SYNOPSIS

Name of the Sponsor: Dynavax Technologies Corporation	**Individual Study Table Referring to Part of the Dossier:**	**For National Authority Use Only**
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Title of Study:

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

Investigator(s) and Study Center(s):

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Publication(s): Ribas A, Medina T, Kummar S, Amin A, Kalbasi A, Drabick J, Barve M, Daniels GA, Wong DJ, Schmidt EV, Candia AF, Coffman R, Leung ACF, and Janssen R. SD-101 in combination with pembrolizumab in advanced melanoma: results of a Phase 1b, multicenter study. Cancer Discovery 2018;8:1250-1257.

Study Period:	**Development Phase:**
01SEP2015 through 24APR2020	Phase 1b/2

Objectives:

Note: As of Protocol Amendment 9, efficacy and exploratory endpoints were no longer collected. The collection of safety endpoints was simplified.

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

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- 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

Methods:

This was 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 was conducted in 2 Phases. Phase 1 evaluated SD-101 given in combination with pembrolizumab in melanoma populations (anti-programmed death receptor-1/ligand 1 [PD-1/L1] naïve and anti-PD-1/L1 experienced with progressive disease [PD]) 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).

Phase 1: Dose Escalation

Phase 1 was a dose-ranging study using a standard 3 + 3 study design. The dose cohorts for SD-101 were 1 mg, 2 mg, 4 mg, and 8 mg. If a maximum tolerated dose (MTD) was not identified, dosing was to stop at 8 mg. Decisions to escalate the dose of SD-101 to the next highest level was based on review of safety data from the time of the first injection (Day 1) through 7 days following the last injection (Day 29). Intra-subject dose escalation was not permitted.

Phase 2: Dose Expansion

Melanoma Cohorts

Melanoma Dose Expansion cohorts in Phase 2 were treated with 8 mg or 2 mg of SD-101 from Phase 1 in combination with 200 mg pembrolizumab Q3W.

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

HNSCC Cohorts

HNSCC Dose Expansion cohorts in Phase 2 were treated with the selected RP2D (8 mg or 2 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 had disease progression on anti-PD-1/L1 therapy in each of Expansion Cohorts 4 and 7 were enrolled.

Number of Subjects Planned:

24 subjects in Phase 1 Dose Escalation and 260 subjects in Phase 2 Dose Expansion.

Number of Subjects Enrolled:

241 subjects were enrolled: 22 subjects in Phase 1 Dose Escalation (1 mg n = 6; 2 mg n = 5, 4 mg n = 5; 8 mg n = 6); 219 subjects in Phase 2 Dose Expansion.

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

A patient must have met 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 could 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:

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- ≤ 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 was 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 was receiving anticoagulant therapy, and as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5) Had provided 2 tissue biopsy samples taken 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 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 have met the following to be eligible for Phase 1:

8) Histologically or cytologically confirmed unresectable or metastatic (stage IV) melanoma

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9) For Phase 1 Escalation Cohorts 1-4, must have at least 1 lesion that qualifies as a target lesion per Response Evaluation Criteria In Solid Tumors (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 have met 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 qualified 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 had documented PD per RECIST v1.1 on a prior treatment regimen containing an anti-PD-1/L1 drug.
13) Expansion Cohort 8: Must have had 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 have met 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.
17) Expansion Cohort 7: Must have all of the following:

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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:

Exclusion Criteria (Phase 1 and Phase 2)

A patient with any 1 of the following criteria was 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.

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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 magnetic resonance imaging (MRI) or computed tomography (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

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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

Test Product, Dose and Mode of Administration, Batch Number:

The study treatments were pembrolizumab and SD-101.

Pembrolizumab 200 mg was administered intravenously every 3 weeks for up to 35 treatments or until disease progression.

SD-101 drug product was administered by intratumoral injection into a single target lesion. In Dose Escalation Cohorts 1-4, patients received 2 mg, 4 mg, 8 mg, or 1 mg SD-101 weekly for 4 weeks followed by 1 dose every 3 weeks (Q3W) for 7 additional doses. In the Dose Expansion Phase, patients received 8 mg or 2 mg SD-101.

Duration of Treatment:

The total duration of subject participation was up to 110 weeks. This included a Screening period beginning up to 28 days prior to the first treatment and a trial completion visit approximately 28 days after the last dose of trial treatment.

Efficacy:

Disease assessment included physical examination, photographic documentation and measurement of superficial lesions, and radiographic imaging with CT or MRI scans at every 9 weeks after the first trial injection until Day 379 and then every twelve weeks for the remainder of the trial.

