oligodeoxynucleotide
ORR	objective response rate
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed death receptor-1
pDC	plasmacytoid dendritic cell
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PR	partial response
PS	performance status
PT	prothrombin time

Abbreviation or Term	Definition
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAR	suspected adverse reaction
SOD	sum of diameters
SUSAR	suspected unexpected serious adverse reaction
TLR9	Toll-like receptor 9
TSH	thyroid stimulating hormone
T-VEC	talimogene laherparepvec
ULN	upper limit of normal
UNS	unscheduled visit/safety follow-up visit
WOCBP	women of childbearing potential

2.0 INTRODUCTION AND RATIONALE

2.1 Melanoma and Head and Neck Squamous Cell Carcinoma

2.1.1 Melanoma

Melanoma is the most serious form of skin cancer and strikes adults of all ages. In the United States (US), melanoma incidence rates have been increasing for at least 30 years and it was estimated that in 2014, approximately 76,100 patients would be diagnosed with malignant melanoma, and that there would be an estimated 9,710 deaths from melanoma (American Cancer Society 2014). Melanoma is more frequent with increasing age with the highest incidence in individuals 65 years of age and older (Howlader, Noone et al. 2014).

Treatment for melanoma includes removal of the primary growth and surrounding normal tissue and sentinel lymph node biopsy to determine stage. More extensive lymph node surgery may be done if lymph node metastases are present. Melanomas with deep invasion or that have spread to lymph nodes may be treated with immunotherapy, radiation therapy, and/or surgery and chemotherapy. Advanced cases of melanoma are treated with palliative surgery, immunotherapy, and/or chemotherapy, and sometimes radiation therapy.

Melanoma is more likely than other skin tumors to metastasize to other parts of the body. The 5-year relative survival rate for persons with melanoma is 91% and highest in disease that is localized at diagnosis. About 84% of melanomas are diagnosed at a localized stage. For localized melanoma, the 5-year survival rate is 98%. However, the 5-year survival rates for regional and distant stage diseases are 63% and 16%, respectively (Howlader, Noone et al. 2014).

Historically, chemotherapeutic regimens approved for use in melanoma produce responses in 10% to 20% of patients with Stage III or IV melanoma with no impact on the overall survival (OS) of these patients (approximately 7 months) (National Cancer Institute 2014). BRAF and MEK inhibitors have been approved for melanoma with an improvement in OS but have median duration of responses less than 1 year (Flaherty, Robert et al. 2012, Sosman, Kim et al. 2012). Signal transduction inhibitors alone and in combination have shown improvements in response rates and OS compared to chemotherapy. A combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, led to an objective response rate (ORR) of 76% with a progression-free survival (PFS) of 9.4 months (Flaherty, Infante et al. 2012). Signal transduction inhibitors are promising but have the potential of selecting resistant tumor clones which will likely limit their ultimate effectiveness. Immunotherapy has the potential to overcome limitations of chemotherapy and possibly signal transduction inhibitors by disinhibiting the tumor immune response to all tumor clones.

Two monoclonal antibodies to programmed death receptor-1 (PD-1), pembrolizumab and nivolumab, have been approved by United States Food and Drug Administration (FDA) for

treatment of metastatic melanoma (Bristol-Myers Squibb Company 2014, Merck & Co. 2015). Pembrolizumab is approved for the treatment of patients with unresectable or metastatic melanoma, for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express programmed death-ligand 1 (PD-L1) as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy, and for patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. In a randomized open-label study, 834 patients with ipilimumab-naive metastatic melanoma were randomized to 1 of 2 doses of pembrolizumab or to ipilimumab (Merck & Co. 2015). Pembrolizumab at 10 mg/kg either every 3 weeks (Q3W) or every 2 weeks (Q2W) demonstrated a statistically significant improvement in both OS and PFS compared to ipilimumab. OS hazard ratios were 0.69 (Q3W), 0.63 (Q2W), both compared to ipilimumab. Median PFS was 4.1 months (Q3W), 5.5 months (Q2W), and 2.8 months (ipilimumab). ORR was 33% (Q3W), 34% (Q2W) and 12% (ipilimumab). In a second trial of 540 patients with metastatic melanoma who had failed prior ipilimumab treatment, patients were randomized to pembrolizumab 2 mg/kg or 10 mg/kg given Q3W or to the investigator's choice of chemotherapy. Both cohorts of pembrolizumab demonstrated a statistically significant improvement in PFS but no statistical difference in the interim OS analysis when compared to the control arm. Median PFS was 2.9 months in both pembrolizumab arms compared to 2.7 months in the chemotherapy control arm (hazard ratio 0.57 [2 mg/kg] and 0.50 [10 mg/kg] compared to control). ORR was 21%, 25%, and 4% for the 2 mg/kg, 10 mg/kg, and control arm, respectively. Nivolumab was studied as a single agent compared to dacarbazine in a randomized double-blind study of 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma (Bristol-Myers Squibb Company 2014). Nivolumab demonstrated a statistically significant improvement in both median OS (not reached versus 10.8 months, hazard ratio [HR] = 0.42, $P < 0.0001$) and PFS (5.1 vs 2.2 months, HR = 0.43, $P < 0.0001$). The ORR was 34% for nivolumab versus 9% for dacarbazine. In a second randomized double-blind trial of 945 patients with previously untreated, unresectable or metastatic melanoma, patients were randomized to nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone. Nivolumab, as a single agent or in combination with ipilimumab, demonstrated a statistically significant improvement in PFS compared to ipilimumab alone. Median PFS was 11.5 months (combination), 6.9 months (nivolumab alone), and 2.9 months (ipilimumab alone). Compared to ipilimumab alone, PFS HRs were 0.42 for the drug combination ($P < 0.0001$) and 0.57 for nivolumab alone ($P < 0.0001$). ORR was 50% (combination), 40% (nivolumab alone), and 14% (ipilimumab alone).

There remains an unmet need to improve disease control and OS for patients with metastatic melanoma, both frontline and following progression from ipilimumab, or 1 of the approved anti-programmed death receptor-1/ligand 1 (anti-PD-1/L1) agents.

2.1.2 Head and Neck Squamous Cell Carcinoma

Head and neck cancer is the sixth most common cancer worldwide, with the predominant histology involving head and neck squamous cell carcinoma (HNSCC) (Vermorken and Specenier 2010). In the US, HNSCC accounts for 3% of cancers diagnosed annually and 2% of cancer-related deaths. The 2016 estimates for number of new cases and anticipated deaths in the US are approximately 62,000 and 13,000, respectively (American Cancer Society 2016). The majority of patients with HNSCC initially present with advanced stage disease (stage III-IV), requiring site-specific multimodal therapy (Vermorken and Specenier 2010). For patients who develop recurrent or metastatic disease that is not amenable to curative intent treatment, cancer-related morbidity is high and survival is dismal (Hoffman 2016). Historically, the most active standard cytotoxic regimens have been platinum-based and associated with response rates of up to 30%, with a median OS expectancy of 6 to 9 months. At present, targeted therapy added to cytotoxic chemotherapy results in median survival of approximately 8 months, underscoring the lack of durable efficacy among the most active regimens for patients with recurrent or metastatic HNSCC, and the urgent need to develop novel therapeutic options which prolong survival while optimizing quality of life (Vermorken and Specenier 2010). Nivolumab was compared to chemotherapy in 240 patients with recurrent or metastatic HNSCC that progressed within 6 months of platinum-based chemotherapy. Nivolumab demonstrated a statistically significant survival advantage (7.5 months versus 5.1 months, HR=0.70; 95% CI, 0.51- 0.96; $P = 0.10$). The ORR was 11.7% for nivolumab versus 7.4% for chemotherapy, and the radiographic PFS was 2.0 months for nivolumab versus 2.4 months for chemotherapy (Hoffman 2016). Single agent pembrolizumab was reported to have an 18.2% ORR in a Phase 1b study of 132 patients with advanced squamous cell carcinoma of the head and neck (Seiwert, Haddad et al. 2015).

There is a large unmet need to improve upon clinical results with anti-PD-1/L1 single agent activity in HNSCC.

2.2 Oligodeoxynucleotides With CpG Motifs in Cancer Immunotherapy

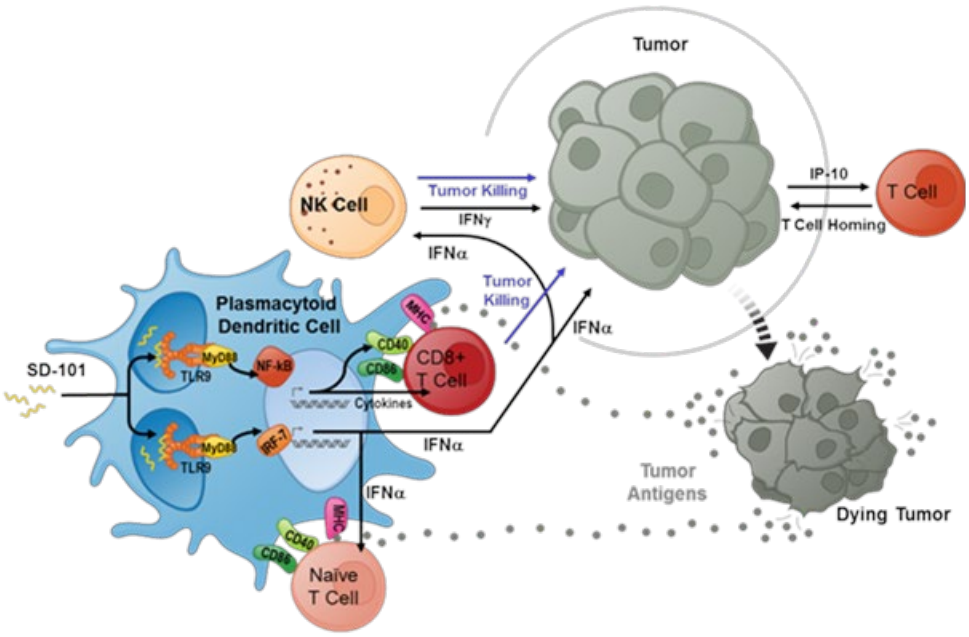
Bacterial deoxyribonucleic acid (DNA) has long been recognized as having potent stimulatory effects on the immune system, including stimulating rejection of transplantable tumors in mice (Yamamoto, Kuramoto et al. 1988). This activity is mediated preferentially by specific DNA motifs containing a cytosine phosphoguanosine (CpG) dinucleotide and can be replicated by short synthetic oligodeoxynucleotides (ODN) (Kuramoto, Yano et al. 1992, Tokunaga, Yano et al. 1992, Roman, Martin-Orozco et al. 1997). CpG-ODNs stimulate specific immune cell types by activation of the innate recognition receptor, Toll-like receptor 9 (TLR9) (Krieg 2006), and have no activity in mice with a homozygous deletion of the TLR9 gene (Campbell, Cho et al. 2009).

Based on studies with cultured human peripheral blood mononuclear cells (PBMCs), CpG-ODNs can stimulate interferon (IFN)-alpha (IFN-α) and interleukin-12 production as well as functional maturation of plasmacytoid dendritic cells (pDCs) (Duramad, Fearon et al. 2005) and can induce proliferation and immunoglobulin production in human B-cells (Krieg, Yi et al. 1995). Signaling by CpG-ODNs through TLR9 requires active uptake of the ODN as TLR9 is present only in specific intracellular compartments (Krieg 2002). TLR9 signaling occurs in 2 distinct intracellular structures, early and late endosomes (Honda, Ohba et al. 2005, Guiducci, Ott et al. 2006), leading to different outcomes. In pDCs, TLR9 signaling in the early endosome leads to induction of type I IFNs, especially IFN-α, whereas signaling in late endosomes results in differentiation of pDCs to potent antigen-presenting cells. Differences in sequence and structure lead to different localization to these 2 intracellular compartments, allowing selection of CpG-ODNs that stimulate low or high levels of type I IFNs (termed CpG-B and CpG-C class ODN, respectively). SD-101 belongs to the CpG-C class of CpG-ODN and was optimized to stimulate very high levels of IFN-α as well as inducing maturation of pDCs to antigen-presenting cells. Results from a Phase 1 trial in healthy normal volunteers (DV3-HNV-01) demonstrated that subcutaneous administration of SD-101 generates a response characterized by a dose-dependent upregulation of type I IFN regulated genes detectable in PBMCs.

In a number of different animal models, intratumoral injection of CpG-ODNs has proven significantly more effective for tumor killing and generation of anti-tumor immunity than systemic administration (Kawarada, Ganss et al. 2001, Lou, Liu et al. 2011). The rationale is that intratumoral delivery of CpG enhances the antigen presenting property of infiltrating dendritic cells promoting cross-presentation of tumor associated antigens and increased natural killer (NK) cell cytotoxic activity against the tumor (Sparwasser, Vabulas et al. 2000, Bauer, Redecke et al. 2001, Marabelle, Kohrt et al. 2014). The net result is activation of both innate and adaptive anti-tumor responses (Figure 2-1). Dynavax has demonstrated in mouse tumor models that SD-101 given intratumorally as a single agent is able to promote an IFN response, infiltration of T cells, and durable tumor control.

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

Figure 2-1: SD-101 Cellular Mechanism of Action



Source: Dynavax internal presentation.
IFN = interferon; MHC = major histocompatibility complex; MyD = Myeloid differentiation; NK = natural killer; pDCs = plasmacytoid dendritic cells; TLR = Toll-like receptor.
Both innate and adaptive immune responses are increased by intratumoral injection of SD-101. SD-101 induces pDCs to secrete high levels of IFN-α, a potent immunomodulatory cytokine able to boost NK-cell cytotoxic activity and induce recruitment of T cells. In addition SD-101 induces pDC maturation and the ability to cross-present tumor associated antigens, promoting a $CD8^+$ T-cell response.

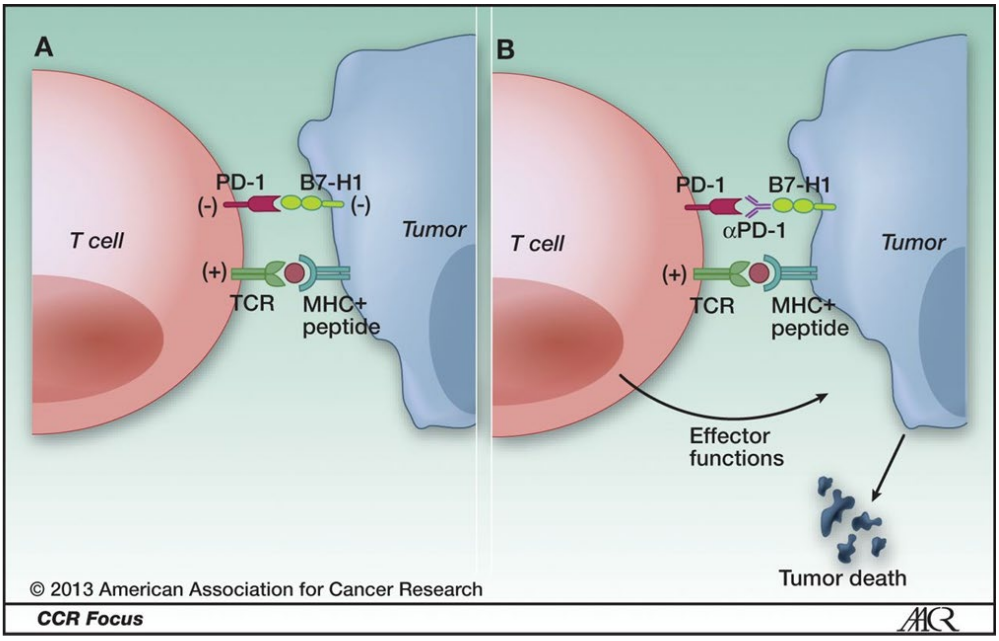
Clinical studies combining radiation therapy which causes tumor cell death and intratumoral CpG-ODN administration have shown efficacy in patients with indolent B-cell lymphomas (Brody, Ai et al. 2010) and cutaneous T-cell lymphoma (Kim, Gratzinger et al. 2012). Regression of non-injected tumor sites in a subset of patients provided clear evidence for generation of systemic anti-tumor immunity in each of these studies. These 2 studies, as well as other published trials of CpG-ODN treatment in cancer patients, were done with CpG-ODNs belonging to the CpG-B class, which induces significantly lower levels of type I IFNs in humans than does SD-101, a CpG-C class ODN.

2.3 PD-1 Blockade With Anti-PD-1 Antibody

The PD-1/ PD-L1 pathway has been shown to be an important pathway inhibiting cytotoxic activity of tumor-infiltrating T cells. PD-L1 (also known as B7-H1) is the counter-receptor of PD-1 (Sznol and Chen 2013). The PD-1 receptor is predominantly expressed on activated T- and B- lymphocytes and downregulates T-cell activation that occurs with recognition by the T-cell receptor of tumor antigens expressed in the context of the major histocompatibility complex (MHC) on tumor cells. High PD-1 expression on antigen-specific T cells, as a consequence of chronic antigenic stimulation in the tumor microenvironment, is thought to be a marker of T-cell exhaustion. PD-L1 expression has been found on tumor cells in a variety of tumors and on myeloid cells infiltrating the tumor and it is a mechanism by which tumors and infiltrating cells can directly engage PD-1 on T cells to evade an effective anti-tumor immune response (Sznol and Chen 2013).

Blockade of PD-1/PD-L1 pathway with antibodies against PD-1 or PD-L1 restore the function of tumor-infiltrating $CD8^+$ and $CD4^+$ T cells in mouse tumor studies (Figure 2-2:) (Sznol and Chen 2013). These data supported clinical development of human antibodies blocking either PD-1 or PD-L1. Two of these agents, pembrolizumab and nivolumab, monoclonal antibodies directed against PD-1, were recently approved for treatment of metastatic melanoma (Webster 2014).

Figure 2-2: Blocking PD-1/PD-L1 Pathway Mechanism of Action



Sznol M , and Chen L Clin Cancer Res 2013;19:1021-1034

Anti-PD-1 = anti-programmed death receptor-1; B7-H1 = B7 – homolog 1; MHC = major histocompatibility complex; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; TCR = T-cell receptor.
A: Ligation of T-cell PD-1 by tumor PD-L1 (B7-H1 in the figure) results in the downregulation of T-cell effector functions that destroy tumor cells.
B: Blockade of this pathway by anti-PD-1 antibodies prevents this downregulation, and allows T cells to maintain their anti-tumor functionality and ability to mediate tumor cell death.

2.4 Combined Anti-PD-1 Therapy and Intratumoral CpG-ODN Treatment of Melanoma

Although anti-PD-1 therapy has shown high rates of durable response in metastatic melanoma patients, only a subset of patients are currently benefiting from monotherapy as many fail to respond or eventually relapse after an initial response (Bristol-Myers Squibb Company 2014, Merck & Co. 2015).

The identification and characterization of factors in the tumor microenvironment at baseline that predict response to anti-PD-1 therapy are currently a priority for the cancer immunotherapy field (Ribas and Tumeh 2014). Recent new studies have found that response to anti-PD-1 therapy is contingent on the presence of infiltrating T cells in the tumor and patients with poor T-cell infiltration at baseline fail to respond to treatment (Tumeh, Harview et al. 2014). This finding is consistent with retrospective studies in selected tumor types, including melanoma, demonstrating a strong association between T-cell content in the tumor and OS (Angell and Galon 2013). In

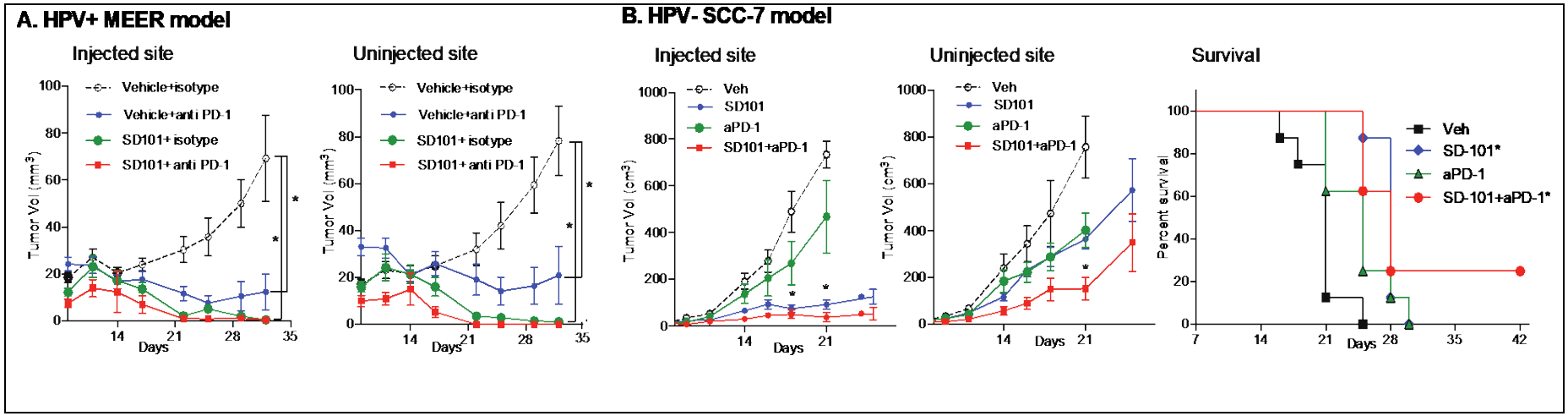
addition, the degree of T-cell infiltration in melanoma is associated with the presence of a type I IFN signature, suggesting that in absence of type I IFN (Bald, Landsberg et al. 2014), the tumor is unable to sustain an immune rich environment which is necessary for the response to anti-PD-1/L1 targeting agents. Therefore, there is a strong rationale for combination therapies that increase type I IFN in the tumor microenvironment and promote T-cell infiltration.

Intratumoral injection of SD-101 is expected to augment the response to anti-PD-1 antibodies by inducing type I IFN and promoting T-cell infiltration and activation at the tumor sites (see the Investigator's Brochure). This hypothesis is supported by the nonclinical data in mouse models of carcinoma (CT26) in which tumors that do not respond to anti-PD-1 therapy fail to upregulate IFN genes and have very low amounts of infiltrating T cells (data on file) consistent with findings in humans as discussed above (Tumeh, Harview et al. 2014). In this CT26 model of transplantable colon carcinoma with PD-1 blockade, this lack of a permissive environment was shown to be modified by addition of intratumoral SD-101 which leads to a conspicuous infiltration of activated T cells that correlates to tumor rejection. In this model the combination of anti-PD-1 antibody and SD-101 has been shown to be far superior in inducing tumor rejection than the single agents alone (see the Investigator's Brochure). In addition, initiating dosing with an anti-PD-1 for 7 days prior to SD-101 led to a more consistent and durable tumor response than when the anti-PD-1 and SD-101 were initially dosed on the same day (data on file).

2.5 SD-101 Alone and in Combination With Anti-PD-1 in Head and Neck Squamous Cell Carcinoma Preclinical Models

Active research for anti-PD-1/L1 therapy and combinations with other immunologic agents are ongoing in clinical studies in multiple tumor types including HNSCC. The preclinical rationale for combining SD-101 and pembrolizumab is based on data with a mouse HNSCC tumor model. Murine (human papillomavirus [HPV]-positive murine tonsil epithelial cells) MEER or HPV-negative murine HNSCC cells (SCC-7) bearing mice were intratumorally treated with SD-101 alone or in combination with anti-PD-1 mAb. When SD-101 was used as a single agent injected intratumorally, it significantly suppressed the growth of tumors at the injected site in both models. In addition, SD-101 suppressed tumor growth at the distant (non-injected) site in the HPV+ MEER model (Figure 2-3 **A**). In the HPV− SCC-7 model, combining SD-101 therapy with anti-PD-1 treatment significantly enhanced the suppression by SD-101 single agent treatment at the distal tumor and improved survival (Figure 2-3 **B**). These anti-tumor effects of SD-101 were accompanied by an increase in IL-12 and type 1 IFN. In summary, SD-101 alone is effective at reducing tumor growth in both HPV+ and HPV− murine HNSCC models and SD-101 further enhances the efficacy of PD-1 blockade (data on file).

