DSP-7888

BBI-DSP-7888-102CI

A PHASE 1B/2, MULTICENTER, OPEN-LABEL STUDY OF DSP 7888 DOSING EMULSION IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS NIVOLUMAB OR PEMBROLIZUMAB IN ADULT PATIENTS WITH ADVANCED SOLID TUMORS

Study Protocol Number:	BBI-DSP-7888-102CI
Study Medication Name:	Nelatimotide and Adegramotide (Ombipepimut-S) (hereafter referred to as DSP-7888) Dosing Emulsion
Developmental Phase:	Phase 1b/2
Indication:	Advanced solid tumors: Phase 1b Platinum-Resistant Ovarian Cancer: Phase 2
Sponsor:	[redacted]
Contract Research Organization (CRO):	[redacted]
Amendment 6.0 Date	22 Jul 2021

SIGNATURE PAGE

Sponsor's Signatory:

The protocol has been approved by [redacted]

DocuSigned by:
[redacted]

7/22/2021

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for DSP-7888. I have read the protocol for Study BBI-DSP-7888-102CI and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACT INFORMATION

Table 1: Contact Information

Role in Study	Name	Address/Email & Telephone Number
Clinical Study Leader	[redacted]	[redacted]
Responsible Physician / 24-Hour Emergency Contact: Phase 1	[redacted]	[redacted]
Responsible Physician / 24-Hour Emergency Contact: Phase 2	[redacted]	[redacted]
Drug Safety Physician	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company: [redacted]	
Name of Investigational Product: Nelatimotide and Adegramotide (Ombipepimut-S) (hereafter referred to as DSP-7888) Dosing Emulsion	
Title of Study: A Phase 1b/2, Multicenter, Open-Label Study of DSP-7888 Dosing Emulsion in Combination with Immune Checkpoint Inhibitors Nivolumab or Pembrolizumab in Adult Patients with Advanced Solid Tumors	
Study center(s): A multicenter study	
Studied period (years): Estimated date first patient enrolled: 21 Dec 2017 Estimated date last patient completed: 30 Sep 2023	**Phase of development:** 1b/2

Objectives:

Phase 1b

Primary: To evaluate the safety and tolerability of, and to identify a recommended intradermal dose of DSP-7888 Dosing Emulsion in combination with nivolumab or pembrolizumab

Secondary: To evaluate the preliminary antitumor activity

Phase 2

Primary: To evaluate the preliminary antitumor activity of DSP-7888 Dosing Emulsion administered with pembrolizumab in terms of the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in patients with platinum-resistant ovarian cancer (PROC)

Secondary: To evaluate the preliminary clinical activity of DSP-7888 Dosing Emulsion in combination with pembrolizumab in terms of duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), 6-month PFS Rate, and overall survival (OS) of DSP-7888 Dosing Emulsion administered in combination with pembrolizumab in PROC. To determine ORR, DCR and PFS per immune RECIST (iRECIST) of DSP-7888 Dosing Emulsion administered in combination with pembrolizumab in PROC and to evaluate the safety and tolerability of DSP-7888 Dosing Emulsion administered with pembrolizumab

Study Design:

This is a Phase 1b/2, open-label, multicenter study of DSP-7888 Dosing Emulsion in combination with checkpoint inhibitors (nivolumab or pembrolizumab) in adult patients with solid tumors, that consists of 2 parts: Phase 1b (a dose search part and an enrichment part) and Phase 2 dose-expansion. In the Phase 1b part of this study there will be 2 arms: Arm 1 and Arm 2. In Arm 1, there will be 6 to 12 patients who will be dosed with DSP-7888 Dosing Emulsion and nivolumab and, in Arm 2, there will be 6 to 12 patients who will be dosed with DSP-7888 Dosing Emulsion and pembrolizumab.

In addition, a Phase 1b enrichment cohort of a further 10 patients, who have locally advanced or metastatic renal cell carcinoma (RCC) or urothelial cancer with primary or acquired resistance to previous checkpoint inhibitors, will be enrolled and will be dosed with DSP-7888 Dosing Emulsion and nivolumab, or DSP-7888 Dosing Emulsion and pembrolizumab, as per the investigator's preference. The purpose of this Phase 1b enrichment cohort is to help evaluate the preliminary

antitumor activity of DSP-7888 Dosing Emulsion at the safe dose level identified in the Phase 1b dose-search part.

Once the recommended dose is determined in the Phase 1b dose search part, PROC patients will be enrolled in the Phase 2 part of the study with DSP-7888 Dosing Emulsion, exploring the combination with pembrolizumab. In Phase 2, a total of approximately 40 patients with PROC will be enrolled. Additional patients may be enrolled to further assess anti-tumor activities in the subgroups of interest. However, the total sample size of Phase 2 part cannot exceed 60 patients.

Phase 1b

After providing written informed consent, patients will undergo screening assessments, which will include a careful review of each patient's medical history.

Patients will be administered doses of DSP-7888 Dosing Emulsion intradermally in both arms of the study (Arm 1 and Arm 2). Arm 1 will include patients with indications approved by the Health Authorities for treatment with nivolumab: advanced melanoma, non-small cell lung cancer (NSCLC), RCC, urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma (HCC), and microsatellite instability-high or mismatch repair-deficient (MSI-H/dMMR) colorectal cancer. Arm 2 will include patients with indications approved by the Health Authorities for treatment with pembrolizumab: melanoma, NSCLC, HNSCC, urothelial carcinoma, MSI-H/dMMR cancer, gastric cancer or gastroesophageal junction adenocarcinoma, and cervical cancer.

In the Phase 1b dose search part of the study, during the Arm 1 induction phase (4 weeks), DSP-7888 Dosing Emulsion will be administered once weekly for 4 weeks, with nivolumab administered every other week. In the subsequent Arm 1 maintenance phase, DSP-7888 Dosing Emulsion will be administered once every 2 weeks with nivolumab until a discontinuation criterion is met. During the Arm 2 induction phase (6 weeks), DSP-7888 Dosing Emulsion will be administered once weekly for 6 weeks, with pembrolizumab administered once every 3 weeks. In the subsequent Arm 2 maintenance phase, DSP-7888 Dosing Emulsion will be administered once every 3 weeks with pembrolizumab until a discontinuation criterion is met.

Both programmed cell death-1 (PD-1) inhibitors (nivolumab and pembrolizumab) will be administered in the approved dose and schedule starting on Day 1 of the study. Study sites will not be limited to any arm of the study, and each arm will investigate the recommended dose in parallel.

Objective disease assessments will be performed according to RECIST (v1.1) and iRECIST, with the first assessment performed at the end of the dose-limiting toxicity (DLT) period (Cycle 3: at 4 weeks for nivolumab arm, at 6 weeks for pembrolizumab arm), and at Weeks 12, 18, and 24 after the first dose of DSP-7888 Dosing Emulsion. After that, objective disease assessments will occur every 12 weeks until patient discontinuation from the study.

The Phase 1b dose search part of the study is completed, and no further patients will be enrolled under the dosing regimen described above (this legacy dosing regimen is also depicted in Appendix 8). For patients enrolled under the Phase 1b enrichment part of the study, the dosing regimen described below will be followed per Amendment 5 of the protocol.

The Phase 1b enrichment cohort (consisting of the additional 10 patients) will include patients with locally advanced or metastatic RCC or urothelial carcinoma who experienced disease progression per iRECIST (immune confirmed progressive disease [iCPD]) during or within 3 months of last dose of the most recent prior anti-PD-1/PD-L1-based treatment.

Patients will be treated with the combination of DSP-7888 Dosing Emulsion and nivolumab, or DSP-7888 Dosing Emulsion and pembrolizumab, as per the treating physician's choice.

The administration of DSP-7888 Dosing Emulsion and anti-PD-1 in the Phase 1b enrichment cohort will differ from that in the Phase 1b dose search part of the study, and will be staggered as follows:

Arm 1 (Enrichment Cohort Only): DSP-7888 Dosing Emulsion + nivolumab combination:

- DSP-7888 Dosing Emulsion 10.5 mg intradermal (ID), will start on Day 1, Q1W for first 4 weeks, then Q2W thereafter
- Nivolumab 240 mg IV, will start on Day 1 of Cycle 3 (Day 29), Q2W

Arm 2 (Enrichment Cohort Only): DSP-7888 + pembrolizumab combination:

- DSP-7888 Dosing Emulsion 10.5 mg ID, will start on Day 1, Q1W for first 3 weeks, then Q3W thereafter
- Pembrolizumab 200 mg IV, will start on Day 1 of Cycle 2 (Day 22), Q3W

Administration of DSP-7888 Dosing Emulsion and anti-PD-1 in the Phase 1b enrichment cohort is also depicted in Figure 3.

Phase 2

Approximately 40 eligible PROC patients are expected to be enrolled in the Phase 2 dose expansion part of the study.

Objective disease assessments will be performed according to RECIST and iRECIST. For Phase 2, patients will be evaluated for objective response to study drug treatment with radiographic imaging every 6 weeks for 24 weeks and then every 12 weeks until progression.

For patients enrolled under Protocol Amendment 4, the administration of DSP-7888 Dosing Emulsion and anti-PD1 in the Phase 2 dose expansion cohort is the same as that in the Phase 1b Arm 2 of the dose search part.

For patients enrolled under Protocol Amendment 5, administration of DSP-7888 Dosing Emulsion and anti-PD1 will be staggered as follows:

- DSP-7888 Doing Emulsion+ pembrolizumab combination:
  - DSP-7888 Dosing Emulsion 10.5 mg ID, will start on Day 1, Q1W for the first 3 weeks, then Q3W thereafter
  - Pembrolizumab 200 mg IV, will start on Day 1 of Cycle 2 (Day 22), Q3W

Phase 1b and Phase 2

The safety and tolerability of DSP-7888 Dosing Emulsion in combination with immunotherapy PD-1 inhibitors will be assessed for the duration of study treatment and follow-up.

All adverse events (AEs) will be collected and recorded for each patient from the date of signing the main ICF for the study until 30 days after last study drug administration. Any serious adverse events (SAEs) related to study-related procedures will be collected starting from completion of the Prescreening informed consent form (ICF) (biomarkers sampling, blood drawings, and biopsy procedures).

Number of patients (planned):

In Phase 1b of the study, there will be approximately 6 to 12 patients for each arm, up to a total of 24 patients. As part of these 24 patients, an enrichment cohort of 10 patients will be enrolled into Phase 1b. If anti-tumor activities are observed in any tumor type, additional patients may be enrolled for further assessment. In Phase 2 of the study, approximately 40 patients will be enrolled. Additional

patients may be enrolled to further assess anti-tumor activities in the subgroups of interest. However, the total sample size of Phase 2 cannot exceed 60 patients. In total, approximately 64-84 patients will be enrolled in the study.

Inclusion Criteria:

Patients must fulfill each of the following requirements:

Phase 1b

Phase 1b Dose Search Part

1. A histologically or cytologically confirmed cancer that is metastatic and is approved to be treated with nivolumab or pembrolizumab with the following origins:

Nivolumab:

- Unresectable or metastatic melanoma
- Metastatic NSCLC
- Advanced RCC
- Recurrent or metastatic squamous cell carcinoma of the head and neck
- Locally advanced or metastatic urothelial carcinoma
- Hepatocellular carcinoma
- MSI-H/dMMR colorectal cancer

Pembrolizumab:

- Unresectable or metastatic melanoma
- Metastatic NSCLC
- Recurrent or metastatic squamous cell carcinoma of the head and neck
- Locally advanced or metastatic urothelial carcinoma
- Unresectable or metastatic MSI-H/dMMR solid tumors
- Recurrent locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma
- Recurrent or metastatic cervical cancer

In addition, the following requirements must be fulfilled:

a) Patients must not be considered eligible for a potentially curative resection

b) Patients who are eligible for PD-1 therapy based on either criterion (i) or (ii) below:

i. Patients progressed on their prior treatment before initiating treatment on current study

Or

ii. Patients who are currently being treated with nivolumab or pembrolizumab and have achieved at least stable disease (SD), and who, in the judgment of their treating physicians, could benefit from the addition of DSP-7888 Dosing Emulsion vaccine to improve or maintain their response

Phase 1b Enrichment Cohort Only:

- Patients with locally advanced or metastatic RCC or urothelial carcinoma who have experienced disease progression per iRECIST (iCPD) during or within 3 months of last dose of the most recent prior anti-PD-1/ PD-L1-based treatment (see Appendix 3)

Both Phase 1b Dose Search Part and Phase 1b Enrichment Cohort:

2. Patients must be positive for at least 1 of the following human leukocyte antigens (HLAs):
   a) HLA-A*02:01
   b) HLA-A*02:06
   c) HLA-A*24:02
   d) HLA-A*03:01
   e) HLA-B*15:01
3. ≥ 18 years of age
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Patients must be able to provide archival tumor tissue with sufficient tumor tissue, or patients must consent to undergo tumor biopsy to acquire sufficient tissue before first administration of study drug
6. Females of childbearing potential must have a negative serum pregnancy test
7. Male or female patients of child-producing potential must agree to use contraception or use prevention of pregnancy measures (true abstinence) during the study and for 6 months (for females and males alike) after the last dose of study drug
8. Total bilirubin of ≤2.0 mg/dL (≤3.0 mg/dL for patients with known Gilbert's syndrome)
9. Aspartate aminotransferase (AST) ≤3.0 × the upper limit of normal (ULN) or <5 × ULN if considered to be due to liver metastases
10. Alanine transaminase (ALT) ≤3.0 × the ULN or <5 × ULN if considered to be due to liver metastases
11. Estimated glomerular filtration rate (GFR) >40 mL/min using the Cockcroft-Gault equation
12. Multigated acquisition (MUGA) scan or echocardiogram (ECHO) with left ventricular ejection fraction (LVEF) >40%
13. Life expectancy ≥3 months
14. Patients must be willing to provide a signed and dated ICF

Phase 2

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Patients must be female ≥18 years of age, able to understand study procedures, and subsequently agreed to participate in the study by providing a written informed consent obtained prior to any prescreening and screening procedures that are standard of care
2. Patients must be positive for at least 1 of the following HLAs as assessed by central laboratory:
   a) HLA-A*02:01

b) HLA-A*02:06

c) HLA-A*24:02

d) HLA-A*03:01

e) HLA-B*15:01

3. Patients must have histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer, with predominantly high-grade (Grade 2 or 3) serous epithelial features
4. Patients must be considered platinum-resistant to last administered platinum-based therapy, defined as patient relapsed within 6 months after the last dose of platinum-based therapy
5. Patients must have completed at least 1 but no more than 4 prior lines of therapy for serous epithelial ovarian, fallopian tube, or primary peritoneal cancer
   a. Maintenance is not considered a separate line of treatment (even if patients who are BRCA mutation-positive received a PARP inhibitor following induction therapy with a platinum doublet, eg, bevacizumab)
   b. Neoadjuvant and adjuvant systemic therapy will be counted as one line of therapy
   c. Patients must have received at least one platinum-based therapy
6. Patients must have progression disease after last therapy and have measurable disease according to RECIST (v.1.1)
7. Patients must have an ECOG performance status of 0 or 1
8. Patients must have adequate organ function, defined as follows:

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1,500 / μL (without granulocyte colony stimulating factor (G-CSF))
Platelets	≥100,000 / μL (without transfusion)
Hemoglobin	≥9.0 g/dL (without transfusion)
Renal	
Serum creatinine OR estimated GFR using the Cockcroft-Gault equation	≤1.5 × ULN **OR** ≥40 mL/min using the Cockcroft-Gault equation for patients with creatinine levels >1.5 × ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN
AST and ALT	≤2.5 × ULN OR ≤5 × ULN for patients with liver metastases
Cardiac	
MUGA or ECHO with LVEF	≥40%
QTcF (QT corrected based on Fridericia's equation) interval	<480 msec

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN, unless the patient is receiving anticoagulant therapy and the PT is within therapeutic range
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	≤1.5 × ULN, unless the patient is receiving anticoagulant therapy and the aPTT is within therapeutic range

9. Patients must provide either a fresh tissue biopsy, if medically feasible, or archival tissue as either a formalin-fixed and paraffin embedded (FFPE) block or newly sectioned tissue on charged slides (equivalent to approximately 8 to 23 slides sectioned at 4-5μm thickness)
10. Patients of childbearing potential must have a negative serum or urine pregnancy test at screening
11. Patients must be either postmenopausal, free from menses for >12 months, surgically sterilized, or willing to use adequate contraception to prevent pregnancy or must agree to abstain from heterosexual activity throughout the study, starting with enrollment through 6 months (for females and males alike) after the last dose of study drug
12. Life expectancy ≥3 months
13. Patients who had stayed on the last treatment for at least 12 weeks without any evidence of progression

Exclusion Criteria:

Patients with any of the following will be excluded from the study:

Phase 1b

Phase 1b Dose Search Part and Phase 1b Enrichment Part:

1. Anticancer chemotherapy (including molecular targeted drugs), immunotherapy, radiotherapy, or investigational agents within 4 weeks of the first dose of DSP-7888 Dosing Emulsion.

   This exclusion is not applicable to patients who meet the inclusion criterion #1b (ii) within Phase 1b dose search part.
2. Major surgery within 4 weeks prior to study treatment
3. Patients who have received a live vaccine within 4 weeks prior to the first dose
4. Any known, untreated brain metastases; patients with treated brain metastases must be clinically stable for 4 weeks after completion of treatment for brain metastases and have radiographic image documentation of stability. Patients must have no clinical symptoms from brain metastases and not have required systemic corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 2) for at least 2 weeks prior to the first dose of study drug
5. Patients who have multifocal glioblastoma
6. Pregnant or breastfeeding
7. Patients who have an active autoimmune disease requiring immunosuppression >10 mg/day prednisone or equivalent (see Appendix 5)

a. Patients with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin prior to study drug administration

8. Patients who have interstitial lung disease or active, noninfectious pneumonitis
9. Known hypersensitivity to a component of protocol therapy:
   a. Patients with known hypersensitivity to any of the components of DSP-7888 Dosing Emulsion
   b. Patients with known hypersensitivity to nivolumab or pembrolizumab are excluded from receiving combination therapy that includes the agent to which they are hypersensitive
10. Uncontrolled concurrent illness including, but not limited to: ongoing or active, uncontrolled bacterial, viral, or fungal infections requiring systemic therapy; clinically significant non-healing or healing wounds; symptomatic congestive heart failure, unstable angina pectoris; severe and/or uncontrolled cardiac arrhythmia; significant pulmonary disease; or, psychiatric illness/social situations that would limit compliance with study requirements
11. Patients with a history of another primary cancer with the exception of: (a) curatively resected nonmelanoma skin cancer; (b) curatively treated cervical carcinoma in situ; (c) localized prostate cancer not requiring systemic therapy; and d) any another cancer from which the patient has been disease-free for ≥2 years that, in the opinion of the investigator and medical monitor for the Sponsor, will not affect patient outcome in the setting of the current diagnosis
12. Patients who have a QT corrected interval, based on Fridericia's equation (QTcF), >480 msec (Common Terminology Criteria for Adverse Events [CTCAE] = Grade 2) or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) at Screening (patients with bundle branch block and a prolonged QTc interval should be reviewed by the medical monitor for potential inclusion)
13. Patients who have a medical history of frequent or sustained ventricular ectopy
14. Patients who have, in the opinion of the treating investigator, any concurrent conditions that could pose an undue medical hazard or interfere with the interpretation of the study results
15. Known history of human immunodeficiency virus (HIV) infection, active hepatitis B, or untreated active hepatitis C

    Note: Patients who have completed a course of antiviral treatment for hepatitis C and are cured are eligible. In cases of negative results, hepatitis B surface antigen (HBsAg) with positive hepatitis B core antibody, and hepatitis B virus DNA testing are required
16. Patients who have baseline signs and symptoms consistent with clinically significant, decreased pulmonary function: (1) blood saturation oxygen level (SpO_2) <90% at rest on room air; (2) dyspnea at rest or required supplemental oxygen within 2 weeks of study enrollment

Phase 2

Patients with any of the following will be excluded from the study:

1. Primary platinum-refractory patients defined as patients who experienced disease progression during the treatment with first-line platinum therapy
2. Patients with a known, untreated brain metastasis; patients with treated brain metastases must be clinically stable for 4 weeks after completion of treatment for brain metastases and have radiographic image documentation of stability; patients must have no clinical symptoms from

brain metastases and not have required systemic corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 5) for at least 4 weeks prior to the first dose

3. Patients who have received prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody or a small molecule targeting other immunoregulatory receptors or mechanisms (examples of such drugs include, but are not limited to, antibodies against, eg, CTLA-4, LAG-3, IDO, PD-L1, IL-2R, GITR)
4. Patients who have received prior treatment with any other Wilms Tumor 1 (WT1)-related agents including peptide vaccine, dendric cell vaccine, and gene therapy
5. Patients who have received treatment for ovarian cancer within the following timeframe prior to the first dose of the study drug
    a. Cytotoxic chemotherapy, hormonal therapy; ≤3 weeks
    b. Targeted therapy except for monoclonal antibody; ≤3 weeks
    c. Immune therapy, biologic therapy (eg, antibodies); ≤4 weeks
    d. Other investigational agents: ≤4 weeks
    e. Radiation therapy (except for localized radiotherapy for analgesic purpose) ≤4 weeks
    f. Radiation therapy (localized radiotherapy for analgesic purpose) ≤1 week
    g. Major surgery regardless of reason ≤4 weeks
6. Patients who have received a live vaccine within 4 weeks prior to the first dose
7. Any known additional malignancy that is progressing or requires active treatment, with the exception of:
    a. curatively treated basal cell or squamous cell carcinoma of skin
    b. curatively treated superficial bladder cancer, carcinoma in situ of the cervix,
    c. any another cancer from which the patient has been disease-free for ≥3 years without any active treatment that, in the opinion of the investigator and medical monitor for the Sponsor, will not affect patient's outcome in the setting of the current diagnosis
8. Patients who have not recovered to <CTCAE Grade 2 or baseline from toxic effect (with exceptions of alopecia and/or neuropathy) of prior cancer therapy
9. Patients who have an active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance dose of corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 5) or any other forms of immunosuppressive therapy within 7 days prior to the first dose of study drug
10. Positive serology for HIV infection, active hepatitis B, or active hepatitis C:
    - In cases of negative results for HBsAg with positive Hepatitis B core antibody, hepatitis B virus (HBV) DNA greater than the lower limits of detection is not acceptable
11. Patients who have a known history of bacillus tuberculosis (TB)
12. Patients with impaired cardiac function or clinically significant cardiac disease:
    - New York Hospital Association (NYHA) Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy

- Unstable angina pectoris ≤6 months before study participation
- Myocardial infarction or stroke ≤6 months before study participation

13. Patients who have an interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids
14. Patients with active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy
15. Patients with any psychiatric condition, substance abuse disorder, or social situation that would interfere with a patient's cooperation with the study requirements and schedule
16. Patients with any condition that would, in the investigator's judgment, interfere with full participation, including administration of study drugs, attending required visits, or interfere with interpretation of study data
17. Patient who are pregnant or breastfeeding
18. Patients who have a known hypersensitivity to DSP-7888 Dosing Emulsion, pembrolizumab, their components, or their excipients
19. Patient has dyspnea at rest (CTCAE ≥Grade 3) or has required supplemental oxygen within 2 weeks of study enrollment
20. Patients with history of bowel obstruction related to underlying disease within 3 months prior to the first dose of study treatment

Duration of treatment:

Patients will have access to study treatment as long as they are benefiting from study treatment in Phase 1b.