Response was assessed using RECIST v1.1

Safety:

Safety assessments included targeted physical exams, laboratory assessments (complete blood count [CBC] with differential, platelet assessment, coagulation testing, thyroid function tests, and serum chemistry [including

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creatinine clearance, liver function tests and lactate dehydrogenase]), and assessment of injection site reactions and adverse events.

Pharmacodynamic Assessment: IFN-α inducible genes were assayed by quantitative polymerase chain reaction of messenger ribonucleic acid 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.

Immunogenicity Assessment: Blood for antibodies to SD-101 was collected.

Statistical Methods:

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

AEs, SAEs, and abnormal laboratory values were summarized by the proportion of patients in the all-treated population who experienced them.

Phase 2 of this trial was 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 are descriptive.

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

Summary and Conclusions:

Analysis groups:

Melanoma patients naïve to anti-PD-1/L1 therapy: N = 86 (2 mg: 45; 8 mg: 41)

Melanoma patients who previously received anti-PD-1/L1 therapy: N = 61 (2 mg: 31; 8 mg: 30)

HNSCC patients naïve to anti-PD-1/L1 therapy: N = 51 (2 mg: 28; 8 mg: 23)

HNSCC patients who previously received anti-PD-1/L1 therapy: N= 32 (2 mg: 23; 8 mg: 9)

Demographic and baseline characteristics:

Melanoma patients naïve to anti-PD-1/L1 therapy: Age (mean) = 65.8 years; males = 68.6%; white = 98.8%; ECOG = 0 = 67.4%; PD-L1 negative = 33.7%; BRAF mutant = 34.9%; stage IV = 72.1%; prior systemic treatment naïve = 73.3%.

Melanoma patients who previously received anti-PD-1/L1 therapy: Age (mean) = 64.0 years; males = 72.1%; white = 90.2%; ECOG=0 = 57.4%; PD-L1 negative = 31.1%; BRAF mutant = 36.1%; stage IV = 78.7%; 2 or more prior lines of systemic treatment = 63.9%.

HNSCC patients naïve to anti-PD-1/L1 therapy: Age (mean) = 64.7 years; males = 78.4%; white = 86.3%; ECOG=0 = 21.6%; oral tumor = 51.0%; human papillomavirus (HPV) positive = 31.4%; PD-L1 negative = 11.8%; metastatic disease = 54.9%; prior systemic treatment naïve = 23.5%.

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HNSCC patients who previously received anti-PD-1/L1 therapy: Age (mean) = 62.2 years; males = 71.9%; white = 87.5%; ECOG=0 = 18.8%; oral tumor = 34.4%; HPV positive = 31.3%; PD-L1 negative = 18.8%; metastatic disease = 43.8%; 2 or more prior lines of systemic treatment = 84.4%.

Key Efficacy Results:

Melanoma patients naïve to anti-PD-1/L1 therapy:

Objective response rate (ORR): 2 mg = 75.6%; 8 mg = 48.8%

ORR in 2 mg: PD-L1 negative = 78.6%; PD-L1 positive = 85.7%

ORR in 8 mg: PD-L1 negative = 40.0%; PD-L1 positive = 69.2%

DOR: 2 mg = not reached; 8 mg = not reached

PFS (median): 2 mg = not reached; 8 mg = 12.9 months

18-month PFS rate: 2 mg = 61.5%; 8 mg = 40.3%

Melanoma patients who previously received anti-PD-1/L1 therapy:

ORR: 2 mg = 22.6%; 8 mg = 13.3%

ORR in 2 mg: PD-L1 negative = 25.0%; PD-L1 positive = 22.2%

ORR in 8 mg: PD-L1 negative = 0%; PD-L1 positive = 23.1%

DOR: 2 mg = not reached; 8 mg = 11.5 months

PFS (median): 2 mg = 2.4 months; 8 mg = 2.4 months

Overall survival (OS) (median): 2 mg = not reached; 8 mg = 20.1 months

HNSCC patients naïve to anti-PD-1/L1 therapy:

ORR: 2 mg = 21.4%; 8 mg = 26.1%

Disease control rate (DCR): 2 mg = 46.4%; 8 mg = 47.8%

ORR in HPV positive = 43.8%; HPV negative = 11.8%

DOR: 2 mg = 7 months; 8 mg = 5.7 months

PFS (median): 2 mg = 2.5 months; 8 mg = 2.3 months

9-month PFS rate: 2 mg = 21.2%; 8 mg = 17.4%

OS (median): 2 mg = Not estimable; 8 mg = 9.0 months

9-month OS rate: 2 mg = 79.9%; 8 mg = 56.9%

HNSCC patients who previously received anti-PD-1/L1 therapy:

ORR: 2 mg = 8.7%; 8 mg = 11.1%

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ORR in 2 mg: HPV positive = 0; HPV negative = 14.3%

ORR in 8 mg: HPV positive = 0; HPV negative = 25.0%

DCR: 2 mg = 21.7%; 8 mg = 33.3%

DOR: 2 mg = NE; 8 mg = 8.1 months

PFS (median): 2 mg = 2.1 months; 8 mg = 1.8 months

OS (median): 2 mg = 5.2 months; 8 mg = 5.6 months

Pharmacodynamic Results:

In the Dose Escalation Phase of the study in patients with melanoma, target engagement occurred at all dose levels. There was a dose response with increasing levels of IFN-inducible gene expression in whole blood.

Pharmacokinetic Results:

Not performed

Safety Results:

Dose escalation: no dose limiting toxicity

Cumulative:

Melanoma patients naïve to anti-PD-1/L1 therapy:

Any treatment-related AE: 2 mg = 100%; 8 mg = 94.9%

Grade 3+ treatment related AEs: 2 mg = 31.8%; 8 mg = 43.6%

Any immune-related AE (irAE): 2 mg = 31.8%; 8 mg = 17.9%

AEs leading to treatment discontinuation: 2 mg = 27.3%; 8 mg = 38.5%

Treatment-related AEs leading to death: 2 mg = 0; 8 mg = 2.6%

Melanoma patients who previously received anti-PD-1/L1 therapy:

Any treatment-related AE: 2 mg = 93.5%; 8 mg = 86.7%

Grade 3+ treatment related AEs: 2 mg = 22.6%; 8 mg = 26.7%

Any immune-related AE (irAE): 2 mg = 3.2%; 8 mg = 6.7%

AEs leading to treatment discontinuation: 2 mg = 6.5%; 8 mg = 20.0%

Treatment-related AEs leading to death: 0

HNSCC patients naïve to anti-PD-1/L1 therapy:

Any treatment-related AE: 2 mg = 74.1%; 8 mg = 100.0%

Grade 3+ treatment related AEs: 2 mg = 14.8%; 8 mg = 34.8%

Any immune-related AE (irAE): 2 mg = 11.1%; 8 mg = 21.7%

Name of the Sponsor: Dynavax Technologies Corporation	Individual Study Table Referring to Part of the Dossier:	For National Authority Use Only
Name of Finished Product: SD-101	**Volume:**	
Name of Active Ingredient: SD-101	**Page:**	

Title of Study:

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

AEs leading to treatment discontinuation: 2 mg = 11.1%; 8 mg = 17.4%

Treatment-related AEs leading to death: 0

HNSCC patients who previously received anti-PD-1/L1 therapy:

Any treatment-related AE: 2 mg = 56.5%; 8 mg = 88.9%

Grade 3+ treatment related AEs: 2 mg = 17.4%; 8 mg = 11.1%

Any immune-related AE (irAE): 2 mg = 4.3%; 8 mg = 0

AEs leading to treatment discontinuation: 2 mg = 17.4%; 8 mg = 11.1%

Treatment-related AEs leading to death: 0

The combination of SD-101 and pembrolizumab was well tolerated in the 4 patient populations evaluated here. The typical adverse reaction to SD-101 is an injection-site reaction or flu-like illness starting the evening of an injection that may include pyrexia, headache, myalgia, malaise, or chills and is treatable with over-the-counter medication. Adding SD-101, an innate immune stimulant, to pembrolizumab, an immune checkpoint blocker, did not lead to an increased rate of irAEs over historical rates for pembrolizumab monotherapy.

Conclusions:

In patients with advanced (Stage IIIc or IV) melanoma and in patients with advanced (recurrent or metastatic) HNSCC who had not previously received anti-PD-1/L1 therapy, the combination of SD-101 and pembrolizumab provided encouraging tumor responses and duration of tumor control with a consistent safety profile as seen in standard of care. The combination of SD-101 with an anti-PD-1 inhibitor warrants further investigation in patients with unresectable or metastatic melanoma, HNSCC, and potentially a variety of other solid tumors.

Date of Report:	08 February 2021