Figure 2-3: Intratumoral SD-101 Reduced Tumor Growth in Murine Models of HPV-Positive (A) and Negative (B) Head and Neck Squamous Cell Carcinoma



ANOVA = analysis of variance; aPD-1 = anti- programmed death receptor-1; HNSCC = head and neck squamous cell carcinoma; HPV = human papillomavirus; PD-1 = programmed death receptor-1; SCC-7 = squamous cell carcinoma-7.
(A) HPV-positive murine tonsil epithelial cells (MEER cells) were subcutaneously implanted in C57BL/6 mice (both flanks). The tumor bearing mice were treated with SD-101 (50 µg per site, Days 12, 15, 18, and 22), or in combination with anti-PD-1 monoclonal Ab (aPD-1, 250 µg, Days 11, 14, 17, and 21).
(B) HPV-negative murine HNSCC cells (SCC-7) were subcutaneously implanted in C3H mice (both flanks). The tumor bearing mice were treated with SD-101 (50 µg, Days 7, 11, 14, 18, and 21) or in combination with anti-PD-1 monoclonal Ab (aPD-1, 250 µg, Days 4, 6, 10, 13, 17, and 20). Tumor growth and survival of the mice were monitored. Significance of survival was analyzed by two-way ANOVA.
*$P < 0.05$ (tumor volumes) and $P < 0.0125$ (survival) versus vehicle treated mice.

2.6 Clinical Experience With SD-101

In the phase 1, single-blind, dose-escalation trial of systemic SD-101 in 20 healthy normal male volunteers, aged 18 years and over (DV3-HNV-01), adverse events (AEs) included flu-like symptoms such as headache, chills, fatigue, and pyrexia, as well as injection-site reactions such as erythema, induration and pain. Dose-limiting toxicities (DLTs) of severe headache, injection-site induration, and neck pain were observed in 1 subject given 5.0 mg of SD-101, resulting in a halt in Dose Escalation and accrual. Transient lymphopenia was the most common laboratory abnormality observed. There was no evidence of complement activation, coagulation abnormalities, or auto-antibody development.

In the phase 1 single-blind, dose-escalation trial of systemic SD-101 in 28 men and women, aged 18 to 55 years, with chronic hepatitis C virus (HCV) infection, SD-101 was administered alone or in combination with ribavirin (DV3-HCV-01). Including doses up to 5.0 mg of SD-101, the majority of AEs were injection-site reactions (erythema, swelling, pain, and pruritus), influenza-like illness, pyrexia, and myalgia. Most AEs were mild or moderate in reported severity. One subject in the 0.1 mg SD-101/ribavirin group experienced a serious adverse event (SAE) of hyperthyroidism that the investigator considered probably related to SD-101 and unrelated to ribavirin. No deaths occurred during the trial.

A phase 1/2 trial of SD-101 in combination with low-dose radiation therapy for untreated low-grade B-cell lymphoma is completed (DV3-LYM-01). A total of 13 patients were dosed in Phase 1 Dose Escalation (4 cohorts comprising 3 patients at each of SD-101 intratumoral doses of 1.0 mg, 2.0 mg, and 4.0 mg, and 4 patients at the 8.0 mg dose). A total of 16 patients were dosed in Dose Expansion (2 cohorts comprising of 7 patients at the 1.0 mg and 9 patients at the 8.0 mg dose levels). SD-101 was well tolerated. Treatment emergent adverse events consisted mainly of Grade 1 to 2 flu like symptoms or local site reactions, with a trend toward more frequent Grade 3 events at the highest tested dose of 8 mg. Intratumoral SD-101 in combination with low-dose radiation resulted in regression of both treated and untreated sites of disease (systemic or abscopal responses) in subjects with previously untreated indolent B-cell lymphoma.

A phase 1 clinical trial of SD-101 in lymphoma patients who had relapsed after allogeneic marrow cell transplantation (IND #111985) was conducted. In this trial, 3 patients received 3 weekly intratumoral doses of SD-101 0.3 mg, and 3 patients received 3 weekly intratumoral doses of SD-101 1.0 mg. Several patients have shown objective abscopal tumor responses. There were no treatment-related severe AEs, and study treatment was generally well tolerated, as noted by the investigator. One unrelated SAE of *Klebsiella* bacteremia was reported in a patient 55 days after the first SD-101 injection (1.0 mg) and 41 days after the third and final injection which resolved. The study is closed.

A Phase 1/2 investigator-sponsored trial (Principal Investigator: Dr. Ronald Levy of Stanford University Medical Center) of SD-101 in combination with local radiation therapy for low-grade B-cell lymphoma patients was conducted and 7 patients were enrolled and treated, and the study is now closed. One SAE of death was reported in a patient who had progressive disease and was subsequently treated with gemcitabine, dexamethasone, carboplatin, and obinutuzumab. The SAE was assessed by the investigator as related to the subsequent cytotoxic chemotherapy and not to study treatment.

In this Phase 1b/2 DV3-MEL-01 (SYNERGY-001) study, Phase 1 Dose Escalation is designed to identify an optimal dose of SD-101 (RP2D) given in combination with pembrolizumab to be evaluated in Phase 2. The selected RP2D going into the Phase 2 Dose Expansion was based on an evaluation of the early available data from Phase 1 Dose Escalation Cohorts (1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg) where SD-101 was injected into a single target lesion. Data review included an evaluation of SD-101 target engagement assessed by IFN activity and effect on immune cells, clinical safety data, and preliminary efficacy data for patients who were anti-PD-1 treatment naïve (n = 9) or experienced with progressive disease (n = 13). Observations included:

1) SD-101 engaged its target, TLR9, as demonstrated by the dose dependent induction of IFN-responsive genes (pharmacodynamic) systemically and in the tumor microenvironment.

2) Nanostring data showed that SD-101 was able to generate an increase in immune cell types in the tumor microenvironment. These increases were generally not dose-dependent.

3) Objective responses were observed at SD-101 dose range of 1.0 mg – 8.0 mg in anti-PD-1/L1 inhibitor naïve patients, with tumor shrinkage at the injected and non-injected lesions.

4) A single patient responded and durable stable disease was seen at the 8.0 mg dose in anti-PD-1/L1 inhibitor experienced patients.

5) There were no DLTs.

6) SD-101 administered intratumorally in combination with IV pembrolizumab demonstrated no worsening of the expected toxicities of each of the individual monotherapies. The most common (≥ 20%) treatment-related AEs were transient low-grade fatigue, myalgia, headache, chills and injection site reactions. Grade ≥ 3 treatment-related AEs were observed in 59.1% patients (most common: myalgia 13.6% and injection site pain 13.6%). Immune- related AEs occurred in 2 patients (2/22 or 9%).

One had a Grade 2 pneumonitis on Day 23 resulting in drug withdrawal and the other had hypophysitis (85 days after last treatment).

Based on preliminary review of the data, the efficacy of 2.0 mg per lesion was higher than 8.0 mg in one lesion in patients who are naïve to anti-PD-1/L1 and the RP2D was updated to 2.0 mg in 1 to 4 lesions and/or regions. The study with the new dosing of 2 mg per injection is ongoing also in patients who are resistant/refractory to anti-PD1/PD-L1 therapy.

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

2.7 About Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure/approved labeling for detailed background information on pembrolizumab.

2.8 Trial Rationale and Doses to be Evaluated

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 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 (Hervas-Stubbs, Perez-Gracia et al. 2011).

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

The starting dose of SD-101 (2.0 mg intratumorally) was chosen based on safety data from the DV3-LYM-01 study and in consideration that the safety profile of SD-101 given together with pembrolizumab is unknown. A lower dose of SD-101 1.0 mg was added in Amendment 4 of this protocol to determine optimal dosing and not because of a safety concern. With Amendment 5, 8.0 mg was selected as the RP2D and another RP2D of 2.0 mg was selected for testing in Amendment 6. The rationale for modifying the SD-101 dose to 2.0 mg/lesion is based on preliminary internal data which suggest that overall objective response could potentially double when dosing at 2.0 mg as compared with 8.0 mg per lesion. Furthermore, increasing the number of tumor lesions for injection may enhance priming of neoantigen-specific anti-tumor T-cells to address potential tumor heterogeneity at different tumor locations. Selection of a 2.0 mg per injection permits injection in up to 4 lesions/regions to reach a maximum of 8.0 mg dose per subject, the highest total dose cleared based on Phase 1b.

Based on the preliminary results for PD-1/PD-L1 naive patients in the ongoing Phase 1b/2 DV3-MEL-01 (SYNERGY-001) study, the number of patients who are resistant/refractory to anti-PD1/PD-L1 therapy was expanded in Amendment 8 to further evaluate 2.0 mg-dosing of SD-101.

The dose of pembrolizumab chosen for this study (200 mg Q3W) is the dose currently recommended in both monotherapy and combination studies with pembrolizumab.

3.0 TRIAL OBJECTIVES

NOTE: As of Amendment 9, Phase 1 of the trial is complete. For Phase 2, the trial will stop collecting efficacy endpoints and exploratory objectives will not be pursued.

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
- To determine an 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)
  - Treatment response of the non-injected lesion(s) (systemic response)
  - Treatment response of all lesions
  - Time to response
- To assess changes in tumor biomarkers

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
- 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

4.0 INVESTIGATIONAL PLAN

4.1 Trial Design

NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected.

This is a phase 1b/2, open-label, multicenter trial designed to evaluate the safety, tolerability, biologic activity, and preliminary efficacy of intratumoral SD-101 injections in combination with intravenous pembrolizumab in patients with metastatic melanoma or recurrent or metastatic HNSCC.

This study will be conducted in 2 phases. Phase 1 evaluates SD-101 given in combination with pembrolizumab in melanoma populations (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease) in up to 4 Dose Escalation cohorts to identify an RP2D to be evaluated in Phase 2. Phase 2 includes up to 4 Dose Expansion cohorts in patients with melanoma (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease) and up to 4 Dose Expansion cohorts of patients with HNSCC (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease). Two RP2Ds were selected to be evaluated in the Dose Expansion phase.

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 naïve
4) Expansion Cohort 4 of approximately 25 HNSCC anti-PD-1/L1 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

Figure 4-1 presents the study design for Phase 1 and Phase 2 at Amendment 9.

Figure 4-1: DV3-MEL-01 Study Design Schema at Amendment 9 – Phase 1 and Phase 2

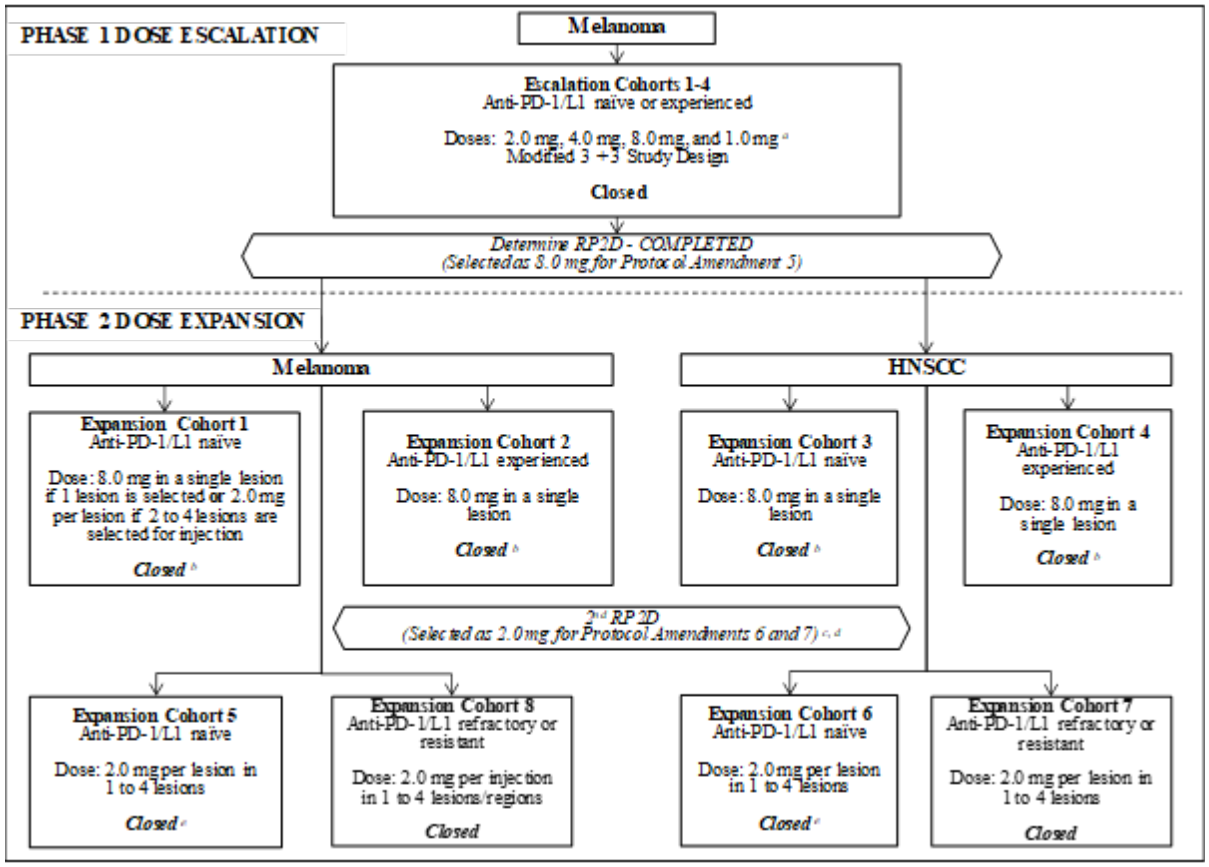


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Figure 4-1 Footnotes

Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1; HNSCC = head and neck squamous cell carcinoma; RP2D = recommended Phase 2 dose.

[a] 1.0 mg of SD-101 was added at Amendment 4

[b] At Protocol Amendment 5, enrollment in Dose Escalation Cohorts 1-4 was CLOSED. Based on available data (including efficacy, safety, and pharmacodynamics biomarkers), the sponsor selected 8.0 mg in a single injectable lesion if 1 lesion is selected or 2.0 mg per lesion if 2 to 4 lesions are selected for injection as the RP2D to be evaluated in the Dose Expansion phase.

[c] At Protocol Amendment 6 and based on available data (including efficacy, safety, and pharmacodynamics biomarkers), the sponsor selected a second Phase 2 dose of 2.0 mg per lesion in 1 to 4 injectable lesions to be evaluated in the Dose Expansion phase. Expansion Cohorts 1, 2, 3, and 4 in which patients were treated with 8.0 mg in a single injectable lesion were CLOSED to further enrollment. Cohort 5 (melanoma anti-PD-1/L1 –naïve), Cohort 6 (HNSCC anti-PD-1/L1 –naïve), and Cohort 7 (HNSCC anti-PD-1/L1 –refractory or resistant) were ADDED with patients receiving 2.0 mg per lesion in 1 to 4 injectable lesion(s).

[d] At Protocol Amendment 7 and based on available data (including efficacy, safety, and pharmacodynamics biomarkers), Cohort 8 (melanoma anti-PD-1/L1–refractory or resistant) was ADDED with patients receiving 2.0 mg per injection in 1 to 4 injectable lesions/regions.

[e] For Protocol Amendment 9 and based on available data from the ongoing trial (including efficacy, safety, and pharmacodynamics biomarkers), Cohorts 5 and 6 were CLOSED. Additionally, Cohort 8 (melanoma anti-PD-1/L1–refractory or resistant) was expanded to approximately 50 patients.

Note: For Protocol Amendment 9, enrollment is closed for all cohorts. Enrolled patients should continue to receive their assigned trial treatments as per the protocol.

The status of cohorts for this DV3-MEL-01 protocol at Amendment 9 is in Table 4-1.

Table 4-1: Status of Cohorts for DV3-MEL-01 Protocol at Amendment 9

Cohort	Anti-PD-1 /L1 Treatment Status	Orig	A 1	A 2	A 3	A 4	A 5	A 6	A 7	A 8	A9
Ph 1 Mel – 1	Naïve or experienced	X	X	X	X	X	Closed	Closed	Closed	Closed	Complete
Ph 1 Mel – 2	Naïve or experienced	X	X	X	X	X	Closed	Closed	Closed	Closed	Complete
Ph 1 Mel – 3	Naïve or experienced	X	X	X	X	X	Closed	Closed	Closed	Closed	Complete
Ph 1 Mel – 4	Naïve or experienced	-	-	-	-	X	Closed	Closed	Closed	Closed	Complete
Ph 2 Mel – 1	Naive	-	-	X	X	X	X	Closed	Closed	Closed	Closed
Ph 2 Mel – 2	Experienced	-	-	X	X	X	X	Closed	Closed	Closed	Closed
Ph 2 Mel – 5	Naive	-	-	-	-	-	-	X	X	Closed	Closed
Ph 2 Mel – 8	Refractory or resistant	-	-	-	-	-	-	-	X	X	Closed
Ph 2 HNSCC – 3	Naive	-	-	-	-	X	X	Closed	Closed	Closed	Closed
Ph 2 HNSCC – 4	Experienced	-	-	-	-	X	X	Closed	Closed	Closed	Closed
Ph 2 HNSCC – 6	Naive	-	-	-	-	-	-	X	X	Closed	Closed
Ph 2 HNSCC – 7	Refractory or resistant	-	-	-	-	-	-	X	X	X	Closed

A = Amendment; Closed = Closed to enrollment; Complete = last patient last visit (LPLV) has been reached for all patients; HNSCC = head and neck squamous cell carcinoma; Mel = melanoma; Orig = original; Ph = phase; X = Open for enrollment.

4.1.1 Phase 1 Dose Escalation: Melanoma (*COMPLETE)*

The Phase 1 will consist of up to 4 Dose Escalation cohorts to evaluate the safety and tolerability of SD-101 given in combination with pembrolizumab in melanoma populations (anti-PD-1/L1 naïve and anti-PD-1/L1 experienced with progressive disease) to identify an RP2D to be evaluated in Phase 2.

Phase 1 employs a modified 3 + 3 study design, evaluating escalating or intermediate dose levels of SD-101 (given with a fixed dose of pembrolizumab) in patients with metastatic melanoma. Cohorts of 3 to 6 patients will be enrolled at each dose level, and each patient will participate in only 1 cohort. Patients at each dose level will be treated and observed for dose-limiting toxicities (DLTs) through the DLT assessment period (Study Day 1-29). Once an RP2D is declared, an additional 6 patients may be enrolled to assess safety at this dose.

Patients in Escalation Cohorts 1-4 will be administered 2.0 mg, 4.0 mg, 8.0 mg, and 1.0 mg, respectively, of SD-101 in combination with 200 mg pembrolizumab Q3W per the Schedule of Trial Events.

The melanoma Dose Escalation cohorts, patient populations, and treatment assignments are outlined in Table 4-2.

Table 4-2: Phase 1 Melanoma Dose Escalation Cohorts (*COMPLETE)*

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	n	Dosing Schema[a]
1	Naïve or experienced	2.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A
2	Naïve or experienced	4.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A
3	Naïve or experienced	8.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A
4	Naïve or experienced	1.0 mg per lesion in 1 injectable lesion (Lesion A)	3 - 6	A[b]

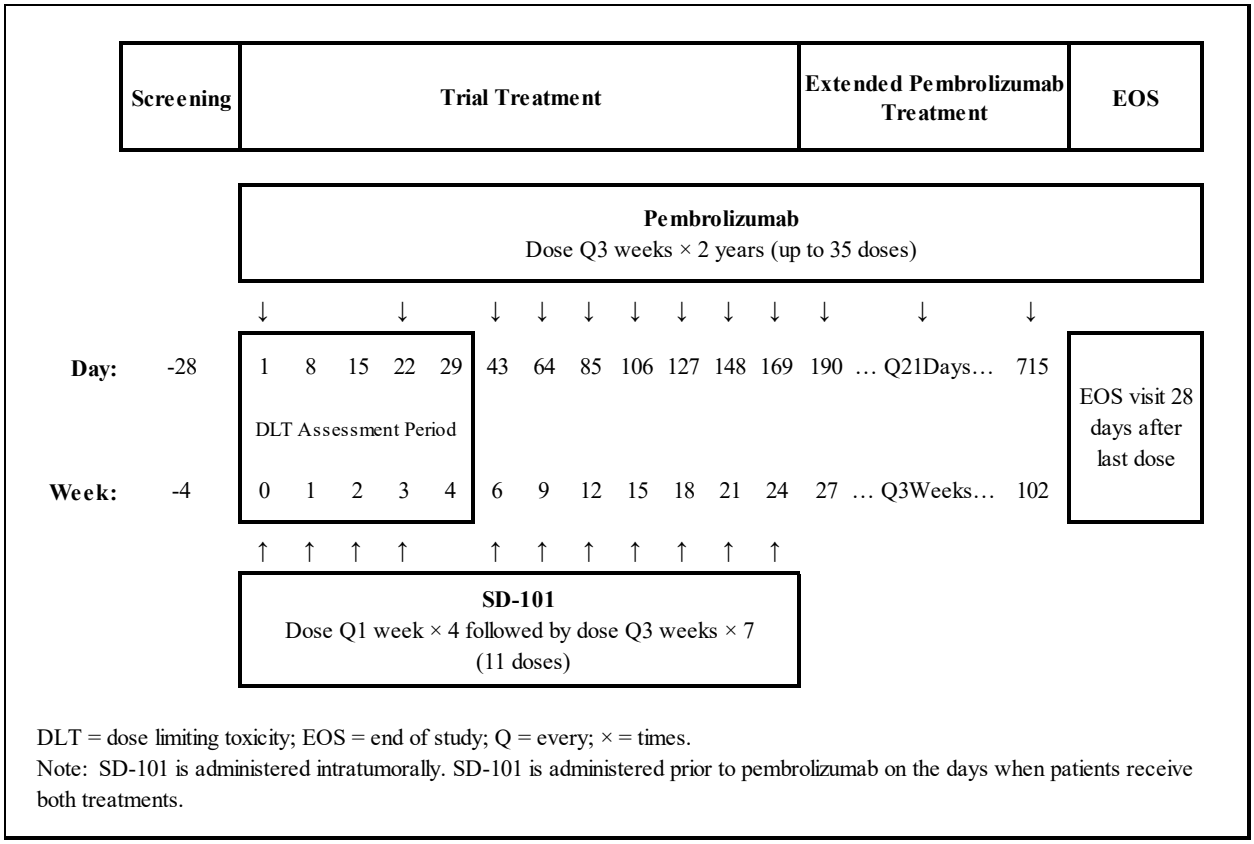
Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1.
[a] Dosing Schema:
A: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 1 course of SD-101 (4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses).
[b] 1.0 mg was added at Protocol Amendment 4.