For Phase 2 of the study, patients will have access to study treatment as long as they are benefiting from study treatment or have received up to a total of 35 treatment cycles (approximately 105 weeks). Patients may continue the study treatment beyond 35 treatment cycles if patients are experiencing clinical benefit after documented discussion with the Sponsor.

Criteria for Evaluation

<u>Phase 1b</u>

Primary Endpoints

- Incidence of DLTs, except for those patients treated in the enrichment cohort
- Incidence and severity of AEs, SAEs
- Dose interruption, reduction, and dose intensity

Secondary Endpoints

The following secondary efficacy endpoints will be evaluated per investigator assessment:

- ORR, defined as proportion of patients who have achieved confirmed complete response (CR) or partial response (PR), evaluated using RECIST (v.1.1) and iRECIST based on investigator assessment
- DCR, defined as the percentage of patients who have achieved best overall response (BOR) of CR, PR, or SD per RECIST (v.1.1) and iRECIST

- DOR, defined as the time from first documentation of a response (CR or PR) until time of first documentation of disease progression by RECIST (v.1.1) and iRECIST, or death by any cause
- PFS, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1) and iRECIST, or death by any cause
- 6-month PFS Rate, defined as the proportion of patients who neither progressed by RECIST (v.1.1) and iRECIST nor died before 6 months (24 weeks) from the first study treatment
- OS, defined as the time from the date of the first dose of study treatment to the date of death by any cause
- Safety assessments:
  - AEs assessed according to CTCAE v4.03
  - DLT observed during the first 2 cycles
  - Dose interruption, reduction, and dose intensity per dose administration record
  - The incidence of treatment-emergent AEs (TEAEs) during the first 2 cycles compared with the third and subsequent cycles
  - The incidence of TEAEs occurring while patients are on treatment or up to 30 days after the last dose of study drug
  - The incidence of AEs that occur from signing the ICF until the first dose of treatment
  - The incidence of SAEs occurring while patients are on treatment through 30 days after the last dose of study drug
  - Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), vital signs, ECOG performance status, electrocardiogram (ECG) parameters, physical examinations, and usage of concomitant medications (additional details in the schedule of assessments)

Exploratory Endpoints

Exploratory Biomarkers:

Biomarkers using peripheral blood samples and tumor tissue samples in patients receiving DSP-7888 Dosing Emulsion in combination with pembrolizumab may be evaluated for correlation with the following immunological changes and/or clinical responses:

- WT1-specific cytotoxic T-lymphocytes (CTL) induction activity in blood samples
- WT1 expression level via chromogenic in situ hybridization (CISH) and PD-L1 expression level via immunohistochemistry (IHC)
- CD8+ cell density in tumor tissues
- Tumor-infiltrating lymphocytes (TILs) profiling in tumor tissues
- Immune profiling in tumor tissues with tumor inflammation signature analysis
- Mutation status and tumor mutation burden (TMB) in tumor tissues

Other Exploratory Endpoints:

- Progression-free survival ratio (PFSr) is defined as PFS1/PFS (-1) ratio using RECIST (v.1.1)
  - PFS1 is defined as the time from the date of first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1), or death by any cause
  - PFS (-1) is defined as the date of initiation of the previous (penultimate) treatment regimen to the date of assessment of progression by RECIST (v.1.1)

Phase 2

Primary Endpoint

The primary endpoint for the efficacy evaluation is ORR, defined as proportion of patients who have achieved confirmed CR or PR, evaluated using RECIST (v.1.1) based on investigator assessment.

Secondary Endpoints

The following secondary efficacy endpoints will be evaluated per investigator assessment:

- DOR, defined as the time from the first documentation of a response (CR or PR) until time of first documentation of disease progression by RECIST (v.1.1), or death by any cause
- DCR, defined as the percentage of patients who have achieved BOR of CR, PR, or SD per RECIST (v.1.1)
- PFS, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1), or death by any cause
- 6-month PFS rate, defined as the proportion of patients who neither progressed by RECIST (v.1.1) nor died before 6 months (24 weeks) from the first study treatment
- OS, defined as the time from the date of first dose of study treatment to the date of death by any cause
- Immune objective response rate (iORR), defined as proportion of patients who have achieved confirmed immune complete response (iCR) or immune partial response (iPR), evaluated using iRECIST based on investigator assessment
- Immune DCR (iDCR), defined as the percentage of patients who have achieved BOR of iCR, iPR, or immune stable disease (iSD), per iRECIST
- Immune PFS (iPFS), defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by iRECIST or death by any cause
- Immune DOR (iDOR), defined as the time from the first documentation of response (iCR or iPR) until time of first documentation of disease progression by iRECIST, or death by any cause
- Safety Assessments: frequency and intensity of AEs assessed according to CTCAE v4.03.

Exploratory Endpoints

Exploratory Biomarkers:

Biomarkers using peripheral blood samples and tumor tissue samples in patients receiving DSP-7888 Dosing Emulsion in combination with pembrolizumab biomarkers may be evaluated for correlation with the following immunological changes and/or clinical responses

- WT1-specific CTL induction activity in blood samples
- WT1 via CISH and PD-L1 expression status (CPS) via IHC in tumor tissue
- CD8+ cell density in tumor tissues
- TILs profiling in tumor tissues
- Immune profiling in tumor tissues with tumor inflammation signature analysis
- Mutation status and mutational burden analysis in tumor tissues

Other Exploratory Endpoints:

- Progression-free survival ratio (PFSr) is defined as PFS1/PFS (-1) ratio using RECIST (v.1.1)
  - PFS1 is defined as the time from the date of first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1), or death by any cause
  - PFS (-1) is defined as the date of initiation of the previous (penultimate) treatment regimen to the date of assessment of progression by RECIST (v.1.1)
- CA-125 response rate is defined as proportion of patients who have achieved response using the Gynecologic Cancer InterGroup (GCIG) CA-125 response definition
- Time to progression with CA-125 is defined as the time from the date of first dose of study treatment to the earlier date of assessment of progression by GCIG CA-125 progression definition or death by any cause
- HLA typing

Statistical Methods:

In general, all efficacy and safety endpoints will be analyzed using descriptive statistics (n, mean, standard deviation, median, and ranges for continuous variables; frequencies and percentages for categorical variables). Kaplan-Meier methods will be used to summarize time-to-event endpoints (OS, PFS, and DOR). Primary efficacy of ORR will be analyzed using the Bayesian approach defined in the statistical analysis plan (SAP). Other efficacy analyses will be performed on the full analysis set (FAS).

Detailed methodology for the statistical analyses of the data collected in this study will be documented in the SAP, which will be maintained by [redacted] The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Patient responses will be assessed based on RECIST v1.1 and iRECIST. Data listings and summaries may include tumor markers, additional imaging, or other response data. Potential relationships between biomarker and other response data may be evaluated. For Phase 2, primary efficacy of ORR with RECIST v 1.1 will be analyzed using the Bayesian approach defined in the SAP, based on ES. Other efficacy analyses will be performed on the FAS. Progression-free survival ratio will be summarized for both the Phase 1b enrichment cohort and for Phase 2.

For Phase 2 Cohort Only

There is no formal hypothesis testing for the Phase 2 cohort. A Bayesian decision-making framework will be employed to quantify whether proof of concept (POC) can be established based on the overall response rate (ORR) by Week 24 from the final analysis for the overall population and/or the CPS < 10 subpopulation. The POC is established at the final analysis if either or both of the following 2 conditions are met:

- In the overall population, 70% credible interval of ORR with 10% in the left tail and 20% in the right tail will be calculated: if lower bound ≥ 8% and upper bound ≥ 21% (where 8% is the reference value [Section 4.3.1] and 21% is the target value of ORR in the overall population), the study will achieve POC.
- In the CPS< 10 subpopulation, 50% credible interval of ORR with 20% in the left tail and 30% in the right tail will be calculated: if lower bound ≥ 5% and upper bound ≥ 15% (where 5% is the reference value [Section 4.3.1] and 15% is the target value of ORR in CPS < 10 subpopulation), the study will achieve POC.

The interim monitoring analysis for futility early efficacy assessment will be conducted using a Bayesian method and will start after the first 20 patients have response evaluation, withdraw, or die by Week 24.

- If the posterior probability of ORR ≥ 21% in the overall population is ≤ 2.5% AND the posterior probability of ORR ≥ 15% in the CPS < 10 subpopulation is ≤ 2.5%, the study is futile and further enrollment will be stopped.
- If the posterior probability of ORR ≥ 21% in overall population is ≥ 80% AND the posterior probability of ORR ≥ 15% in CPS < 10 subpopulation is ≥ 70%, then early success is met and further enrollment may be stopped.
- Otherwise, the enrollment will continue as is until 40 patients.

The above decision rules for interim analysis are non-binding.

A total of 20 to 40 patients will be enrolled for this cohort. Additional patients may be enrolled to further assess anti-tumor activities in the subgroups of interest. However, the total sample size of Phase 2 part cannot exceed 60 patients.

Adverse events will be assessed according to CTCAE v4.03, when appropriate, and will be evaluated by grade and System Organ Class (SOC). Adverse event listings and tabulated summaries of categorized AEs will be generated by dose level and patients overall, for each study arm, and study phase. Additionally, the number of patients enrolled, number evaluable for dose search, and number with DLTs will be described for each dose level, patients overall, and each study arm in Phase 1b, the dose search part of the study. Vital signs, laboratory data, and ECG data, stratified by dose level and overall for each study arm and phase, will be summarized for changes over time at each postbaseline visit, together with the change from baseline.

Antitumor activity will be evaluated and will be summarized using descriptive statistics. Analyses will be performed both for all patients enrolled and for patients evaluable for response in the FAS. Data listings and summaries may include tumor markers, additional imaging, or other response data. Potential relationships between drug administration, PD, and other response data may be evaluated. Kaplan-Meier estimates of OS and PFS will be generated.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Special Terms

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BBI	Boston Biomedical, Inc (former name of [redacted]
BOR	best overall response
cGCP	current Good Clinical Practice
CISH	chromogenic in situ hybridization
CPS	combined positive score
CR	complete response
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
DCR	disease control rate
DDS	dose-determining set
DLT	dose-limiting toxicity
DOR	duration of response
DSP-7888 Dosing Emulsion	Ombipepimut-S (Nelatimotide and Adegramotide) / Ombipepimut-S Suspension with Montanide
DSP-7888 (Adegramotide/Nelatimotide [INN] and Ombipepimut-S [USAN])	code name for the dipeptide vaccine of DSP-7888-H and DSP-7888-K
DSP-7888-H	DSP-7888-H (adegramotide [INN]) helper peptide
DSP-7888-K	DSP-7888-K (nelatimotide [INN]) cytotoxic T lymphocyte-inducing (killer) peptide

ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group (performance status)
eCRF	electronic case report form
ES	efficacy set
FAS	full analysis set
FFPE	formalin-fixed and paraffin-embedded
GCIG	Gynecologic Cancer InterGroup
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practices
HBsAg HBV	hepatitis B surface antigen hepatitis B virus
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNSCC	head and neck squamous cell carcinoma(s)
HNSTD	highest non-severely toxic dose
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iCPD	immune confirmed progressive disease per iRECIST
iCR	immune complete response
iDCR	immune disease control rate
iDOR	immune duration of response
IEC	independent ethics committee
IHC	immunohistochemistry
INR	international normalized ratio
IRB	institutional review board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
iORR	immune objective response rate
iPFS	immune progression-free survival

iPR	immune partial response
irAE	Immune related adverse event
iSD	immune stable disease
ISR	injection site reaction
iUPD	immune unconfirmed progressive disease per iRECIST
IV	intravenous(ly)
LoQ	limit of quantification
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MSI-H/dMMR	microsatellite instability-high or mismatch repair-deficient
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	no-observed adverse effect level
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PD-1	programmed cell death protein 1
PFS	progression-free survival
PFSr	progression-free survival rate
PK	pharmacokinetic(s)
PR	partial response
PROC	platinum-resistant ovarian cancer
PT	prothrombin time
PTT	partial thromboplastin time
Q1W	once every week

Q3W	once every 3 weeks
QTcF	corrected QT using the Fridericia equation
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
[redacted]	[redacted] Inc., the Sponsor
SOA	schedule of assessments
SOC	System Organ Class
SpO_2	blood saturation oxygen level
SRC	Safety Review Committee
SS	Safety set
TB	bacillus tuberculosis
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TMB	tumor mutation burden
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WT1	Wilms Tumor 1

4. INTRODUCTION

4.1. Disease Background

It is estimated that in 2017, there will be 1,688,780 new cases of cancers in the United States (US) alone, with an estimated 600,920 cancer deaths; there were 8.8 million cancer deaths worldwide in 2015 (American Cancer Society, 2017; World Health Organization [WHO]). Consequently, there is a significant unmet medical need for the development of novel treatments for advanced solid tumors.

Ovarian cancer comprises multiple histologic subtypes, with epithelial ovarian cancer constituting approximately 90% of malignant ovarian cancers (National Comprehensive Cancer Network [NCCN] Guidelines 2019). Ovarian cancer is the seventh most common neoplasm for women worldwide, with more than 238,000 cases and >150,000 deaths in 2012 (Torre, 2018). In 2018, it was estimated that 22,240 new diagnoses and 14,070 deaths from ovarian cancer would occur in the US; less than 40% of women with ovarian cancer are cured (Siegel, 2018). More than 70% of patients with ovarian cancer present with stage III or IV disease, and a high percentage of patients with high-grade serous histology present with advanced disease (Kobel, 2010; Seidman, 2004). Approximately 90% of ovarian cancer patients with serous histology are positive, with Wilms Tumor 1 (WT1) in their tumors (McCluggage, 2015). Primary cytoreductive (debulking) surgery followed by platinum-based chemotherapy, with or without concurrent and maintenance bevacizumab, represents the currently recommended standard first-line systemic treatment, although most patients develop recurrence, with a median progression-free survival (PFS) time of 12 to 18 months (Jiang, 2014). Furthermore, patients who relapse within 6 months of completing first-line therapy have been classified as being "platinum resistant," and typically have low response rates to subsequent chemotherapy (15%), with a PFS of 3 to 4 months and a median survival under a year (Davis, 2014). Thus, more efficient treatment methods are warranted to improve the survival of ovarian cancer patients.

4.2. Investigational Product Background and Mechanism of Action

Nelatimotide and Adegramotide Dosing Emulsion (Ombipepimut-S Suspension with Montanide; hereafter referred to as DSP-7888 Dosing Emulsion) is a synthetic peptide vaccine that consists of 2 synthetic peptide constructs: nelatimotide (INN) (DSP-7888-K [killer peptide; an MHC Class I peptide]) and adegramotide (INN) (DSP-7888-H [helper peptide; an MHC Class II peptide]). Both constructs are derived from the WT1 protein. DSP-7888 Dosing Emulsion, a DSP-7888 solution mixed with montanide ISA 51 VG (labeled as DSP-7888-M). This will be administered at the study site by staff trained in the administration of intradermal drugs. Specifically, DSP-7888-K is a conjugate consisting of the $WT1_{126-134}$ peptide sequence and the modified $WT1_{235-243}$ peptide sequence, whereas DSP-7888-H corresponds to the $WT1_{34-51}$ sequence. The emulsion acts as a depot and enhances the immunogenicity of the DSP-7888-K and DSP-7888-H peptides.

DSP-7888 Dosing Emulsion is applicable for the patient who has at least 1 of 5 human leukocyte antigen (HLA) types: HLA-A*02:01, HLA-A*02:06, HLA-A*24:02, HLA-A*03:01, and HLA-B*15:01, which are expected to cover approximately 76.4% of North American Natives, 68.9% of Caucasians, 65.3% of Hispanics, 56.8% of Asians, and 42.2% of African Americans in the US population (Cao, 2001).

DSP-7888 Dosing Emulsion is administered intradermally or subcutaneously and is expected to be presented on the surface of antigen-presenting cells as an MHC Class I peptide complex that can be recognized by $CD8^+$ cytotoxic T lymphocytes (CTLs.) As a consequence, vaccination with DSP7888 Dosing Emulsion may stimulate the host immune system to induce a CTL response against cancer cells overexpressing the WT1 protein, resulting in cell lysis and inhibition of cancer cell proliferation. Addition of the MHC Class II peptide is expected to show efficacy over that observed with a treatment regimen of the MHC Class I peptide alone. Intradermal administration is selected in this study based on the data showing higher WT1-specific CTL induction activity in patients who received intradermal administration of DSP-7888 Dosing Emulsion than those who had received subcutaneous administration of DSP-7888 Dosing Emulsion. Further details can be found in the Investigator's Brochure.

4.3. Rationale for Study

4.3.1. Rationale for the Study Population

The combination of cancer vaccines like DSP-7888 Dosing Emulsion with checkpoint inhibitors (programmed cell death-1 [PD-1]/programmed death ligand 1 [PD-L1]) represents a feasible option to improve clinical benefit and a way to reverse resistance to immunomodulators (Morse, 2015). The vaccine significantly enhances infiltration by $CD8^+$ T cells that allows the priming and intratumoral recruitment of these cells, and could possibly transform a "non-inflamed," non-permissive tumor that is resistant to checkpoint inhibitors into a sensitive, "inflamed" tumor that is responsive to checkpoint inhibitor blockade. Interferon gamma production by antitumor-specific T cells could also upregulate PD-L1 on tumor cells as a resistance mechanism to adaptive immunity, thereby promoting PD-L1/PD-1 after vaccination (Morse, 2015).

The proposed panel of tumor types selected for the Phase 1b part of the study was based on higher expression of WT1 in these tumors, as well as promising clinical activities of checkpoint inhibitors in those tumor types (Goto, 2016). However, for the Phase 2 part of this study, ovarian cancer has been selected, as approximately 90% of the patients are WT1-positive in their tumors (Goldstein, 2002; Hwang, 2004).

The data of KEYNOTE-100 (an open-label Phase 2 study of pembrolizumab monotherapy for patients with recurrent ovarian cancer) demonstrated that pembrolizumab monotherapy in recurrent ovarian cancer elicited modest antitumor efficacy (objective response rate [ORR]:8.0%). Moreover, patients with Combined Positive Score ([CPS] ie, PD-L1 expression in tumor cells and immune cells) ≥10 had an ORR of 17.1% compared to an ORR of approximately 5% in patients with CPS <10. Although several studies, including KEYNOTE-100, demonstrate an activity of checkpoint inhibitors in recurrent ovarian cancer (Matulonis, 2019), and the patients who respond to checkpoint inhibitors have a long-term benefit from the treatment, they are not comparable to the results in other solid tumors (eg melanoma). The combination of cancer vaccines, like DSP-7888 Dosing Emulsion with checkpoint inhibitor, could possibly transform a "non-inflamed" tumor such as ovarian cancer into "inflamed" tumor to enhance infiltration by $CD8^+$ T cells. In a preclinical model of leukemia, it has been demonstrated that cancer vaccines cooperated with checkpoint blockade and allowed for immune control of cancers with low nonsynonymous mutation loads (Manlove, 2016). In a preclinical study of DSP-7888 Dosing Emulsion, the activity of DSP-7888-induced CTLs was further enhanced by treatment

with anti-PD-1 antibody. Additionally, antitumor activities of DSP-7888 and anti-PD-1 antibody were enhanced by their combination in the HLA-transgenic mouse model compared with DSP-7888 Dosing Emulsion alone or anti-PD-1 antibody alone (Goto, 2016).

4.3.1.1. Rationale for Dose Selection

A GLP repeat-dose toxicity study with DSP-7888 Dosing Emulsion demonstrated that neither a low dose (3.5 mg, consisting of 2.0 mg killer peptide + 1.5 mg helper peptide) nor a high dose (17.5 mg, consisting of 10.0 mg killer peptide + 7.5 mg helper peptide) resulted in treatment-related effects on body weight, food consumption, ophthalmologic examination, electrocardiography, body temperature, blood pressure, respiratory rate, immunophenotyping in peripheral blood, or organ weights in the cynomolgus monkeys. The main toxicities observed were ISRs (erythema, induration, and crust), which were more pronounced in the high-dose group. Under the conditions of this study, the NOAEL of DSP-7888 Dosing Emulsion was not determined. The HNSTD was declared as the high dose of DSP-7888 Dosing Emulsion (DSP-7888-K 10 mg/body + DSP-7888-H 7.5 mg/body).

In the Phase 1b dose search part, the higher starting dose of 10.5 mg (Level 1) of DSP-7888 Dosing Emulsion was selected based on studies that showed higher WT1-specific CTL induction with this dose. Patients with 10.5 mg administration showed stronger and earlier CTL induction than patients with 3.5 mg administration with similar safety profiles (Miyakoshi, 2016).

The recommended dose from Phase 1b dose search part will be used in the Phase 1b enrichment part and the Phase 2 part. In the absence of any dose-limiting toxicities (DLTs) identified in Phase 1b of the study, 10.5 mg of DSP-7888 Dosing Emulsion will be the recommended Phase 2 dose.