4.1.1.1 Dosing Schedule (*COMPLETE)*

Phase 1 portion of this trial is a Dose Escalation of SD-101 with a fixed dose of pembrolizumab as depicted in Figure 4-2. SD-101 will be administered intratumorally as 4 weekly doses

followed by 1 dose Q3W for 7 additional doses. Pembrolizumab 200 mg will be administered intravenously Q3W starting on Day 1 for up to 35 treatments (approximately 2 years) or until disease progression. SD-101 will be administered before pembrolizumab on days when both drugs are scheduled to be used.

Figure 4-2: Trial Flow Diagram for Phase 1 Dose Escalation Cohorts 1 to 4 *(COMPLETE)*



DLT = dose limiting toxicity; EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

4.1.1.2 DLT Assessment *(COMPLETE)*

Cohorts of 3 to 6 patients will be enrolled at each dose level, and each patient will participate in only 1 cohort. Patients at each dose level will be treated and observed for DLT through the DLT assessment period (Study Day 1-29). In addition to use of a modified 3 + 3 Dose Escalation design to assess a maximum tolerated dose (MTD), Phase 1 implements a staggered enrollment for a cohort. Patients enrolled under staggered enrollment in Phase 1 are referred to as sentinel patients in the protocol. The starting dose of SD-101 will be 2.0 mg administered intratumorally and will be given to 1 sentinel patient. If the sentinel patient does not experience a DLT within

72 hours, the second patient in the cohort may be dosed. If no DLT is experienced in the second patient after 72 hours, the third patient (and up to 3 additional patients) may be dosed. If a DLT is experienced in the first sentinel patient within 72 hours of injection, a second sentinel patient may be dosed with SD-101 following a safety review by the Safety Review Team (comprised of the Dynavax Medical Monitor, Phase 1 coordinating investigator, and other key safety Dynavax personnel as described in the Cohort Safety Review Plan) and an evaluation of *safe to proceed*. If no DLT is observed after 72 hours in the second sentinel patient, the third and subsequent patients in the cohort may be enrolled.

If there is no DLT observed (Section 9.1) in the group of 3 or more patients, the next cohort will be enrolled, and escalation will proceed to the next highest dose with a sentinel patient receiving SD-101 at least 72 hours prior to dosing of subsequent patients.

If a DLT is observed in 1 patient in the first 3 patients enrolled in a cohort, enrollment will proceed and the cohort size will be increased up to 6 patients. If only 1 DLT is observed in 6 patients in a cohort, escalation will proceed, and the next cohort may begin enrollment.

A minimum of 3 patients will be enrolled in each Cohort. Dose escalation will proceed if no DLT is observed in all patients enrolled. If 1 DLT is observed in any cohort after 3 patients have been enrolled, the cohort size will be increased to 6 patients. The maximum allowed DLTs per cohort to allow subsequent Dose Escalation is 1 DLT observed in 6 patients. The sponsor may also choose to enroll up to 6 patients initially into a cohort. Dose escalation will proceed if no more than 1 DLT is observed in 6 patients.

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

If ≥ 2 of 6 patients experience a DLT in any cohort, Dose Escalation will cease and the previous lower dose of SD-101 may be designated the MTD. However, the sponsor may also decide to investigate an additional lower or intermediate dose cohort(s) than have already been tested. Patients will be enrolled and evaluated as described above for previous Dose Escalation cohorts except that staggered enrollment with a sentinel patient will not be required. Three to 6 patients will be enrolled at the intermediate or lower dose and DLT assessments performed, with expansion to 6 patients as required and applicable. A maximum of 0 DLTs in the first 3 patients or 1 DLT in the first 6 patients will define this dose as the MTD.

The planned dose cohorts for SD-101 are 2.0 mg, 4.0 mg, and 8.0 mg. Dose Escalation will continue until an MTD is determined or a maximum planned dose (ie, a total body dose of 8.0 mg) is reached. In addition, a 1.0 mg dose cohort, added in Amendment 4 of this protocol, will not require staggered enrollment with a sentinel patient as long as any higher dose cohort

has completed the DLT assessment period and met protocol criteria for Dose Escalation as described in this section. Decisions to escalate the dose of SD-101 to the next highest level will be based on review of safety data from the time of the first injection (Day 1) through Day 29 (the DLT assessment period). If 1 DLT in 6 patients or 2 Grade 2 AEs considered drug-related (except for malaise, headache, myalgia, fatigue, or chills) occur in 3 patients in a dose cohort, the Dose Escalation increment for the next dosing cohort will be decreased from 100% to 50%. Intra-patient Dose Escalation is not permitted.

The RP2D of SD-101 given in combination with pembrolizumab will be chosen based on all available data including efficacy, safety, and pharmacodynamic biomarkers (eg, IFN-inducible gene signature and tumor-infiltrating lymphocytes). The RP2D will not exceed the MTD.

Disease response and study treatment management for Dose Escalation will be assessed by the investigator based on RECIST v1.1 and immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) (ie, scans obtained at least 4 weeks later that qualify as PD per RECIST v1.1 [Appendix 6]). This assessment of disease response and progression is consistent with current pembrolizumab studies and is implemented due to observed *pseudoprogression* as well as late responses with immunotherapy. The protocol also allows patients who are clinically stable and have unconfirmed PD to continue on pembrolizumab and SD-101 per investigator decision. All patients who develop confirmed progressive disease must discontinue all study treatment unless requested by an investigator and approved by a Dynavax Medical Monitor. Patients who discontinue pembrolizumab must discontinue SD-101. Pembrolizumab may be continued as a single agent if SD-101 is discontinued per investigator decision as described in Section 9.2.

4.1.2 Phase 2 Dose Expansion – Cohorts *(CLOSED)*

NOTE: As of Amendment 9, enrollment in Phase 2 of the trial is closed. Enrolled patients should continue receiving their assigned treatment per protocol.

4.1.2.1 Melanoma Cohorts

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.

For metastatic melanoma, planned enrollment is approximately 60 patients in Expansion Cohort 1 and approximately 25 each in Expansion Cohort 2 and Cohort 5, and approximately 50 in Cohort 8. Patients in Cohort 2 will have had disease progression on anti-PD-1/L1 therapy, those in Cohort 8 will have had refractory or resistant response to anti-PD-1/L1 therapy, and patients in Cohorts 1 and 5 will be naïve to anti-PD-1/L1 therapy.

The melanoma expansion cohorts, patient populations, and treatment assignments are outlined in Table 4-3.

Table 4-3: Phase 2 Melanoma Dose Expansion Cohorts *(CLOSED)*

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	n	Dosing Schema[a]
1	Naïve	8.0 mg in a single injectable lesion if 1 lesion is selected (Lesion A) **or** 2.0 mg per lesion if 2 to 4 lesions are selected for injection (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 60	B
2	Experienced[b]	8.0 mg in a single injectable lesion (Lesion A)	Approximately 25	A
5	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 25	A1
8	Refractory or resistant[c]	2.0 mg in 1 ml per injection in 1 to 4 separate lesions for lesions measuring up to 5 cm in the longest diameter; or for lesions larger than 5 cm, 2.0 mg in 1 ml per injection in 1 to 4 separate regions where the injections are ≥ 5 cm apart (maximum total dose is 8.0 mg)	Approximately 50	A1

Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1.

[a] Dosing Schema:
A: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
B: SD-101 dosing starts on Day 22 at the second dose of pembrolizumab and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
A1: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 1 course of SD-101 (4 weekly then every 3 weeks on schedule with pembrolizumab up to Week 51)

[b] Received prior treatment regimen containing an anti-PD-1/L1 drug.

[c] Received at least 2 doses of an anti-PD-1/L1 therapy and experienced PD within 3 months after last dose of anti-PD-1/L1 therapy. Anti-PD-1/L1 refractory or resistant patients must have documented PD per RECIST v.1.1, which has been confirmed by a second scan at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.

4.1.2.2 HNSCC Cohorts

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.

In Phase 2 HNSCC, approximately 25 anti-PD-1/L1 naïve patients in each of Expansion Cohorts 3 and 6, and approximately 25 patients who have disease progression on anti-PD-1/L1 therapy in each of Expansion Cohorts 4 and 7 will be enrolled.

The HNSCC Dose Expansion cohorts, patient populations, and treatment assignments are outlined in Table 4-4.

Table 4-4: Phase 2 HNSCC Dose Expansion *(CLOSED)*

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	n	Dosing Schema[a]
3	Naïve	8.0 mg in a single injectable lesion (Lesion A)[b]	Approximately 25	B
4	Experienced[c]	8.0 mg in a single injectable lesion (Lesion A)[b]	Approximately 25	A
6	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 25	A1
7	Refractory or resistant[d]	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	Approximately 25	A1

Anti-PD-1/L1 = anti-programmed death receptor-1/ligand 1.

[a] Dosing Schema:
A: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
B: SD-101 dosing starts on Day 22 at the second dose of pembrolizumab and patients receive 2 courses of SD-101 (each course, separated by 9 weeks, is 4 weekly doses and then every 3 weeks on schedule with pembrolizumab for 7 additional doses)
A1: SD-101 and pembrolizumab dosing both start on Day 1 and patients receive 1 course of SD-101 (4 weekly then every 3 weeks on schedule with pembrolizumab up to Week 51)

[b] Patients will receive 8.0 mg per lesion in 1 lesion with the option of injecting into up to 4 regions within the lesion in approximate equally divided volumes of an 8.0 mg dose.

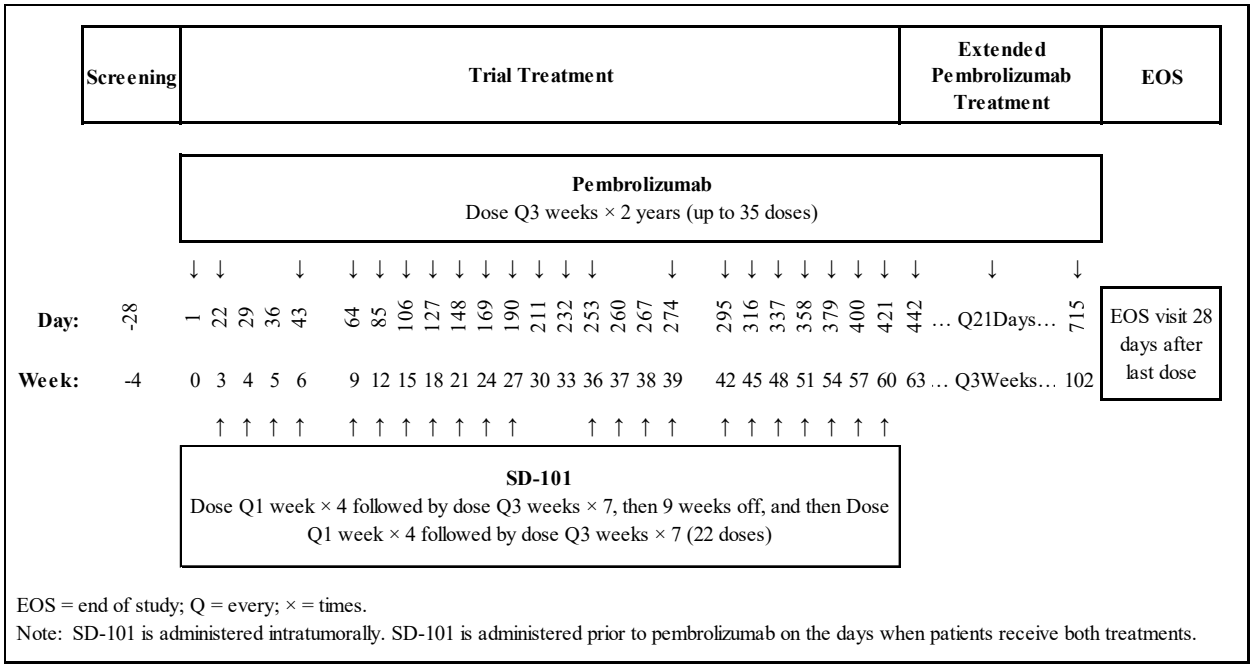
[c] Received prior treatment regimen containing an anti-PD-1/L1 drug.

[d] Received at least 2 doses of an anti-PD-1/L1 therapy, where the last dose of anti-PD-1/L1 therapy was within 6 months of study enrollment (Day 1) and have either refractory response (PD occurred within 3 months duration of the start of treatment on anti-PD-1/L1 therapy) OR resistant response (PD occurred beyond 3 months duration of treatment on anti-PD-1/L1 therapy and within 6 months after the last dose of treatment on anti-PD-1/L1 therapy). Anti-PD-1/L1 refractory or resistant patients must have documented PD per RECIST v.1.1, which has been confirmed by a second scan at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.

4.1.3 Phase 2 Dose Expansion – Dosing Schedule

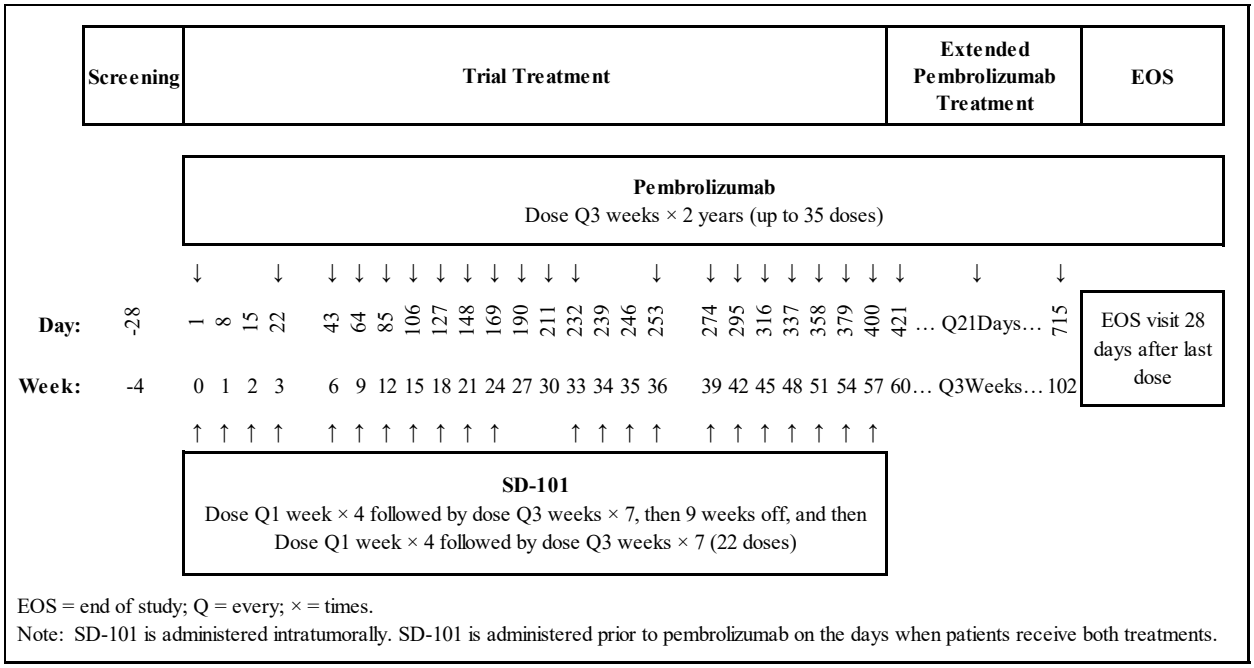
As presented in the Trial Flow Diagrams for the Dose Expansion Cohorts 1 to 4, patients with metastatic melanoma or HNSCC will receive 2 courses of the SD-101 dose regimen, with 9 weeks off between the 2 courses. In Cohorts 1 and 3 (Figure 4-3), patients will have a lead-in dose of pembrolizumab at Day 1 and start the treatment course on Day 22; whereas, in Cohorts 2 and 4 (Figure 4-4), SD-101 and pembrolizumab treatments will both start on Day 1. Metastatic melanoma or HNSCC patients in Cohorts 5, 6, 7, and 8 (Figure 4-5) will receive 1 course of SD-101 and dosing with SD-101 and pembrolizumab both start on Day 1. Pembrolizumab 200 mg will be administered intravenously Q3W until disease progression or up to 2 years. SD-101 will be administered before pembrolizumab on days when both drugs are scheduled to be used.

Figure 4-3: Trial Flow Diagram for Dose Expansion Cohorts 1 and 3 (*CLOSED*)



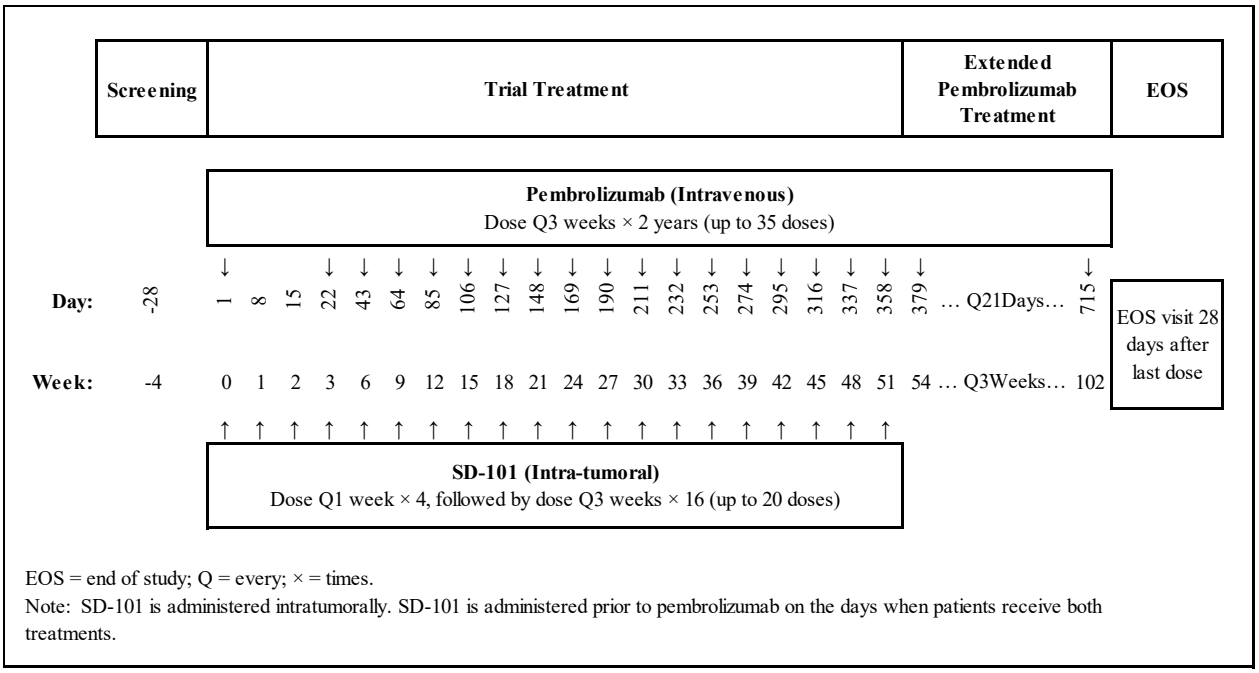
EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

Figure 4-4: Trial Flow Diagram for Dose Expansion Cohorts 2 and 4 (*CLOSED*)



EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

Figure 4-5: Trial Flow Diagram for Dose Expansion Cohorts 5, 6, 7, and 8 (*CLOSED*)



EOS = end of study; Q = every; × = times.
Note: SD-101 is administered intratumorally. SD-101 is administered prior to pembrolizumab on the days when patients receive both treatments.

4.1.4 Phase 1 and Phase 2 – Assessments

NOTE: As of Amendment 9, Phase 1 of the trial is complete and enrollment in Phase 2 is closed. Phase 2 of the trial has been modified to continue dosing per protocol. The trial will stop collecting all efficacy endpoints. Assessments of disease response should be made per Investigator based on local standard of care and assessment guidelines. This section has been modified accordingly.

All patients will undergo safety assessments, pharmacodynamic assessments, tumor response assessments, and tumor biopsies performed at specified trial visits, as indicated in the Schedule of Trial Events (Appendix 1 through Appendix 4).

Once informed consent is obtained, disease assessments prior to treatment will include:

- Complete physical examination including assessment of superficial lesions with photographic documentation and measurement of these lesions

- Radiographic imaging including computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, brain, and other areas (Appendix 7), as clinically indicated. CT imaging is preferred. In addition, screening imaging for HNSCC patients requires imaging of the neck. The screening radiographic imaging will serve as baseline and must be obtained within 4 weeks of study enrollment, ie, receiving the first trial treatment.
- Laboratory assessments
- Baseline confirmation of PD-L1 expression from a biopsy of the target lesion (Lesion A) that will be injected with SD-101 in Phase 2 Expansion patients. A baseline biopsy should be collected within 28 days prior to the initiation of study treatment. Archival tissue of the target lesion within 3 months of screening is acceptable.
- Copy of pathology report confirming diagnosis

Disease assessment will include physical examination, photographic documentation and measurement of superficial lesions, and radiographic imaging (Appendix 7) with CT or MRI (with preference for CT) scans.

Repeat tumor biopsies will be conducted for all Cohorts. Biopsies of the target lesion (Lesion A) which has been injected with SD-101 are required at the time points as outlined in the Schedule of Trial Events (Appendix 1 through Appendix 4). At each biopsy collection time point, 2 tissue biopsy samples will be collected per the study laboratory manual. Lesion A should be of a sufficient size such that the intratumoral biopsy does not compromise the investigator's ability to assess the lesion size changes per Response Evaluation Criteria in Solid Tumors (RECIST) over time. Biopsies from Lesion A are required. Additional biopsies from other injected lesions are optional, but strongly encouraged. Of note, 1 to 3 additional biopsies may be collected from other injected lesions if a cohort allows for injecting up to 4 lesions. Separate and additional biopsies from a non-injected lesion are also optional but strongly encouraged. If Lesion A or other biopsied lesions have regressed, further biopsies are not required. If an injected lesion has completely regressed, and there is no other replacement lesion (Section 6.2.2.2), SD-101 will be injected peritumorally for up to the next 3 doses of SD-101. Further details on tumor biopsies are in Section 10.1.2.

In Phase 1, response will be assessed by evaluating Lesion A, all sites of disease outside Lesion A, and all lesions combined. In Phase 2, response will be assessed by evaluating all lesions injected with SD-101, lesion(s) not injected with SD-101, and all lesions combined.

Disease response and study treatment management for Dose Expansion will be assessed by the investigator based on RECIST v1.1 and irRECIST (ie, scans obtained at least 4 weeks later that qualify as PD per RECIST v1.1 [Appendix 6]). This assessment of disease response and progression is consistent with current pembrolizumab studies and was implemented due to

observed *pseudoprogression* as well as late responses with immunotherapy. The protocol also allows patients who are clinically stable and have unconfirmed PD to continue pembrolizumab and SD-101 per investigator decision and Dynavax Medical Monitor approval. All patients who develop confirmed disease progression per local assessment guidelines should be discontinued from the study. Pembrolizumab may be continued as a single agent if SD-101 is discontinued per investigator decision as described in Section 9.2. Patients who discontinue pembrolizumab must discontinue SD-101.

4.2 Duration of Trial

The total duration of patient participation in this trial is up to approximately 110 weeks. This includes a Screening period beginning up to 28 days prior to the first trial treatment, and a trial completion visit approximately 28 days after the last dose of trial treatment.

4.3 Trial Endpoints

NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected. The collection of safety endpoints has been simplified. This section has been modified accordingly.

4.3.1 Phase 1 – Dose Escalation

4.3.1.1 Primary Endpoints

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

4.3.1.2 Exploratory Endpoints

- ORR per RECIST v1.1
- Disease control rate (DCR) per RECIST v1.1
- Time to response per RECIST v1.1
- Changes in tumor-infiltrating lymphocytes, PD-L1 expression, and other gene expression in tumor biopsies

4.3.2 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. All imaging endpoints will be based on

investigator evaluation. A central imaging laboratory for study image collection and radiographic endpoint determination will be used per sponsor decision.

4.3.2.1 Primary Endpoints – No longer collected as of Amendment 9

- ORR per RECIST v1.1

4.3.2.2 Secondary Endpoints

- Incidence of injection-site reactions, AEs, and SAEs

The following Secondary Endpoints (Phase 2) will not be collected as of Amendment 9:

- Time to response using RECIST v1.1
- Duration of response per RECIST v1.1
- Radiographic PFS per RECIST v1.1

4.3.2.3 Exploratory Endpoints – No longer collected as of Amendment 9

- Radiographic primary and secondary endpoints evaluated using irRECIST (Appendix 6, Immune-related RECIST)
- Changes in correlative biomarkers including tumor-infiltrating lymphocytes and PD-L1 expression at baseline and after SD-101 treatment
- Changes in potential tumor neoantigens in patients with recurrent or metastatic HNSCC
- Changes in the expression of IFN-inducible genes in whole blood in patients with metastatic head and neck squamous cell carcinoma

4.4 Randomization

None of the patients in this trial will be randomized.

4.5 Blinding

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

4.6 Appropriateness of Measurements

The measures of safety in the trial are routine clinical and laboratory procedures. AEs will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (National Cancer Institute 2010) (Table 11-1). The measurement of injection-site reactions is based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Center for Biologics Evaluation and Research 2007)

(Appendix 5). The primary measure of response of lesions in this trial is based on standard RECIST v1.1 guidelines (Appendix 6).

4.7 Trial Termination

The End-of-Study (EOS) date is defined as the date of the last visit of the last participant. However, the sponsor reserves the right to terminate the trial at any time. Reasons for discontinuation include but are not limited to:

- Inability to enroll sufficient patients into the trial
- Good clinical practices (GCP) compliance issues that compromise the validity of the trial

Procedures for withdrawal of individual patients can be found in Section 5.3.

5.0 SELECTION OF PATIENTS

As of Amendment 9, enrollment is closed and this section is no longer applicable.

The trial population in Phase 1 Escalation Cohort 1-4 will include men and women with metastatic melanoma with at least 1 site of disease that qualifies as a target lesion per RECIST v1.1 and is accessible for intratumoral injection. Patients must meet the inclusion and exclusion criteria as described in detail in Sections 5.1 and 5.2 to be enrolled (defined as receiving the first trial treatment [ie, pembrolizumab or SD-101]) in the trial. An estimated 24 patients will be enrolled in Phase 1.

The trial population in Phase 2 metastatic melanoma will include approximately 160 men and women with metastatic melanoma with at least 2 target lesions per RECIST v1.1 and at least 1 of the qualifying lesions must be accessible for intratumoral injection; the target lesion could be the injectable lesion.

The trial population in Phase 2 HNSCC will include approximately 100 men and women with recurrent or metastatic HNSCC with at least 1 target lesions per RECIST v1.1, and which must be accessible for intratumoral injection. Phase 2 expansion cohorts are described in Sections 4.1.1.1 and 4.1.2.2.

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through inclusion/exclusion criteria and routine safety monitoring.

5.1 Inclusion Criteria

A patient must meet all the following criteria to be eligible for enrollment (defined as receiving the first trial treatment [ie, pembrolizumab or SD-101]) in the trial:

Phase 1 and Phase 2

1) Willing and able to provide written informed consent for the trial
2) Aged 18 years and older
3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1
4) Patient must have adequate organ function as indicated by the following laboratory values:

Hematological

- Absolute neutrophil count (ANC) ≥ 1,500 /mcL
- Platelet count ≥ 100,000 /mcL
- Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L

Renal

- Serum creatinine ≤ 1.5 × upper limit of normal (ULN) OR
- Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl) ≥ 60 mL/min for subject with creatinine levels > 1.5 × institutional ULN

Hepatic

- Serum total bilirubin:
  - ≤ 1.5 × ULN **OR**
  - < 3 × ULN for persons with Gilbert's syndrome **OR**
  - Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 × ULN
- Aspartate transaminase (AST) and alanine transaminase (ALT) (also known as serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase)
  - ≤ 2.5 × ULN **OR**
  - ≤ 5 × ULN for patients with liver metastases

Coagulation

- International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless patient is receiving anticoagulant therapy, and as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
- Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless patient is receiving anticoagulant therapy, and as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5) Have provided 2 tissue biopsy samples taken of the target lesion (Lesion A) as a single biopsy split into 2 samples or 2 separate biopsies that meet the minimal sample size requirement per the study laboratory manual. One sample is for determining PD-L1 expression level by immunohistochemistry and can be an archival sample of the anticipated target lesion that has been collected within 3 months of screening. The other sample is for RNA expression profiling and must be a fresh biopsy.
6) Life expectancy of at least 6 months
7) Female patients of childbearing potential, as defined in Section 5.2.1, must have a negative urine or serum pregnancy test within 72 hours prior to taking the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative then a serum test is required which must be negative for the patient to enroll. Women of childbearing potential (WOCBP) must be willing to use 2 medically acceptable methods of contraceptive from Day 1 through 120 days after the last dose of trial treatment. The 2 medically acceptable birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

   Male patients of reproductive potential, as described in Section 5.2.1, must agree to use an adequate method of contraception from Day 1 through 120 days after the last dose of trial treatment.

   Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

Inclusion Criteria (Phase 1 only: Melanoma)

A patient must meet the following to be eligible for Phase 1:

8) Histologically or cytologically confirmed unresectable or metastatic (stage IV) melanoma
9) For Phase 1 Escalation Cohorts 1-4, must have at least 1 lesion that qualifies as a target lesion per RECIST v1.1 except for the minimum measurement of 10 mm in diameter for superficial lesions, is easily accessible (palpable or can be visualized by ultrasound), and is amenable to multiple intratumoral injections. If superficial, the target lesion must be documented photographically.

Inclusion Criteria (Phase 2 only: Melanoma)

A patient must meet the following to be eligible for Phase 2 (as applicable to the expansion cohorts):

10) Histologically or cytologically confirmed recurrent or unresectable or metastatic (stage IV) melanoma
11) Must have at least 2 lesions that qualify as a target lesion per RECIST v1.1, and 1 of the qualifying lesions must be easily accessible (palpable or can be visualized by ultrasound) and amenable to multiple intratumoral injections. The target lesion should be of sufficient size such that the required tumor biopsies do not significantly affect tumor assessment per RECIST v1.1. If superficial, the target lesion must measure at least 10 mm in diameter, be measured by calipers, and be documented photographically. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.
12) Expansion Cohort 2: Must have documented PD per RECIST v1.1 on a prior treatment regimen containing an anti-PD-1/L1 drug (see Appendix 6 for definition of PD per RECIST v1.1)
13) Expansion Cohort 8: Must have all of the following:
    a) Received at least 2 doses of an anti-PD-1/L1 therapy
    b) PD occurred within 3 months after last dose of anti-PD-1/L1 therapy
    c) Documented PD per RECIST v.1.1, which has been confirmed by a second assessment at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression

Inclusion Criteria (Phase 2 only: HNSCC)

A patient must meet the following to be eligible for Phase 2 (as applicable to the expansion cohorts):

14) Histologically or cytologically confirmed recurrent or metastatic HNSCC that could not be treated with curative intent.

15) Must have at least 1 lesion that qualifies as a target lesion per RECIST v1.1, and which must be easily accessible (palpable or can be visualized by ultrasound) and amenable to multiple intratumoral injections. The target lesion should be of sufficient size such that the required tumor biopsies do not significantly affect tumor assessment per RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.

16) Expansion Cohort 4: Must have documented confirmed PD per RECIST v1.1 on a prior treatment regimen containing an anti-PD-1/L1 drug (see Appendix 6 for definition of PD per RECIST v1.1)

17) Expansion Cohort 7: Must have all of the following:

    a) Received at least 2 doses of an anti-PD-1/L1 therapy, where the last dose of anti-PD-1/L1 therapy was within 6 months of study enrollment (Day 1)

    b) Refractory response, ie, PD occurred within 3 months duration of the start of treatment on anti-PD-1/L1 therapy; OR resistant response, ie, PD occurred beyond 3 months duration of treatment on anti-PD-1/L1 therapy and within 6 months after the last dose of treatment on anti-PD-1/L1 therapy

    c) Documented PD per RECIST v.1.1, which has been confirmed by a second assessment at least 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression

5.2 Exclusion Criteria

A patient with any 1 of the following criteria is not eligible for enrollment in the trial:

Phase 1 and Phase 2

1) Received systemic chemotherapy or biological cancer therapy (except anti-PD-1/L1 therapy) within 3 weeks prior to study enrollment

2) Received prior radiotherapy within 2 weeks of start of study therapy. A shorter washout period may be permitted after approval by the Medical Monitor.

3) Received small molecule inhibitor targeted therapy, such as tyrosine kinase inhibitors, within 2 weeks prior to study enrollment
4) Has not recovered to CTCAE Grade 1 or better from the AEs due to cancer therapeutics prior to study enrollment

   NOTE: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia or Grade 2 AEs that qualify as Grade 2 due to replacement hormonal or steroid therapy are exceptions to this criterion and may qualify for the study with approval by a Dynavax Medical Monitor.

   If a patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to enrollment.
5) Received a transfusion of blood products (including platelets or red blood cells) or colony-stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study enrollment
6) Is expected to require any other form of anti-cancer therapy while in the trial
7) Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy (including immune modulators or systemic corticosteroids) within 7 days prior to study enrollment
8) Positive for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection as determined by laboratory tests for HBsAg, anti-HBc, and anti-HBs; anti-HCV; and anti-HIV -1/2, respectively
9) History of or current uveal or mucosal ocular melanoma
10) Active infection including cytomegalovirus
11) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 120 days after the last dose of trial treatment
12) Active autoimmune disease requiring systemic treatment in the past 2 years or a disease that requires immunosuppressive medication including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome, or autoimmune thrombocytopenia. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
13) Current pneumonitis or history of (non-infectious) pneumonitis that required steroids
14) An immune-related AE from a previous immunotherapeutic agent that has not resolved to Grade 1 or less prior to study enrollment. The exception is a Grade 2 AE which qualifies as Grade 2 due to replacement steroid therapy which may be allowed with approval by a Dynavax Medical Monitor.
15) Known active central nervous system metastases or carcinomatous meningitis

NOTE: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of trial treatment and with any neurologic symptoms returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

16) Use of any investigational agent within the last 28 days prior to study enrollment

17) Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

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

19) History of sensitivity to any component of SD-101 or hypersensitivity reaction to treatment with a monoclonal antibody and/or any of its excipients

20) Any known additional malignancy that is progressing or requires active treatment. Exceptions are cutaneous melanoma or HNSCC under study per protocol, or basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy.

Exclusion Criteria (Phase 2, Melanoma Expansion Cohorts 1 and 5 only)

21) Melanoma considered resectable with curative intent

22) Prior therapy with an anti-PD-1/L1 agent

23) Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients

Exclusion Criteria (Phase 2, Melanoma Expansion Cohorts 2 and 8 only)

24) Melanoma considered resectable with curative intent

25) Any prior combination therapy involving agents given by intratumoral injection that target the innate immune pathway or system such as oncolytic viral or microbial therapy (eg, T-VEC [talimogene laherparepvec]), toll-like receptors (TLR) agonists, STING or RIG-1 and an anti-PD-1/L1 inhibitor

Exclusion Criteria (Phase 2, HNSCC Expansion Cohorts 3 and 6 only)

26) HNSCC considered resectable with curative intent

27) Prior therapy with an anti-PD-1/L1 agent

28) Require anticoagulation therapy

Exclusion Criteria (Phase 2, HNSCC Expansion Cohorts 4 and 7 only)

29) HNSCC considered resectable with curative intent

30) Any prior combination therapy involving agents given by intratumoral injection that target the innate immune pathway or system such as oncolytic viral or microbial therapy (eg, T-VEC), TLR agonists, STING or RIG-1 and an anti-PD-1/L1 inhibitor.

31) Require treatment on anticoagulation therapy

5.2.1 Contraception

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. All female patients are considered to be WOCBP except if they have been postmenopausal for at least 2 years or surgically sterile for at least 1 year.

Postmenopause is defined as:

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

  FSH level testing is not required for women > 62 years old with amenorrhea for > 1 year.

NOTE:

- Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

- For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
- Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

5.3 Removal of Patients From the Trial

Patients may choose to withdraw from the trial at any time. The reason for withdrawal will be recorded on the case report form (CRF).

Patients may also be discontinued from the trial by the investigator for any of the following reasons:

- Patient does not receive the first dose of SD-101
- Pembrolizumab is discontinued because of toxicity
- Patient begins new cancer treatment for melanoma or HNSCC (as applicable)
- Noncompliance with trial procedures as determined by the investigator or sponsor
- At the discretion of the investigator if it is felt to no longer be in the best interest of the patient to remain in the trial
- If patient becomes pregnant and/or starts breastfeeding
- The sponsor decides to terminate the trial

The investigator or designee should discuss with the Dynavax Medical Monitor prior to withdrawing a patient from the trial before trial completion. When a patient discontinues the trial, they should undergo an EOS/Safety Follow-up Visit 28 days after the last dose of trial treatment as described in Section 10.8. Required procedures are listed in Appendix 1 through Appendix 4. Additional information about stopping treatment or terminating the trial may be found in Sections 7.6, 9.1 and 9.2.

6.0 TRIAL TREATMENT AND SUPPLIES

The identities and instructions for administration, storage, and handling of SD-101 and pembrolizumab are described below. Both SD-101 and pembrolizumab are considered as, and referred to as, trial drug(s) or trial treatment in this protocol.

6.1 Trial Treatments

6.1.1 Pembrolizumab

Pembrolizumab [Keytruda® (US)], a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of cancer.

Pembrolizumab is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and water for injection, USP.

Further details regarding formulation of pembrolizumab are provided in the current approved product labels and Investigator's Brochure for pembrolizumab.

A fixed dose of 200 mg of pembrolizumab will be administered via intravenous infusion Q3W for up to 35 treatments (approximately 2 years).

6.1.2 SD-101

SD-101 is a clear to slightly opalescent, colorless to pale yellow solution, free of visible particles and will be supplied by Dynavax in single-use vials. Dilution with sterile 0.9%, preservative-free sodium chloride for injection to the appropriate concentration for dosing will be required for all doses; instructions for dilution are provided in the Pharmacy Manual. The dose cohorts for SD-101 are 1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg.

6.2 Instructions for Administration

6.2.1 Pembrolizumab

Pembrolizumab will be administered using a 30-minute intravenous infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5/+10 minutes).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Designated site personnel will be responsible for preparing and administering pembrolizumab and will be required to record limited information during each infusion (eg, infusion date/time, lot number and expiry date for product administered, total dose/volume administered). See Pharmacy Manual for further details.

Pembrolizumab will be administered after SD-101 on days when both drugs are scheduled to be used.

6.2.2 SD-101

SD-101 will be administered before pembrolizumab on days when both drugs are scheduled to be used. Designated trial-site personnel will be responsible for preparing and administering the trial injection with SD-101. At minimum, syringes will be labeled with the protocol number, patient initials, and patient number.

Prior to injection, the site should be thoroughly cleansed and then wiped with alcohol. Ultrasound may be used to assist injection. Notation in the source documents should specify location and size (in 2 dimensions) in as much detail as possible. Injection should be made as close to the center of the tumor as possible. All of the drug should be injected.

Note: Intratumoral injections are not allowed if a tumor is fully encasing or in close proximity to major blood vessel(s). In this situation another tumor site must be accessible for intratumoral injections.

Table 6-1 summarizes the dosage and administration of SD-101 for Phase 1 and Phase 2 cohorts.

Table 6-1: Dosage and Dose Administration for Phase 1 and Phase 2 Cohorts

Cohort	Anti-PD-1/L1 Experience	SD-101 Dose	Maximum Total Per-patient SD-101 Dose
Phase 1 Melanoma Dose Escalation Cohorts			
1	Naïve or experienced	2.0 mg per lesion in 1 injectable lesion (Lesion A)	2.0 mg
2	Naïve or experienced	4.0 mg per lesion in 1 injectable lesion (Lesion A)	4.0 mg
3	Naïve or experienced	8.0 mg per lesion in 1 injectable lesion (Lesion A)	8.0 mg
4	Naïve or experienced	1.0 mg per lesion in 1 injectable lesion (Lesion A)	1.0 mg
Phase 2 Melanoma Dose Expansion Cohorts			
1	Naïve	8.0 mg in a single injectable lesion if 1 lesion is selected (Lesion A) **or** 2.0 mg per lesion if 2 to 4 lesions are selected for injection (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
2	Experienced	8.0 mg in a single injectable lesion (Lesion A)	8.0 mg
5	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
8	Refractory or resistant	2.0 mg in 1 ml per injection in 1 to 4 separate lesions for lesions measuring up to 5 cm in the longest diameter; or for lesions larger than 5 cm, 2.0 mg in 1 ml per injection in 1 to 4 separate regions where the injections are ≥ 5 cm apart (maximum total dose is 8.0 mg)	8.0 mg
Phase 2 HNSCC Dose Expansion			
3	Naïve	8.0 mg per lesion in 1 lesion with the option of injecting into up to 4 regions within the lesion in approximate equally divided volumes of an 8.0 mg dose	8.0 mg
4	Experienced	8.0 mg per lesion in 1 lesion with the option of injecting into up to 4 regions within the lesion in approximate equally divided volumes of an 8.0 mg dose	8.0 mg
6	Naïve	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg
7	Refractory or resistant	2.0 mg per lesion in 1 to 4 injectable lesions (Lesion A, Lesion B, Lesion C, Lesion D)	8.0 mg

Please refer to the Pharmacy Manual for additional details on dose administration.

6.2.2.1 Phase 1 Metastatic Melanoma - *COMPLETE*

In Phase 1 Escalation Cohorts 1-4, SD-101 is injected intratumorally into a target lesion (Lesion A), the same site used throughout the trial. If at any point during treatment, the lesion for injection has completely regressed the remaining SD 101 injections will be given peritumorally by injection into the site of Lesion A.

6.2.2.2 Phase 2 Metastatic Melanoma - *CLOSED*

Lesion A must be selected and must meet the requirement of being amenable to multiple intratumoral injections of SD-101, and a target lesion as defined per RECIST v1.1. Biopsy and intratumoral injection of Lesion A may be performed on different days but must be completed within the window period allowed per protocol.

The same site(s) will be used throughout the trial unless a lesion has completely regressed. If a selected lesion regresses and/or becomes inaccessible for injection, a replacement lesion, which could be either a target, non-target, or new lesion per RECIST v1.1, may be chosen for injection and will be injected at subsequent dosing time points. Injection into a new lesion may occur only after consultation with the Dynavax MM.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.

If at any point during treatment, the lesion for injection has completely regressed and there is no other replacement lesion, SD-101 will be injected peritumorally for up to the next 3 doses of SD-101.

Please refer to the Pharmacy Manual for details.

6.2.2.3 Phase 2 HNSCC - *CLOSED*

Lesion A must be selected and must meet the requirement of being amenable to multiple intratumoral injections of SD--101, and a target lesion as defined per RECIST v1.1. Biopsy and intratumoral injection of Lesion A may be performed on different days but must be completed within the window period allowed per protocol.

If a selected lesion has regressed to where injection can no longer be made to any region within the same lesion, a replacement lesion, which could be either a target, non-target, or new lesion per RECIST v1.1, may be chosen for injection and will be injected in a similar manner at

subsequent dosing points. Injection into a new lesion may occur only after consultation with the Dynavax MM.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Approval from the Medical Monitor is required to inject a previously radiated lesion.

If at any point during treatment, the lesion for injection has completely regressed and there is no other replacement lesion, SD-101 will be injected peritumorally for up to the next 3 doses of SD-101.

Please refer to the Pharmacy Manual for details.

6.3 Labeling

6.3.1 Pembrolizumab

During the course of the study, labeled pembrolizumab for clinical study use (MK-3475) will be provided.

At a minimum, pembrolizumab (MK-3475) will be labeled with the following information: product name, product lot number, contents, volume, concentration, sponsor name, and a statement indicating that the drug is for investigational use only. Additionally, at a minimum, the intravenous bag will be labeled with the protocol number, patient initials, and patient number.

6.3.2 SD-101

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

6.4 Storage and Handling Instructions

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

6.4.1 Pembrolizumab

Pembrolizumab vials of solution for injection (MK-3475) must be stored at refrigerated conditions (2°C to 8°C) and protected from light.

Note: Vials should be stored in the labeled box in which they are received to ensure the drug is protected from light.

A detailed description of the storage and handling instructions for pembrolizumab (MK-3475) is provided in the Pharmacy Manual.

6.4.2 SD-101

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

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

6.5 Control and Accountability of Investigational Medicinal Product

All investigational medicinal products must be received by a trained designated person at the trial site, handled and stored safely and properly, and kept in a secured location with limited access.

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

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

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

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

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

Refer to the Pharmacy Manual for detailed instructions on trial treatments.

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

6.6 Treatment Compliance

All trial injections and infusions will be administered by designated personnel only.

7.0 TREATMENT OF PATIENTS

7.1 Treatments Administered

All patients will receive 200 mg of pembrolizumab administered intravenously Q3W (± 3 days) for up to 35 treatments (approximately 2 years) or until disease progression. All patients must have an ANC count of ≥ 1500 cells/mcL at screening and on the day of dosing in order to receive SD-101. ANC labs should be drawn on the day of dosing; however, if this is not possible, ANC labs can be drawn the day before dosing of SD-101. If ANC count < 1500 cells/mcL or Grade ≥ 3 neutropenia develops while on study, then patients must have an ANC count of ≥ 1500 cells/mcL on the day of dosing in order to receive SD-101.

Concurrently, they will receive the following regimens of SD-101:

- Phase 1 Escalation Cohorts 1-4: 4 weekly doses of SD-101 starting from Day 1 followed by 1 dose Q3W for 7 additional doses; up to 11 total doses (Figure 4-3). Both SD-101 and pembrolizumab start on the same study day.
- Phase 2 Expansion Cohorts 1-4: 2 courses of SD-101, each consisting of 4 weekly doses of SD-101 followed by 1 dose Q3W for 7 additional doses, with 9 weeks off between the courses, for up to 22 total doses (Figure 4-4 and Figure 4-5). Cohorts 1 and 3 patients will receive a single dose of pembrolizumab before commencing the first treatment course with SD-101, and patients in Cohorts 2 and 4 will start both SD-101 and pembrolizumab on the same study day.
- Phase 2 Expansion Cohorts 5-8: 4 weekly doses of SD-101 starting from Day 1 followed by 1 dose Q3W for 16 additional doses; up to 20 total doses. Both SD-101 and pembrolizumab start on the same study day.

For the Phase 1 Dose Escalation, SD-101 doses are 1.0 mg, 2.0 mg, 4.0 mg, and 8.0 mg. Patients will be assigned to the current dose being evaluated per sponsor decision at the time they are enrolled in the trial.

Intra-patient Dose Escalation or dose reduction is not permitted.

7.2 Treatment Period

All patients will receive 200 mg of pembrolizumab Q3W for up to 2 years from Day 1.

In Phase 1 Dose Escalation, patients in Escalation Cohorts 1-4 will receive SD-101 from Day 1 through Day 169 (Figure 4-2).