For those patients enrolled under Protocol Amendment 5, the administration schedule of DSP-7888 dosing emulsion and anti-PD-1 antibody will differ from that in the completed Phase 1b dose search part, and will be staggered as follows:

1. Timing of integration of anti-PD-1 antibody into DSP-7888 Dosing Emulsion:
    - DSP-7888 Dosing Emulsion + nivolumab combination:
        - DSP-7888 Dosing Emulsion 10.5 mg ID, beginning on Day 1, Q1W for first 4 weeks, then Q2W thereafter
        - Nivolumab 240 mg IV, beginning on Day 1 of Cycle 3 (Day 29), Q2W
    - DSP-7888 Dosing Emulsion + pembrolizumab combination:
        - DSP-7888 Dosing Emulsion 10.5 mg ID, beginning on Day 1, Q1W for first 3 weeks, then Q3W thereafter
        - Pembrolizumab 200 mg IV, beginning on Day 1 of Cycle 2 (Day 22), Q3W

Cancer vaccines, including neoantigens, are currently being explored in combination with anti-PD-1 and anti-PD-L1 antibodies in several clinical trials with the intent to reinvigorate T cell-mediated tumor killing and enhance the anti-PD-1 effect. However, since the PD-1 pathway plays an important role in the balance of T cell activation and tolerance (Patsoukis N, 2017), identifying the optimal timing or sequencing of PD-1 blockade with respect to T cell receptor (TCR) engagement and the status of T cell priming is essential to achieve maximum therapeutic

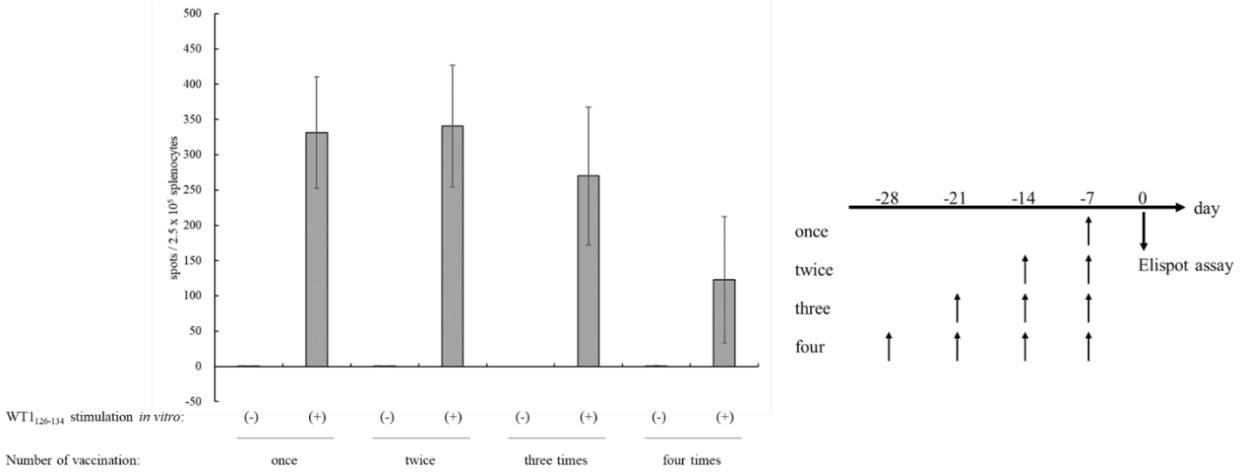
benefits. In mouse tumor models that are known to be resistant to anti-PD-1 therapy, PD-1 blockade in suboptimally primed CD8+ T cell conditions results in the generation of dysfunctional PD-1^{+}CD38hi CD8^{+} cells, leading to resistance to anti-PD-1 antibody and therapeutic failure. On the other hand, optimal antigenic stimulation reverses anti-PD-1 resistance. These results suggest that (1) concomitant treatment with anti-PD-1 in suboptimal priming conditions confers resistance to immunotherapy that can be reversed by proper antigen stimulation and (2) appropriate sequencing of immunomodulatory agents is crucial for therapeutic outcomes (Verma, 2019). In addition, Pauken et al. show that constitutive loss of PD-1 during acute infection causes overactivation of CD8+ T cells during the effector phase and impairs memory and recall responses. These data indicate PD-1 is required for optimal memory (Pauken, 2020). Based on the recent finding above, anti-PD-1 antibody therapy will be integrated in a staggered schedule into DSP-7888 Dosing Emulsion from Day 29 (Arm 1) or Day 22 (Arm 2), based on the choice of combination therapy, when optimal priming of WT1-specific CTL by DSP-7888 Dosing Emulsion has been expected.

2. Duration of induction phase for combination with pembrolizumab:

Per Protocol Amendment 5, the long duration of the 6-week induction phase is shortened to 3 weeks.

A nonclinical in vivo pharmacology study was conducted to evaluate the trend of induction of HLA-A*02:01-restricted T cells that recognize the $WT1_{126\text{-}134}$ peptide using HLA-A*02:01 transgenic mice. A weekly DSP-7888-like cancer vaccine, which was prepared by mixing MONTANIDE ISA 51 VG and aqueous antigenic peptide solution containing Nelatimotide Trifluoroacetate and Adegramotide Acetate but without any additives, was administered once, twice, three, or four times. 7 days after the final administration, splenocytes were prepared from each mouse and evaluated to measure the number of HLA-A*02:01-restricted T cells that recognize the $WT1_{126\text{-}134}$ peptide with IFN-γ ELISPOT assay. As a result, there was a statistically downward trend in the induction with an increasing number of administrations of the weekly cancer vaccine. (p=0.0466; Figure 1).

Figure 1: Effect of the Number of Doses of Cancer Vaccine on the Induction of $WT1_{126-134}$ -reactive T Cells



Legend: The number of $WT1_{126-134}$-reactive T cells induced by the DSP-7888-like cancer vaccine in HLA-A*02:01 transgenic mice. HLA-A*02:01 Tg mice were intradermally administered DSP-7888-like cancer vaccine containing 0.1 mg of Nelatimotide Trifluoroacetate and 0.1 mg of Adegramotide Acetate once, twice, three, or four times (n = 3 animals/group). 7 days after the final administration, splenocytes were prepared from each mouse and evaluated to measure the number of HLA-A*02:01-restricted T cells that recognize the $WT1_{126-134}$ peptide with IFN-γ ELISPOT assay. Values are the mean ± standard deviation of each group of IFN-γ ELISPOT assay. p=0.0466 (Jonckheere-Terpstra).

4.3.2. Current Status of [redacted] Sponsored Studies

DSP-7888 Dosing Emulsion is currently under clinical investigation in 2 studies including the DSP-7888 102CI study and a multi-national Phase 3 study in patients with recurrent or progressive glioblastoma. These 2 studies are ongoing, and additional information regarding DSP-7888 Dosing Emulsion can be found in the current Investigator's Brochure.

DSP-7888 Dosing Emulsion has been well tolerated thus far. Overall, the most frequently observed adverse event (AE) is injection site reaction (ISR).

Thirteen patients already have been enrolled into the Phase 1b dose search part of this study as of 16 Dec 2019,7 in the nivolumab arm and 6 in the pembrolizumab arm. Tumor evaluation data from select renal cell carcinoma (RCC) and urothelial carcinoma patients indicate preliminary signs of antitumor activity in this cohort. Therefore, the Sponsor intends to conduct additional evaluation of the effect of DSP-7888 Dosing Emulsion in these 2 disease indications in the Phase 1b enrichment part. The protocol allows for enrollment of up to 24 patients in the Phase 1b portion of the study, and additional patients may be enrolled for further assessment if anti-tumor activities are observed in any tumor type.

4.3.3. Nonclinical Studies

4.3.3.1. Primary Pharmacology

4.3.3.1.1. In Vitro Pharmacology

Two in vitro pharmacology studies (R-PH-DSP-7888-001 and R-PH-DSP-7888-002) were conducted to test the induction of $CD8^+$ T cells that recognize $WT1_{126-134}$ peptide, $WT1_{37-45}$

peptide, and modified $WT1_{235-243}$ peptide in human peripheral blood mononuclear cells (PBMCs) stimulated with a mixture of DSP-7888-K and DSR-127629 (the amino acid sequence of the latter compound is the same as that of DSP-7888-H). The mixture elicited $CD8^+$ T cells that recognized the synthetic $WT1_{126-134}$ peptide or the synthetic $WT1_{37-45}$ peptide in HLA-A*02:01+ PBMCs, and elicited $CD8^+$ T cells that recognized the synthetic modified $WT1_{235-243}$ peptide in HLA-A*24:02+ PBMCs. In addition, the frequency of HLA-A*03:01- or HLA-B*15:01-restricted CD8+ T cells that recognized the synthetic WT1126-134 peptide (in PBMCs from patients enrolled in Study BBI-DSP7888-201G) was increased by treatment with DSP-7888 Dosing Emulsion.

4.3.3.1.2. In Vivo Pharmacology

Two in vivo pharmacology studies (R-PH-DSP-7888-003 and R-PH-DSP-7888-004) were conducted to test whether DSP-7888 Dosing Emulsion elicits: (1) HLA-A*02:01-restricted CTLs that recognize $WT1_{126-134}$ peptide or WT_{37-45} peptides in HLA-A*02:01 transgenic mice, and (2) HLA-A*24:02-restricted CTLs that recognize modified $WT1_{235-243}$ peptide in HLA-A*24:02 transgenic mice. Another study (R-PH-DSP-7888-005) was conducted to test whether DSP-7888-H has the ability to enhance the induction of $WT1_{126-134}$ peptide-reactive T cells in HLA-A*02:01 transgenic mice.

DSP-7888 Dosing Emulsion elicited HLA-A*02:01-restricted CTLs that recognized the synthetic $WT1_{126-134}$ peptide or the synthetic $WT1_{37-45}$ peptide in HLA-A*02:01 transgenic mice, and elicited HLA-A*24:02-restricted CTLs that recognized the synthetic modified $WT1_{235-243}$ peptide in HLA-A*24:02 transgenic mice. DSP-7888 Dosing Emulsion including DSP-7888-H elicited a greater number of T cells reactive to the synthetic $WT1_{126-134}$ peptide.

4.3.3.1.3. Safety Pharmacology

No dedicated safety pharmacology studies have been conducted with DSP-7888 Dosing Emulsion. Safety pharmacology endpoints, including routine clinical observations, respiratory rate, blood pressure, electrocardiography, and body temperature were evaluated in the Good Laboratory Practices (GLP)-compliant 4-week intermittent (once weekly) intradermal toxicity study in cynomolgus monkeys, followed by a 4-week recovery period (Study SBL198-332). In that study, there were no clinical findings to indicate effects on behavior, respiratory rate, blood pressure, electrocardiogram (ECG) parameters, or body temperature following intradermal administration of DSP-7888 Dosing Emulsion.

4.3.3.2. Pharmacokinetics

The pharmacokinetics (PK) of DSP-7888 Dosing Emulsion were evaluated in the same non-rodent (cynomolgus monkey) species used for toxicology studies. Additionally, in vitro studies were conducted to assess the stability of DSP-7888-K and DSP-7888-H in human and monkey blood. Concentrations were presented as the DSP-7888-K or DSP-7888-H equivalents unless otherwise indicated.

4.3.3.2.1. In Vivo Pharmacokinetics in Monkey

In vivo studies in monkeys (SBL198-338 and JCL14101436) were conducted to investigate the PK of DSP-7888 Dosing Emulsion. Male cynomolgus monkeys (n = 2) were given a single

intradermal administration of DSP-7888 Dosing Emulsion at a dose volume of 0.1 mL/site to 10 different injection sites on the back of each animal (1.0 mL/body; containing 10 mg/body as DSP-7888-K, 7.5 mg/body as DSP-7888-H). Plasma concentrations of DSP-7888-K and DSP-7888-H were then measured at 0.25, 0.5, 1, 2, 4, 8, and 24 hours postdose. DSP-7888-K was detected only 0.25 hours after dosing (27.8 ng/mL) and was below the limit of quantification (LoQ) (<20 ng/mL) from 0.5 to 24 hours postdose. DSP-7888-H was also detected only 0.25 hours after dosing (36.7 ng/mL) and was below the LoQ (<20 ng/mL) from 0.5 to 24 hours postdose.

These results indicated that DSP-7888-K and DSP-7888-H transiently appeared in systemic circulation, but the plasma concentrations declined rapidly to below the LoQ following a single intradermal administration of DSP-7888 Dosing Emulsion to the monkey.

4.3.3.2.2. In Vitro Stability in Human and Monkey Blood

The in vitro stability of DSP-7888-K and DSP-7888-H in human and monkey blood was investigated (Study JCL14081377).

DSP-7888-K and DSP-7888-H (at a final concentration of 20 μg/mL) were incubated at 37°C in the blood of both humans and monkeys. The mean half-lives of DSP-7888-K in human and monkey blood were 0.14 and 0.11 hours, respectively. The mean half-lives of DSP-7888-H in human and monkey blood were 0.10 and 0.18 hours, respectively.

4.3.3.3. Toxicology

Based on the technical feasibility of replicating the planned clinical dose, dosing schedule, and routes of administration of DSP-7888 Dosing Emulsion, the cynomolgus monkey was chosen as the species in which to evaluate the potential toxicity of DSP-7888 Dosing Emulsion. Additionally, because previously published clinical data with other WT1 peptide vaccines (Sakai, 2015; Oka, 2004; Soeda, 2010; Kaida, 2011) described ISRs following repeated vaccinations, the cynomolgus monkey was considered an appropriate animal model in which to evaluate local skin reactions following repeated injections of DSP-7888 Dosing Emulsion. A 4-week toxicity study was performed using the intradermal route of administration to evaluate potential toxicities, including local skin reactions, of DSP-7888 Dosing Emulsion.

The objective of this GLP-compliant study (SBL198-332) was to evaluate the toxicity of DSP-7888 Dosing Emulsion and assess the reversibility of toxicity observed in the animals when DSP-7888 Dosing Emulsion was administered intradermally to cynomolgus monkeys once weekly for up to 4 weeks, with a 4-week recovery period (total 5 dose times). Two dose levels (low-dose and high-dose) were intradermally administered once weekly: DSP-7888-K 2.0 mg/body + DSP-7888-H 1.5 mg/body (low-dose group) and DSP-7888-K 10 mg/body + DSP-7888-H 7.5 mg/body (high-dose group).

All animals survived until their scheduled sacrifice. Administration of control dosing emulsion and DSP-7888 Dosing Emulsion at both low- and high-dose levels did not result in any treatment-related effects on body weight, food consumption, ophthalmologic examination, electrocardiography, body temperature, blood pressure, respiratory rate, immunophenotyping in peripheral blood, or organ weights.

In the high-dose group, during the dosing period, erythema, induration, and crust were observed in all males and females; erosion was observed in 1 male and 2 females; and ulcer was observed in 1 male and 2 females at dose administration sites. At the fifth injection site, erythema, induration, crust, erosion, and/or ulcer were observed in the high-dose group during the recovery period. In the low-dose group, erythema and induration were observed in all males and females, and crust was observed in 1 male and 2 females at dose administration sites. In the control dosing emulsion group, erythema was observed in 2 males and 4 females, and induration was observed in all females at the dose administration sites. However, these skin reactions showed a tendency toward resolution at the end of the recovery period; injection sites in some animals were treated with irrigation, disinfection, antibiotics, and/or gauze to prevent secondary infection.

Alterations in hematology parameters (high platelet count, high fibrinogen levels) and/or blood chemistry (high C-reactive protein [CRP], high globulin concentration, low albumin concentration, and/or low albumin/globulin ratio) were noted in the animals in the high-dose group; erosion and/or ulcer at the injection site were concurrently observed in these animals. Based on the results, the alterations in hematology and/or blood chemistry parameters were concluded to be secondary to inflammatory changes at the injection site. The alterations were fully resolved by the end of recovery period.

Positive occult blood reaction in urine during the dosing and recovery period, and an increase in osmotic pressure during the dosing period were noted in females in the high-dose group in urinalysis; however, the findings were not considered to be adverse since they were not accompanied by any histopathologic lesions in the kidneys.

At necropsy, induration at the injection site in the control dosing emulsion and in the low-dose and the high-dose groups, erythema and crust at the injection site in the low- and the high-dose groups, ulcer and edema in the subcutaneous tissue at the injection site, and erosion at the injection site in the high-dose group were observed in males and/or females at the final dose of the dosing and/or recovery periods. In the high-dose group, edema in the subcutaneous tissue was observed at the fifth injection site at the end of the dosing period, although that finding was not observed at the first, second, third, or fourth injection site. At the end of the recovery period, edema in the subcutaneous tissue was not observed at any injection site in the high-dose group. Additionally, in the high-dose group, enlargement of the axillary lymph nodes in one male and inguinal lymph nodes in one female were observed at the end of the dosing period, whereas that finding was not noted at the end of recovery period.

In histopathology, oil droplet, lymphocyte/plasma cell infiltration, macrophage/giant cell infiltration, and/or neutrophil infiltration in the dermis/subcutis, and crust in the control dosing emulsion, the low-dose, and the high-dose groups; thickening of the epidermis, erosion/ulcer, edema in the dermis/subcutis, bulla in the epidermis in the low-dose and the high-dose groups; and fibrosis in the dermis and hemorrhage in the subcutis in the high-dose group were observed in the injection sites at the end of the dosing and recovery periods. In the high-dose group, at the end of dosing period, very slight to moderate edema in the dermis/subcutis and/or bulla in the epidermis were observed at the fourth and fifth injection sites, although these findings were not noted at the first, second, or third injection sites. At the end of recovery period, edema in the dermis/subcutis and bulla in the epidermis were not observed at any injection site except that slight edema in the dermis/subcutis was observed at the second injection site.

Based on the results, it is considered that the findings in clinical signs, hematology, blood chemistry, necropsy, and histopathology related to inflammatory changes at the injection site were fully or partially resolved. Oil droplet, lymphocyte/plasma cell infiltration, macrophage/giant cell infiltration, and/or neutrophil infiltration were observed in the sinus and/or the capsule in the axillary and/or inguinal lymph nodes in the control dosing emulsion, the low-dose, and/or the high-dose groups. No changes, except for those at the injection sites or in the lymph nodes, were noted in any organs or tissues in the DSP-7888 Dosing Emulsion-treated groups.

Under the conditions of this study, the no-observed adverse effect level (NOAEL) of DSP-7888 Dosing Emulsion was not determined. The highest non-severely toxic dose (HNSTD) was declared as the high dose of DSP-7888 Dosing Emulsion (DSP-7888-K 10 mg/body + DSP-7888-H 7.5 mg/body).

4.3.4. Clinical Studies

DSP-7888 Dosing Emulsion is being evaluated in 3 clinical studies in patients with advanced malignancies: Studies DB650027 and DB601001 in Japan and Study BBI-DSP-7888-201G under an IND in the US and under CTAs in other countries. One study has been completed, study BBI-DSP-7888-101, in patients with advanced malignancies. No deaths have been attributed to DSP-7888 Dosing Emulsion in the completed and ongoing clinical studies. Injection site reaction is the most common AE of DSP-7888 Dosing Emulsion identified in the clinical studies (see Section 8.3.5 regarding management of the ISRs).

5. STUDY OBJECTIVES AND ENDPOINTS

A summary of objectives, endpoints, and assessments of the study is presented in Table 3 below.

Table 3: Study Objectives, Endpoints, and Assessments

Phase 1b

	Objectives	Endpoints
Phase 1b		
Primary Objective	To evaluate the safety and tolerability, and identify a recommended intradermal dose of DSP-7888 Dosing Emulsion in combination with nivolumab or pembrolizumab	1. Incidence of DLTs, except for those patients treated in the enrichment cohort 2. Incidence and severity of AEs, serious AEs (SAEs) 3. Dose interruption, reduction, and dose intensity
Secondary Objective	To evaluate the preliminary antitumor activity of DSP-7888 Dosing Emulsion in combination with nivolumab and pembrolizumab in terms of ORR, disease control rate (DCR), duration of response (DOR), 6-month progression-free survival (PFS) Rate, overall survival (OS)	1. ORR, defined as proportion of patients who have achieved confirmed complete response (CR) or partial response (PR), evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) (v.1.1) and immune RECIST (iRECIST) based on investigator assessment 2. DCR, defined as the percentage of patients who have achieved best overall response (BOR) of CR, PR, or stable disease (SD) per RECIST (v.1.1) and iRECIST 3. DOR, defined as the time from the first documentation of a response (CR or PR) until time of first documentation of disease progression by RECIST (v.1.1) and iRECIST, or death by any cause 4. PFS, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1) and iRECIST, or death by any cause 5. 6-month PFS Rate, defined as the proportion of patients who neither progressed by RECIST (v.1.1) and iRECIST nor died before 6 months (24 weeks) from the first study treatment 6. OS, defined as the time from the date of the first dose of study treatment to the date of death by any cause

	Objectives	Endpoints
Exploratory Objective	To characterize pharmacodynamic (PD) or potential predictive biomarkers and their relationship to clinical activity	Biomarkers using peripheral blood samples and tumor tissue samples in patients receiving DSP-7888 Dosing Emulsion in combination with pembrolizumab may be evaluated for correlation with the following immunologic changes and/or clinical responses 1. WT1-specific CTL induction activity in blood samples 2. WT1 expression level via chromogenic in situ hybridization (CISH) and PD-L1 expression level via immunohistochemistry (IHC) 3. CD8+ cell density in tumor tissues 4. Tumor infiltrating lymphocytes (TILs) profiling in tumor tissues 5. Immune profiling in tumor tissues with tumor inflammation signature analysis 6. Mutation status and tumor mutation burden (TMB) in tumor tissues
	To determine the PFS rate as an evaluation of treatment benefit of DSP-7888 Dosing Emulsion administered with nivolumab or pembrolizumab	PFS rate is defined as PFS1/PFS (-1) ratio using RECIST (v.1.1) 1. PFS1 is defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1), or death by any cause 2. PFS (-1) is defined as the date of initiation of the previous (penultimate) treatment regimen to the date of assessment of progression by RECIST (v.1.1)

Abbreviations: AEs = adverse events; CTL = cytotoxic T lymphocyte; DCR = disease control rate; DOR = duration of response; IHC = immunohistochemistry; iRECIST = Immune Response Evaluation Criteria In Solid Tumors; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events; TIL = tumor-infiltrating lymphocytes; TMB = tumor mutation burden; WT1 = Wilms Tumor 1

*Note: It should be ensured that 8 to 23 slides of archival samples and/or the equivalent amount of archival tissue block and/or fresh biopsy samples from enrolled patients are available at Pre-screening/Screening. From patients who consent to providing additional samples by signing the additional informed consent for these optional samples, an additional 6 to 8 slides will be collected for future biomarker analysis. These samples must contain sufficient tumor tissue. Details of the biopsy time points are described in the schedule of assessments (SOA) in Table 7, Table 8, and Table 9.