In Phase 2 Dose Expansion, patients naïve to anti-PD-1/L1 in Cohorts 1 and 3 will receive SD-101 from Day 22 through Day 421 (Figure 4-3) and patients experienced with anti-PD-1/L1 in Cohorts 2 and 4 will receive SD-101 from Day 1 through Day 400 (Figure 4-4). Patients in Cohorts 5, 6, 7, and 8 will receive SD-101 from Day 1 through Day 358 (Figure 4-5).

Pembrolizumab will be continued until completion of planned dosing (up to 2 years) or required discontinuation as described in Section 7.6. SD-101 will be continued until completion of planned dosing, confirmed disease progression, or required discontinuation as described in Section 9.2 (whichever occurs sooner).

Details of the dosing for Phase 1 and Phase 2 are provided in the Schedule of Trial Events (Appendix 1 through Appendix 4).

SD-101 will be administered before pembrolizumab on days when both drugs are scheduled to be used.

Note: If pembrolizumab treatment is temporarily withheld, treatment of SD-101 and pembrolizumab will start on the same day once pembrolizumab is resumed. Delayed dosing of SD-101 would be preferred over completely skipping a dose as long as the interval between SD-101 dosing is not less than 5 days with subsequent return of SD-101 dosing to per protocol schedule of events. See Section 7.6 for details regarding delayed or skipped doses.

The protocol may be discontinued by Dynavax Technologies Corporation at any time (Section 4.7).

7.3 Treatment Precaution

IFN-α has been shown to inhibit cytochrome P450 (CYP) enzyme 1A2 (Brennan 2012). Since SD-101 induces IFN-α, SD-101 may inhibit metabolism of drugs by CYP 1A2. CYP 1A2 substrates with narrow therapeutic ranges should be used with caution. The following drugs should be used with caution through 7 days after each subsequent dose of SD-101: caffeine,

theophylline, warfarin, tricyclic antidepressants, clozapine, fluvoxamine, ciprofloxacin, propranolol, and verapamil.

7.4 Prohibited Treatments or Therapies

Patients may receive other medications that the investigator deems to be medically necessary, with the exception of the medications listed below, which are prohibited during the trial. Patients who in the assessment by the investigator require the use of any of the following treatments for clinical management should be removed from the trial (see Section 5.3):

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Dynavax Medical Monitor.
  - Note: Inhaled steroids are allowed for management of asthma.
- Surgery, unless approved by the Dynavax Medical Monitor

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

The Exclusion Criteria (Section 5.0) describe other medications and therapies that are prohibited in this trial.

7.5 Permitted Therapy

Topical or inhaled or intranasal corticosteroids (with minimal systemic absorption) and non-absorbed intra-articular steroid injections are permitted to treat AEs and may be continued with permission of the Dynavax Medical Monitor. Systemic corticosteroids required for the control of infusion reactions or immune-related AEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg per day of prednisone or equivalent) before the next administration of SD-101 or pembrolizumab. A brief (< 24 hours) course of steroids for prophylaxis against contrast dye allergy is permitted for patients undergoing tumor assessments per institutional standard. Guidelines for steroid use to treat immunologic AEs are listed in Section 7.7.

Acetaminophen (maximum 3 g per day), ibuprofen, and/or ondansetron may be used post-SD-101 treatment to treat flu-like symptoms and pre-dose as prophylaxis. Pre- and post-SD-101 treatment prophylaxis with these agents is allowed but not encouraged for the first SD-101 dose for a patient in Phase 1 unless recommended per the Dynavax Medical Monitor. The sponsor may make further recommendations with regards to prophylaxis treatments for potential flu-like symptoms as the study is ongoing. See Section 9.3 for additional details.

Efforts should be made to keep all other concurrent medications at stable doses during the trial and to refrain from starting any new medications, unless clinically indicated. Therapy to prevent or treat local and/or systemic reactions following administration of either trial drug may include analgesics, antipyretics, and antihistamines.

7.6 Dose Modification, Dose Delays, and Missed Doses

NOTE: As of Amendment 9, irRECIST for the determination of disease progression is no longer applicable and this section has been revised accordingly.

Only a limited number of patients have been treated with SD-101, and to date, the most common toxicities include transient Grade 1 to 2 flu-like symptoms. In mice, SD-101 has been injected intratumorally concurrently with a neutralizing anti-mouse PD-1 antibody. In multiple experiments using high doses of SD-101 (approximately 2 mg/kg), no evidence of acute morbidity or mortality in mice was observed that could be due to the interaction of the 2 agents.

To protect patient safety, patients will be closely monitored for any additional or synergistic toxicities observed with the combination.

Withhold SD-101 for any Grade ≥ 3 injection-site reaction or drug-related AE that is not a DLT (see Section 9.1). SD-101 treatment may be resumed once the AE has resolved to Grade 0 or 1 with standard treatment. SD-101 must also be held for an ANC count of < 1500 cells/mcL.

Patients will be treated at the dose in their assigned Cohort and individual dose adjustment (reduction or increase) of SD-101 or pembrolizumab will not be permitted.

Delayed dosing of SD-101 would be preferred over completely skipping a dose as long as the interval between SD-101 dosing is not less than 5 days with subsequent return of SD-101 dosing to per protocol schedule of events. If the 5-day interval cannot be adhered to, then the injection must be skipped to allow a minimum of 5-day interval window between the off-scheduled injection and next injection on schedule. After a delayed or skipped dose, dosing will return to the original interval as described under Schedule of Trial Events.

For Phase 1, if ≥ 2 doses are missed during the DLT assessment period for any reason or if ≥ 4 doses are missed due to AEs following the DLT period, then SD-101 should be permanently discontinued. For Phase 2, if ≥ 4 doses are missed due to AEs, then SD-101 should be permanently discontinued.

If SD-101 dosing is delayed for more than 3 days, then the hematology and chemistry laboratory collections listed in the Schedule of Trial Events (Appendix 1 through Appendix 4) or the planned day of dosing that were missed should be done prior to dosing on that day (eg, if Day 22 dosing is delayed and SD-101 is dosed on Day 26, then all the Day 22 labs should be repeated pre-dose on Day 26).

SD-101 should be withheld if a patient requires greater than 10 mg per day of prednisone or equivalent to treat an AE (Section 9.3.2). SD-101 may be resumed when the corticosteroid is discontinued and pembrolizumab is resumed.

If an HNSCC subject develops an AE which requires anticoagulation therapy, the Investigator in consultation with the Medical Monitor will determine whether SD-101 injection should be continued or interrupted.

SD-101 should be permanently discontinued for any of the following:

- SD-101 dosing is delayed for more than 6 weeks
- DLT that occurs during the DLT assessment period in Phase 1 (Section 9.1)

- Clinically significant immune-related event
- Pembrolizumab is permanently discontinued

SD-101 will be permanently discontinued for any of the following adverse reactions (ARs):

- Severe or life-threatening ARs, including any of the following:
  - Any Grade 4 (life-threatening) AR
  - Grade 3 or 4 pneumonitis
  - Grade 4 diarrhea/colitis
  - Grade 4 hyperthyroidism
  - Grade 3 AST or ALT of > 5 × ULN or Grade 3 total serum bilirubin > 3 × ULN
  - AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week in patients with liver metastasis who begin treatment with a baseline Grade 2 AST or ALT of > 3 and ≤ 5 × ULN
  - Grade 3 or 4 nephritis
  - Any severe or Grade 3 AR that recurs
  - Inability to reduce corticosteroid dose (used for treatment of AEs) to 10 mg or less of prednisone or equivalent per day within 12 weeks of starting corticosteroids
- Observation of any other toxicities that in the opinion of the investigators suggests that there may be a significant increase in either the incidence or severity of any events seen with either single agent. In this case, the sponsor and investigators will review all safety data.

Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as listed in Table 7-1. If a patient`s AE prevents pembrolizumab dosing then SD-101 injection should be held if the AE also could at least be possibly related to SD-101. Delayed dosing of SD-101 would be preferred over completely skipping a dose as long as the interval between SD-101 dosing is not less than 5 days with subsequent return of SD-101 dosing to per protocol schedule of events. See Section 7.7 for use of corticosteroids.

Grade 2 - 3 fatigue does not require the withholding of pembrolizumab or SD-101 treatment.

It is at the discretion of the investigator whether to continue a patient on study treatment until repeat imaging is obtained. If repeat imaging confirms PD, patients will be discontinued from the study.

Two dosing delays of pembrolizumab due to toxicity will be permitted. In the event of a third occurrence of a toxicity which would require dosing delay, pembrolizumab will be discontinued permanently.

If a subject resumes pembrolizumab treatment after a dose interruption, the interval between pembrolizumab dosing should not be less than 3 weeks (± 3 days) with subsequent return of pembrolizumab dosing to per protocol schedule of events.

Dosing interruptions for SD-101 or pembrolizumab are permitted in the case of medical/surgical events. For Phase 2, dosing interruptions for logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and/or holidays) are permitted. Patients should be placed back on trial treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Dynavax Medical Monitor.

The reason for any interruption in treatment should be documented in the patient's study record.

7.7 Dose Modification and Toxicity Management for Immune-Related Adverse Events Associated With Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7-1.

Table 7-1: Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions:

Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Table 7-1: Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab (Cont'd)

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

Table 7-1: Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab (Cont'd)

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Table 7-1: Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab (Cont'd)

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician. NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

AE = adverse event; ALT = alanine transaminase; AR = adverse reaction; AST = aspartate transaminase; CTCAE = Common Terminology Criteria for Adverse Events; irAE = immune-related AE; IV = intravenous; T1DM = type 1 diabetes mellitus.

7.8 Replacement of Patients

NOTE: As of Amendment 9, enrollment is closed and this section is no longer applicable.

Patients who complete screening but are not treated or patients who do not complete at least 3 injections of SD-101 during the DLT assessment period for reasons other than drug-related toxicity will be replaced. Patients who withdraw from the trial during the DLT assessment interval prior to Day 29 for reasons other than a drug-related toxicity may be replaced.

Patients who received < 90% of pembrolizumab during the DLT assessment period (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will be replaced.

Phase 2 patients who do not receive the following may be replaced at the decision of the Dynavax Medical Monitor:

- At least 1 dose of SD-101 and pembrolizumab
- Baseline and at least 1 post-baseline imaging
- Baseline and at least 1 post-baseline tumor biopsy

8.0 ASSESSMENT OF RESPONSE

NOTE: As of Amendment 9, efficacy and exploratory endpoints will no longer be collected. The collection of safety endpoints has been simplified. Assessments of disease response to treatment should be made per Investigator based on local standard of care.

Response assessments will be performed at specified time points as listed in the Schedule of Trial Events (Appendix 1 through Appendix 4).

8.1 Interferon-inducible Genes

NOTE: As of Amendment 9, this section is no longer applicable.

IFN-inducible gene expression will be measured in Phase 1 to indirectly determine the induction of IFN-α by different doses of SD-101. In addition to DLT assessment, the levels of IFN-inducible gene expression may be used to determine the optimal RP2D of SD-101 for further evaluation of combination therapy in oncology trials. The rationale for utilizing IFN-inducible gene expression as a factor in choosing an optimal dose of SD-101 is to ensure that an appropriately active dose of SD-101 will be used since preclinical data have suggested that high doses of CpGs may paradoxically lower CpG stimulated immune response due to a

compensatory mechanism of the immune system. Induction of IFN-α responsive genes is considered a surrogate for the activity of SD-101 since engagement of TLR9, the target of SD-101, indirectly resulting in an upregulation of these genes. Specifically, fold increases in IFN-inducible genes will be analyzed per individual gene and as a combination of genes on a cohort basis to provide assurances that an appropriately active dose of SD-101 will be used.

IFN-inducible gene expression may also be measured in up to 12 patients in each of the Phase 2 Expansion HNSCC cohorts to understand HNSCC tumor responses.

8.2 Response Evaluation and Criteria

NOTE: As of Amendment 9, Section 8.2 and its subsections (8.2.1, 8.2.1.1, and 8.2.1.2) are no longer applicable. All disease response assessments, including the timing, type, and evaluation of imaging, are to be performed and assessed per the Investigator based on local standard of care; the data will not be collected and no longer need to be recorded in the CRF. Confirmation of progression by repeat imaging is not mandatory. Decisions on treatment discontinuation should be made per Investigator based on local standard of care and in accordance with the stopping rules outlined in Section 9.2. The text in these sections is retained as a reference only to aid Investigators in making treatment decisions and is not mandatory.

All baseline efficacy evaluations will be performed at Screening. Baseline radiographic and superficial measurement (as applicable for superficial lesions) must be performed no more than 4 weeks prior to study enrollment. The same imaging method used at baseline should be used throughout the study unless a change is required due to AEs (eg, new radiographic contrast allergy) per local radiology guidelines.

Evaluation of superficial lesions requires both photographic and manual (caliper) measurement at all time points that radiographic imaging is required per Schedule of Trial Events (Appendix 1 through Appendix 4). Although radiographic imaging collected at the scheduled time points is preferred, it is allowed to be obtained the day prior to study treatment.

Response to treatment and disease progression will be evaluated by the investigator and recorded on the CRF every 9 weeks after the first trial injection until Day 379 and then every 12 weeks thereafter for the remainder of the trial. All treatment response and disease progression require confirmation of response (complete response [CR] or partial response [PR]) using RECIST v1.1 and irRECIST, which is the study-specific irRECIST that requires confirmation of disease progression with an additional scan obtained at least 4 weeks later that also meets the criteria of PD per RECIST v1.1 (Appendix 6, Immune-related RECIST). Patients with suspected disease progression should continue to follow trial procedures until they have confirmed disease

progression. It is at the discretion of the investigator whether to continue a patient on study treatment until repeat imaging is obtained (per irRECIST patient management). This clinical judgment decision by the investigator should be based on the patient's overall clinical stability defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
2) No decline in ECOG PS
3) Absence of rapid progression of disease
4) Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If repeat imaging confirms PD due to any of the scenarios listed in Appendix 6, Immune-related RECIST, patients will be discontinued from study therapy. If repeat imaging does not confirm PD by irRECIST and the patient continues to be clinically stable, treatment may continue and follow the regular radiographic imaging schedule. If a patient requires another anti-cancer therapy, radiographic imaging and measurement of superficial lesions will be discontinued.

Please refer to Section 10.8 for EOS visit and procedures regarding discontinuation from the trial.

8.2.1 Response Criteria

8.2.1.1 RECIST v1.1 and Immune-related RECIST

NOTE: As of Amendment 9, this section is no longer applicable. All disease response assessments are to be performed and assessed per the Investigator based on local standard of care; the data will not be collected and no longer need to be recorded in the CRF. The analysis of ORR and DCR may be performed based on data collected prior to Amendment 9.

Response of lesions and disease status will be assessed using standard RECIST 1.1 for the primary evaluation of response and the study specific modified RECIST referred to as irRECIST for an exploratory evaluation. The primary difference between RECIST v1.1 and irRECIST is the requirement for confirmation of PD with additional imaging at least 4 weeks later that also qualifies as PD per RECIST v1.1. Details are listed in Appendix 6, Immune-related RECIST. Throughout the trial, each respective investigator will determine and manage disease status (progression or response) of patients per RECIST v1.1 and irRECIST at the specified imaging time points (Appendix 1 through Appendix 4) or more frequently as clinically indicated.

RECIST v1.1 was adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST v1.1 will be used with the following adaptations (see Appendix 6, Immune-related RECIST):

- Determination of 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 [SOD]).
- Continued treatment while awaiting radiologic confirmation of progression is encouraged if the patient is clinically stable.

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

In Phase 2, ORR and DCR will be evaluated, which will comprise all lesions as well as for injected and non-injected lesions independently. The ORR will include patients with CR or PR. The DCR will include patients with CR, PR, or stable disease. The ORR and DCR will be determined using both RECIST v1.1 and irRECIST. Details of analyses will be provided in a separate study statistical analysis plan.

8.2.1.2 Radiographic Assessment

NOTE: As of Amendment 9, this section is no longer applicable. All disease response assessments, including the timing, type, and evaluation of imaging, are to be performed and assessed per the Investigator based on local standard of care; the data will not be collected and no longer need to be recorded in the CRF. Decisions on treatment discontinuation should be made per Investigator based on local standard of care and in accordance with the stopping rules outlined in Section 9.2.

Disease assessment will include CT (preferred) or MRI scan of chest, abdomen and pelvis, brain, and other areas as clinically indicated (Appendix 7). Screening imaging for all patients requires imaging of the brain, chest, abdomen, pelvis, and other areas as clinically indicated. In addition, screening imaging for HNSCC patients requires imaging of the neck. Post-baseline imaging for melanoma patients includes chest, abdomen, pelvis, and other areas as clinically indicated. Post-baseline imaging for HNSCC patients includes chest, abdomen, pelvis, neck, and other

areas as clinically indicated. The same imaging techniques used at baseline MUST be used at all subsequent time points to permit accurate and comparable measurement of lesions. Post-baseline radiographic assessment must image all anatomic areas in which there are malignant disease/metastases demonstrated on screening imaging.

Patients are required to have their baseline radiographic evaluations within 4 weeks of study enrollment and will have their first post-baseline radiographic assessment in the trial on Day 64 (± 3 days), unless there is clinical indication warranting earlier imaging, and will have follow-up assessments every 9 weeks (± 3 days) until Day 379 then every 12 weeks (± 3 days) thereafter until the end of the trial. Although radiographic imaging collected at the scheduled time points is preferred, it is allowed to be obtained the day prior to study treatment.

Trial treatment will be discontinued for a patient if the patient shows confirmed disease progression (unless requested by an investigator with written approval by a Dynavax Medical Monitor) as described in Section 9.2.

Radiographic imaging will be continued until start of a new anti-cancer treatment or the end of the trial.

8.3 Biomarker Analysis

NOTE: As of Amendment 9, this section is no longer applicable.

Biopsies of Lesion A and 1 or more other accessible lesions will be analyzed for changes in correlative biomarkers (changes over time relative to baseline) including tumor-infiltrating lymphocytes and PD-L1 expression.

9.0 MANAGEMENT OF TRIAL TREATMENT TOXICITIES

NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to continue dosing per protocol. The collection of safety endpoints has been simplified. Decisions on treatment discontinuation should be made per Investigator based on local standard of care. This section has been updated accordingly.

Safety will be evaluated through the careful monitoring of all clinical and laboratory AEs. Safety assessments may include vital signs, weight, physical examinations, ECOG PS, electrocardiograms (ECGs) and laboratory safety tests (eg, complete blood count [CBC], serum chemistry, PTT or aPTT, urinalysis, thyroid function). See Section 10.3.6 for additional details of laboratory testing. Special attention will be given to immune-related adverse effects (eg, gut, skin, liver, endocrine organs).

All AEs will be graded and recorded throughout the trial according to National Cancer Institute (NCI) CTCAE, Version 4.03. The severity of the local post-injection reactions, including those that become AEs because they persist more than 7 days, will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 5). Characterization of toxicities will include time to onset, severity, and duration. Safety endpoints will include all types of drug-related AEs and SAEs regardless of causality.

Phase 1 will be reviewed by a Safety Review Team comprised of the Dynavax Medical Monitor, Phase 1 coordinating investigator, and other key safety Dynavax personnel as described in the Cohort Safety Review Plan. Before Dose Escalation at each dose level of SD-101 and at any other time during Phase 1 or Phase 2 that warrants additional review due to emerging safety data, the investigators will discuss and review the safety data with the Dynavax Medical Monitor.

9.1 Dose-limiting Toxicity Definitions and Stopping Rules *(COMPLETE)*

Standard safety monitoring will be employed for DLT assessment and dose-escalation decisions. All AEs will be considered in DLT assessment unless an event is clearly unrelated to trial treatment.

Before Dose Escalation at each dose level of SD-101 and at any other time that safety data warrant review, the investigators will participate in a teleconference with the Dynavax Medical Monitor to review all safety data. Additionally, at all times during the course of the study, an increased frequency of Grade 3 immune-related AEs to 2 times that which would be anticipated with pembrolizumab alone will require a halt in accrual and a review of all safety data by the sponsor and investigators.

All AEs, including DLTs, are to be reported according to instructions in the Study Reference Manual and graded using NCI CTCAE, Version 4.03 (National Cancer Institute 2010). If a patient experiences a DLT, he or she will be treated according to clinical practice and will be monitored for resolution of the toxicity.

The safety profiles of SD-101 (see Investigator's Brochure) and pembrolizumab (Merck & Co. 2015) as monotherapies have been previously described. The safety profile of the combination of the drugs is unknown. Toxicity of the combination of SD-101 and pembrolizumab may likely manifest as there might be an increase in the frequency, severity, or duration of known toxicity such as flu-like illness due to SD-101 or immune-related AEs due to pembrolizumab. The outcome of a DLT considered related to SD-101 will be discontinuation of SD-101. Toxicity due to pembrolizumab will lead to dose interruption and/or discontinuation as described in Section 7.6 and be managed according to Section 7.7. DLTs considered related to the combination of the

2 drugs will be reviewed and assessed in a teleconference with the Dynavax Medical Monitor and the investigators.

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.

If a patient experiences a DLT, they should not receive further injections of SD-101. If SD-101 is discontinued, a patient may continue to receive pembrolizumab alone with approval by the Dynavax Medical Monitor until required discontinuation per Section 9.2.

After a patient is discontinued from trial treatment and if progressive disease has been confirmed, a mandatory EOS visit should be performed approximately 28 days after the last administration of trial treatment (See Section 10.8 for details).

9.1.1 Staggered Dosing for Phase 1 *(COMPLETE)*

For Dose Escalation cohorts in Phase 1, SD-101 and pembrolizumab will be administered first to a sentinel patient. In the 2.0 mg cohort, if after 72 hours no DLT has occurred, the second patient may be treated. If after 72 hours no DLT has occurred, the third patient may be treated. In the 4.0 mg, and 8.0 mg cohorts, a sentinel patient will be treated. If after 72 hours no DLT has occurred, the dose will be considered as tolerated in the sentinel patient and the remaining 2 patients will receive SD-101 and pembrolizumab. Lower or intermediate dose cohorts will not require staggered enrollment with a sentinel patient and may be enrolled concurrently with the higher dose cohorts.

If DLT occurs in the first sentinel patient within 72 hours, dosing will not continue with the remainder of the cohort until review of the sentinel patient safety data by the investigators and medical monitors. Dosing of a second sentinel patient with SD-101 and pembrolizumab may be considered if agreed upon by the investigators and sponsor. If no DLT is observed for the second cohort patient within 72 hours, then the remaining patients in the cohort may be enrolled and treated. If the second sentinel patient in the dose cohort experiences DLT within 72 hours and DLT is confirmed in safety review, then 2 DLTs will have been observed and the dose will be considered not tolerated. No further patients will be enrolled or dosed at that dose level.

9.1.2 Safety Review and Dose Escalation *(COMPLETE)*

Prior to proceeding with Dose Escalation, the safety data during the DLT Assessment Period will be evaluated for the entire dose cohort. The cohort safety data will be reviewed at that time for DLTs and declared as either tolerated or not tolerated, based on the number of patients experiencing DLTs as follows:

- 0 - 1 patients with DLT: dose tolerated
- 2 or more patients with DLT: dose not tolerated

If no more than 1 DLT is observed in all patients in the current cohort, Dose Escalation will proceed and the sentinel patient in the next cohort will receive the assigned dose. The same process will be followed sequentially for all dose cohorts.

If a dose is declared not tolerated, additional patients may be enrolled in a lower or intermediate dose cohort following discussions between the investigators and the sponsor to determine the MTD. Once the proposed RP2D has been declared, an additional 6 patients may be enrolled and evaluated at this dose for safety. If 6 patients have not been dosed and cleared of DLT at the proposed RP2D or a higher dose level, additional patient(s) will be enrolled and undergo DLT evaluation to meet this 6-patient minimum prior to declaration of an RP2D and enrollment of Phase 2 patients. Sites will be notified in real time when the MTD has been defined or when study stopping rules have been applied to prevent unnecessary patient exposure.

The outcome of each safety review will be documented and disseminated via e-mail to all participating clinical sites upon the completion of each meeting. Official documentation submitted to clinical sites will note whether any DLTs or significant safety data trends were observed. It will also include instructions to all personnel with respect to decisions regarding expansion of enrollment within a particular cohort, Dose Escalation or halting of further enrollment or dosing in the study.

9.2 Reasons for Stopping a Patient From Receiving Additional Treatment

NOTE: As of Amendment 9, the use of irRECIST for determination of disease progression is no longer applicable and this section has been revised accordingly. It is at the discretion of the investigator as per local standard of care and assessment guidelines whether to repeat imaging for confirmation and whether to continue a patient on study treatment until repeat imaging is obtained.

Patients will be discontinued from either trial treatment by the investigator for any of the following reasons:

- Noncompliance with trial procedures as determined by the investigator or sponsor
- Pregnancy in patient and/or initiation of breast feeding (see Section 10.3.7)
- Use of or need for prohibited medications (as described in Section 7.4)
- Confirmed PD per local standard of care and local assessment guidelines
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AEs
- Adverse drug reaction that requires study drug discontinuation per protocol (see Section 7.6)

- Need for > 2 dose delays due to toxicity as per the dose modification guidelines described in Section 7.6
- If in the opinion of the investigator, a change or discontinuation of therapy would be in the best interest of the patient
- Patient has completed 35 doses and/or 2 years (Study Day 715) of pembrolizumab therapy

The investigator or designee must notify Dynavax when a patient has been discontinued from treatment. If SD-101 is discontinued prior to completion of planned study dosing, a patient may continue on pembrolizumab alone per investigator decision and approval of the Dynavax Medical Monitor.

In patients who have initial evidence of radiographic PD, it is at the discretion of the investigator whether to repeat imaging for confirmation and whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including ECOG PS, clinical symptoms, and laboratory data. Patients may receive pembrolizumab and SD-101 treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Patients who discontinue pembrolizumab must discontinue SD-101. If pembrolizumab treatment is temporarily withheld, treatment of SD-101 and pembrolizumab will start on the same day once pembrolizumab is resumed. Pembrolizumab may be continued as a single agent if SD-101 is discontinued per investigator decision. Delayed dosing of SD-101 would be preferred over completely skipping a dose as long as the interval between SD-101 dosing is not less than 5 days with subsequent return of SD-101 dosing to per protocol schedule of events. See Section 7.6 for details regarding delayed or skipped doses.

> **Note: Written informed consent must be obtained from a subject prior to receiving study treatment after disease progression has been confirmed.**

9.3 Management of Patient Safety

NOTE: As of Amendment 9, Phase 1 of the trial is complete. Phase 2 of the trial has been modified to simplify collection of safety endpoints. This section has been updated accordingly.

If a patient experiences any flu-like symptoms during the 24 to 48 hour period following SD-101 injection, then the patient may take acetaminophen, maximum 3 g per day, ibuprofen (at labeled dosing), or ondansetron as needed for 24 to 48 hours post-injection. If symptoms are severe and unresponsive to standard therapy, codeine may also be used. For subsequent injections of SD-101, acetaminophen, ibuprofen, or ondansetron may be taken prophylactically before and after SD-101 injection. For prophylaxis, recommended dosing of acetaminophen and/or ibuprofen is 2 hours before and 6 hours after dosing with continuation for 24 to 48 hours. Doses and frequencies of acetaminophen, ibuprofen, ondansetron, and codeine should be per the product label.

9.3.1 Management of Injection-site Reactions

Injection-site reactions should be managed conservatively, as they are expected to spontaneously subside. Local pruritus can be treated with diphenhydramine and pain can be treated with oral medications as described in the previous section. If significant symptoms of pain and induration persist for more than 12 hours, applications of an ice pack locally for 30 minutes every 2 hours, as needed, may be instituted. Use of ice pack prior to 12 hours after the onset of symptoms is discouraged as it may interfere with the action of the drug. The site is not to be injected if local pain, tenderness, or swelling persists from a previous injection or other cause has not resolved to Grade 0 or 1 for local site reactions (see Appendix 5). The injection may be delayed until the symptoms have resolved or the injection may be skipped (see Section 7.6).

An unscheduled visit (UNS) (Section 10.9) should be performed if there is suspected disease progression or patient safety concerns. All supportive therapies will be recorded in the patient's CRF. All patients are required to have an EOS visit (Section 10.8) 28 days after discontinuation of all study treatments.

9.3.2 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 9-1 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

Table 9-1: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hr	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • Intravenous fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grades 3 or 4 **Grade 3**: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4**: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Intravenous fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing

Source: From Merck guidance (on file with sponsor)
IV = Intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDS = nonsteroidal anti-inflammatory drugs.

Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

10.0 TRIAL PROCEDURES

NOTE: As of Amendment 9, trial procedures have been simplified. This section has been updated accordingly.

All tests and evaluations required at specified time points are listed in the Schedule of Trial Events (Appendix 1 through Appendix 4). The results of these tests and evaluations must be entered in the patient's source document and also recorded on the patient's CRF. All other tests and evaluations, including disease assessment and safety monitoring, are to be performed at the discretion of the investigator per local standard of care; these data will not be collected or recorded on the patient's CRF. Adverse events should be reported through safety reporting as described in Sections 10.3.9 and 10.3.10.

10.1 Informed Consent and Screening Log

The investigator or designee must review the informed consent form (ICF) with each prospective patient to be certain that the prospective patient understands the procedures and risks of the trial. Prospective patients who wish to participate in the trial must provide written informed consent by signing the ICF before undergoing any screening procedures. Patients may undergo trial screening tests prior to giving written informed consent provided that these tests are considered part of standard care.

The information from the consent form should be translated and communicated to the patient in language understandable to the patient.

A copy of the signed and dated consent form should be given to the patient before participation in the trial. The initial ICF and any subsequent revised written ICF, and written information must receive the Institutional Review Board (IRB) approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

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

Additional requirements for informed consent are presented in Section 14.3.

10.1.1 Eligibility

After written consent is obtained, screening procedures must be carried out per the Schedule of Trial Events (Appendix 1 through Appendix 4). A patient must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the trial. A copy of the pathology report confirming diagnosis of metastatic melanoma or recurrent or metastatic HNSCC must be obtained prior to enrollment. Assignment of patient number and dose is described in the Study Reference Manual.

10.1.2 Tumor Biopsy

Tumor biopsies from Lesion A (the target lesion to be injected) are required at Screening within 28 days prior to the first dose of SD-101. Two samples are required. The 2 samples can be taken as a single biopsy split into 2 samples or 2 separate biopsies and must meet the minimal sample size requirement per the study laboratory manual (ie, a minimum of 4 to 6 mm specimen, obtained via punch, core needle [14 gauge or smaller gauge needle], or surgical excision). One sample is for determining the expression level of PD-L1, and the other sample is for RNA expression profiling. The PD-L1 expression could be from an archival tissue sample of the target lesion if collected within 3 months of screening. A fresh biopsy needs to be obtained for the RNA profiling.

Subsequent tumor biopsies, which are taken after the start of study treatment, are obtained at time points specified per the schedule of trial events (Appendix 1 through Appendix 4) and are collected pre-injection on treatment days or within the visit window. Two samples are required for these subsequent biopsies. A single biopsy can be split into 2 samples or 2 separate biopsies can be collected. Biopsies are required to meet the minimal sample size as indicated in the study laboratory manual. One sample will be used for immunohistochemistry and the second sample will be used for RNA expression profiling to identify and assess changes in immune cells and gene expression responses in the tumor microenvironment. Lesion A should be of a sufficient size such that the intratumoral biopsy does not compromise the investigator's ability to assess the lesion size changes per RECIST over time. If Lesion A is completely regressed, subsequent replacement lesion(s) do(es) not need to be biopsied. For Lesion A, biopsies would not be done in cases where it is judged by the investigator and in consultation with the Dynavax Medical Monitor to be not appropriate or feasible for either medical or technical reasons.

Written patient consent is required for biopsies. Tumor biopsies may be obtained via punch, core needle, or surgical excision. Biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes). If a core biopsy is performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis (eg, immunohistochemistry of PD-L1, PD-L2, and other immunological markers; ribonucleic acid

[RNA] signature profiling), mutational load (HNSCC only), and formation of neoantigens (HNSCC only). (Details of tumor biopsy procedures including tumor biopsy processing and shipping procedures are provided in the study laboratory manual.)

Tumor biopsies should be collected prior to injection of SD-101. When collecting biopsies, local anesthetics may be used with the exception of topical anti-inflammatories or topical steroids. Local anesthetics should be given such that subsequent SD-101administration will not result in dilution of the study drug (ie, avoid needle tracking between procedures and administer local anesthetic not directly in the tumor or away from the targeted site of intratumoral injection of SD-101).

A biopsy from a non-injected lesion and an injected lesion other than Lesion A at the same baseline and treatment time points as required for Lesion A is optional but highly desired. In addition, a biopsy of Lesion A, an injected lesion other than Lesion A, and a non-injected lesion at disease progression is optional but highly desirable. Collections are to be done pre-injection and may occur pre-injection on treatment days or within the visit window prior to treatment.

Exceptions for not performing biopsies are when there is a potential safety risk to the patient as determined by the Investigator in consultation with the Dynavax Medical Monitor.

10.2 Trial Visits

Procedures should be performed as close to the scheduled time as possible. The window for weekly study visits is ± 1 day and ± 3 days for every 3 week visits. The window for 24-hour visits is ±3 hours. Windows for protocol specified imaging is ± 3 days. The visit schedule during the SD-101 dosing varies for the Phase 1 and Phase 2 Cohorts. After completion of SD-101 dosing (Trial Treatment Period), the visit schedule follows pembrolizumab dosing (Extended Pembrolizumab Treatment) with study visits Q3W until EOS.

A detailed outline of all scheduled trial procedures is provided in the Schedule of Trial Events (Appendix 1 through Appendix 4). Procedures should be performed at the trial center where the patient is being treated. Patients who fail screening may be rescreened per approval by the sponsor.

The exact time at which a procedure is performed must be recorded in the patient's trial records or appropriate worksheet (if applicable). Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

Blood collections for safety evaluation assume priority over other procedures. Whenever possible, blood samples should be obtained by fresh peripheral venipuncture. If a patient does not have peripheral access, the sample may be collected from a central catheter immediately after

an initial withdrawal of at least 10 mL of blood; or preferably, after a series of other blood sample collections from the central catheter.

The patient will be assessed for AEs per the Schedule of Trial Events (Appendix 1 through Appendix 4).

During Extended Pembrolizumab Treatment, sites will administer pembrolizumab Q3W and follow standard of care laboratory and assessment practices. Sites are required to report SAEs that occur during the Extended Pembrolizumab Treatment as described in Section 10.3.10 but are not required to document in the eCRF laboratory, imaging, or other patient assessments performed to monitor safety or to assess disease response or treatment during the Extended Pembrolizumab Treatment period.

If pembrolizumab treatment is temporarily withheld, treatment of SD-101 and pembrolizumab will start on the same day once pembrolizumab is resumed. Delayed dosing of SD-101 would be preferred over completely skipping a dose as long as the interval between SD-101 dosing is not less than 5 days with subsequent return of SD-101 dosing to per protocol schedule of events (see Section 7.6 for details regarding delayed or skipped doses). If both study drugs are on hold, the study visit(s) during the hold period may be skipped, with the exception that radiographic imaging must be performed according to schedule.

10.3 Safety Assessments

The safety assessments are listed below. The Schedule of Trial Events is provided in Appendix 1 through Appendix 4.

10.3.1 Medical and Medication History

Medical history includes clinically significant diseases, surgeries, cancer history, and all medications (eg, prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the Screening Visit. Baseline melanoma and HNSCC disease status, histology, stage, and molecular profiling of genetic alterations or mutations (if available) will be recorded. Prior treatment includes treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Results from any prior genetic screening tests and any immunohistochemical (IHC) tests, such as for PD-L1, will be recorded. The date of last prior cancer treatment and the response to that treatment must be documented. Radiographic studies performed prior to trial entry may be collected for review by the investigator.

10.3.2 ECOG Performance Status Assessment

An assessment of PS will be performed using the ECOG PS scale of 0 to 5 (Appendix 8).

10.3.3 Vital Signs

Vital signs will be recorded and will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oximetry. Vital signs taken at injection visits will include oral temperature.

10.3.4 Physical Examinations

The investigator or qualified designee will conduct physical examinations. A complete physical examination will be conducted at Screening and EOS/Safety Follow-up Visit, and a targeted physical examination (based on interval history and/or AEs) including assessment of superficial lesions will be conducted at other visits per the Schedule of Trial Events (Appendix 1 through Appendix 4).

10.3.5 Electrocardiogram

An ECG (12-lead with standard parameters of heart rate, shape, size and duration of P wave, P-R interval, QRS, QT interval, QTc interval, and T wave configuration) will be performed at Screening, after treatment on Day 15 and 29, and EOS for Phase 1 and at Screening for Phase 2. Additional ECGs should be obtained to evaluate AEs as applicable per standard of care.

10.3.6 Safety Laboratory Assessments

Laboratory assessments are listed below and will be performed according to the Schedule of Trial Events (Appendix 1 through Appendix 4). Sample collections prior to injection and infusion on treatment days are preferred; however, these samples are allowed to be obtained the day prior to dosing. Routine laboratory tests (serum chemistry, hematology) for screening, including pregnancy testing may be obtained per standard of care and used for screening laboratory and determination of study eligibility as long as obtained within 28 days of first dose of pembrolizumab. Laboratories obtained within 7 days of Day 1 visit, with the exception of a CBC with ANC, do not need to be repeated on Day 1.

- Hepatitis and HIV testing at Screening Visit: serum hepatitis B, hepatitis C, and HIV testing per institutional standard of care as determined by laboratory tests for HBsAg, anti-HBc, and anti-HBs; anti-HCV; and anti-HIV -1/2, respectively

- Chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, AST, ALT, LDH, bilirubin, alkaline phosphatase, and C-reactive protein (CRP)
- Hematology: hemoglobin, hematocrit, white blood cell count with differential, and platelet count
- Thyroid function tests: free T3, free T4, and thyroid stimulating hormone (TSH)
- Coagulation: PT and aPTT
- Reserve serum aliquot specimens will be collected and stored frozen for possible future testing.
- Urinalysis with microscopy

Additional details for specific tests are provided in the Laboratory Manual.

10.3.7 Pregnancy

10.3.7.1 Pregnancy Testing

All WOCBP (as defined in Section 5.2.1) who are being considered for participation in the trial will be tested for pregnancy with a serum or urine β-hCG test within 72 hours prior to taking the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, then a serum test is required which must be negative for the patient to enroll. Additional pregnancy testing should be scheduled per local regulations where applicable.

10.3.8 Injection-site Reaction Assessments

Assessments of injection-site reactions will be collected for a minimum of 90 minutes following each of the first 4 initial weekly SD-101 injections in Phase 1 as outlined in the Schedule of Trial Events (Appendix 1 through Appendix 4) at the clinical site and as reported by the patient on the Diary Card for 7 days in Phase 1.

With Protocol Amendment 6, Diary Cards are discontinued in Phase 2; however, injection site reactions listed on the Toxicity Grading scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials (Appendix 5) that persist for more than 7 days will be recorded as AEs (Section 11.1).

Prior to the first 4 initial weekly injections of SD-101 in Phase 1 (Appendix 1), patients will receive a new Diary Card with instructions to measure and record local injection-site reactions and solicited AEs that occur post SD-101 injection. The completed Diary Cards will be reviewed with the patients at their next study visit.

For the first 4 weekly injections of SD-101 in the first course in Phase 1, Dynavax will capture all injection-site reactions that occur, even if the diameter of the largest dimension does not meet a Grade 1 on the severity scale (Appendix 5). 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*).

All data documented by the patient on Diary Cards will be collected, reviewed by the trial nurse/coordinator with the patient, and recorded on the appropriate CRF.

Injection-site reactions need to be recorded also on the AE eCRF for the following:

1) The duration of the injection-site reaction exceeds 7 days
2) The verbatim term for the injection-site reaction is different than the terms listed for the diary and provided for recording on the injection-site reaction eCRF
3) The injection-site reaction qualifies as an SAE.

10.3.9 Adverse Events

All AEs, as defined in Section 11.2, will be evaluated from immediately after the first trial treatment on Day 1 through 28 days after last dose of trial treatment.

10.3.10 Serious Adverse Events

All SAEs, as defined in Section 11.3.1, will be evaluated from the time the consent is signed through 90 days following cessation of trial treatment or EOS (whichever is later), or 28 days following cessation of trial treatment if the patient initiates new anti-cancer therapy. Any SAE must be reported to Dynavax or its designee within 24 hours of the knowledge of the event.

An SAE, whether assessed as related or not related to study treatment, will be followed until considered stable, resolved, or until EOS, or the patient initiates new anti-cancer therapy (whichever is earlier).

10.3.11 Concomitant Medications

Any prescription medication, over-the-counter drug or natural/herbal preparations, including vitamins and dietary supplements, and transfusions, including those for the treatment of any AEs, taken by the patient from Screening through 28 days after permanent discontinuation of all study treatment must be recorded in EDC.

10.4 Disease Assessments

NOTE: As of Amendment 9, all disease response assessments, including the timing and type of imaging, are to be performed per the Investigator based on local standard of care; the data will not be collected and no longer need to be recorded in the CRF. This section has been updated accordingly.

Disease assessment will consist of: 1) clinical assessment of superficial lesions, and 2) radiographic imaging (See Section 8.2.1.2). Such assessments will be performed at baseline no more than 28 days prior to the first dose of trial treatment and at the discretion of the investigator as per local standard of care thereafter (Appendix 1 through Appendix 4).

10.4.1 Confirmation of Progressive Disease (Based on irRECIST)

NOTE: As of Amendment 9, irRECIST is no longer applicable and this section has been deleted accordingly. All imaging will be performed as per local standard of care guidelines. It is at the discretion of the investigator whether to repeat imaging for confirmation and whether to continue a patient on study treatment.

Determination of PD is per local standard of care and local assessment guidelines.

10.5 Pharmacodynamic Assessments

NOTE: As of Amendment 9, this section is no longer applicable.

- Phase 1: Blood will be collected for assessing IFN-inducible gene expression. Collections are to be done pre-injection on treatment Days 1 and 8 (Appendix 1). On Day 9, the sample is to be collected 24 hours after the Day 8 injection.
- Phase 2: Blood will be collected for possible future testing of RNA gene expression. Collections are to be done at Screening and pre-injection on study days as specified in Appendix 2 and Appendix 4.

For both phases of the study, an extra aliquot of serum will be collected and stored frozen for possible future testing at time points outlined in Appendix 1 through Appendix 4.

10.6 Immunogenicity Assessments

NOTE: As of Amendment 9, this section is no longer applicable.

To determine if antibodies to SD-101 are generated following administration of SD-101, blood will be collected as outlined in Appendix 1 through Appendix 4.

10.7 Exploratory Assessments

NOTE: As of Amendment 9, Sections 10.7.1, 10.7.2, and 10.7.3 are no longer applicable.

10.7.1 Expression Profiling

Exploratory assessments for PD-L1 expression by immunohistochemistry, and RNA expression profiling to determine the infiltration of lymphocytes and other immune-related responses may be assessed and correlated with clinical response.

10.7.2 Neoantigen and DNA Mutational Analyses

Studies of genetic mutations, polymorphisms, and rearrangements are increasingly important in understanding and ultimately predicting responses to cancer therapies targeting the anti-tumor immune response. For recurrent or metastatic HNSCC, sequence analysis of selected samples of tumor and blood may be conducted as an exploratory assessment.

In addition to understanding the anti-tumor responses, the sequence analysis can identify mutations that, when expressed by a tumor, are potentially immunogenic (ie, neoantigens) and can inform additional targeting therapeutic strategies for future clinical studies. Confirmation of the identification of neoantigens will be done using PBMCs, which will be stimulated with peptides corresponding to the identified neoantigens and analyzed for activation through secretion of cytokines by ELISpot. Sequencing may be conducted for biopsies collected in the HNSCC trial. PBMCs for confirmation of the identification of neoantigens may be obtained at sites that are able to isolate and freeze viable PBMCs at the time of biopsy collection in the HNSCC portion of the trial. Collection time points are indicated in the Schedule of Trial Events located in Appendix 2 and Appendix 4. The Laboratory Manual will provide details on the procedure for sample collection.

10.7.3 Human Papillomavirus Status

For HNSCC patients only, HPV status (positive + or negative) at Screening will be determined from either archival test results or new testing as described in the Schedule of Trial events Appendix 2 through Appendix 4.

10.8 End-of-Study/Safety Follow-up Visit

NOTE: As of Amendment 9, trial procedures have been simplified. This section has been updated accordingly.

The EOS /Safety Follow-up Visit is required after permanent discontinuation of trial treatments (both SD-101 and pembrolizumab), regardless of the reason for discontinuation [to be completed 28 (± 3) days after last dose of trial treatment].

10.9 Unscheduled Visit for Safety or Disease Progression

NOTE: As of Amendment 9, all disease assessments will be performed as per local standard of care guidelines. Confirmation of disease progression by repeat imaging is not mandatory.

A UNS should be performed if there is suspected disease progression or patient safety concerns. Procedures for the visit are at the discretion of the investigator according to local standard of care guidelines.

If the patient has permanent discontinuation of trial treatments (both SD-101 and pembrolizumab), an EOS Visit (Section 10.8) should be scheduled 28 days after the date of last trial treatment administration.

10.10 Duration of Follow-up

NOTE: As of Amendment 9, follow-up procedures have been simplified. This section has been updated accordingly.

All patients must be followed for at least 28 days after their last dose of trial treatment (Section 11.0). Patients who discontinue trial treatment without documented disease progression should be assessed per local standard of care guidelines until the EOS/Study Follow-up visit is complete.

11.0 INVESTIGATOR'S RESPONSIBILITIES

This trial will be conducted in accordance with the protocol, the International Council for Harmonisation (ICH) E6(R2) GCP guidelines and applicable US Code of Federal Regulations (CFR) and local regulatory requirements. Investigators are responsible for monitoring the safety of patients throughout the course of the trial and for providing appropriate medical care. The investigator will perform all tasks directly or is responsible for overseeing and training qualified site personnel as delegated to perform trial tasks. In addition, investigators are responsible for alerting Dynavax to any event that seems unusual and for reporting all AEs, event of clinical interests (ECIs), SAEs, pregnancies, and deaths in the appropriate CRFs.

11.1 Injection-site Reactions

Local injection-site reactions will be assessed and documented per Section 10.3.8. Local injection-site reactions are considered AEs if they persist longer than 7 days and need to be recorded and reported per protocol Section 11.2. The severity of the injection-site reactions will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 5).

The severity of all injection-site reactions that are not listed on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 5) will be assessed and confirmed by the investigator and will be graded using the adapted NCI CTCAE Version 4.03 grading scale (Table 11-1).

Further information is provided in the Study Reference Manual.

11.2 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the trial treatment.

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

Progression of the cancer under study is not considered an AE or SAE and should not be reported as an AE or SAE.