Phase 2

	Objectives	Endpoints
Phase 2		
Primary	To evaluate the preliminary antitumor activity of DSP-7888 Dosing Emulsion administered with pembrolizumab in terms of ORR in patients with platinum-resistant ovarian cancer (PROC)	ORR, defined as the proportion of patients who have achieved confirmed CR or PR, evaluated using RECIST (v.1.1) based on investigator assessment
Secondary	To evaluate the preliminary clinical activity of DSP-7888 Dosing Emulsion in combination with pembrolizumab in terms of DOR, DCR, PFS, 6 months PFS Rate, and OS of DSP-7888 Dosing Emulsion administered in combination with pembrolizumab in PROC	1. DOR, defined as the time from the first documentation of a response (CR or PR) until time of first documentation of disease progression by RECIST (v.1.1), or death by any cause 2. DCR, defined as the percentage of patients who have achieved BOR of CR, PR, or SD per RECIST (v.1.1) 3. PFS, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1), or death by any cause 4. 6 months PFS Rate, defined as the proportion of patients who neither progressed by RECIST (v.1.1) nor died before 6 months (24 weeks) from the first study treatment 5. OS, defined as the time from the date of the first dose of study treatment to the date of death by any cause
	To determine ORR, DCR, PFS, and iDOR per iRECIST of DSP-7888 Dosing Emulsion administered in combination with pembrolizumab in PROC	1. immune ORR (iORR), defined as proportion of patients who have achieved confirmed immune complete response (iCR) or immune partial response (iPR), evaluated using iRECIST based on investigator assessment 2. immune DCR (iDCR), defined as the percentage of patients who have achieved BOR of iCR, iPR, or iSD per iRECIST 3. immune PFS (iPFS), defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression* by iRECIST, or death by any cause

	Objectives	Endpoints
		4. immune DOR (iDOR), defined as the time from the first documentation of response (iCR or iPR) until time of first documentation of disease progression by iRECIST, or death by any cause * The event date to be used for calculation of PFS should be the first date at which progression criteria are met (ie, the date of immune unconfirmed progressive disease [iUPD]) provided that immune confirmed progressive disease [iCPD] is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date
	To evaluate the safety and tolerability of DSP-7888 Dosing Emulsion administered with pembrolizumab	Frequency and intensity of AEs using Common Terminology Criteria for Adverse Events (CTCAE) v 4.03
Exploratory	To determine the PFS rate as an evaluation of treatment benefit of DSP-7888 Dosing Emulsion administered with pembrolizumab	PFS rate is defined as PFS1/PFS (-1) ratio using RECIST (v.1.1) 1. PFS1 is defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST (v.1.1), or death by any cause 2. PFS (-1) is defined as the date of initiation of the previous (penultimate) treatment regimen to the date of assessment of progression by RECIST (v.1.1)
	To evaluate the antitumor activity of DSP-7888 Dosing Emulsion administered with pembrolizumab in terms of the CA-125 response rate and time to progression with CA-125 criteria in PROC	1. CA-125 response rate is defined as proportion of patients who have achieved response using the Gynecologic Cancer InterGroup (GCIG) CA-125 response definition 2. Time to progression with CA-125 is defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by GCIG CA-125 progression definition or death by any cause
	To characterize PD or potential predictive biomarkers and their relationship to clinical activity	Biomarkers using peripheral blood samples and tumor tissue samples in patients receiving DSP-7888 Dosing Emulsion in combination with pembrolizumab may be evaluated for correlation with the following immunologic changes and/or clinical responses

	Objectives	Endpoints
		1. WT1-specific CTL induction activity in blood samples 2. WT1 expression level via CISH and PD-L1 expression status (CPS) via IHC in tumor tissue 3. CD8+ cell density in tumor tissues 4. TILs profiling in tumor tissues 5. Immune profiling in tumor tissues with tumor inflammation signature analysis 6. Mutation status and mutational burden analysis in tumor tissues 7. HLA typing

*Note: These samples must contain sufficient tumor tissue. Details of the biopsy time points are described in the SOA in Table 7, Table 8, and Table 9.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

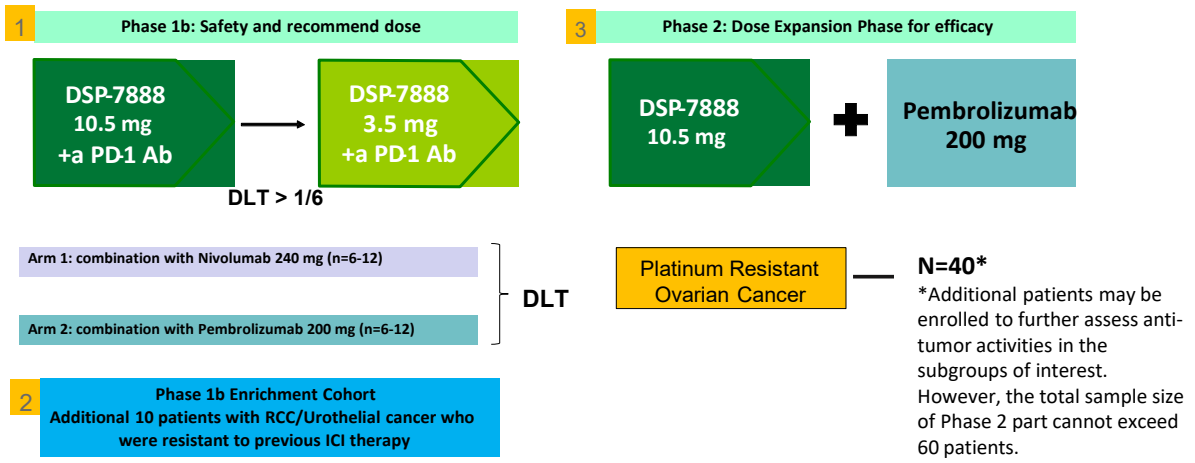
This is a Phase 1b/2, open-label, multicenter study of DSP-7888 Dosing Emulsion in combination with checkpoint inhibitors (nivolumab or pembrolizumab) in adult patients with solid tumors, that consists of 2 parts: Phase 1b (a dose search part and an enrichment part) and Phase 2 dose expansion (Figure 2). In the Phase 1b part of this study there will be 2 arms: Arm 1 and Arm 2. In Arm 1, there will be 6 to 12 patients who will be dosed with DSP-7888 Dosing Emulsion and nivolumab and, in Arm 2, there will be 6 to 12 patients who will be dosed with DSP 7888 Dosing Emulsion and pembrolizumab.

In addition, a Phase 1b enrichment cohort of a further 10 patients, who have locally advanced or metastatic renal cell carcinoma (RCC) or urothelial cancer with primary or acquired resistance to previous checkpoint inhibitors, will be enrolled and will be dosed with DSP-7888 Dosing Emulsion and nivolumab, or DSP-7888 Dosing Emulsion and pembrolizumab, as per the investigator's preference. The purpose of this Phase 1b enrichment cohort is to help evaluate the preliminary antitumor activity of DSP-7888 Dosing Emulsion at the safe dose level identified in the Phase 1b dose search part.

Once the recommended dose is determined in the Phase 1b dose search part, PROC patients will be enrolled in the Phase 2 part of the study with DSP-7888 Dosing Emulsion, exploring the combination with pembrolizumab. In Phase 2, a total of approximately 40 patients with PROC will be enrolled.

Objective disease assessments will be performed according to Table 7 (Phase 1b Arm 1), Table 8, (Phase 1b Arm 2), and Table 9 (Phase 2).

Figure 2: Overall Study Design



Note: The DSP-7888 Dosing Emulsion 3.5 mg + a PD-1 inhibitor cohort will only open if >1 out of 6 patients from the DSP-7888 Dosing Emulsion 10.5 mg + a PD-1 inhibitor cohort report a DLT.

6.1.1. Phase 1b

6.1.2. Dose Search Part

After providing written informed consent, patients will undergo screening assessments, which will include a careful review of each patient's medical history.

Patients will be administered doses of DSP-7888 Dosing Emulsion intradermally in both arms of the study (Arm 1 and Arm 2). Arm 1 will include patients with indications approved by the Health Authorities for treatment with nivolumab: advanced melanoma, non-small cell lung cancer (NSCLC), RCC, urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma (HCC), and microsatellite instability-high or mismatch repair-deficient (MSI H/dMMR) colorectal cancer. Arm 2 will include patients with indications approved by the Health Authorities for treatment with pembrolizumab: melanoma, NSCLC, HNSCC, urothelial carcinoma, MSI-H/dMMR cancer, gastric cancer or gastroesophageal junction adenocarcinoma, and cervical cancer (Figure 3).

In the Phase 1b dose search part of the study, during the Arm 1 induction phase (4 weeks), DSP-7888 Dosing Emulsion will be administered once weekly for 4 weeks, with nivolumab administered every other week. In the subsequent Arm 1 maintenance phase, DSP-7888 Dosing Emulsion will be administered once every 2 weeks with nivolumab until a discontinuation criterion is met. Arm 2 will include patients with indications approved by the Health Authorities for treatment with pembrolizumab: melanoma, NSCLC, HNSCC, urothelial carcinoma, MSIH/-dMMR cancer, gastric cancer or gastroesophageal junction adenocarcinoma, and cervical cancer. During the Arm 2 induction phase (6 weeks), DSP-7888 Dosing Emulsion will be administered once weekly for 6 weeks, with pembrolizumab administered once every 3 weeks. In the subsequent Arm 2 maintenance phase, DSP 7888 Dosing Emulsion will be administered once every 3 weeks with pembrolizumab until a discontinuation criterion is met.

Both programmed cell death-1 (PD-1) inhibitors (nivolumab and pembrolizumab) will be administered in the approved dose and schedule starting on Day 1 of the study. Study sites will not be limited to any arm of the study, and each arm will investigate the recommended dose in parallel.

The Phase 1b dose search part of the study is completed, and no further patients will be enrolled under the dosing regimen described above (this legacy regimen is also depicted in Appendix 8). For patients enrolled under the Phase 1b enrichment part of the study, the dosing regimen described below will be followed per Amendment 5 of the protocol.

6.1.3. Enrichment Part

The Phase 1b enrichment cohort (consisting of the additional 10 patients) will include patients with locally advanced or metastatic RCC or urothelial carcinoma who experienced disease progression per iRECIST (immune confirmed progressive disease [iCPD]) during or within 3 months of last dose of the most recent prior anti-PD-1/PD-L1-based treatment.

Patients will be treated with the combination of DSP-7888 Dosing Emulsion and nivolumab, or DSP 7888 Dosing Emulsion and pembrolizumab, as per the treating physician's choice.

The administration of DSP-7888 Dosing Emulsion and anti-PD1 therapy in the Phase 1b enrichment cohort will differ from that in the Phase 1b dose search part of the study, and will be staggered as follows:

Arm 1 (Enrichment Cohort Only): DSP-7888 + nivolumab combination:

- DSP-7888 Dosing Emulsion will start on Day 1, Q1W for first 4 weeks, then Q2W thereafter
- Nivolumab will start on Day 1 of Cycle 3 (Day 29), Q2W

Arm 2 (Enrichment Cohort Only): DSP-7888 + pembrolizumab combination:

- DSP-7888 Dosing Emulsion will start on Day 1, Q1W for first 3 weeks, then Q3W thereafter
- Pembrolizumab will start on Day 1 of Cycle 2 (Day 22), Q3W

6.1.4. Phase 2

A Phase 2, multicenter, open-label, single-arm, study will be conducted to evaluate the efficacy and safety of DSP-7888 Dosing Emulsion in combination with pembrolizumab in patients with advanced high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were previously treated with platinum-based therapy and experienced resistance to platinum-based therapy, defined as patient relapsed within 6 months after last dose of platinum-based therapy. Patients must have received 1 to 4 previous treatment regimens.

The Phase 2 dose of DSP-7888 Dosing Emulsion will be the recommended dose as determined in the Phase 1b Arm 2 part of the study.

Approximately 40 eligible PROC patients are expected to be enrolled in the Phase 2 dose expansion part of the study.

For patients enrolled under Protocol Amendment 4, the administration of DSP-7888 Dosing Emulsion and anti-PD1 in the Phase 2 dose expansion cohort is the same as that in the Phase 1b Arm 2 of the dose search part. For patients enrolled under Protocol Amendment 5, administration of DSP-7888 Dosing Emulsion and anti-PD1 will be staggered as follows:

DSP-7888 + pembrolizumab combination:

- DSP-7888 Dosing Emulsion will start on Day 1, Q1W for first 3 weeks, then Q3W thereafter
- Pembrolizumab will start on Day 1 of Cycle 2 (Day 22), Q3W

6.1.4.1. Duration of Treatment

The study consists of 4 periods: Prescreening period, Screening period, Treatment period, and Follow-up period (See Appendix 7).

Each patient will participate in the trial from the time the patient signs the Prescreening informed consent form (ICF) until completion of survival follow-up (see Figure 2).

Human leukocyte antigen (HLA)-eligible patients in the Prescreening period will move on to a Screening period within a 28-day window from Cycle 1 Day1. Following Screening, all eligible

patients will receive treatment of DSP-7888 Dosing Emulsion in combination with pembrolizumab or nivolumab, dependent upon phase of the study.

For those patients enrolled under Protocol Amendment 5, DSP-7888 Dosing Emulsion will start on Day 1, pembrolizumab will start on Day 1 of Cycle 2 (Day 22), and then once every 3 weeks thereafter until the patient completes 35 cycles (approximately 24 months) of study treatment (if the patient is experiencing clinical benefit, and in the opinion of the investigator it is in the patient's best interest to continue the study beyond 35 cycles, the patient may continue treatment after documented discussion with the Sponsor). Reasons for treatment discontinuation are described in Section 7.3.1.

Once patients discontinue or complete treatment, they will enter the follow-up period including disease assessment follow-up for any patient who discontinues study treatment for a reason other than immune confirmed PD (iCPD), and/or survival follow-up.

6.1.4.2. Prescreening Period

After signing the HLA screening ICF, patients will be evaluated for HLA subtype eligibility. Blood samples must be submitted to a centralized laboratory for HLA testing to determine patient eligibility for enrollment into the study. Patients found to be HLA eligible will move on to participate in further screening assessments for the complete evaluation of all other study eligibility criteria. Patients may proceed with the HLA screening ICF and HLA test while still receiving the prior therapy.

6.1.4.3. Screening Period

A Screening period will start once the patient signs the main ICF, and all procedures should be completed within 28 days from Cycle 1 Day 1. In the Screening period, patient eligibility will be determined based on the eligibility criteria, and patients will undergo screening assessments according to the Schedule of Assessments (SOA). Tissue samples (fresh or archival) will be required for exploratory biomarker analysis. Post-treatment biopsies are requested per SOA, unless collecting the tumor biopsy is determined to be not medically feasible by the treating investigator.

6.1.4.4. Treatment Period

Per Amendment 5, the treatment period consists of 2 treatment phases: Induction phase and Maintenance phase.

1. Induction phase (First cycle)
    - DSP-7888 Dosing Emulsion 10.5 mg intradermal injection, once weekly (Q1W), Days 1, 8, and 15 of Cycle 1
2. Maintenance phase (All cycles after Cycle 1 up to Cycle 35)
    - DSP-7888 Dosing Emulsion 10.5 mg intradermal injection, Day 1 of Cycle 2 (Q3W) and each subsequent cycle
    - Pembrolizumab 200 mg IV infusion Day 1 of Cycle 2 (Q3W) and each subsequent cycle until discontinuation or up to Cycle 35

On the days when both DSP-7888 Dosing Emulsion and pembrolizumab are administered, DSP-7888 Dosing Emulsion should be administered first. Study treatment may be modified for AEs per dose modification guidelines or based on the clinical judgment of the treating investigator.

Patients will be asked to undergo study specific visits and procedures according to SOA. Patients will be evaluated for objective response to study drug treatment with radiographic imaging (computer tomography [CT] scan or magnetic resonance imaging [MRI]) using RECIST (v.1.1) every 6 weeks for 24 weeks, and then every 12 weeks until progression. If a patient experiences objective disease progression according to RECIST (v 1.1) and is clinically stable, the patient will continue on treatment with study drug until the patient experiences iCPD per iRECIST.

Clinical stability is defined as:

- No worsening of performance status
- No clinically relevant increase in disease-related symptoms
- No requirement for intensified management of disease-related symptoms (such as analgesics, radiation, or palliative care)

Patients who remain on study treatment following objective disease progression per RECIST (v.1.1) will continue to be evaluated for objective response to study treatment according to the SOA and to iRECIST.

Patients also will be monitored for serum CA-125 using GCIG CA-125 criteria as part of clinical evaluation of response according to the SOA. Progressive disease may not be determined by CA-125 progression alone.

Adverse event monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) CTCAE version 4.03. Patients will be evaluated for AEs from the time of signing the main ICF until 30 days after their last dose of study treatment.

Blood samples will be required for safety labs, CA-125 assessment, as well as the biomarker assay during the treatment period, and a fresh tumor tissue sample is requested post-treatment for biomarker assessment if medically feasible.

6.1.4.5. Follow-up Period

The follow- up period will begin once a patient has discontinued study treatment. Follow-up period includes disease assessment follow-up (for patients who discontinue study treatment for a reason other than iCPD per iRECIST) and survival follow-up.

Patients who discontinue study treatment without experiencing iCPD will continue to undergo tumor assessment and evaluation of CA-125 (Phase 2), according to the SOA until up to 24 months after last dose of study drug, the start of new anticancer therapy, iCPD per iRECIST, death, loss to follow-up, withdrawal of consent, or the end of the study, whichever occurs first.

Patients who discontinue study treatment when experiencing iCPD per iRECIST with study drug, or patients who discontinue study treatment without experiencing iCPD per iRECIST, but who experience iCPD per iRECIST or start new anticancer therapy during disease follow-up will be assessed for survival and new anticancer treatment status per the SOA, until up to 24 months

after the last dose of study drug, death, withdrawal of consent, loss to follow-up, or end of the study, whichever occurs first.

The safety and tolerability of DSP-7888 Dosing Emulsion in combination with immunotherapy PD-1 inhibitors will be assessed for the duration of study treatment and follow-up (see Table 7, Table 8, and Table 9 for the respective SOAs).

All AEs will be collected and recorded for each patient from the date of signing the main ICF for the study until 30 days after last study drug administration. Any pregnancies that occur within 180 days after last study drug administration are to be captured. An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition (see Table 7, Table 8, and Table 9).

Particular attention should be given to the follow up of any **Grade 3 or higher** injection site reactions ongoing at the End of Treatment period until resolution, return to baseline, determined to be a stable or chronic condition or until the patient is lost to follow up or the patient has died. Please record the data within EDC per eCRF instructions. In the instance of resolution with sequelae, please be sure to enter the sequelae as a separate AE (eg skin discoloration, persistent induration, scarring “from ISR”). To facilitate this careful follow up, please consider use of video teleconference with the patient during the follow up period post study.

Objective disease assessments will be performed according to RECIST and iRECIST. For Phase 1b, the first assessment will be performed during Cycle 3, at 4 weeks for the nivolumab arm and at 6 weeks for the pembrolizumab arm, and at Weeks 12, 18, and 24, after the first dose of DSP-7888 Dosing Emulsion. After that, objective disease assessments will occur every 12 weeks until patient discontinuation from the study. For Phase 2, patients will be evaluated for objective response to study drug treatment with radiographic imaging every 6 weeks for 24 weeks and then every 12 weeks until progression.

Figure 3: Schematic of Study Arm 1 and Study Arm 2 in Phase 1b

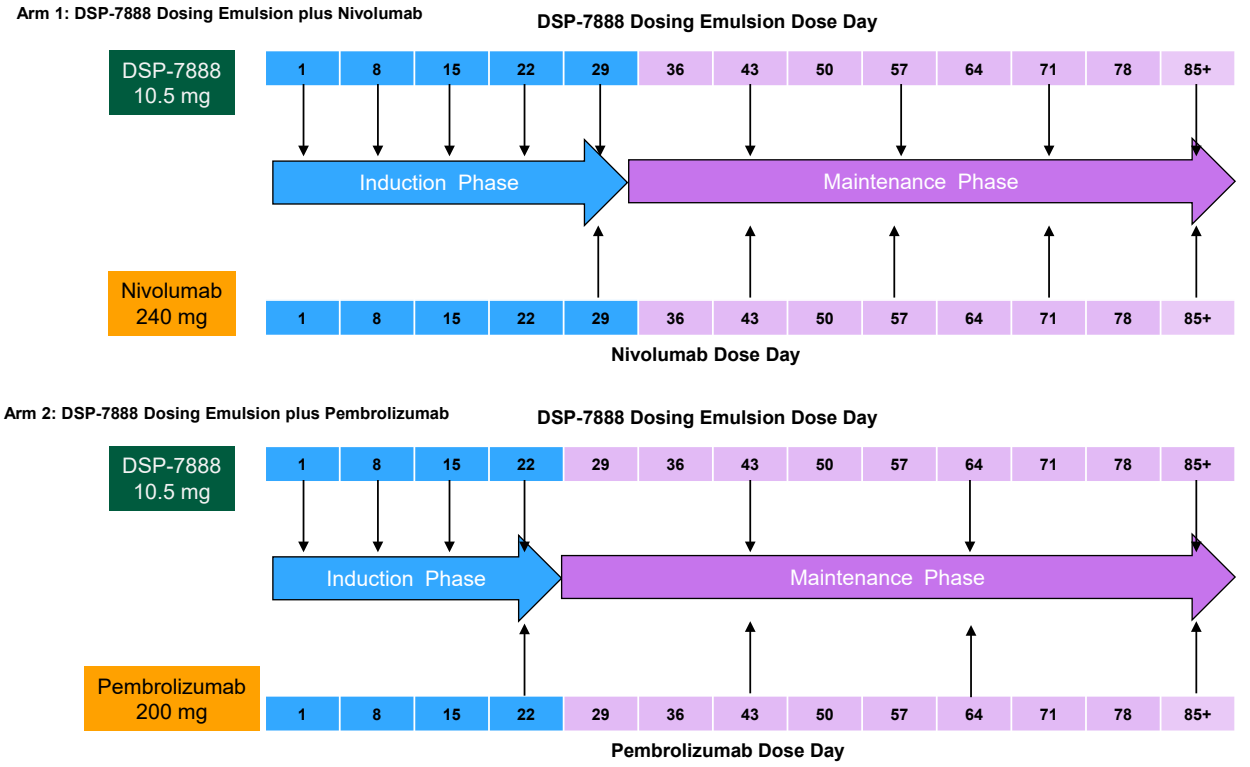
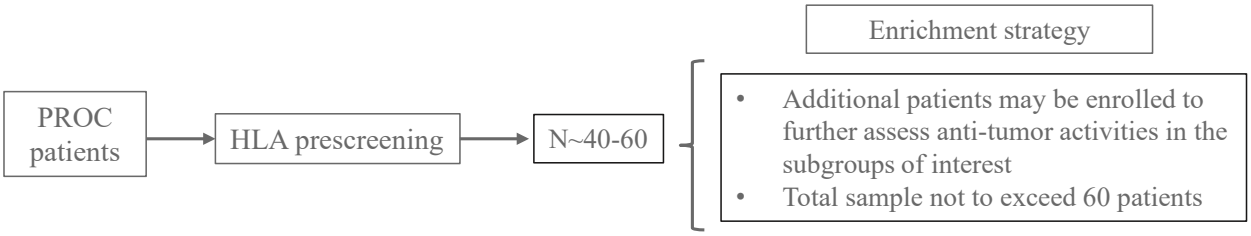


Figure 4: Schematic of Phase 2 of Study



6.2. Planned Number of Patients

In Phase 1b of the study, there will be approximately 6 to 12 patients for each arm, up to a total of up to 24 patients. In the enrichment cohort, 10 patients will be enrolled. If anti-tumor activities are observed in any tumor type, additional patients may be enrolled for further assessment. In Phase 2 of the study, approximately 40 patients will be enrolled. Additional patients may be enrolled to further assess anti-tumor activities in the subgroups of interest. However, the total sample size of Phase 2 cannot exceed 60 patients.

6.3. Treatment Assignment

6.3.1. Phase 1b

The administration of DSP-7888 Dosing Emulsion and anti-PD1 therapy in the Phase 1b enrichment cohort will be staggered as follows:

Arm 1 (Enrichment Cohort Only): DSP-7888 + nivolumab combination:

- DSP-7888 Dosing Emulsion 10.5 mg will start on Day 1, Q1W for first 4 weeks, then Q2W thereafter
- Nivolumab 240 mg will start on Day 1 of Cycle 3 (Day 29), Q2W

Arm 2 (Enrichment Cohort Only): DSP-7888 + pembrolizumab combination:

- DSP-7888 Dosing Emulsion 10.5 mg will start on Day 1, Q1W for first 3 weeks, then Q3W thereafter
- Pembrolizumab 200 mg will start on Day 1 of Cycle 2 (Day 22), Q3W

Patients in this study will receive DSP-7888 Dosing Emulsion at assigned dose levels, according to Table 4 and Table 6 and according to the study arm. Each study arm will begin at Dose Level I, and dose de-escalation will proceed independently of the other arms if a safety concern occurs in Dose Level I. For a given patient, the appropriate PD-1 combination partner will be determined by the treating investigator (see Table 5) for dose schedule. Dose adjustments of DSP-7888 Dosing Emulsion are allowed as per protocol. As per their labels and package inserts, dose adjustments for nivolumab and pembrolizumab are not recommended.

The Phase 1b enrichment cohort (10 patients) will be treated with the combination of DSP-7888 Dosing Emulsion and nivolumab, or DSP-7888 Dosing Emulsion and pembrolizumab, as per the treating physician's choice, following the dosing guidelines and schedule stated above in this section.

For an individual patient, the combined treatment of DSP-7888 Dosing Emulsion and nivolumab or DSP-7888 Dosing Emulsion and pembrolizumab will continue until the investigator determines that the patient is no longer likely to receive clinical benefit from DSP-7888 Dosing Emulsion. However, to assess the benefit of radiologic imaging in accordance with the iRECIST criteria, in cases of suspected progression, the protocol requires a confirmatory scan performed 4 to 8 weeks following the initial scan that shows the suspected progression.

Patients will continue to receive study treatment independent of radiologic assessment or progression:

1. Provided that the investigator considers it to be safe for the patient
2. Provided that the investigator determines that there is potential benefit for the patient
3. When the patient is willing to continue

Table 4: Phase 1b Study Dose Level and Schedule

DSP-7888 Dosing Emulsion Dose Level	DSP-7888 Dosing Emulsion Dose and Schedule
DSP-7888 Dosing Emulsion Dose Level I	Nivolumab Arm (Arm 1): 10.5 mg weekly for 4 weeks for induction phase, then every 2 weeks for maintenance phase Pembrolizumab Arm (Arm 2): 10.5 mg weekly for 3 weeks for induction phase, then every 3 weeks for maintenance phase
DSP-7888 Dosing Emulsion Dose Level II	Nivolumab Arm (Arm 1): 3.5 mg weekly for 4 weeks for induction phase, then every 2 weeks for maintenance phase Pembrolizumab Arm (Arm 2): 3.5 mg weekly for 3 weeks for induction phase, then every 3 weeks for maintenance phase
DSP-7888 Dosing Emulsion Dose Level III	Nivolumab Arm (Arm 1): 1.75 mg weekly for 4 weeks for induction phase, then every 2 weeks for maintenance phase Pembrolizumab Arm (Arm 2): 1.75 mg weekly for 3 weeks for induction phase, then every 3 weeks for maintenance phase

Table 5: PD-1 Inhibitor Dose

PD1 Inhibitor	Dose and Schedule
Nivolumab	In Arm 1, 240 mg administered intravenously (IV) over 30 minutes (±5)* every 14 days (2 weeks/cycle) starting from Day 1 of Cycle 3 (Day 29), then maintenance phase (after Cycle 3).
Pembrolizumab	In Arm 2, 200 mg/8 mL administered through IV infusion over 30 (±5) minutes every 21 days (3 weeks) starting from Day 1 of Cycle 2 (Day 22), then maintenance phase (after Cycle 2).

*The administration time change from 60 to 30 minutes is based on the updated dosage and administration guidance of the new nivolumab product label released in July 2018.

6.3.2. Phase 2 (Dose-Expansion Part)

Patients will have access to study treatment as long as they are benefiting from study treatment or have received up to a total of 35 treatment cycles (approximately 105 weeks). Patients may continue the study treatment beyond 35 treatment cycles if the patient is experiencing clinical benefit, after documented discussion with the Sponsor.

DSP-7888 Dosing Emulsion and pembrolizumab will be administered at the recommended dose level from the Phase 1 part of the study, following the same schedule as listed in Table 6.

Table 6: Phase 2 Study Dosing Schedule

Investigational Product	Frequency	Dosage	Route of Administration
DSP-7888 Dosing Emulsion	Q1W for first 3 weeks Q3W post 3 weeks	10.5mg	Intradermal injection (ID)
Pembrolizumab	Q3W, starting from Day 1 of Cycle 2 (Day 22)	Solution for infusion 200mg/8mL	IV infusion

6.4. Dose-limiting Toxicities (Phase 1b Dose Search Part Only)

A dose-limiting toxicity (DLT) is defined by the occurrence of 1 of the toxicities defined below, occurring during the first 28 days of Arm 1 (DSP-7888 Dosing Emulsion induction phase in combination with nivolumab; Arm 1) and the first 42 days of Arm 2 (DSP-7888 Dosing Emulsion induction phase in combination with pembrolizumab; Arm 2).

Evaluable patients are defined per Dose-Determining Set (DDS), as defined in Section 12.1.2.3. Patients who discontinue before meeting the DDS criteria may be replaced to fully evaluate a given dose level. The criteria for the determination of DLT will apply to a given administration schedule independently.

No intrapatient dose escalation/de-escalation is allowed during the DLT evaluation period.

The following treatment-related AEs will be considered a DLT:

Non-hematologic

- Any treatment-related Grade 3 or higher non-hematologic clinical (non-laboratory) AE, with the following exceptions:
  - Grade 3 nausea/vomiting or Grade 4 vomiting that resolves to Grade 1 or 2 in 72 hours or less with appropriate supportive care
  - Grade 3 or 4 diarrhea that resolves to Grade 1 or 2 in 72 hours or less with appropriate supportive care
  - Grade 3 fatigue lasting <5 days
  - Grade 3 hypertension that can be controlled with medical therapy within 7 days
- Any treatment-related Grade 3 or higher non-hematologic laboratory abnormality if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for ≥7 days

Hematologic

- Any treatment-related hematologic toxicity specifically defined as:
  - Thrombocytopenia Grade 4 or higher, or Grade 3 associated with bleeding
  - Neutropenia Grade 4 for ≥7 days, or Grade 3 or 4 associated with infection or febrile neutropenia
  - Anemia Grade 4, or Grade 3 or 4 requiring blood transfusion

Immune-related

- Grade 3 or higher CTCAE v. 4.03 immune system disorder-related adverse reactions that persist as Grade 3 for >14 days, despite appropriate treatment, except for allergic reactions and autoimmune reaction
- Any Grade 3 or higher allergic reaction

- Any Grade 2 or higher autoimmune reaction with the following exceptions:
  - Grade 2 elevation of transaminases/hepatitis that recovers to Grade 0 or 1 within 10 days (for patients with liver metastases, elevation of transaminases due to hepatitis that recovers to baseline within 10 days)
  - Grade 2 hypothyroidism that recovers to Grade 0 or 1 within 7 days without steroids
  - Grade 2 diarrhea/colitis that spontaneously recovers to Grade 0 or 1 within 7 days with supportive care but without steroids
  - Grade 2 immune-related rash/dermatitis
- Any treatment-related Grade 4 ISR or Grade 3 ISR that requires hospitalization.

Any patient who experiences a DLT should be permanently removed from study treatment and should not be replaced.

Note that DSP-7888 Dosing Emulsion dosing has been managed with dose interruptions and/or adjustments for ISRs/AEs. Therefore, a DSP-7888 Dosing Emulsion dose interruption/delay for an AE related to an ISR that does not meet a DLT definition, as described above, will be considered a non-DLT modification. Non-DLT dose modifications will not be considered in determining the recommended dose for DSP-7888 Dosing Emulsion; however, they will be considered in determining further management of the DSP-7888 Dosing Emulsion dosing schedule in the expansion part, in combination with the selected PD-1 inhibitor.

6.5. Defining Recommended Dose of DSP-7888 Dosing Emulsion with Nivolumab or Pembrolizumab (Only Phase 1b Dose Search Part)

The determination of the recommended dose of DSP-7888 Dosing Emulsion in combination with nivolumab or pembrolizumab will be based on the criteria defined herein.

Initially, 6 patients will be enrolled into each of the arms according to a rolling 6 study design at the DSP-7888 Dosing Emulsion Dose Level I (of 10.5 mg weekly) in combination with either nivolumab 240 mg (every 2 weeks; Arm 1) or pembrolizumab 200 mg (every 3 weeks; Arm 2).

The recommended dose of DSP-7888 Dosing Emulsion in combination with a given PD-1 inhibitor agent will be determined in each study arm. Dose adjustments will proceed independently in each study arm. The recommended dose of DSP-7888 Dosing Emulsion must be less than or equal to a dose level at which 1 out of 6 patients enrolled experience a DLT (see definition of a DLT in Section 6.4). A dose level is eligible for consideration as the recommended dose if 0 or 1 of 6 patients enrolled experience a DLT at that dose level.

Criteria for determining whether a given dose level is eligible to be considered a recommended dose of DSP-7888 Dosing Emulsion are based on the number of patients with DLTs out of the total number of DLT-eligible patients in a given cohort. The criteria are as specified below:

- If 0 or 1 of 6 patients at the starting dose level experience a DLT, the dose level is eligible for consideration as the recommended dose of DSP-7888 Dosing Emulsion
- If 2 or more of 6 patients at a given dose level experience a DLT, the dose will be decreased. Further enrollment will be at the lower dose level. If 0 or 1 of 6 patients at

the lower dose level experience a DLT, the dose level is eligible for consideration as the recommended dose of DSP-7888 Dosing Emulsion

The determination of the recommended dose of DSP-7888 Dosing Emulsion in a given study arm also will be based on overall tolerability, including a review of persistent Grade 2 AEs and a review of AEs occurring beyond the first 2 cycles.

The safety and tolerability of DSP-7888 Dosing Emulsion in combination with immunotherapy PD-1 inhibitors will be assessed for the duration of study treatment and 30 days follow-up.

6.6. Safety Review Committee

The Safety Review Committee (SRC) for Phase 1b dose-escalation will be chaired by the [redacted]. The SRC will include the Principal Investigator (or delegate) from each of the investigational sites. The SRC will also include a representative from [redacted] PV (or designee), an [redacted] Biostatistician (or designee), and a representative from [redacted] Clinical Research. The SRC will review the safety and tolerability of DSP-7888 Dosing Emulsion in combination with nivolumab and pembrolizumab in each cohort to decide the next dose level to be tested. In addition, all immune-related AEs occurring in Arm 1 and Arm 2 will be evaluated throughout the conduct of this study. The SRC's review and assessment will include all available safety data from each cohort, together with available PD data. The SRC's review will also include an assessment of all cases, individually and in aggregate, for those patients who meet the criteria for DLT in order to determine the clinical significance and basis for their inclusion or exclusion in the decision for dose change.

The SRC will review and agree on the recommended maximum tolerated dose prior to enrolling patients in the dose-expansion part. In the dose-search cohort (Phase 1b), the stopping rule will follow the rule of the 3+3 design. All decisions made by the SRC will be documented and provided in writing to the investigators before dosing any new patients.

In Phase 2 of the study, the Sponsor will decide the necessity for a study suspension, protocol amendment, continuation of enrollment, or termination of the study if the following criteria are met:

- Any cases of death (other than death related to progressive disease) that occur from the start of treatment with DSP-7888 Dosing Emulsion and up to 30 days from the last DSP-7888 Dosing Emulsion administration, and deemed by the Sponsor to be related to any of the study's drugs
- If the percentage of patients in this study presenting with drug-related (assessed by Sponsor) Grade 4 or higher AE within a particular medical concept (eg, hypersensitivity) is higher than that reported in patients treated with DSP-7888 Dosing Emulsion within the clinical program, and as reported in the literature

6.7. Procedures

The safety and tolerability of DSP-7888 Dosing Emulsion in combination with immunotherapy PD-1 inhibitors will be assessed for the duration of study treatment and follow-up. Refer to Table 7,Table 8, and Table 9 for the respective schedules of assessments. Adherence to the study

design requirements, including those specified in the Schedule of Assessments is essential and required for study conduct.

Table 7: Schedule of Assessments (Arm 1, Combination of DSP-7888 Dosing Emulsion and Nivolumab [14-Day Study Cycles])

Tests and Procedures	Pre-Screening	Pre-Study Evaluation	On-Study Evaluations[a]									End of Treatment	Follow-Up For OS
			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7+		
Week			0	1	2	3	4	6	8	10	12+	30 days after last DSP-7888 Dosing Emulsion dose	Every 3 months after date off treatment
Day	Any time before enrollment	Within 28 days prior to first dose of study drug	1	8	15	22	29	43	57	71	85+		
Window		*28 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*+7 days*[b]	
Pre-screening consent	X												
HLA-typing (A/B locus and DRB1 locus)	X												
Informed consent		X											
Inclusion/exclusion review		X											
Medical and cancer history		X											
Physical examination		X	X		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X	
Serum pregnancy test, if applicable		X											
ECOG performance status		X			X		X	X	X	X	X	X	
Complete vital signs		X	X		X		X	X	X	X	X	X	
Body weight		X	X		X		X	X	X	X	X	X	
Hematology		X		X	X	X	X	X	X	X	X	X	
Clinical chemistry		X		X	X	X	X	X	X	X	X	X	
Thyroid function test		X			X		X	X	X	X	X	X	
Urinalysis		X		X	X	X	X	X	X	X	X	X	
Pulse oximetry		X	X		X		X	X	X	X	X	X	
Blood samples for Hepatitis B/C & HIV		X											
ECHO/MUGA		X			X			X			X[d]	X	
12-lead electrocardiogram		X	X[e]		X[e]			X			X[f]	X	
Tumor tissue samples for biomarkers[g]		X[h]									X[i]		
Tumor tissue samples for future biomarker analysis[j]		X									X[i]		

Tests and Procedures	Pre-Screening	Pre-Study Evaluation	On-Study Evaluations[a]									End of Treatment	Follow-Up For OS
			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7+		
Week			0	1	2	3	4	6	8	10	12+	30 days after last DSP-7888 Dosing Emulsion dose	Every 3 months after date off treatment
Day	Any time before enrollment	Within 28 days prior to first dose of study drug	1	8	15	22	29	43	57	71	85+		
Window		*28 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*±2 days*	*+7 days*[b]	
Blood samples for CTL induction[k]		X[l]			X[m]		X[m]		X[m]		X[m,n]	X	
Blood samples for future biomarker analysis[o]		X[l]			X[m]		X[m]		X[m]		X[m,n]	X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	
Adverse events[p]		X	X	X	X	X	X	X	X	X	X	X	
Administer DSP-7888 Dosing Emulsion			X	X	X	X	X	X	X	X	X		
Administer nivolumab							X	X	X	X	X		
Follow-up for overall survival													X[q]
Objective disease assessment[r]		X	First post-treatment assessment at Week 4 (Cycle 3), followed by one at Week 12 (Cycle 7), then 2 subsequent assessments every 6 weeks at Week 18, Week 24 (Cycle 10, Cycle 13), and finally every 12 weeks (Cycle 19 and every 6 cycles) until disease progression.[s]									

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTL = cytotoxic T lymphocyte; ECG = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; FFPE = formalin-fixed and paraffin embedded; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; ICF = informed consent form; iRECIST = immune Response Evaluation Criteria in Solid Tumors MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; OS = overall survival; PD-L1 = programmed death ligand 1; PET = positron emission tomography; PBMC = peripheral blood mononuclear cells; RECIST = Response Evaluation Criteria in Solid Tumors; TIL = tumor-infiltrating lymphocytes; TIS = tumor immune signature; WT1 = Wilms Tumor 1

[a] All tests must be performed PRIOR to injection of study treatment, with the exception of ECG.

[b] Complete End of Treatment assessment procedures before patient receives new anti-cancer treatment.

[c] Inspection of prior injection sites will be done at each administration of the vaccine.

[d] . From Cycle 4, ECHO/MUGA tests for ejection fraction will be done on Day 1 every 6th cycle (eg, Cycle 10, 16, 22).

[e] Obtained at least 2 hours post-dose of DSP-7888 Dosing Emulsion.

[f] From Cycle 4, 12-lead electrocardiograms will be performed on Day 1 of every 3rd Cycle (eg, Cycle 7, 10, 13).

[g] It should be ensured that a total of at least 23 slides of archival samples and/or the equivalent amount of archival tissue block and/or fresh biopsy samples from the enrolled patients are available. These samples must contain sufficient tumor tissue.

[h] Collection of tumor tissue samples at Pre-Study evaluation is mandatory. Either archival tissue or fresh biopsy samples at Pre-study evaluation would be acceptable. Collection of fresh biopsy samples is required, if medically feasible.

[i] Sample to taken at week 12 (Cycle 7), see Section 10.1 for the timepoints and circumstances for tumor tissue sample collection for post treatment evaluations after Week 12 (Cycle 7). Tumor tissue samples will be collected at End of Treatment only if patient discontinues from study prior to Week 12.

[j] Either archival tissue or fresh biopsy samples will be collected only after the patient signs an additional separate informed consent for these optional samples. A total of 6 to 8 slides will be sent to the central laboratory for analyses.

[l] If blood is not collected at Screening, it may be obtained on Day 1 prior to administration of protocol therapy.

[m] Samples to be taken pre-dosing with DSP-7888 Dosing Emulsion.

[n] Sample to be taken every 2 cycles pre-dosing until dosing is discontinued (eg, Cycle 7, 9, 11, 13).

[o] Additional informed consent is needed prior to collection at Pre-Study evaluation. Serum, PBMC and ctDNA (plasma) are included as a blood sample. PBMC will be prepared from whole blood at the Central Laboratory. The whole blood sample for PBMC preparation should be shipped from the clinical site to the central laboratory on the sample collection date. Blood samples for ctDNA (plasma) is collected at Screening only.

[p] Use CTCAE v4.03 term, if appropriate (Note: the verbatim term should be reported, not the associated CTCAE term). All AEs must be reported for each patient from the date of ICF signature until 30 days after the last dose of study drug administration.

[q] Follow-up until end of life or end of the study, whichever occur first. Follow up to occur every 3 months and/or on an ad-hoc basis for safety or regulatory purposes, or a prespecified analysis

[r] Assessment consists of chest/abdomen/pelvis CT/MRI. A bone scan and MRI of the brain will be conducted when clinically indicated. Imaging technology should be consistent across the study, CT component of PET/CT assessments are sufficient to be used if PET/CT scan was done at baseline.

[s] Images are assessed according to RECIST v1.1 and iRECIST.

Table 8: Schedule of Assessment (Arm 2 of Phase 1b, Combination of DSP-7888 Dosing Emulsion and Pembrolizumab [21-Day Study Cycles])

Tests and Procedures	Pre-Screening	Pre-Study Evaluation	On-Study Evaluations[1]									End of Treatment	Follow-Up For OS
			Cycle 1			Cycle 2			Cycle 3	Cycle 4	Cycle 5+		
Week			0	1	2	3	4	5	6	9	12	30 days after last DSP-7888 Dosing Emulsion dose	Every 3 months after date off treatment
Day	Any time before enrolment	Within 28 days prior to first dose of study drug	1	8	15	22	29	36	43	64	85		
Window		*28 days*	*±2 days*			*±2 days*			*±2 days*	*±2 days*	*±2 days*	*+7 days*[18]	
Pre-screening consent	X												
HLA-typing (A/B locus and DRB1 locus)	X												
Informed consent		X											
Inclusion/exclusion review		X											
Medical, cancer history		X											
Physical examination		X	X			X[2]			X[2]	X[2]	X[2]	X	
Serum pregnancy test, if applicable		X											
ECOG performance status		X				X			X	X	X	X	
Complete vital signs		X	X			X			X	X	X	X	
Body Weight		X	X			X			X	X	X	X	
Hematology		X		X	X	X			X	X	X	X	
Clinical chemistry		X		X	X	X			X	X	X	X	
Thyroid function test		X				X			X	X	X	X	
Urinalysis		X		X	X	X			X	X	X	X	
Pulse oximetry		X	X			X			X	X	X	X	
Blood samples for Hepatitis B/C & HIV		X											
ECHO/MUGA		X				X			X		X[3]	X	
12-lead electrocardiogram		X	X[4]			X[4]			X		X[5]	X	
Tumor tissue samples for biomarkers		X[6]									X[7]		
Tumor tissue samples for future biomarker analysis[8]		X									X[7]		
Blood samples for CTL induction[9]		X[10]				X[11]			X[11]		X[11,12]	X	
Blood samples for future biomarker analysis[13]		X[10]				X[11]			X[11]		X[11,12]	X	
Concomitant medications		X	X	X	X	X			X	X	X	X	

Tests and Procedures	Pre-Screening	Pre-Study Evaluation	On-Study Evaluations[1]									End of Treatment	Follow-Up For OS
			Cycle 1			Cycle 2			Cycle 3	Cycle 4	Cycle 5+		
Week			0	1	2	3	4	5	6	9	12	30 days after last DSP-7888 Dosing Emulsion dose	Every 3 months after date off treatment
Day	Any time before enrolment	Within 28 days prior to first dose of study drug	1	8	15	22	29	36	43	64	85		
Window		*28 days*	*±2 days*			*±2 days*			*±2 days*	*±2 days*	*±2 days*	*+7 days*[18]	
Adverse events[14]		X	X	X	X	X			X	X	X	X	
Administer DSP-7888 Dosing Emulsion			X	X	X	X			X	X	X		
Administer pembrolizumab						X			X	X	X		
Follow-up for overall survival													X[15]
Objective disease assessment[16]		X	First post-treatment assessment at Week 6 (Cycle 3), then 3 subsequent assessments at Week 12, Week 18, Week 24 (Cycle 5, Cycle 7, Cycle 9), and finally every 12 weeks (Cycle 13 and every 4 cycle) until disease progression.[17]										

AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTL = cytotoxic T lymphocyte; ECG = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; ICF = informed consent form; IHC = immunohistochemistry; iRECIST = immune Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; OS = overall survival; PD-L1 = programmed death ligand 1; PET = positron emission tomography; PMBC = peripheral blood mononuclear cells; RECIST = Response Evaluation Criteria in Solid Tumors; TIL = tumor infiltrating lymphocytes; TIS = tumor immune signature; TMB = tumor mutational burden; WT1 = Wilms Tumor 1

1. All tests must be performed PRIOR to injection of study treatment, with the exception of ECG.
2. Inspection of prior injection sites will be done at each administration of the vaccine.
3. From Cycle 3, ECHO/MUGA tests for ejection fraction will be done on Day 1 of every 4th cycle (eg, Cycle 7, 11, 15).
4. Obtained at least 2 hours post-dose of DSP-7888 Dosing Emulsion.
5. From Cycle 3, 12-lead electrocardiograms will be performed on Day 1 of every 2nd Cycle (eg, Cycle 5, 7, 9).
6. Collection of tumor tissue samples at pre-study evaluation is mandatory. Either archival tissue or fresh biopsy samples at Pre-study evaluation would be acceptable.
7.Sample to be taken at Week 12 (Cycle 5), see Section 10.1 for the timepoints and circumstances for tumor tissue sample collection for post-treatment evaluations after Week 12 (Cycle 5). Tumor tissue samples will be collected at End of Treatment only if patient discontinues from study prior to Week 12. Additional informed consent is needed prior to collection.
8. Either archival tissue or fresh biopsy samples will be collected only after the patient signs an additional informed consent for these optional samples. A total of 6 to 8 slides will be sent to the central laboratory for analyses.
9. PBMCs will be prepared from whole blood at the Central Laboratory. The whole blood sample for PBMC preparation should be shipped from the clinical site to the Central Laboratory on the sample collection date.
10. If blood is not collected at Screening, it may be obtained on Day 1 prior to administration of protocol therapy.
11. Samples to be taken pre-dosing with DSP-7888 Dosing Emulsion.
12. Sample to be taken every 2 cycles, pre-dosing until dosing is discontinued (eg, Cycle 5, 7, 9, 11, 13).
13. Additional informed consent is needed prior to collection at Pre-Study evaluation. Serum, PBMC and ctDNA (plasma) are included as a blood sample. PBMC will be prepared from whole blood at Central Laboratory. The whole blood sample for PBMC preparation should be shipped from clinical site to central laboratory on the sample collection date. Blood sample for ctDNA (plasma) is collected at Screening only.
14.Use CTCAE v4.03 term, if appropriate (Note: the verbatim term should be reported, not the associated CTCAE term. All AEs must be reported for each patient from the date of ICF signature until 30 days after the last dose of study drug administration.