An uncomplicated pregnancy is not an AE or SAE and should not be reported as an AE/SAE. Patients should be followed as described in Section 11.5.

The reporting period for all non-serious AEs begins at the time of the first trial treatment (Day 1) through 28 days after last dose of trial treatment. Patients who are withdrawn due to an AE should have an AE assessment completed 28 days or more after their last trial treatment. All AEs will be captured on the AE CRF.

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

The investigator will follow all related AEs observed during the trial until the AEs are considered resolved or until 28 days after last dose of trial treatment or the patient begins new anti-cancer therapy, whichever is earlier. Dynavax or the Dynavax designee may request additional follow-up on specific unresolved events.

11.2.1 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as ECIs and must be reported to the sponsor.

ECIs must be reported following the reporting period for AEs (the initiation of study treatment through 28 days after permanent discontinuation of trial treatment) or, if they qualify as an SAE, following the reporting period for SAEs (through 90 days following cessation of trial treatment or EOS (whichever is later), or 28 days following cessation of trial treatment if the patient initiates new anti-cancer therapy). Any ECIs (as defined in this section) or follow up to an ECI that occurs in any patient **must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event** (regardless of whether the investigator assesses the event as probably or possibly related to study drug). Reporting must be made by electronic media and on the Safety Report Form (regardless of whether the investigator assessed the event as serious or not serious) per SAE reporting procedures. Electronic reporting procedures can be found in the electronic data capture (EDC) data entry guidelines. Safety reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

ECIs for this trial include:

1) An overdose of SD-101 or pembrolizumab, as defined in Section 11.2.2.

   OR

2) An elevated AST or ALT lab value that is greater than or equal to 3 X the ULN and an elevated total bilirubin lab value that is greater than or equal to 2 X the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 X the ULN, as determined by way of protocol-specified laboratory testing or UNS laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

11.2.2 Overdoses

An overdose of SD-101 is defined as more than twice the protocol-specified dose.

An overdose of pembrolizumab is defined as ≥1000 mg (≥ 5 x the prescribed dose).

An overdose of SD-101 or pembrolizumab, regardless of the presence of an associated AE or SAE, is considered an ECI and must be documented and reported according to the ECI requirements described in Section 11.2.1.

Additionally, an AE or SAE associated with an overdose of SD-101 or pembrolizumab must be documented and reported according to the respective requirements for AEs or SAEs.

11.2.3 New Cancer (Not the Cancer Being Investigated Under the Study)

Any new non-serious or serious cancer (not the cancer being investigated under the study), whether or not the new cancer is related to the trial treatment (SD-101 and/or pembrolizumab), **must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event per SAE reporting procedures**.

The occurrence of any non-serious new cancer will follow the reporting period for AEs (Section 11.2) and the occurrence of any serious new cancer will follow the reporting period for SAEs (Section 11.3).

11.2.4 Definition of Adverse Reaction

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

11.2.5 Definition of Suspected Adverse Reaction

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

11.2.6 Definition of Unexpected Adverse Event or Unexpected Suspected Adverse Reactions

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

11.3 Serious Adverse Events

11.3.1 Definition of Serious Adverse Events

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

- Results in death;
- Is life-threatening;

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

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

  Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient. Examples of such events are allergic bronchospasm requiring treatment in an emergency room, serious blood dyscrasias, or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

11.3.2 Serious Adverse Event Reporting Requirements

Any SAE that occurs from the time the consent is signed through 90 days following cessation of trial treatment or EOS (whichever is later), or 28 days following cessation of trial treatment if the patient initiates new anti-cancer therapy, whether or not the SAE is related to the trial treatment (SD-101 and/or pembrolizumab), **must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event**. The contact information for reporting SAEs is provided in the Study Reference Manual. General SAE reporting instructions are as follows:

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

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

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

The relationship of the SAE to trial treatment will be assessed by the investigator (Section 11.4.2). Follow-up information should be actively sought and submitted as it becomes available.

The investigator will assess relationship to trial treatment. In addition, the sponsor will assess relationship to trial treatment and determine expectedness to SD-101 based on the current SD-101 Investigator's Brochure and to pembrolizumab based on the pembrolizumab Investigator's Brochure. The sponsor will report all SD-101 suspected and unexpected serious

adverse reactions (SUSARs) to regulatory authorities as expedited reports in accordance with applicable regulatory requirements (eg, 21 CFR 312.32[c] in the US). All other SAEs will be reported as part of regulatory safety updates, as required, such as in annual reports. Merck will be responsible for pembrolizumab global reporting requirements.

11.4 Adverse Event Severity and Relationship to Trial Treatment

11.4.1 Severity Grading of Adverse Events

The severity of predefined AEs and other health changes will be assessed and confirmed by the investigator and will be graded using the NCI CTCAE Version 4.03 grading scale by system organ class (National Cancer Institute 2010). If the appropriate grading or description cannot be applied, then the investigator may elect to use the adapted NCI CTCAE, Version 4.03 (Table 11-1) to assess the AE.

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

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

Source: Adapted from NCI CTCAE, Version 4.03 (National Cancer Institute 2010)

ADL = Activities of Daily Living; AE = adverse event; CTCAE = common terminology criteria for adverse events; NCI = National Cancer Institute.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

NOTE: For all AEs and SAEs, if there is a change in the severity after onset of either an AE or SAE, the AE or SAE should be reported as a single entry with the maximum severity grading captured.

11.4.2 Relationship of Adverse Events to Trial Treatment

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

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

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

AE = adverse event.

The investigator will follow all related AEs observed during the trial until the AEs are considered resolved or until trial termination.

The investigator will follow all SAEs, whether assessed as possibly, or probably related, or not related to study treatment, until the SAEs are considered stable, resolved, or until EOS, or the patient begins new anti-cancer therapy (whichever is earlier).

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

11.5 Reporting and Documentation of Pregnancy

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

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

Pregnancies and breastfeedings that occur from Day 1 through 120 days after the last dose of trial treatment or 28 days following cessation of trial treatment if the patient initiates new anti-cancer therapy (whichever is earlier) must be reported by the investigator. The sponsor or designee must be notified as soon as possible once the trial site learns of a pregnancy or breastfeeding. Pregnancy report forms provided by the sponsor or designee must be completed and submitted to Dynavax or designee. The contact information for reporting pregnancy is provided in the Study Reference Manual.

12.0 STATISTICAL METHODS

NOTE: As of Amendment 9, Phase 1 of the trial is complete. All analyses related to data collected in Phase 1 will be performed as detailed in this section. As of Amendment 9, the trial will stop collecting efficacy and exploratory data, and the collection of safety data has been simplified. Thus, after trial completion, only selected analyses related to data collected in Phase 2 of the trial will be performed, and exploratory objectives will not be pursued.

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, changes are made to primary or exploratory objectives and/or hypotheses, or to the statistical methods related to those objectives and/or hypotheses, then those changes, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR. No imputations will be made for missing data. Additional details of the statistical analyses to be performed will be provided in the trial Statistical Analysis Plan.

12.1 General

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.

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

ORR will be presented as the proportion of patients who achieved CR or PR. The DCR will be presented as the proportion of patients who achieved CR, PR, or stable disease.

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

Final analyses will be carried out after the last participant has completed their last trial visit, the trial database has been authorized by Dynavax as complete and final, and major protocol deviations have been identified. 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. Efficacy and safety data from each cohort may be analyzed and reported separately from other cohorts. In addition, safety data will be summarized overall and for each separate tumor indication.

12.2 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 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 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 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 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 6, approximately 25 anti-PD-1/L1 naïve HNSCC patients will be enrolled. This will allow 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 7, approximately 25 patients who are refractory or resistant to anti-PD-1/L1 therapy will be enrolled. This will allow 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%.

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%.

12.3 Analysis Endpoints

12.3.1 Safety Endpoints

The primary safety endpoint in Phase 1 of the trial is incidence of DLTs. Other safety measures evaluated in all parts of the trial are injection-site reactions, all other AEs, laboratory safety assessments, and vital signs.

12.3.2 Efficacy Endpoints

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 referred to as irRECIST

for an exploratory evaluation (Appendix 6). Throughout the trial, each respective investigator will determine and manage disease status (progression or response) of patients per RECIST v1.1 and irRECIST at the specified imaging time points (Appendix 1 through Appendix 4) or more frequently as clinically indicated.

Endpoints will include ORR, DCR, time to response, and duration of response for Lesion A and lesions not injected with SD-101 independently and combined.

12.3.3 Exploratory Biomarker Endpoints

The primary candidate biomarker to be investigated is PD-L1 expression levels in tumor tissue at baseline, which will be assessed by immunohistochemistry. Other candidate biomarkers which may be investigated include tumor-infiltrating lymphocytes, expression of PD-L2 and PD-1, RNA signature profiles, and quantitative RNA expression of candidate genes of interest, including PD-L1.

12.4 Trial Analysis Populations

The safety population will include all enrolled patients who receive at least 1 dose of both pembrolizumab and SD-101. 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 cohort. The efficacy 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 PD-L1 status (positive or negative [ie, < 1% positivity]) and specific prior anti-PD-1/PD-L1 therapy. Further details of statistical considerations will be provided in a separate Statistical Analysis Plan.

12.5 Demographic and Baseline Characteristics

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

12.6 Pharmacodynamic Analyses

IFN-α inducible genes will be assayed by quantitative polymerase chain reaction of mRNA isolated from blood from before administration of the first and second doses of SD-101 and

approximately 24 hours after administration of the second dose of SD-101. The fold increase in gene expression after administration of the second dose of SD-101 relative to administration before the first and second doses will be analyzed as a surrogate for the activity of SD-101. The core group of genes measured will be ISG-54, Mx-B, IFN-α, TNF-α, IP-10, IRF-7, GBP-1, MCP-1, and MCP-2. Other genes may be tested to elucidate anti-tumor immune responses and the patterns seen in the core genes. The fold increases will be analyzed per individual gene and as the geometric mean of their combination or a subset of the same.

12.7 Safety Analyses

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

12.8 Response Analyses

ORR, DCR, time to response, and duration of response, comprising the response of lesions injected with SD-101 and all non-injected lesions and the ORR and DCR of lesions injected with SD-101 and non-injected lesions respectively, will be analyzed descriptively. The ORR will be defined as the proportion of patients who achieve a best objective response of either CR or PR (see Appendix 6).

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

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.

12.9 Source Documents

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

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

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

12.10 Direct Access to Source Data/Documents

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

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

13.0 DATA QUALITY ASSURANCE

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

14.0 ETHICS

14.1 Institutional Review Board/Independent Ethics Committee

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

14.2 Ethical Conduct of the Trial

This trial will be conducted in accordance with ICH E6(R2) GCP guidelines and applicable local legal and regulatory requirements.

The trial will be submitted to required clinical trial registries such as www.clinicaltrials.gov.

14.3 Informed Consent

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

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

14.4 Patient Confidentiality

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

15.0 DATA HANDLING AND RECORD KEEPING

15.1 Case Report Forms

Electronic case report forms (eCRF) will be used at the clinical trial site to collect trial data for enrolled patients. Screening failure patients will not be captured on eCRFs. When data are available, authorized clinical trial site personnel will carefully and accurately record the data on the eCRF. Sites must ensure that all source documents are maintained according to ICH/GCP guidance and support the data that are entered onto the eCRFs.

The eCRF data will be captured in a system validated according to procedures that comply with the 21 CFR Part 11 and the ICH E6(R2) GCP guidelines, Section 5.5. The eCRFs will be reviewed and signed by the principal investigator or someone clinically qualified and identified on the delegation log as someone that can sign-off on the eCRF.

15.2 Data Handling

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

Outside the EDC system, when appropriate, the CRO will receive FDA 21 CRF 11 compliant external lab data transfers from a validated laboratory information management system. After database lock, the investigator will receive a copy of the patient data for archiving at the trial site.

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

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

15.3 Coding of Adverse Events, Drugs, and Diseases

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

15.4 Record Retention

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

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

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

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

16.0 USE OF INFORMATION AND PUBLICATION

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

All efforts should be made for abstracts and publications to be jointly authored by investigators and Dynavax. Dynavax will be furnished with a copy of any proposed publication. Dynavax's comments shall be given without undue delay, and not later than within 60 days.

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

It is understood by the investigator that the information generated in this trial may be used by Dynavax in connection with the development of the product and therefore may be disclosed to government agencies in various countries.

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

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

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

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. Dynavax will not quote from

publications by investigators in its scientific information or promotional material without full acknowledgment of the source (ie, author and reference).

17.0 REFERENCES

American Cancer Society (2014). Cancer Facts & Figures 2014. Atlanta, American Cancer Society.

American Cancer Society. (2016). "Cancer Facts & Figures 2016."

Angell, H. and J. Galon (2013). "From the immune contexture to the Immunoscore: the role of prognostic and predictive immune markers in cancer." Curr Opin Immunol **25**(2): 261-267.

Bald, T., J. Landsberg, D. Lopez-Ramos, M. Renn, N. Glodde, P. Jansen, E. Gaffal, J. Steitz, R. Tolba, U. Kalinke, A. Limmer, G. Jönsson, M. Hölzel and T. Tüting (2014). "Immune Cell–Poor Melanomas Benefit from PD-1 Blockade after Targeted Type I IFN Activation." Cancer Discovery **4**(6): 674-687.

Bauer, M., V. Redecke, J. W. Ellwart, B. Scherer, J. P. Kremer, H. Wagner and G. B. Lipford (2001). "Bacterial CpG-DNA triggers activation and maturation of human CD11c-, CD123+ dendritic cells." J Immunol **166**(8): 5000-5007.

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

Bristol-Myers Squibb Company (2014). OPDIVO (nivolumab) (Prescribing Information). Princeton, NJ.

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

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

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

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

Eisenhauer, E. A., P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe

and J. Verweij (2009). "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)." European Journal of Cancer **45**(2): 228-247.

Flaherty, K. T., J. R. Infante, A. Daud, R. Gonzalez, R. F. Kefford, J. Sosman, O. Hamid, L. Schuchter, J. Cebon, N. Ibrahim, R. Kudchadkar, H. A. Burris, 3rd, G. Falchook, A. Algazi, K. Lewis, G. V. Long, I. Puzanov, P. Lebowitz, A. Singh, S. Little, P. Sun, A. Allred, D. Ouellet, K. B. Kim, K. Patel and J. Weber (2012). "Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations." N Engl J Med **367**(18): 1694-1703.

Flaherty, K. T., C. Robert, P. Hersey, P. Nathan, C. Garbe, M. Milhem, L. V. Demidov, J. C. Hassel, P. Rutkowski, P. Mohr, R. Dummer, U. Trefzer, J. M. Larkin, J. Utikal, B. Dreno, M. Nyakas, M. R. Middleton, J. C. Becker, M. Casey, L. J. Sherman, F. S. Wu, D. Ouellet, A. M. Martin, K. Patel, D. Schadendorf and M. S. Group (2012). "Improved survival with MEK inhibition in BRAF-mutated melanoma." N Engl J Med **367**(2): 107-114.

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

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.

Hoffman, J. (2016) "Nivolumab Improves Survival in Head and Neck Cancer."

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

Howlader, N., A. M. Noone, M. Krapcho, J. Garshell, D. Miller, A. S. F, C. L. Kosary, M. Yu, J. Ruhl, Z. Tatalovich, A. Mariotto, D. R. Lewis, H. S. Chen, E. J. Feuer and K. A. E. Cronin. (2014). "SEER Cancer Statistics Review, 1975-2011 based on November 2013 SEER data submission, posted to the SEER website, April 2014." from http://seer.cancer.gov/csr/1975_2011/.

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

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

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

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

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

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

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

Marabelle, A., H. Kohrt, C. Caux and R. Levy (2014). "Intratumoral immunization: a new paradigm for cancer therapy." Clin Cancer Res **20**(7): 1747-1756.

Merck & Co., I. (2015). KEYTRUDA® (pembrolizumab) (Prescribing Information). White House Station, NJ.

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

National Cancer Institute. (2014). "PDQ® Melanoma Treatment. Date last modified November 7, 2014." from http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional.

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

Ribas, A. and P. C. Tumeh (2014). "The future of cancer therapy: selecting patients likely to respond to PD1/L1 blockade." Clin Cancer Res **20**(19): 4982-4984.

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

Seiwert, T. Y., R. I. Haddad, S. Gupta, R. Mehra, M. TAHARA, R. Berger, S.-H. Lee, B. Burtness, D. T. Le, K. Heath, A. Blum, M. Dolled-Filhart, K. Emancipator, K. Pathiraja, J. D.

Cheng and L. Q. Chow (2015). "Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort." J Clin Oncol **33**(No 18_suppl (June 20 Supplement), 2015: LBA6008).

Sosman, J. A., K. B. Kim, L. Schuchter, R. Gonzalez, A. C. Pavlick, J. S. Weber, G. A. McArthur, T. E. Hutson, S. J. Moschos, K. T. Flaherty, P. Hersey, R. Kefford, D. Lawrence, I. Puzanov, K. D. Lewis, R. K. Amaravadi, B. Chmielowski, H. J. Lawrence, Y. Shyr, F. Ye, J. Li, K. B. Nolop, R. J. Lee, A. K. Joe and A. Ribas (2012). "Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib." N Engl J Med **366**(8): 707-714.

Sparwasser, T., R. M. Vabulas, B. Villmow, G. B. Lipford and H. Wagner (2000). "Bacterial CpG-DNA activates dendritic cells in vivo: T helper cell-independent cytotoxic T cell responses to soluble proteins." Eur J Immunol **30**(12): 3591-3597.

Sznol, M. and L. Chen (2013). "Antagonist Antibodies to PD-1 and B7-H1 (PD-L1) in the Treatment of Advanced Human Cancer." Clinical Cancer Research **19**(5): 1021-1034.

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

Tumeh, P. C., C. L. Harview, J. H. Yearley, I. P. Shintaku, E. J. M. Taylor, L. Robert, B. Chmielowski, M. Spasic, G. Henry, V. Ciobanu, A. N. West, M. Carmona, C. Kivork, E. Seja, G. Cherry, A. J. Gutierrez, T. R. Grogan, C. Mateus, G. Tomasic, J. A. Glaspy, R. O. Emerson, H. Robins, R. H. Pierce, D. A. Elashoff, C. Robert and A. Ribas (2014). "PD-1 blockade induces responses by inhibiting adaptive immune resistance." Nature **515**(7528): 568-571.

Vermorken, J. B. and P. Specenier (2010). "Optimal treatment for recurrent/metastatic head and neck cancer." Ann Oncol **21 Suppl 7**: vii252-vii261.

Webster, R. M. (2014). "The immune checkpoint inhibitors: where are we now?" Nat Rev Drug Discov **13**(12): 883-884.

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

APPENDIX 1: SCHEDULE OF TRIAL EVENTS (PHASE 1 DOSE ESCALATION COHORTS 1-4) - *COMPLETE*

Screening Through Day 29

Trial Period:	**Screening**	**Trial Treatment** (± 1 day for weekly visits)					
Day:	- 28 to -1[a]	1	8	9[b]	15	22	29
		DLT Assessment Period[c]					
Study Procedures							
Informed consent	X						
Inclusion/Exclusion criteria	X						
Demographics/Medical history/Prior medications[g]	X	X					
Vital signs[h]	X	X	X		X	X	X
Physical examination[i]	X	X	X		X	X	X
ECOG Performance Status	X						X
12-Lead ECG[j]	X				X		X
Review AEs[k]		X	X		X	X	X
Review SAEs	X	X	X		X	X	X
Concomitant medications[l]	X	X	X		X	X	X
HIV and hepatitis testing[m]	X						
Serum chemistry and CRP[n]	X	X	X		X	X	X
Hematology[o]	X	X	X		X	X	X
Coagulation[p]	X	X	X		X	X	X
Thyroid function tests[q]	X						X
Urinalysis with microscopy		X	X		X	X	X
Pregnancy testing[r]	X						
Blood for IFN-alpha inducible gene expression (pharmacodynamic)[s]		X	X	X			
SD-101anti-drug antibodies[t]	X						
Reserve serum aliquot[u]		X	X	X	X	X	X

APPENDIX 1: SCHEDULE OF TRIAL EVENTS (PHASE 1 DOSE ESCALATION COHORTS 1-4) - *COMPLETE* (CONT'D)

Screening Through Day 29 (Cont'd)

Trial Period:	**Screening**	**Trial Treatment** (± 1 day for weekly visits)					
Day:	- 28 to -1[a]	1	8	9[b]	15	22	29
		DLT Assessment Period[c]					
Efficacy Measurement							
Clinical assessment of superficial lesions[y]	X						
Radiographic imaging[z]	X						
Drug Administration and Observation							
Pembrolizumab therapy[aa]		X				X	
Diary card issuance and/or review[bb]		X	X		X	X	
SD-101 intratumoral injection [aa]		X	X		X	X	
SD-101 Post-treatment observation (minimum 90 minutes)[cc]		X	X		X	X	
Injection-site reaction assessment[k]		X	X		X	X	
Tumor Biopsies							
Tumor biopsies (consent required)[dd]	X						X

APPENDIX 1: SCHEDULE OF TRIAL EVENTS (PHASE 1 DOSE ESCALATION COHORTS 1-4) - *COMPLETE* (CONT'D)

Day 43 Through End of Study

Trial Period:	**Trial Treatment (± 3 days for every 3 week visits)**																	**Extended Pembrolizumab Treatment**[d] (Note: pembrolizumab is administered every 3 weeks, but study visits are every 3 months ± 3 days)								**EOS / Safety FU**[e] **(± 3 days)**	**UNS**[f]
Day:	43	64	85	106	127	148	169	190	211	232	253	274	295	316	337	358	379	421	463	505	547	589	631	673	715	28 days after last dose	
Study Procedures																											
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Physical examination[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
12-Lead ECG[j]																										X	
Review AEs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Review SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Concomitant medications[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Serum chemistry and CRP[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Hematology[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Coagulation[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Thyroid function tests[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Urinalysis with microscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X	X
SD-101 anti-drug antibodies[t]			X				X								X											X	
Reserve serum aliquot[u]			X				X				X				X	X			X							X	

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APPENDIX 1: SCHEDULE OF TRIAL EVENTS (PHASE 1 DOSE ESCALATION COHORTS 1-4) - *COMPLETE* (CONT'D)

Day 43 Through End of Study (Cont'd)

Trial Period:	**Trial Treatment (± 3 days for every 3 week visits)**																	**Extended Pembrolizumab Treatment**[d] (Note: pembrolizumab is administered every 3 weeks, but study visits are every 3 months ± 3 days)								**EOS / Safety FU**[e] **(± 3 days)**	**UNS**[f]
Day:	43	64	85	106	127	148	169	190	211	232	253	274	295	316	337	358	379	421	463	505	547	589	631	673	715	28 days after last dose	
Efficacy Measurements																											
Clinical assessment of superficial lesions[y]		X			X			X			X			X			X		X		X		X		X		X
Radiographic imaging[z]		X			X			X			X			X			X		X		X		X		X		X
Drug Administration and Observation																											
Pembrolizumab therapy[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Diary card issuance and/or review [bb]	X	X	X	X	X	X	X																				
SD-101 intratumoral injection[aa]	X	X	X	X	X	X	X																				
SD-101 Post-treatment observation (minimum 30 minutes)[cc]	X	X	X	X	X	X	X																				
Injection-site reaction assessment[k]	X	X	X	X	X	X	X																				
Tumor Biopsies																											
Tumor biopsies (consent required)[dd]			X				X																				

APPENDIX 2: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 1 AND 3 – ANTI-PD-1/L1 NAÏVE) – *CLOSED*

NOTE: As of Amendment 9, Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected, and the collection of safety endpoints has been simplified. The final study visit will be the EOS/Safety Follow-up. All other procedures to monitor disease progression and safety should be performed at the investigator's discretion according to local standard of care; these data do not need to be collected on the CRF. This Schedule of Trial Events has been amended and assessments that are no longer required have been deleted.