15. Follow-up until end of life or end of the study, whichever occur first. Follow up to occur every 3 months and/or on an ad-hoc basis for safety or regulatory purposes, or a prespecified analysis
16. Assessment consists of chest/abdomen/pelvis CT/MRI. A bone scan and MRI of the brain will be conducted when clinically indicated. Imaging technology should be consistent across the study, CT component of PET/CT assessments are sufficient to be used if PET/CT scan was done at baseline.
17. Images are assessed according to RECIST v1.1 and iRECIST.
18. Complete End of Treatment assessment procedures before patient receives new anti-cancer treatment.

Table 9: Schedule of Assessments (Phase 2, Combination of DSP-7888 Dosing Emulsion and Pembrolizumab for Ovarian Cancer)

Period	Pre-screening	Screening period	Treatment Period (All procedure must be performed PRIOR to injection of study treatment)										Follow-up Period		Notes
Treatment Cycle			1			2			3	4	5+*	EOT (30 day after last dose)	Disease follow up**	Survival Follow up	*Cycle 5 and subsequent cycles up to Cycle 35
Day			1	8	15	1	8	15	1	1	1				**Applicable for only if patients who discontinue study treatment for a reason other than disease progression
Week (from 1st dose)			0	1	2	3	4	5	6	9	12				
Scheduling Window (Days)	-	-28 to 1*	0	±2	±2	±2	±2	±2	±3	±3	±7	+7[a]	±7	±14	*Procedures in screening should be completed within 28 days from Cycle 1 Day1
Study Drug Administration															
DSP-7888 Dosing Emulsion			X	X	X	X			X	X	X				
Pembrolizumab						X			X	X	X				
Administrative procedure															
HLA screening informed consent	X														
Informed Consent*		X													*Main informed consent and informed consent for future biomarker (optional) for willing participants
Inclusion and Exclusion criteria		X													
Demography and Medical History		X*													*including COVID-19 history and vaccination history
Prior and Concomitant Medications		X	X	X	X	X			X	X	X	X			
Cancer history and Cancer Prior Treatment		X													

Period	Pre-screening	Screening period	Treatment Period (All procedure must be performed PRIOR to injection of study treatment)										Follow-up Period		Notes
Treatment Cycle			**1**			**2**			**3**	**4**	**5+***	**EOT (30 day after last dose)**	**Disease follow up****	**Survival Follow up**	*Cycle 5 and subsequent cycles up to Cycle 35 **Applicable for only if patients who discontinue study treatment for a reason other than disease progression
Day			**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Week (from 1st dose)			**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**				
Scheduling Window (Days)	**-**	**-28 to 1***	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	**+7[a]**	**±7**	**±14**	*Procedures in screening should be completed within 28 days from Cycle 1 Day1
New anticancer therapy													X	X	*Every 12 weeks up to 105 weeks and/or on an ad-hoc basis for safety or regulatory purposes, or a prespecified analysis.
Safety assessment															
Physical Examination*		X	X			X			X	X	X	X			*Inspection of prior injection site will be done
Vital Sign and Weight		X*	X	X	X	X			X	X	X	X			*Height will be measured only at screening
12-lead ECG		X							X			X			
ECHO/MUGA		X													
ECOG performance status		X	X	X	X	X			X	X	X	X			
Adverse Events	X*	X**	X	X	X	X			X	X	X	X**			* SAE related to study procedure will be reported to [redacted] Safety **AE must be collected from the date of main ICF to 30 days after last dose

Period	Pre-screening	Screening period	Treatment Period (All procedure must be performed PRIOR to injection of study treatment)										Follow-up Period		Notes
Treatment Cycle			**1**			**2**			**3**	**4**	**5+***	**EOT (30 day after last dose)**	**Disease follow up****	**Survival Follow up**	*Cycle 5 and subsequent cycles up to Cycle 35 **Applicable for only if patients who discontinue study treatment for a reason other than disease progression
Day			**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Week (from 1st dose)			**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**				
Scheduling Window (Days)	**-**	**-28 to 1***	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	**+7[a]**	**±7**	**±14**	*Procedures in screening should be completed within 28 days from Cycle 1 Day1
Efficacy assessment															
Tumor imaging/response assessment*		X							X		X**	X***	X****		*Assessed by RECIST 1.1 and followed by iRECIST after progressive disease per RECIST 1.1. **Cycle 5, 7, 9 and subsequent assessments every 4 Cycle (Cycle 13, 17, 21 etc.) ***Not mandated if last assessment performed less than 28 days from EOT ****Every 12 weeks from last assessment
CA-125 sample collection/response assessment		X	X			X			X	X	X*	X	X**		* Every 2 Cycle (eg, Cycle 5,7,9) **Every 12 weeks from last assessment
Survival status														X*	*Every 12 weeks up to 105 weeks and/or on an ad-hoc basis for safety or regulatory purposes, or a prespecified analysis.
Clinical laboratory assessment															
HLA-typing*	X														*Performed by Central Lab (A and B locus and DRB1 locus). One tube for HLA typing, and the second tube stored for exploratory endpoints.
Pregnancy Test		X*													*if applicable. Either serum or urine
HBV, HCV and HIV		X													
Hematology		X	X			X			X	X	X	X			
Serum Chemistry		X	X			X			X	X	X	X			

Period	Pre-screening	Screening period	Treatment Period (All procedure must be performed PRIOR to injection of study treatment)										Follow-up Period		Notes
Treatment Cycle			**1**			**2**			**3**	**4**	**5+***	**EOT (30 day after last dose)**	**Disease follow up****	**Survival Follow up**	*Cycle 5 and subsequent cycles up to Cycle 35 **Applicable for only if patients who discontinue study treatment for a reason other than disease progression
Day			**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Week (from 1st dose)			**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**				
Scheduling Window (Days)	**-**	**-28 to 1***	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	**+7[a]**	**±7**	**±14**	*Procedures in screening should be completed within 28 days from Cycle 1 Day1
Urinalysis		X	X			X			X	X	X	X			
Coagulation Parameters		X										X			
T3, FT4 and TSH		X				X			X		X*	X			* Every 2 Cycle (eg, Cycle 5,7,9)
Biomarker sample collection															
Blood samples for CTL induction*		X				X			X		X**	X			*Samples to be taken at screening and, during treatment, prior to each dose**Cycle 5, 7, 9 and subsequent assessments every 4 Cycle (Cycle 13, 17, 21 etc.)
Blood samples for future biomarker (optional) *		X				X			X		X**	X			*Only patients who provides informed consent for future biomarker samples to be taken prior to dosing. Serum, PBMC and ctDNA (plasma) are included as a blood sample. PBMC will be prepared from whole blood at Central Laboratory. The whole blood sample for PBMC preparation should be shipped from clinical site to central laboratory on the sample collection date. **Cycle 5, 7, 9 and subsequent assessments every 4 cycles (Cycle 13, 17, 21 etc.) ctDNA only at screening, Cycle 3 Day1, Cycle 5 Day1, next visit when patients have PR or CR with RECIST criteria, and EOT.

Period	Pre-screening	Screening period	Treatment Period (All procedure must be performed PRIOR to injection of study treatment)										Follow-up Period		Notes
Treatment Cycle			**1**			**2**			**3**	**4**	**5+***	**EOT (30 day after last dose)**	**Disease follow up****	**Survival Follow up**	*Cycle 5 and subsequent cycles up to Cycle 35 **Applicable for only if patients who discontinue study treatment for a reason other than disease progression
Day			**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Week (from 1st dose)			**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**				
Scheduling Window (Days)	**-**	**-28 to 1***	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±7**	**+7[a]**	**±7**	**±14**	*Procedures in screening should be completed within 28 days from Cycle 1 Day1
Tumor tissue collection		X*									X**	X**			* Fresh biopsy (if medically feasible), archival tumor block, or newly cut slides are required at screening. **Cycle 5, or EOT if earlier, if medically feasible
Tumor samples for future biomarker (optional)		X*									X**	X**			*Only patients who provides informed consent for future biomarker. Either archival tissue or fresh biopsy samples will be collected and a total of 6 to 8 slides will be sent to the central laboratory for analyses **Cycle 5, or EOT if earlier, if medically feasible

[a] Complete End of Treatment assessment procedures before patient receives new anti-cancer treatment.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Inclusion Criteria

Patients must fulfill each of the following requirements:

Phase 1b

Phase 1b Dose Search Part

1. A histologically or cytologically confirmed cancer that is metastatic and is approved to be treated with nivolumab or pembrolizumab with the following origins:

Nivolumab:

- Unresectable or metastatic melanoma
- Metastatic NSCLC
- Advanced RCC
- Recurrent or metastatic squamous cell carcinoma of the head and neck
- Locally advanced or metastatic urothelial carcinoma
- Hepatocellular carcinoma
- MSI-H/dMMR colorectal cancer

Pembrolizumab:

- Unresectable or metastatic melanoma
- Metastatic NSCLC
- Recurrent or metastatic squamous cell carcinoma of the head and neck
- Locally advanced or metastatic urothelial carcinoma
- Unresectable or metastatic MSI-H/dMMR solid tumors
- Recurrent locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma
- Recurrent or metastatic cervical cancer

In addition, the following requirements must be fulfilled:

a. Patients must not be considered eligible for a potentially curative resection
b. Patients who are eligible for PD-1 therapy based on either criterion (i) or (ii) below:
    i. Patients progressed on their prior treatment before initiating treatment on current study

    Or

    ii. Patients who are currently being treated with nivolumab or pembrolizumab and have achieved at least stable disease (SD), and who, in the judgment of

their treating physicians, could benefit from the addition of DSP-7888 Dosing Emulsion vaccine to improve or maintain their response

Phase 1b Enrichment Cohort Only:

- Patients with locally advanced or metastatic RCC or urothelial carcinoma who have experienced disease progression per iRECIST (iCPD) during or within 3 months of last dose of the most recent prior anti-PD-1/ PD-L1-based treatment (see Appendix 3)

Both Phase 1b Dose Search Part and Phase 1b Enrichment Cohort:

2. Patients must be positive for at least 1 of the following human leukocyte antigens (HLAs):
   a. HLA-A*02:01
   b. HLA-A*02:06
   c. HLA-A*24:02
   d. HLA-A*03:01
   e. HLA-B*15:01
3. ≥ 18 years of age
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Patients must be able to provide archival tumor tissue with sufficient tumor tissue, or patients must consent to undergo tumor biopsy to acquire sufficient tissue before first administration of study drug
6. Females of childbearing potential must have a negative serum pregnancy test
7. Male or female patients of child-producing potential must agree to use contraception or use prevention of pregnancy measures (true abstinence) during the study and for 6 months (for females and males alike) after the last dose of study drug
8. Total bilirubin of ≤2.0 mg/dL (≤3.0 mg/dL for patients with known Gilbert's syndrome)
9. Aspartate aminotransferase (AST) ≤3.0 × the upper limit of normal (ULN) or <5 × ULN if considered to be due to liver metastases
10. Alanine transaminase (ALT) ≤3.0 × the ULN or <5 × ULN if considered to be due to liver metastases
11. Estimated glomerular filtration rate (GFR) >40 mL/min using the Cockcroft-Gault equation
12. Multigated acquisition (MUGA) scan or echocardiogram (ECHO) with left ventricular ejection fraction (LVEF) >40%
13. Life expectancy ≥3 months
14. Patients must be willing to provide a signed and dated ICF

Phase 2

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Patients must be female ≥ 18 years of age, able to understand study procedures, and subsequently agreed to participate in the study by providing a written informed consent obtained prior to any prescreening and screening procedures that are standard of care
2. Patients must be positive for at least 1 of the following HLAs as assessed by central laboratory:
   a. HLA-A*02:01
   b. HLA-A*02:06
   c. HLA-A*24:02
   d. HLA-A*03:01
   e. HLA-B*15:01
3. Patients must have histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer, with predominantly high-grade (Grade 2 or 3) serous epithelial features
4. Patients must be considered platinum-resistant to last administered platinum-based therapy, defined as patient relapsed within 6 months after the last dose of platinum-based therapy
5. Patients must have completed at least 1 but no more than 4 prior lines of therapy for serous epithelial ovarian, fallopian tube, or primary peritoneal cancer
   a. Maintenance is not considered a separate line of treatment (even if patients who are BRCA mutation-positive received a PARP inhibitor following induction therapy with a platinum doublet, eg, bevacizumab)
   b. Neoadjuvant and adjuvant systemic therapy will be counted as one line of therapy
   c. Patients must have received at least one platinum-based therapy
6. Patients must have progression disease after last therapy and have measurable disease according to RECIST (v.1.1)
7. Patients must have an ECOG performance status of 0 or 1
8. Patients must have adequate organ function, defined as follows:

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1,500 / μL (without granulocyte colony stimulating factor (G-CSF))
Platelets	≥100,000 / μL (without transfusion)
Hemoglobin	≥9.0 g/dL (without transfusion)
Renal	
Serum creatinine OR estimated GFR using the Cockcroft-Gault equation	≤1.5 × ULN **OR** ≥40 mL/min using the Cockcroft-Gault equation for patients with creatinine levels >1.5 × ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN

AST and ALT	≤2.5 × ULN OR ≤5 × ULN for patients with liver metastases
Cardiac	
MUGA or ECHO with LVEF	≥40%
QTcF (QT corrected based on Fridericia's equation) interval	<480 msec
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN, unless the patient is receiving anticoagulant therapy and the PT is within therapeutic range
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	≤1.5 × ULN, unless the patient is receiving anticoagulant therapy and the aPTT is within therapeutic range

9. Patients must provide either a fresh tissue biopsy, if medically feasible, or archival tissue as either a formalin-fixed and paraffin embedded (FFPE) block or newly sectioned tissue on charged slides (equivalent to approximately 8 to 23 slides sectioned at 4-5µm thickness)
10. Patients of childbearing potential must have a negative serum or urine pregnancy test at screening
11. Patients must be either postmenopausal, free from menses for >12 months, surgically sterilized, or willing to use adequate contraception to prevent pregnancy or must agree to abstain from heterosexual activity throughout the study, starting with enrollment through 6 months (for females and males alike) after the last dose of study drug
12. Life expectancy ≥3 months
13. Patients who had stayed on the last treatment for at least 12 weeks without any evidence of progression

7.2. Exclusion Criteria

Phase 1b

Phase 1b Dose Search and Phase 1b Enrichment Part:

1. Anticancer chemotherapy (including molecular targeted drugs), immunotherapy, radiotherapy, or investigational agents within 4 weeks of the first dose of DSP-7888 Dosing Emulsion

   This exclusion is not applicable to patients who meet the inclusion criterion #1b (ii) within Phase 1b dose search part.
2. Major surgery within 4 weeks prior to study treatment
3. Patients who have received a live vaccine within 4 weeks prior to the first dose
4. Any known, untreated brain metastases; patients with treated brain metastases must be clinically stable for 4 weeks after completion of treatment for brain metastases and have

radiographic image documentation of stability. Patients must have no clinical symptoms from brain metastases and not have required systemic corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 5) for at least 2 weeks prior to the first dose of study drug

5. Patients who have multifocal glioblastoma
6. Pregnant or breastfeeding
7. Patients who have an active autoimmune disease requiring immunosuppression > 10 mg/day prednisone or equivalent (see Appendix 5)
    a. Patients with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin prior to study drug administration
8. Patients who have interstitial lung disease or active, noninfectious pneumonitis
9. Known hypersensitivity to a component of protocol therapy:
    a. Patients with known hypersensitivity to any of the components of DSP-7888 Dosing Emulsion
    b. Patients with known hypersensitivity to nivolumab or pembrolizumab are excluded from receiving combination therapy that includes the agent to which they are hypersensitive
10. Uncontrolled concurrent illness including, but not limited to: ongoing or active, uncontrolled bacterial, viral, or fungal infections requiring systemic therapy; clinically significant non-healing or healing wounds; symptomatic congestive heart failure; unstable angina pectoris; severe and/or uncontrolled cardiac arrhythmia; significant pulmonary disease; or, psychiatric illness/social situations that would limit compliance with study requirements
11. Patients with a history of another primary cancer with the exception of: (a) curatively resected nonmelanoma skin cancer; (b) curatively treated cervical carcinoma in situ; (c) localized prostate cancer not requiring systemic therapy; and d) any another cancer from which the patient has been disease-free for ≥2 years that, in the opinion of the investigator and medical monitor for the Sponsor, will not affect patient outcome in the setting of the current diagnosis
12. Patients who have a QT corrected interval, based on Fridericia's equation (QTcF), >480 msec (Common Terminology Criteria for Adverse Events [CTCAE] = Grade 2) or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) at Screening (patients with bundle branch block and a prolonged QTc interval should be reviewed by the medical monitor for potential inclusion)
13. Patients who have a medical history of frequent or sustained ventricular ectopy
14. Patients who have, in the opinion of the treating investigator, any concurrent conditions that could pose an undue medical hazard or interfere with the interpretation of the study results

15. Known history of human immunodeficiency virus (HIV) infection, active hepatitis B, or untreated active hepatitis C

    Note: Patients who have completed a course of antiviral treatment for hepatitis C and are cured are eligible. In cases of negative results, hepatitis B surface antigen (HBsAg) with positive hepatitis B core antibody, and hepatitis B virus DNA testing are required

16. Patients who have baseline signs and symptoms consistent with clinically significant, decreased pulmonary function: (1) blood saturation oxygen level (SpO_2) <90% at rest on room air; (2) dyspnea at rest or required supplemental oxygen within 2 weeks of study enrollment

Phase 2

Patients with any of the following will be excluded from the study:

1. Primary platinum-refractory patients defined as patients who experienced disease progression during the treatment with first-line platinum therapy
2. Patients with a known, untreated brain metastasis; patients with treated brain metastases must be clinically stable for 4 weeks after completion of treatment for brain metastases and have radiographic image documentation of stability; patients must have no clinical symptoms from brain metastases and not have required systemic corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 5) for at least 4 weeks prior to the first dose
3. Patients who have received prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody or a small molecule targeting other immunoregulatory receptors or mechanisms (examples of such drugs include, but are not limited to, antibodies against, eg, CTLA-4, LAG-3, IDO, PD-L1, IL-2R, GITR)
4. Patients who have received prior treatment with any other Wilms Tumor 1 (WT1)-related agents including peptide vaccine, dendric cell vaccine, and gene therapy
5. Patients who have received treatment for ovarian cancer within the following timeframe prior to the first dose of the study drug
    a. Cytotoxic chemotherapy, hormonal therapy; ≤3 weeks
    b. Targeted therapy except for monoclonal antibody; ≤3 weeks
    c. Immune therapy, biologic therapy (eg, antibodies); ≤4 weeks
    d. Other investigational agents: ≤4 weeks
    e. Radiation therapy (except for localized radiotherapy for analgesic purpose) ≤4 weeks
    f. Radiation therapy (localized radiotherapy for analgesic purpose) ≤1 week
    g. Major surgery regardless of reason ≤4 weeks
6. Patients who have received a live vaccine within 4 weeks prior to the first dose
7. Any known additional malignancy that is progressing or requires active treatment, with the exception of:
    a. curatively treated basal cell or squamous cell carcinoma of skin
    b. curatively treated superficial bladder cancer, carcinoma in situ of the cervix,

c. any another cancer from which the patient has been disease-free for ≥3 years without any active treatment that, in the opinion of the investigator and medical monitor for the Sponsor, will not affect patient's outcome in the setting of the current diagnosis

8. Patients who have not recovered to <CTCAE Grade 2 or baseline from toxic effect (with exceptions of alopecia and/or neuropathy) of prior cancer therapy
9. Patients who have an active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance dose of corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 5) or any other forms of immunosuppressive therapy within 7 days prior to the first dose of study drug
10. Positive serology for HIV infection, active hepatitis B, or active hepatitis C:
    - In cases of negative results for HBsAg with positive Hepatitis B core antibody, hepatitis B virus (HBV) DNA greater than the lower limits of detection is not acceptable
11. Patients who have a known history of bacillus tuberculosis (TB)
12. Patients with impaired cardiac function or clinically significant cardiac disease:
    - New York Hospital Association (NYHA) Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy
    - Unstable angina pectoris ≤6 months before study participation
    - Myocardial infarction or stroke ≤6 months before study participation
13. Patients who have an interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids
14. Patients with active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy
15. Patients with any psychiatric condition, substance abuse disorder, or social situation that would interfere with a patient's cooperation with the study requirements and schedule
16. Patients with any condition that would, in the investigator's judgment, interfere with full participation, including administration of study drugs, attending required visits, or interfere with interpretation of study data
17. Patient who are pregnant or breastfeeding
18. Patients who have a known hypersensitivity to DSP-7888 Dosing Emulsion, pembrolizumab, their components, or their excipients
19. Patient has dyspnea at rest (CTCAE ≥Grade 3) or has required supplemental oxygen within 2 weeks of study enrollment
20. Patients with history of bowel obstruction related to underlying disease within 3 months prior to the first dose of study treatment

7.3. Withdrawal Criteria

7.3.1. Reasons for Discontinuation of Protocol Therapy

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of partial consent means that the patient does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on the study (eg, participate in all subsequent study visits or procedures). Patients may decline to continue receiving investigational product at any time during the study. These patients, as well as those who have stopped receiving investigational product for other reasons (eg, investigator or Sponsor concern) should continue the schedule of study observations. The patients may withdraw consent for continued treatment and still provide consent to be followed up in the follow-up period.

Patients will be discontinued from protocol therapy for any of the following reasons:

- Patients completes 35 cycles (approximately 105 weeks) of study treatment (Phase 2 part only)

  Note: if the patient is experiencing clinical benefit, and if, in the opinion of the investigator, it is in the patient's best interest to continue the study beyond 35 cycles, the patient may continue treatment, after documented discussion with the Sponsor
- Documented disease progression (see Appendix 2)
- The need for a prohibited treatment for a concomitant illness or AE
- An AE that precludes further administration of DSP-7888 Dosing Emulsion (see Section 8.3.1 and Section 8.3.2)
- Patient withdraws consent for continued administration of DSP-7888 Dosing Emulsion, nivolumab, or pembrolizumab

  Note: if a patient withdrawals consent from study treatment, the patient may maintain his/her consent to participate in the follow-up portion of the study
- The investigator believes it is in the patient's best interest to discontinue protocol treatment or to initiate alternative treatment
- Pregnancy
- Lost to follow-up (3 attempts to contact the patient must be made by the investigative site by phone or email before a patient is considered lost to follow-up)
- Patient moves out of the investigator's catchment area or is unable to continue to come to the investigational site
- At Sponsor's request

7.3.2. Reasons for Discontinuation from the Clinical Study

Reasons for discontinuation from the study include:

- Patient withdraws consent for continued participation
- Lost to follow-up
- Death of the patient
- The Sponsor deems it necessary to discontinue the study

Withdrawal of full consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any patient may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the patient the most appropriate way to withdraw to ensure the patient's health.

No patients will be replaced during the dose-expansion part of the clinical study. Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment.

Patients withdrawing from the study will be requested to complete the same final evaluations as patients completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for patients who complete the study.

Reasonable efforts will be made to contact patients who are lost to follow-up. These efforts must be documented in the patient's file.

The Sponsor has the right to terminate the study at any time. In this event, the investigator(s) will be informed of the reason for study termination.

8. TREATMENT OF PATIENTS

8.1. Description of Study Drugs

8.1.1. DSP-7888 Dosing Emulsion Investigational Product

DSP-7888 Dosing Emulsion, also known as Adegramotide/Nelatimotide (INN) and Ombipepimut-S (USAN), is a synthetic peptide vaccine that consists of 2 synthetic peptide constructs: Nelatimotide (INN) (DSP-7888-K [killer peptide; an MHC Class I peptide]) and Adegramotide (INN) (DSP-7888-H [helper peptide; an MHC Class II peptide]). Both constructs are derived from the WT1 protein. DSP-7888 Dosing Emulsion, consisting of DSP-7888 in suspension with montanide 51 VG (labeled as DSP-7888-M), will be administered at the study site by staff trained in the administration of intradermal drugs.

8.1.2. Nivolumab

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Nivolumab will be administered at 240 mg every 2 weeks, as per the approved label.

On the days when both DSP-7888 Dosing Emulsion and nivolumab are administered, DSP-7888 Dosing Emulsion should be administered first. Nivolumab will be obtained by the clinical site.

8.1.3. Pembrolizumab

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks interaction with its ligands, PD-L1 and PD-L2. This binding results in the activation of T-cell–mediated immune responses against tumor cells. Blocking PD-1 activity has resulted in decreased tumor growth in genetically identical mouse tumor models. Pembrolizumab will be administered at a dose of 200 mg/8 mL IV over 30 (±5) minutes every 21 days (3 weeks). On the days when both DSP-7888 Dosing Emulsion and pembrolizumab are administered, DSP-7888 Dosing Emulsion should be administered first. Pembrolizumab may be obtained by the clinical site in Phase 1b of the study. For Phase 2 of the study, pembrolizumab will be provided by [redacted]

8.2. Treatment Dose and Schedule (Phase 1 and Phase 2)

Treatment dosing and treatment schedules for DSP-7888 Dosing Emulsion, nivolumab, and pembrolizumab are provided in Table 10.

Table 10: DSP-7888 Dosing Emulsion, Nivolumab, and Pembrolizumab Treatment Dose and Schedule

DSP-7888 Dosing Emulsion					**Treatment Schedule** **DSP-7888 Dosing Emulsion, Nivolumab, Pembrolizumab**	
Dose Level	**Dose Intensity**	**Number of Injection* Sites**	**Amount Per Injection* Site (mL)**	**Total Amount to Administer Per Dosing Day (mL)**	**Nivolumab Arm** (Arm 1)	**Pembrolizumab Arm** (Arm 2) of Phase 1b and Phase 2
DSP-7888 Dosing Emulsion Dose Level I	10.5 mg	6	0.1	0.6	**DSP-7888 Dosing Emulsion** induction phase: weekly for 4 weeks then maintenance phase: every 2 weeks **nivolumab 240 mg** administered IV over 30 (±5) minutes every 14 days (2 weeks) in only maintenance phase	**DSP-7888 Dosing Emulsion** induction phase: weekly for 3weeks then maintenance phase: every 3 weeks **pembrolizumab 200 mg/8mL** administered IV over 30 (±5) minutes every 21 days (3 weeks) in only maintenance phase
DSP-7888 Dosing Emulsion Dose Level II	3.5 mg	2	0.1	0.2		
DSP-7888 Dosing Emulsion Dose Level III (only used for dose reduction)	1.75 mg	1	0.1	0.1		

Abbreviations: IV = intravenous(ly)

8.3. Dose Modification

Any study treatment may be interrupted at any time for any grade toxicity considered intolerable by the patient, based on the investigator's and patient's judgment.

In the case of any patient who has missed 4 or more consecutive doses of either study drug, that study drug should be permanently discontinued, but the patient may continue on the other nonmissed study drug. If the patient is experiencing clinical benefit and, in the opinion of the investigator it is in the patient's best interest to remain on study, the patient may continue treatment on a case-by-case basis, after documented discussion with the Sponsor.

Dose modification by treatment is described in the following sections.

8.3.1. DSP-7888 Dosing Emulsion Dose Modification in Phase 1b

The dose of DSP-7888 Dosing Emulsion should be held for any Grade 3 or Grade 4 toxicity that is related to DSP-7888 Dosing Emulsion and that is present on a scheduled dosing day. Dosing may be resumed at a reduced dose once the toxicity has resolved to Grade 1 or less. If the toxicity occurs at a dose of 10.5 mg, dosing may resume at the dosage of 3.5 mg. If the toxicity occurs at a dose of 3.5 mg, dosing may resume at a dose of 1.75 mg. No intrapatient dose reduction is allowed during the DLT evaluation period.

On days when DSP-7888 Dosing Emulsion is held for toxicity, nivolumab (Arm 1) or pembrolizumab (Arm 2) should be administered if scheduled for that day. If toxicities related to DSP-7888 Dosing Emulsion preclude administration of DSP-7888 Dosing Emulsion for 4 consecutive treatments, DSP-7888 Dosing Emulsion should be discontinued; and the medical monitor and Sponsor should be consulted for case review and possible approval of continuing therapy with nivolumab (Arm 1) or pembrolizumab (Arm 2) alone.

After the induction phase, dose reduction is permitted due to ISRs if the investigator or subinvestigator has judged that a dose reduction is medically required.

Patients who experience Grade 3 or higher toxicities with a DSP-7888 Dosing Emulsion dose of 1.75 mg will be removed from the study.

8.3.2. DSP-7888 Dosing Emulsion Dose Modification in Phase 2

Both dose interruption and dose reductions are allowable for DSP-7888 Dosing Emulsion.

8.3.2.1. Dose Reduction

After the induction phase, dose reduction to 3.5 mg and subsequently to 1.75 mg is permitted due to ISR if the investigator considers that a dose reduction is medically required. No further dose reductions from 1.75 mg will be allowed. Re-escalation of the dose after dose reduction is not permitted.

8.3.2.2. Dose Interruption

DSP-7888 Dosing Emulsion must be interrupted for any CTCAE (v.4.03) Grade 3 or 4 AE that the investigator considers to be related to DSP-7888 Dosing Emulsion. If toxicity is resolved to Grade 1 or less/baseline, the patient may restart treatment with DSP-7888 Dosing Emulsion but with a dose level reduction.

EXCEPTION: Because more serious ISRs (eg, Grade 3) may take longer to resolve due to the tissue injury, resolution to Grade 2 only is required for restart of treatment with DSP-7888 Dosing Emulsion. However, no dose reduction is required for following cases:

- Grade 3 or 4 hematologic laboratory abnormality which resolves to Grade1 or less within 7 days without supportive care (blood transfusion or G-CSF agents)
- Grade 3 or 4 non-hematologic laboratory abnormality which resolves to Grade1 or less within 7 days
- Grade 3 ISR that does not require hospitalization; patients may continue on the study treatment per investigator's judgment
- Grade 3 fatigue, fever, malaise, edema per CTCAE (v.4.03), which resolves to Grade1 or less within 5 days, with appropriate supportive care
- Grade 3 nausea, vomiting, diarrhea per CTCAE (v.4.03), which resolves within 3 days, with appropriate supportive care

Before discontinuation of dosing for any of the above reasons, a conversation with the Medical Monitor may be applicable.

If toxicity is not resolved to Grade 1 or less (or Grade 2 or less in the case of ISRs, as described above) within 4 consecutive missing doses and, in the opinion of the investigator, the patient is clinically stable and receiving benefit from study drug, the patient may restart treatment with DSP-7888 Dosing Emulsion at a reduced dosed on a case-by-case basis, only after consultation with the Sponsor.

8.3.3. Pembrolizumab and Nivolumab Dosing Management in Phase 1b and Phase 2

The product labels/package inserts (refer to pembrolizumab and nivolumab), have identified several immune system toxicities as related to the use of pembrolizumab and nivolumab. Dose management (dose withholding or permanent discontinuation) should be performed based on the recommendations in the respective product label.

8.3.4. Settings and Recommendations for DSP-7888 Dosing Emulsion Injections

Whenever possible, injections should be administered into the area surrounding the regional lymph nodes in the upper arm, the lower abdomen, or the femoral area.

To the extent possible, injections of study drug should be administered to separate parts of the body and separated from one another. Rotation of injection sites is recommended. Injection sites should not be chosen in the area of any ongoing skin condition (eg, an area of psoriasis).

8.3.5. Evaluation and Management of Injection Site Reactions

8.3.5.1. Evaluation of Injection Site Reactions

The type of ISR should be reported for the AE verbatim term (eg injection site redness should be reported as injection site redness, and not injection site reaction). Injection site reactions will be graded according to CTCAE v4.03 (Table 11).

Table 11: Grading of Injection Site Reactions (CTCAE v4.03)

Grade 1	Grade 2	Grade 3	Grade 4
Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated

Factors other than the appearance of the ISR should be taken into consideration when evaluating the severity of an ISR. A pinpoint ulcer, for example, truly may not be indicative of a Grade 3 ISR; other factors, such as the presence of fever or the need for systemic analgesia, also should be considered in determining ISR severity, and in guiding decisions regarding temporary discontinuation and/or dose reductions of DSP-7888 Dosing Emulsion.

8.3.5.2. Management Guidelines for Grade 1 Injection Site Reactions

Irrigation with physiologic saline is recommended. Topical steroids should be applied as appropriate. A mid-strength Class 4 topical steroid is recommended (National Psoriasis Foundation, 1996-2020). Examples include:

- Flurandrenolide ointment, 0.05%
- Mometasone furoate cream, 0.1%
- Triamcinolone acetonide cream/spray, 0.1%
- Fluocinolone acetonide ointment, 0.03%
- Desoximetasone cream or ointment, 0.05%
- Hydrocortisone valerate ointment, 0.2%

Topical antiseptics or antimicrobials that are likely to cause a skin reaction by initiating an immune response should not be used; however, antibiotics may be used in the presence of infectious findings or positive culture results.

8.3.5.3. Management Guidelines for Grade 2/3 Injection Site Reactions

- Irrigation with physiologic saline and use of topical steroids, as described for Grade 1 ISRs above, should be instituted. If topical steroids are not sufficient for ISRs, local (subcutaneous) injection of steroids may be considered
- Topical antibiotics should not be used unless cultures indicate infection
- Open areas may be protected with a non-stick dressing
- Patients with Grade 3 ISRs that do not require hospitalization may remain on study and receive full dose per investigator's judgment
- If an abscess forms, incision and drainage should be carried out to avoid exacerbation of the inflammatory response around the site. After the drainage, the site should be washed with physiologic saline followed by application of topical steroids, as appropriate. Most abscesses should be sterile, but cultures should be obtained (see Section 8.3.5.2 for recommendations for when the culture is positive)

- Emergency measures should be implemented for ISRs > Grade 3

8.4. Packaging and Labeling

[redacted] may supply the DSP-7888 bulk product. The study packaging will be performed by a contract manufacturing organization designated by [redacted] Company).

[redacted] will supply the pembrolizumab (Keytruda - NDC # 0006-3026-02) for Phase 2 of the study. It will be delivered to a contract manufacturing organization designated by INC Research.

All packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) for Medicinal Products, Regulatory Requirements for Investigational Drug Labeling, and any other relevant regulatory requirements.

8.5. Prior and Concomitant Therapy

Patients should receive treatment for all inter-current medical conditions or AEs at the discretion of the investigator in conformance with community or institutional medical standards.

All information regarding concomitant treatments (medications or procedures) must be recorded on the patient's case report form/electronic case report form (CRF/eCRF) (including the name of the medication or procedure and duration of treatment).

Palliative and supportive care for disease-related symptoms will be offered to all patients in this study. Patients may receive palliative radiation therapy or palliative surgery for symptomatic lesion(s) as long as the lesion is not the only evaluable one.

Study drug administration should be interrupted during and following these therapies until the patient has adequately recovered from the effects of treatment, as judged by the treating investigator.

Patients on the study will be permitted to receive COVID-19 vaccinations that are authorized for use by the Health Authorities of the country/region.

If possible, a COVID-19 vaccination should be administered on non-study drug injection days. Because DSP-7888 Dosing Emulsion is a peptide vaccine, the COVID-19 vaccine should be administered preferably 48 hours after the DSP-7888 Dosing Emulsion administration to avoid confounding of immediately occurring AEs. The COVID-19 vaccine should also be given at a different injection site from the DSP-7888 Dosing Emulsion injection site.

8.6. Permitted Treatment

The following medications are allowed:

- Corticosteroids (equivalent to ≤10 mg/day prednisone; see Appendix 5), and topical, ophthalmic, and inhalation corticosteroids are permitted as needed. If a patient experiences an immune-related AE (irAE), use of steroids is permitted based on the Management of Immunotherapy-related Toxicities (NCCN Guidelines 2018 Version 1)

- Medically indicated isolated dosing of steroids for patient with CT IV contrast allergy is allowed

8.7. Prohibited Medication/Therapy

- All other antineoplastic therapy, including cytotoxic agents, hormonal agents, monoclonal antibodies, immunomodulatory agents, or investigational agents, with the exception of:
  - Luteinizing hormone-releasing hormone (LHRH) agonists, anti-estrogens, or aromatase inhibitors started and maintained at a stable dose for at least 90 days before the planned first dose of study drug
- Systemic radiopharmaceuticals during the study
- Other investigational agents
- Patients may not receive any immunosuppressive agents, except for irAE management, based on the NCCN Guidelines 2018 Version 1
- Pharmacologic doses of systemic corticosteroids (equivalent to >10 mg/day prednisone; see Appendix 5) except for irAE management based on the NCCN Guidelines 2018 Version 1. Note: Corticosteroids (equivalent to ≤10 mg/day prednisone; see Appendix 5), and topical, ophthalmic, and inhalation corticosteroids are permitted, as needed.
- Treatment aimed at preventing the induction of AEs by the study drug
- Surgery for the treatment of neoplastic disease. (Note: palliative surgery for symptomatic lesion[s] is permitted as long as the lesion is not the only evaluable one.)
- Radiation therapy for the treatment of neoplastic disease. (Note: palliative radiation therapy for symptomatic lesion[s] is permitted.)
- Hyperthermia/thermotherapy for the treatment of neoplastic disease
- Patients should not receive live vaccines (eg, Flu-Mist®); vaccines containing killed organisms are permitted

8.8. Note on Nivolumab/Pembrolizumab and Systemic Immunosuppression

Nivolumab is a human monoclonal antibody; as such, pharmacokinetic (PK) interaction studies have not been conducted. As monoclonal antibodies are not metabolized by cytochrome P450 enzymes or other drug-metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the PK of nivolumab. As for pembrolizumab, no data are available on potential drug interactions.

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab or pembrolizumab, should be avoided because of their potential interference with PD activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.

8.9. Treatment Compliance

The administration of investigational product will occur at the clinical site; therefore, the study staff will be able to confirm compliance by maintenance of comprehensive accountability logs and pharmacy records.

8.10. Randomization

Not applicable.

8.11. Blinding

Not applicable.

9. STUDY DRUG MATERIALS AND MANAGEMENT

Full details on study drug materials and their management are provided in Section 8.1, Section 8.2, and Section 8.3.

10. PHARMACODYNAMIC AND TUMOR TISSUE ASSESSMENTS

10.1. Tumor Tissue Collection Procedure

Patients will provide written informed consent before any study-related procedures are performed.

Tumor tissue samples will be collected as specified in Table 7, Table 8, and Table 9.

For the prestudy evaluation tissue samples, a total of at least 23 slides of archival samples and/or the equivalent amount of archival tissue block and/or fresh biopsy samples from the enrolled patients are collected. From patients who consent to providing additional samples by signing the additional informed consent for these optional samples, an additional 6 to 8 slides will be collected for future biomarker analysis.

10.1.1. Phase 1b and Phase 2

For the post-treatment evaluation tissue samples, from patients who consent to providing post-treatment tumor samples by signing additional consent, a tumor sample that will provide sufficient material for 23 slides will be obtained. However, if it is not medically feasible to collect, less than 23 slides will be acceptable for post-treatment evaluations. From patients who consent to providing additional samples by signing the additional informed consent for these optional samples, an additional 6 to 8 slides will be collected for future biomarker analysis. The time points and circumstances for tumor tissue sample collection for post-treatment evaluations are described below:

At Week 12, a post-treatment evaluation tissue sample will be collected.

After Week 12, from consenting patients, another post-treatment tissue sample will be collected (only applicable for Phase 1b patients), as follows:

- For patients with SD at Week 12 who receive subsequent response evaluation which shows PR, a biopsy will be collected at the time of PR evaluation
- For patients with suspected pseudo progression at Week 12 who receive subsequent response evaluation which shows PR/SD, a biopsy will be collected at the time of PR/SD evaluation
- For patients with PR at Week 12, no further biopsy will be collected
- For patients with PD/SD at Week 12 who discontinue treatment, no further biopsy will be collected

Tumor tissue samples will be collected at End of Treatment only if the patient discontinues from the study prior to Week 12.

10.1.2. Follow-Up Procedures

The follow-up period will begin once a patient has discontinued the study treatment. The follow-up period includes disease assessment follow-up (for patients who discontinue study treatment for a reason other than iCPD, per iRECIST) and survival follow-up.

Patients who discontinue study treatment without experiencing iCPD will continue to undergo tumor assessment and evaluation of CA-125, according to the SOA, until up to 105 weeks after the last dose of study drug, the start of new anticancer therapy, iCPD per iRECIST, death, loss to follow-up, withdrawal of consent, or the end of the study, whichever occurs first.

Patients who discontinue study treatment who are experiencing iCPD per iRECIST with study drug, or patients who discontinue study treatment without experiencing iCPD per iRECIST, but experience iCPD per iRECIST or start new anticancer therapy during disease follow-up will be assessed for survival and new anticancer treatment status per the SOA until up to 24 months after the last dose of study drug, death, withdrawal of consent, loss to follow-up, or end of study, whichever occurs first.

10.2. Pharmacodynamic Variables (Biomarkers)

- WT1-specific CTL induction will be measured throughout the study
- WT1 via CISH, PD-L1 expression status (CPS), and CD8+cell density via IHC
- TIL and TIS profiling in tumor
- Mutation status and TMB

In addition to the biomarkers above, blood samples for serum/PBMC/ct DNA(Plasma) and tumor tissue will be collected for future biomarker analysis, only if patients consents for additional informed consent(optional). The timing of sample collections will be conducted according to Table 7, Table 8, and Table 9.

When data are available, change from baseline will be estimated and correlated with efficacy outcomes. Parameters at baseline obtained from tissue samples will be estimated and correlated with efficacy outcomes.

11. ASSESSMENTS OF SAFETY AND EFFICACY

11.1. Assessment of Safety

11.1.1. Safety Parameters

Safety will be evaluated based on the AEs recorded at each contact with the patient, physical examinations, and the results of laboratory tests. Toxicity will be graded according to the CTCAE v4.03.

11.1.1.1. Vital Signs

Vital signs will include systolic and diastolic blood pressures, pulse, respiratory rate, temperature, and weight. Blood pressure and heart rate will be recorded in a standardized manner, ie, after the patient has rested in the sitting position for at least 5 minutes. Vital signs will be recorded according to Table 7, Table 8, and Table 9. Height and body mass index will be recorded at Screening only.

11.1.1.2. Physical Examination

A physical examination will include examination of the skin; head-ears-eyes-nose-throat (HEENT); chest, including the lungs and the heart; abdomen; neurologic, and extremities and areas of major lymph node chains. Physical examinations will be conducted according to Table 7, Table 8, and Table 9.

Inspection of previous injection sites should be made prior to administration of DSP-7888 Dosing Emulsion.

11.1.1.3. Cardiac Assessments

Cardiac assessments, including ECHO/MUGA scans for ejection fraction; 12-lead resting ECG in triplicate, including heart rate, PR interval, QRS duration, QTcF intervals, and ECG findings; and pulse oximetry assessments will be obtained during Screening and then according to Table 7, Table 8, and Table 9.

11.1.1.4. Laboratory Assessments

The hematology and clinical chemistry laboratory analyses will be performed at local laboratories. Reference ranges will be supplied and used by the investigator to assess the laboratory data for clinical significance and pathologic changes.

11.1.1.4.1. Hematology

A complete blood cell count (CBC) will include measures of red blood cells (RBC), hemoglobin (Hb), white blood cells (WBC) with differential, and platelet count. A CBC will be performed according to Table 7, Table 8, and Table 9.

11.1.1.4.2. Clinical Chemistry

Collect samples for serum chemistry tests, including sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, ALT, AST, alkaline phosphatase (ALP), creatinine, lactate

dehydrogenase (LDH), gamma-glutamyl transferase (GGT), amylase, CRP (Phase 1b Screening only, Phase 2 all visits), albumin, globulin, total bilirubin, conjugated bilirubin, unconjugated bilirubin, glucose, cholesterol, triglycerides, blood urea nitrogen (BUN), and uric acid.

11.1.1.4.3. Thyroid Function Test

Collect samples for thyroid function tests including thyroid-stimulating hormone (TSH), FT4, and T3.

11.1.1.4.4. Other Laboratory Variables

Screening for HBsAg, hepatitis C antibody, and HIV will be performed at Screening/Baseline only. In cases of negative results, HBsAg with positive hepatitis B core antibody and hepatitis B virus DNA testing are required.