Screening Through Day 421

Trial Period:	**Screening**	**Trial Treatment**																										
		(every week ± 1 day)						(every 3 weeks ± 3 days)									(every week ± 1 day)				(every 3 weeks ± 3 days)						
Day:	-28 to -1[a]	1	22	29	30[b,ee]	36	43	50	64	85	106	127	148	169	190	211	232	253	260	267	274	295	316	337	358	379	400	421
Study Procedures																												
Informed consent	X																											
Inclusion/Exclusion Criteria	X																											
Demographics/Medical history/Prior medications[g]	X	X																										
Vital signs[h]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																										
Physical examination[i]	X																											
ECOG Performance Status	X																											
12-Lead ECG[j]	X																											
Review AEs[k]		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SAEs	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[l]	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HPV status, and hepatitis testing[m]	X																											

APPENDIX 2: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 1 AND 3 – ANTI-PD-1/L1 NAÏVE) – CLOSED (CONT'D)

Screening Through Day 421 (Cont'd)

Trial Period:	Screening	Trial Treatment																												
		(every week ± 1 day)						(every 3 weeks ± 3 days)										(every week ± 1 day)				(every 3 weeks ± 3 days)							
Day:	-28 to -1[a]	1	22	29	30[b,ee]	36	43	50	64	85	106	127	148	169	190	211	232	253	260	267	274	295	316	337	358	379	400	421
Study Procedures																														
Serum chemistry and CRP[n]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																												
Hematology[o]	X																													
Coagulation[p]	X																													
Thyroid function tests[q]	X																													
Urinalysis with microscopy																														
Pregnancy testing[r]	X																													
Efficacy Measurements																														
Clinical assessment of superficial lesions[y]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																												
Radiographic imaging[z]	X																													
Drug Administration and Observation																														
Pembrolizumab therapy[aa]		X	X				X		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X		
SD-101 intratumoral injection[aa]			X	X		X	X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		
SD-101 post-treatment observation[cc]			X	X		X	X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		
Injection-site reaction assessment[k]			X	X		X	X																							
Tumor Biopsies																														
Tumor biopsies (consent required)[dd]	X							X			X				X															

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APPENDIX 2: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 1 AND 3 – ANTI-PD-1/L1 NAÏVE) – *CLOSED* (CONT'D)

Day 442 Through End of Study

Trial Period:	**Extended Pembrolizumab Treatment**[d] (Note: pembrolizumab is administered every 3 weeks ± 3 days)														**EOS/ Safety F/U**[e] **(± 3 days)**	**UNS**[f]
Day:	442	463	484	505	526	547	568	589	610	631	652	673	694	715	28 days after last dose	
Study Procedures																
Vital signs[h]	As of Amendment 9, per local standard of care at the discretion of the investigator.														X	X
Physical examination[i]															X	X
ECOG Performance Status															X	X
Review AEs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry and CRP[n]	As of Amendment 9, per local standard of care at the discretion of the investigator.														X	X
Hematology[o]															X	X
Thyroid function tests[q]															X	X
Urinalysis with microscopy															X	X
Efficacy Measurements																
Clinical assessment of superficial lesions[y]	As of Amendment 9, per local standard of care at the discretion of the investigator.															
Radiographic imaging[z]																
Drug Administration and Observation																
Pembrolizumab therapy[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

APPENDIX 3: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 2 AND 4 – ANTI-PD-1/L1 EXPERIENCED) – *CLOSED*

NOTE: As of Amendment 9, Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected, and the collection of safety endpoints has been simplified. The final study visit will be the EOS/Safety Follow-up. All other procedures to monitor disease progression and safety should be performed at the investigator's discretion according to local standard of care; these data do not need to be collected on the CRF. This Schedule of Trial Events has been amended and assessments that are no longer required have been deleted.

Screening Through Day 400

Trial Period:	**Screening**	**Trial Treatment**																										
		(every week ± 1 day)						(every 3 weeks ± 3 days)									(every week ± 1 day)				(every 3 weeks ± 3 days)							
Day:	-28 to -1[a]	1	8	9[b, ge]	15	22	29	43	64	85	106	127	148	169	190	211	232	239	246	253	274	295	316	337	358	379	400	
Study Procedures																												
Informed consent	X																											
Inclusion/Exclusion Criteria	X																											
Demographics/Medical history/Prior medications[g]	X	X																										
Vital signs[h]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																										
Physical examination[i]	X																											
ECOG Performance Status	X																											
12-Lead ECG[j]	X																											
Review AEs		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SAEs	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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APPENDIX 3: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 2 AND 4 – ANTI-PD-1/L1 EXPERIENCED) – *CLOSED* (CONT'D)

Screening Through Day 400 (Cont'd)

Trial Period:	Screening	Trial Treatment																										
		(every week ± 1 day)						(every 3 weeks ± 3 days)									(every week ± 1 day)				(every 3 weeks ± 3 days)						
Day:	-28 to -1[a]	1	8	9[b, ee]	15	22	29	43	64	85	106	127	148	169	190	211	232	239	246	253	274	295	316	337	358	379	400
Concomitant medications[l]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HPV status, and hepatitis testing[m]	X																										
Serum chemistry and CRP[n]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																									
Hematology[o]	X																										
Coagulation[p]	X																										
Thyroid function tests[q]	X																										
Urinalysis with microscopy																											
Pregnancy testing[r]	X																										
Efficacy Measurements																											
Clinical assessment of superficial lesions[y]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																									
Radiographic imaging[z]	X																										
Drug Administration and Observation																											
Pembrolizumab therapy[aa]		X				X		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
SD-101 intratumoral injection[aa]		X	X		X	X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
SD-101 post-treatment observation[cc]		X	X		X	X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Injection-site reaction assessment[k]		X	X		X	X																					
Tumor Biopsies																											
Tumor biopsies (consent required)[dd]							X			X				X													

APPENDIX 3: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 2 AND 4 – ANTI-PD-1/L1 EXPERIENCED) – *CLOSED* (CONT'D)

Day 421 Through End of Study

Trial Period:	**Extended Pembrolizumab Treatment**[d] (Note: pembrolizumab is administered every 3 weeks ± 3 days)															**EOS/ Safety F/U**[e] **(± 3 days)**	**UNS**[f]
Day:	421	442	463	484	505	526	547	568	589	610	631	652	673	694	715	28 days after last dose	
Study Procedures																	
Vital signs[h]	As of Amendment 9, per local standard of care at the discretion of the investigator.															X	X
Physical examination[i]																X	X
ECOG Performance Status																X	X
12-Lead ECG[j]																	
Review AEs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry and CRP[n]	As of Amendment 9, per local standard of care at the discretion of the investigator.															X	X
Hematology[o]																X	X
Thyroid function tests[q]																X	X
Urinalysis with microscopy																X	X
Efficacy Measurements																	
Clinical assessment of superficial lesions[y]	As of Amendment 9, per local standard of care at the discretion of the investigator.																X
Radiographic imaging[z]																	X
Drug Administration and Observation																	
Pembrolizumab therapy[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

APPENDIX 4: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 5 AND 6 [ANTI-PD-1/L1 NAÏVE] AND COHORTS 7 AND 8 [ANTI-PD-1/L1 REFRACTORY OR RESISTANT]) - *CLOSED*

NOTE: As of Amendment 9, Phase 2 of the trial has been modified to continue dosing per protocol; however, efficacy and exploratory endpoints will no longer be collected, and the collection of safety endpoints has been simplified. The final study visit will be the EOS/Safety Follow-up. All other procedures to monitor disease progression and safety should be performed at the investigator's discretion according to local standard of care; these data do not need to be collected on the CRF. This Schedule of Trial Events has been amended and assessments that are no longer required have been deleted.

Screening Through Day 358

Trial Period:	**Screening**	**Trial Treatment**																					
		(every week ± 1 day)						(every 3 weeks ± 3 days)									(every 3 weeks ± 3 days)						
Day:	- 28 to -1[a]	1	8	9[b, cc]	15	22	29	43	64	85	106	127	148	169	190	211	232	253	274	295	316	337	358
Study Procedures																							
Informed consent	X																						
Inclusion/Exclusion Criteria	X																						
Demographics/Medical history/Prior medications[g]	X	X																					
Vital signs[h]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																					
Physical examination[i]	X																						
ECOG Performance Status	X																						
12-Lead ECG[j]	X																						
Review AEs[k]		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SAEs	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[l]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HPV status, and hepatitis testing[m]	X																						

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APPENDIX 4: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 5 AND 6 [ANTI-PD-1/L1 NAÏVE] AND COHORTS 7 AND 8 [ANTI-PD-1/L1 REFRACTORY OR RESISTANT]) (CLOSED) (CONT'D)

Screening Through Day 358 (Cont'd)

Trial Period:	Screening	Trial Treatment																					
		(every week ± 1 day)						(every 3 weeks ± 3 days)									(every 3 weeks ± 3 days)						
Day:	- 28 to - 1[a]	1	8	9[b, ee]	15	22	29	43	64	85	106	127	148	169	190	211	232	253	274	295	316	337	358
Serum chemistry and CRP[n]	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[o]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																					
Coagulation[p]	X																						
Thyroid function tests[q]	X																						
Urinalysis with microscopy																							
Pregnancy testing[r]	X																						
Efficacy Measurements																							
Clinical assessment of superficial lesions[y]	X	As of Amendment 9, per local standard of care at the discretion of the investigator.																					
Radiographic imaging[z]	X																						
Drug Administration and Observation																							
Pembrolizumab therapy[aa]		X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-101 intratumoral injection[aa]		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-101 post-treatment observation[cc]		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site reaction assessment[k]		X	X		X	X																	
Tumor Biopsies																							
Tumor biopsies (consent required)[dd]							X			X				X									

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APPENDIX 4: SCHEDULE OF TRIAL EVENTS (PHASE 2 EXPANSION COHORTS 5 AND 6 [ANTI-PD-1/L1 NAÏVE] AND COHORTS 7 AND 8 [ANTI-PD-1/L1 REFRACTORY OR RESISTANT]) (CLOSED) (CONT'D)

Day 379 Through End of Study

Trial Period:	Extended Pembrolizumab Treatment[d] (Note: pembrolizumab is administered every 3 weeks ± 3 days)																	EOS/ Safety F/U[e] (± 3 days)	UNS[f]
Day:	379	400	421	442	463	484	505	526	547	568	589	610	631	652	673	694	715	28 days after last dose	
Study Procedures																			
Vital signs[h]	As of Amendment 9, per local standard of care at the discretion of the investigator.																	X	X
Physical examination[i]																		X	X
ECOG Performance Status																		X	X
Review AEs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry and CRP[n]	As of Amendment 9, per local standard of care at the discretion of the investigator.																	X	X
Hematology[o]																		X	X
Thyroid function tests[q]																		X	X
Urinalysis with microscopy																		X	X
Efficacy Measurements																			
Clinical assessment of superficial lesions[y]	As of Amendment 9, per local standard of care at the discretion of the investigator.																		X
Radiographic imaging[z]																			X
Drug Administration and Observation																			
Pembrolizumab therapy[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

APPENDIX 1-4 FOOTNOTES

AE = adverse event; ALT = alanine transaminase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; CRP = C-reactive protein; CT = computed tomography; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOS = End-of-Study; F/U = follow-up; Hgb = hemoglobin; HIV = human immunodeficiency virus; IFN = interferon; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = progressive disease; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; PT = prothrombin time; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid stimulating hormone; UNS = unscheduled visit/Safety Follow-up Visit; WBC = white blood cell; WOCBP = women of childbearing potential.

Screening[a]	Routine laboratory tests (serum chemistry, hematology) for screening should be performed within 28 days prior to enrollment or can be obtained from a standard of care visit within 28 days of first dose of pembrolizumab. Laboratories obtained within 7 days of Day 1 visit, with the exception of a CBC with ANC, do not need to be repeated on Day 1.
24-hour postdose visit[b]	The window for 24-hour postdose visit is ±3 hours.
DLT Assessment Period[c]	DLT assessment period is Study Day 1 through Study Day 29.
Extended Pembrolizumab Treatment[d]	During Extended Pembrolizumab Treatment, pembrolizumab will be administered Q3W with standard of care procedures performed by the site. Data related to dosing, concomitant medications, AEs, and SAEs must be entered in the CRF.
EOS / Safety FU[e]	After a patient is discontinued from both trial treatments, a mandatory EOS/Safety Follow-up visit will be performed 28 (± 3) days after the last administration of trial treatment, regardless of the reason for permanent discontinuation.
UNS[f]	A UNS should be performed if there is suspected disease progression or patient safety concerns. Procedures for the visit are at the discretion of the investigator according to local standard of care guidelines. All disease assessments will be performed as per local standard of care guidelines. Confirmation of disease progression by repeat imaging is not mandatory.
Demographics/Medical history/Prior medications[g]	Medical history includes clinically significant diseases, surgeries, cancer history, response to cancer treatment, and all medications (eg, prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the Screening Visit. Baseline melanoma and HNSCC disease status, histology, stage and molecular profiling of genetic alterations or mutations (if available) will be recorded. Prior treatment includes treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Results of any prior genetic screening tests and any immunohistochemical (IHC) tests, such as for PD-L1, will also be recorded. The date of last prior cancer treatment must be documented. Radiographic studies performed prior to trial entry may be collected for review by the investigator.
Vital signs[h]	Includes oral temperature (only at trial injection visits), heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oximetry.
Physical examination[i]	The investigator or qualified designee will conduct physical examinations. A complete physical examination is conducted at Screening and EOS, and a targeted physical examination (based on interval history and/or AEs) including assessment of superficial lesions is conducted at all other visits per the Schedule of Trial Events.
12-Lead ECG[j]	Electrocardiogram (12-lead ECG) should be performed at Screening, after treatment on Days 15 and 29, and at EOS in Phase 1, and collected at Screening only in Phase 2.

APPENDIX 1-4 FOOTNOTES (CONT'D)

Review AEs[k]	In Phase 1, assessments of injection-site reactions will be collected for a minimum of 90 minutes through the first 4 weekly injections and for 30 minutes following the remaining injections of SD-101 at the clinical site. Injection-site reactions will be graded based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 5). In Phase 2, injection-site reactions that persist for more than 7 days will be recorded as AEs. All other AEs and laboratory safety measurements will be graded per NCI CTCAE Version 4.03. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. AEs will be collected through 28 days after the last dose of trial treatment.
Concomitant medications[l]	All concomitant medications taken by the patient from Screening through the EOS visit will be reported.
HIV and hepatitis testing[m]	Serum hepatitis B, hepatitis C, and HIV testing as determined by laboratory tests for HBsAg, anti-HBc, and anti-HBs; anti-HCV; and anti-HIV -1/2, respectively. For HNSCC patients only, HPV status (positive + or negative) at Screening will be determined from either archival test results or new testing.
Serum chemistry and CRP[n]	Per local standard of care at the discretion of the investigator.
Hematology[o]	Per local standard of care at the discretion of the investigator.
Coagulation[p]	Per local standard of care at the discretion of the investigator.
Thyroid function tests[q]	Per local standard of care at the discretion of the investigator.
Pregnancy testing[r]	For WOCBP, serum or urine pregnancy test must be negative within 72 hours prior to the first trial treatment. If the urine test is positive or cannot be confirmed as negative then a serum test is required which must be negative for the patient to enroll. Dipstick can be used. Additional pregnancy testing should be scheduled per local regulations where applicable. All female patients are considered to be WOCBP except if they have been postmenopausal for at least 2 years or surgically sterile for at least 1 year.
Blood for IFN-alpha inducible gene expression (pharmacodynamic)[s]	**Phase 1 Dose Escalation Cohorts 1-4 only:** IFN-inducible gene expression measured at pre-dose on Day 1 (baseline), at Day 8 prior to injection, and at Day 9 which is 24 hours after injection.

APPENDIX 1-4 FOOTNOTES (CONT'D)

Diary card issuance and/or review[bb]	Prior to each of the first 4 initial weekly doses of SD-101 in Phase 1, patients will receive a new Diary Card with instructions to measure and record local injection- site reactions and solicited AEs that occur post SD-101 injection. Note that injection-site reactions are not required to be recorded separately on the AE eCRF unless the duration is greater than 7 days. The completed Diary Cards will be reviewed with the patients at their next study visit.
SD-101 Post-treatment observation (minimum 90 minutes)[cc]	Patients will remain in clinic for 90 minutes after each of the first 4 weekly SD-101 injections in their first course and for 30 minutes after subsequent injections.
Tumor biopsies (consent required)[dd]	Tumor biopsy of Lesion A will be performed within 28 days prior to the first dose of SD-101. Two samples are required at each time point. See specific guidance for samples in Section 10.1.2. Lesion A should be of a sufficient size such that the intratumoral biopsy does not compromise the investigator's ability to assess the lesion size changes per RECIST over time. Biopsies may be obtained via punch, core needle, or surgical excision. Biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes). (See specific guidance for minimum needle gauge in the Study Reference Manual). Collections are to be done pre- injection on treatment days and may occur pre-injection on treatment days or within the visit window prior to treatment. Repeat samples may be required if adequate tissue is not provided. Details of tumor biopsy procedures including processing and shipping are provided in the study laboratory manual. Biopsies will be collected on: • Phase 1 Dose Escalation Cohorts 1-4 only: Screening, Days 29, 85 and 169 visits. • Phase 2 Dose Expansion Cohorts 1 and 3 only: Screening, Days 50, 106, and Day 190 visits. • Phase 2 Dose Expansion Cohorts 2 and 4 to 8 only: Screening, Days 29, 85, and Day 169 visits.
Day 9 and Day 30 visits[ee]	These visits are for HNSCC patients in Phase 2 Dose Expansion: Cohort 3 on Day 30, and Cohorts 4, 6 and 7 only on Day 9.

APPENDIX 5: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

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

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

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

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

APPENDIX 6: RECIST V1.1 AND IMMUNE-RELATED RECIST RESPONSE DEFINITION

NOTE: As of Amendment 9, this Appendix is for information only. Use of the guidelines outlined within is at the discretion of the investigator and is not mandatory. All disease response assessments, including the timing, type, and evaluation of imaging, are to be performed and assessed at the investigator's discretion per local standard of care. Confirmation of progression by repeat imaging is not mandatory. Decisions on treatment discontinuation should be made per investigator based on local standard of care. All imaging will be performed as per local standard of care guidelines.

Assessments will use RECIST v1.1 guidelines (Eisenhauer, Therasse et al. 2009), which are included in the Study Reference Manual, and study specific modification of the RECIST v1.1 guidelines referred to as irRECIST.

RECIST v1.1

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 time point.

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 SOD for the baseline time point. All other lesions should be identified as non-target lesions and be recorded at baseline.

Post-baseline radiographic response assessment

At each post-baseline imaging time point, the long axis diameter of all target lesions is measured and recorded. A response of the target lesions is assessed by determination of the overall SOD of the lesions (SOD for that imaging time point). A response for each baseline non-target lesion is determined and recorded. The presence of any new lesions is 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 SOD of target lesions, taking as reference the baseline SOD.

Progressive disease (PD): At least 20% increase in the SOD of target lesions, taking as reference the smallest prior SOD 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 SOD 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 time point, 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 mm 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 Table 1 below.

Table 1: Overall Response Definitions Using RECIST v1.1

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

Source: (Eisenhauer, Therasse et al. 2009)
CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Immune-related RECIST

irRECIST is a modification of RECIST v1.1 which requires confirmation of initial PD per RECIST v1.1 with an additional scan obtained at least 4 weeks later that also meets the criteria of PD progression per RECIST v1.1. In determining whether or not PD is confirmed per irRECIST, the investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

The following are scenarios where PD is confirmed at repeat imaging if ANY of the following occurs by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse

- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

The following are scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

The rationale of the modification is to address observed *pseudoprogression* as well as late responses that are expected with immunotherapy. Guidance for continued imaging and treatment following an initial determination of PD per RECIST v1.1 is provided in the protocol in Section 10.4.1.

APPENDIX 7: IMAGING MODALITIES

NOTE: As of Amendment 9, all post-baseline imaging is to be performed according to local standard of care. The modality, anatomic areas, and timing of imaging is at the discretion of the investigator. This section has been updated accordingly.

Contrast enhanced CT (preferred) or enhanced MRI are the preferred imaging modalities to be used. Chest x-rays performed during the Screening phase (and repeated at any time during the trial if clinically indicated) may be used as supportive data, as an accessory to the chest CT scans.

All imaging data are to be collected on film or in digital format.

CT/MRI of the Chest/Abdomen/Pelvis

CT/MRI imaging of the chest, abdomen, and pelvis is required at Screening, regardless of the location of known metastases. For HNSCC, imaging of the neck is also required. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest, abdomen and pelvic scans, in patients where there is clinical suspicion of malignant disease/metastases. Such additional CT/MRIs will be required at Screening only when malignant disease/metastases is known/suspected.

Brain MRI/CT

Brain scans (MRI or CT) are required at Screening. Brain scans should be conducted during the course of the trial if the Screening scan was positive as clinically indicated.

Non-radiographic Assessments/Digital Photography

These should be made at the sites and recorded in the source documents at the time points indicated in Appendix 1 through Appendix 4. Visible skin lesions should be measured clinically and documented digitally using standardized photographic images, including a ruler for scale as part of the image. Superficial lesions not well captured by imaging scans should be documented using standardized photographic images, including a ruler for scale as part of the image to track the lesion size.

Image Acquisition Guidelines

Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at baseline. Image acquisition guidelines should be consistent with the American College of Radiology imaging guidelines and local imaging guidelines. All

measurable and non-measurable lesions should be assessed at Screening and at any tumor assessment time points indicated as mandatory in Appendix 1 through Appendix 4. Additional assessments may be performed, as clinically indicated, if there is a suspicion of progression or for confirmation of response. The investigator will base response to treatment on local assessment guidelines. Imaging-based evaluation is preferred to physical examination. Helical (spiral) CT scans of chest, abdomen and pelvis are preferred. If not available, conventional (non-helical, non-spiral CT) should be used.

Intravenous contrast should be used for all CT scans. Oral contrast should be used for CT abdomen and pelvis. If intravenous contrast is contraindicated, CT may be performed without contrast. If oral contrast is indicated, milk or other suitable substitution per local imaging standards may be used. CT scan of the chest is preferred compared to MRI of the chest.

However, for patients who cannot receive intravenous contrast, MRI may be used as an alternative imaging modality. Intravenous imaging agent (gadolinium or acceptable alternative per local institutional standards) should be used for all MRI scans. Patients who develop contrast allergy after trial enrollment may be followed by MRI for subsequent tumor measurements or have non-contrast CT scans per approval by a Dynavax Medical Monitor and per institutional standard practice. Sections should be contiguous, similarly sized and consistent from

visit-to-visit. Section thickness must be based on institutional standards (eg, from 5 to 8 mm; 10 mm cuts are not recommended). Chest x-ray, ultrasound, and positron emission tomography scans are not acceptable methods to measure baseline disease status for the purposes of this trial.

APPENDIX 8: ECOG PERFORMANCE STATUS INDEX

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

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: (Oken, Creech et al. 1982).
Available at: http://www.ecog.org/general/perf_stat.html. Accessed 21 February 2015.