11.1.1.4.5. Urinalysis

A urinalysis will include measurements of pH, specific gravity, protein, nitrite, glucose, ketones, occult blood, bilirubin, and urobilinogen. If any dipstick determinations are 2+ or greater, a microscopic examination of urine will be performed. If a dipstick determination of protein is 2+ or higher, a 24-hour urine collection must be done. Urine testing will be performed according to Table 7, Table 8, and Table 9.

11.1.1.4.6. Pregnancy Testing

In Phase 1b, pregnancy testing in women of childbearing potential may be obtained with a serum human chorionic gonadotropin test. In Phase 2, pregnancy testing may be obtained via either serum or urine testing. A pregnancy test will be performed during Screening and then if clinically indicated per the investigator's judgment.

11.1.2. Adverse and Serious Adverse Events

11.1.2.1. Definitions

11.1.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study patient administered an investigational agent that does not necessarily have a causal relationship with the treatment administered. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the investigational agent, whether or not considered related to the investigational agent. An AE can arise from any use of the drug, and from any route of administration, formulation or dose, including an overdose.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity or frequency.
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigations (eg, laboratory results, x-ray findings). See Section 11.1.2.3.5 for further guidance on clinically significant laboratory findings.

Pregnancy is not an AE; however, if a female patient or partner of a male patient becomes pregnant during the conduct of the study, the Investigator must notify [redacted] according to the procedures provided in Section 11.1.2.4.4.

11.1.2.1.2. Adverse Reactions and Suspected Adverse Reactions

All noxious and unintended responses to an investigational agent related to any dose should be considered adverse drug reactions. Suspected adverse reactions are any AEs for which there is a reasonable possibility that the investigational agent caused the AE. Adverse reactions may also include medication errors and uses outside of what is foreseen in the protocol, including misuse, abuse, and overdose (intentional or unintentional) of the investigational agent.

11.1.2.1.3. Serious Adverse Event

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience
  - Note: "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event as it occurred; it does not refer to an event that might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless the hospitalization is for the following:
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF).
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience
- Results in congenital anomaly or birth defect
- Results in persistent or significant disability or incapacity
- Is considered to be an important medical event.

  Note: Important medical events are those that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2.2. Procedures for Eliciting, Recording, and Reporting Adverse Events

11.1.2.2.1. Eliciting and Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit.

All AEs occurring from the signing of informed consent until 30 days after the last dose of investigational therapy will be recorded in the eCRF. Any SAEs related to study-related procedures will be collected starting from ICF for biomarkers sampling, blood drawings, and biopsy procedures. All SAEs attributable to study-related procedures will be collected starting from completion of the Prescreening ICF (biomarkers sampling, blood drawings, and biopsy procedures).

An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

All SAEs occurring from the signing of informed consent through 30 days after the last investigational agent administration will be reported to [redacted] or designee as outlined in Section 11.1.2.3.

At each required visit during the study, all AEs that have occurred since the previous visit must be reviewed. The Investigator or appropriate designee must determine if the AE is serious or non-serious.

11.1.2.2.2. Relationship to Investigational Agent

A medically qualified Investigator must assess the relationship of any AE to the use of the investigational agent, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between investigational agent exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known mechanism of action or toxicities associated with the investigational product.
- **Dechallenge**: the AE resolved or improved with decreasing the dose or stopping use of the investigational agent. Judgment should be used if multiple products are discontinued at the same time.
- **Rechallenge**: the AE recurred or worsened upon re-exposure to the investigational agent.

The causal relationship between the investigational agent and the AE will be assessed using one of the following categories:

- Not Related/Unrelated: Suggests that there is no causal association between the investigational agent and the reported event.

- Unlikely Related: Suggests that the clinical picture is highly consistent with a cause other than the investigational agent, but attribution cannot be made with absolute certainty and a relationship between the investigational agent and AE cannot be excluded with complete confidence.
- Possibly Related: Suggests that treatment with the investigational agent may have caused or contributed to the AE (ie, the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the investigational agent but could also have been produced by other factors).
- Probably Related: Suggests that a reasonable temporal sequence of the event with the investigational agent administration exists and the likely causal association of the event with the investigational agent. This will be based upon the known pharmacological action of the investigational agent, known or previously reported adverse reactions to the investigational agent or class of drugs, or judgment based on the Investigator's clinical experience.
- Definitely Related: Temporal relationship to the investigational agent, other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, re-appearance on re-challenge.

11.1.2.2.3. Adverse Event Severity

The severity of AEs will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v4.03. For events not specifically found in CTCAE, the following definitions will be used to estimate grade of severity:

- 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 activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," (outlined in Section 11.1.2.1.3 which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

11.1.2.2.4. Assessment of Expectedness

The Reference Safety Information for assessing the expectedness of an AE in this study is to be the section identified as the Reference Safety Information in the most recent DSP-7888 Investigator's Brochure.

The Reference Safety Information for assessing the expectedness of an AE for a comparator or co-suspect drug in this study is the US Package Insert for nivolumab or pembrolizumab.

11.1.2.3. Specific Instructions for Recording Adverse Events on the eCRF

11.1.2.3.1. Diagnosis Versus Signs and Symptoms

If a diagnosis is known at the time of reporting, the diagnosis rather than the individual signs and symptoms should be recorded in the eCRF (eg, record only hepatitis rather than elevated transaminases, bilirubin, jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up and should replace the individual signs and/or symptoms as the event term on the eCRF.

11.1.2.3.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF (eg, dehydration secondary to diarrhea).

11.1.2.3.3. Medication Errors, Misuse and Abuse of Investigational Agent

Overdose, medication error, misuse and abuse are defined as follows:

- *Overdose*: refers to the administration of a quantity of investigational agent given per administration or cumulative, which is above the maximum dose according to the protocol. Clinical judgment should always be applied.
- *Medication error*: refers to an unintentional error in dispensing or administration of the investigational agent not in accordance with the protocol.
- *Off-label use*: relates to situations where the investigational agent is intentionally used for medical purpose not in accordance with the protocol.
- *Misuse*: refers to situations where the investigational agent is intentionally and inappropriately used not in accordance with the protocol.
- *Abuse*: corresponds to the persistent or sporadic, intentional excessive use of the investigational agent, which is accompanied by harmful physical or psychological effects.
- *Occupational exposure*: refers to the exposure to the investigational agent as a result of one's professional or non-professional occupation.

Overdoses, medication errors, abuse or misuse regardless of whether there was an associated AE will be collected as part of investigational agent dosing information and/or as a protocol violation, as required.

Any AE associated with an overdose, medication error, misuse or abuse of study drug should be recorded on the AE eCRF with the diagnosis of the AE.

11.1.2.3.4. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF. If a persistent AE becomes more severe in severity, it should be recorded as a new AE on the eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. Each individual instance of a recurrent AE should be recorded on an SAE Report Form and/or AE eCRF.

11.1.2.3.5. Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be recorded on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form and/or eCRF. Abnormal laboratory values assessed as not clinically significant (NCS) should be documented as such in the source document.

Abnormal laboratory values will be reported as an AE if the laboratory result:

- Requires an adjustment in the investigational agent(s) or discontinuation of treatment
- Meets seriousness criteria
- Requires additional testing or surgical intervention
- Is associated with accompanying symptoms

11.1.2.3.6. Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 11.1.2.1.3). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis of the disease under study should not be reported as an AE/SAE, as they are considered to be disease progression.

11.1.2.3.7. COVID-19

Because much is still unknown about how SARS-CoV-2 affects the human body, patients who have tested positive for COVID-19 will be identified and relevant information collected. All patients should provide documentation of any testing for COVID-19, if available, along with the test results, at screening for enrollment and/or during the study. Prior test results should be reported, if available, for any patient who has previously tested positive for COVID-19

SARS-CoV-2 titers (antiviral immunoglobulin G [IgG] and immunoglobulin M [IgM]). These data will be entered into the patient's study-specific record.

Any patient-reported illness of COVID-19 during the study should be recorded as an AE. If a patient reports infection with COVID-19, the investigator may discuss with the Medical Monitor whether the patient can continue on study.

11.1.2.3.8. Deaths

All events leading to the clinical outcome of death occurring during the SAE reporting period (from the signing of the informed consent through 30 days after the last investigational agent administration) are to be reported to Sponsor or designee as an SAE and recorded on the AE eCRF.

11.1.2.4. Reporting of Expedited Safety Observations by the Investigator Including Serious Adverse Events

11.1.2.4.1. Immediate Reporting of Serious Adverse Events by Investigator to Sponsor

All SAEs, from the signing of informed consent through 30 days after last dose, including SAEs from screen failures, will be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event, even if the experience does not appear to be related to the investigational agent.

Serious AEs should be communicated on an SAE report form as follows:

[redacted] **Pharmacovigilance Department Contacts**	
Email:	[redacted]
Fax:	[redacted]

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented on a follow-up form. All follow-up information must be reported in the same timelines as initial information.

At any time after completion of the AE reporting period (ie, 30 days post-treatment), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to the investigational agent, the event must be reported to the Sponsor or designee.

11.1.2.4.2. Immediate Reporting of Occupational Exposure, Overdose, or New Cancers

Any **occupational exposure** or exposure of an individual not enrolled in the study to the investigational medicinal product must be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event, even if the exposure does not result in an AE. Unintentional exposures should be communicated on the SAE Report Form, as described above for SAEs.

Any **overdose** to the investigational medicinal product must be reported to the Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event, even if the overdose does not result in an AE. Overdose should be communicated on the SAE Report Form, as described above for SAEs.

Any **new cancers** must be reported to Sponsor or designee within **24 hours** of the Investigator's first knowledge of the event. New cancers should be communicated on the SAE Report Form, as described above for SAEs.

11.1.2.4.3. Reporting COVID-19 Infections

Suspected or confirmed COVID-19 infections, including asymptomatic infections and positive COVID-19 tests are Adverse Events of Special Interest (AESIs) and therefore immediately reportable events, even if the events do not meet SAE criteria.

Serious COVID-19 events will be reported on an SAE Report form within 24 hours of the investigator's awareness, according to Section 11.1.2.4.1.

Nonserious COVID-19 events will be reported on a COVID-19 Report form within 5 calendar days of the investigator's awareness, to the same email/fax for reporting SAEs described in Section 11.1.2.4.1.

Updates or follow-up information for COVID-19 events should be reported on an SAE Report form (serious events) or a COVID-19 Report form (nonserious events) within the same timelines as the initial reports.

11.1.2.4.4. Reporting Pregnancies

If a female patient or the female partner of a male patient becomes pregnant during the course of study, the Investigator must report the pregnancy to the Sponsor or designee using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event.

If not all information on the Pregnancy Reporting Form is available at the time of the initial report, follow-up Pregnancy reports will be completed and submitted within **24 hours** of becoming aware of the new information. The Investigator is required to follow up on the pregnancy until it has completed. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within **24 hours** of becoming aware. SAEs associated with the pregnancy, including fetal death, miscarriage or congenital anomalies, must be reported as a serious adverse event according to Section 11.1.2.4.

If the female partner of a male patient becomes pregnant, the Investigator must obtain consent to collect pregnancy information from the pregnant partner (including the status of the newborn, if applicable).

11.1.2.4.5. Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations.

11.1.2.4.6. Safety Notifications by the Sponsor to the Investigator

Investigators will receive prompt notification of any suspected adverse drug reaction that is both serious and unexpected, or any finding that suggests a significant risk for patients, in accordance with local laws and regulations. The Investigator will promptly inform his/her IRB/IEC of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

11.2. Assessment of Efficacy

Tumor response will be determined by the investigator according to RECIST v1.1 and iRECIST. Tumor response according to iRECIST will be used for treatment decision-making and other supporting disease-specific efficacy measurements. Tumor evaluations during treatment period in Arm 1 will be performed at Weeks 4, 12, 18, and 24, followed by every 12 weeks until disease progression. Tumor evaluations during treatment period in Arm 2 will be at Weeks 6, 12, 18, and 24, followed by every 12 weeks until disease progression.

Tumor evaluations during the treatment period in Phase 2 will be at Weeks 6, 12, 18, and 24, followed by every 12 weeks until disease progression or the completion of 35 treatment cycles. Patients who discontinue study treatment without experiencing iCPD will continue to undergo tumor assessment according to the SOA until up to 24 months after the last dose of study drug, the start of new anticancer therapy, iCPD per iRECIST, death, loss to follow-up, withdrawal of consent, or the end of the study, whichever occurs first.

12. STATISTICS

12.1. Statistical Methods

Detailed methodology for the statistical analyses of the data collected in this study will be documented in the statistical analysis plan (SAP), which will be maintained by [redacted]. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

In general, all efficacy and safety endpoints will be analyzed using descriptive statistics (n, mean, standard deviation, median, and ranges for continuous variables; frequencies and percentages for categorical variables).

All deviations related to conduct of the study, patient management, or patient assessment will be identified, evaluated, and closed before database lock and will be described in the final CSR. Protocol deviations are not allowed for inclusion or exclusion criteria.

12.1.1. Determination of Sample Size

12.1.1.1. Dose-search Part (Phase 1b)

In the dose-search part of the study, there will be 6 to 12 patients for each arm (up to a total of 24 patients). If a patient is terminated before having any evaluable data, the patient will be replaced until the planned sample size is reached.

In the enrichment cohort, 10 patients will be enrolled to help evaluate the preliminary antitumor activity and the safety profile of DSP-7888 Dosing Emulsion.

If anti-tumor activities are observed in any tumor type, additional patients may be enrolled for further assessment.

12.1.1.2. Dose-Expansion Part (Phase 2)

There is no formal hypothesis testing for the Phase 2 cohort. Approximately 40 eligible PROC patients are expected to be enrolled in the Phase 2 dose expansion part of the study. A Bayesian decision-making framework will be employed to quantify whether proof of concept (POC) can be established based on the overall response rate (ORR) by Week 24 from the final analysis for overall population and/or CPS < 10 subpopulation. The POC is established at the final analysis if either or both of the following two conditions are met:

- In the overall population, 70% credible interval of ORR with 10% in the left tail and 20% in the right tail will be calculated: if lower bound ≥ 8% and upper bound ≥ 21% (where 8% is the reference value [Section 4.3.1; Matulonis, 2019]) and 21% is the target value of ORR in the overall population), the study achieve POC.
- In the CPS< 10 subpopulation, 50% credible interval of ORR with 20% in the left tail and 30% in the right tail will be calculated: if lower bound ≥ 5% and upper bound ≥ 15% (where 5% is the reference value [Section 4.3.1; Matulonis, 2019] and 15% is the target value of ORR in CPS < 10 subpopulation), the study achieves POC.

Statistical analysis may be conducted to evaluate the relationship between ORR and the PD-L1 level and/or WT1 using statistical methods, such as ROC curve or contingency table.

In Phase 2 of the study, approximately 40 patients will be enrolled. Additional patients may be enrolled to further assess anti-tumor activities in the subgroups of interest. However, the total sample size of Phase 2 cannot exceed 60 patients. In total, approximately 64-84 patients will be enrolled in the study.

12.1.2. Analysis Datasets

12.1.2.1. Full Analysis Set

The Full Analysis Set (FAS) consists of all patients who receive at least 1 full or partial dose of study treatment (DSP-7888 Dosing Emulsion, nivolumab, or pembrolizumab). Patients will be classified according to the treatment assigned (dose level and schedule).

Patients who were screened but never started treatment will be listed but not included in the FAS. Screening failures will not be included in any of the summary tables.

12.1.2.2. Safety Set

The Safety Set (SS) consists of all patients who receive at least 1 full or partial dose of study treatment (DSP-7888 Dosing Emulsion, nivolumab, or pembrolizumab). Patients will be classified according to the treatment received (dose level and schedule), where treatment received is defined as the assigned treatment if the patients took at least 1 dose of that treatment or the first treatment received if the assigned treatment was never received.

12.1.2.3. Dose-Determining Set

The DDS includes all patients from the FAS (Phase 1b, dose-search part only) who met the minimum exposure criterion and had sufficient safety evaluations or experienced a DLT during in the first 2 cycles of treatment.

A patient is considered to have met the minimum exposure criterion if he/she received at least 50% of the planned doses of DSP-7888 Dosing Emulsion (≥3 doses) and nivolumab/pembrolizumab (≥1 dose) during the first 2 cycles.

Patients who do not experience a DLT during the first 2 cycles are considered to have sufficient safety evaluations if they have been observed for 2 cycles after the first dose, and are considered by both the Sponsor and investigators to have enough safety data to conclude that a DLT did not occur.

12.1.2.4. Efficacy Set

The Efficacy Set (ES) includes all patients from the FAS who have responded to treatment (CR/PR), assessed as progressed on treatment without regard to length of treatment, or have been on treatment for 6 months or more without regard to tumor response status.

12.1.3. Handling of Missing Data

No missing data will be imputed, except missing start/end date of concomitant medication. The rule of imputation will be defined in the SAP.

12.1.4. Demographic and Baseline Characteristics

Baseline is defined as the last non-missing measurement taken before receiving the first dose of study drug. All applicable demographic and baseline characteristics will be summarized with descriptive statistics.

12.1.5. Data Analyses

12.1.5.1. Efficacy Analysis

Kaplan-Meier methods will be used to summarize time-to-event endpoints (OS, PFS, and DOR). Primary efficacy of ORR will be analyzed using the Bayesian approach defined in the SAP; other efficacy analyses will be performed on the FAS.

Patient responses will be assessed based on RECIST v1.1 and iRECIST. Data listings and summaries may include tumor markers, additional imaging, or other response data. Potential relationships between PD and other response data may be evaluated. In Phase 2, primary efficacy of ORR will be analyzed using the Bayesian approach defined in the SAP; other efficacy analyses will be performed on the FAS.

Progression-free survival ratio (PFSr) will be summarized for both the Phase 1b enrichment cohort and for Phase 2.

12.1.5.2. Safety Analysis

Adverse events will be assessed according to CTCAE v4.0,3 when appropriate, and will be evaluated by grade and System Organ Class (SOC). Adverse event listings and tabulated summaries of categorized AEs will be generated by dose level and patients overall, for each study arm, and study phase. Additionally, the number of patients enrolled, number evaluable for dose search, and number with DLTs will be described for each dose level, by patients overall, and for each study arm in Phase 1b, the dose-search part of the study. Vital signs, laboratory data, and ECG data stratified by dose level and overall for each study arm and phase will be summarized for changes over time at each post-baseline visit, together with the change from baseline.

12.1.5.3. Pharmacodynamics, Biomarkers, and Exploratory Analysis

Additional antitumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics. Analyses will be performed both for all patients enrolled and for patients evaluable for response in the FAS. Data listings and summaries may include tumor markers, additional imaging, or other response data. Potential relationships between drug administration, PD, and other response data may be evaluated. Kaplan-Meier estimates of OS and PFS will be generated.

All exploratory analyses intended to be discussed in the Clinical Study Report (CSR) will be defined in the SAP. The biomarker data will be listed and summarized by treatment and tumor type, where possible. Correlation with the efficacy data may be explored by statistical methods and graphic presentation. The details of the analysis will be described in the SAP. Additional analyses may be performed on a program or company level. These will be planned and reported separately from this study.

12.1.5.4. Interim Analysis

No formal interim analysis is planned. However, safety will be reviewed on an ongoing basis for the dose-search part (Phase 1b).

In Phase 2, the interim monitoring analysis will be conducted using Bayesian method and start after the first 20 patients have response evaluation or withdraw or die by Week 24 for futility and early efficacy assessment.

- If the posterior probability of ORR ≥ 21% in overall population is≤ 2.5% AND the posterior probability of ORR ≥ 15% in CPS < 10 subpopulation is ≤ 2.5%, the study is futile and further enrollment will be stopped.
- If the posterior probability of ORR ≥ 21% in overall population is ≥ 80% AND the posterior probability of ORR ≥ 15% in CPS < 10 subpopulation is ≥ 70%, then early succeed met and further enrollment may be stopped.
- Otherwise, the enrollment will continue as is until 40 patients.

The above decision rules for interim analysis are non-binding.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Data for each patient will be recorded on a CRF. Data collection must be completed for each patient who signs an ICF and is administered study drug. Screen failures will not have completed CRFs, but the site is to maintain all signed ICF and medical records, as well as documentation of the reason for screen failure.

In accordance with current Good Clinical Practice (cGCP) and International Council on Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

During the COVID-19 public health emergency, traditional on-site monitoring might be difficult for reasons such as: (1) sites may not be able to accommodate monitoring visits (eg, due to staffing limitations or site closures) or (2) monitors may not be able to travel to trial sites. When planned on-site monitoring visits are not possible, the reason should be documented and available for review by [redacted] and during FDA inspections. On-site monitoring visits may be replaced with remote monitoring visits during the COVID-19 public health emergency (Food and Drug Administration, January 2021).

13.2. Audits and Inspections

Study centers and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

13.3. Institutional Review Board/Independent Ethics Committee

The investigator must obtain IRB or IEC approval for the study. Initial IRB/IEC approval of the protocol and all materials approved by the IRB/IEC for this study, including the patient ICF and any recruitment materials must be maintained by the study site/investigator and made available for inspection by the study monitor or any regulatory authorities with an interest in this study.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, [redacted] may conduct a quality assurance audit. Refer to Section 13.2 for more details regarding the audit process

15. ETHICS

15.1. Ethics Review

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to [redacted] before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. [redacted] will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Good Clinical Practice, applicable regulatory requirements and the [redacted] policy on Bioethics.

15.3. Informed Consent

The Principal Investigator(s) at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures. If an informed consent cannot be obtained and documented from a prospective trial participant (or legally authorized representative) as signed paper copy, the consent form may be provided electronically by the Investigator/designee.

Where a prospective trial participant (or legally authorized representative) is unable to print the informed consent document provided electronically by the Investigator/designee, an electronic signature process is not available, and the prospective trial participant must meet time-sensitive eligibility criteria, the investigator may consider using the alternative process to satisfy FDA requirements for obtaining and documenting informed consent and IRB approved process Food and Drug Administration, January 2021).

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

16. DATA HANDLING AND RECORDKEEPING

16.1. Data Protection

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the patients' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff, with adequate precautions to ensure confidentiality of those data; and in accordance with the Health Insurance Portability and Accountability Act, as well as national and/or local laws and regulations applicable to personal data protection.

If applicable, the Sponsor will provide CT/MRI scans for potential central independent radiology assessment.

16.2. Source Documents

The Sponsor or [redacted]) will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of the Sponsor or [redacted]).

Study centers will enter data directly into an electronic data capture (EDC) system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified, and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be compliant with CFR 21 Part 11.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and the World Health Organization (WHO) Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

16.3. Inspection of Records

[redacted] will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. If on-site monitoring visits are not possible [redacted] will be allowed to do remote monitoring to maintain oversight of the clinical site.

16.4. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for [redacted] or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17. PUBLICATION POLICY

The publication policy for the study will be described in the clinical study agreement. To avoid disclosures that could jeopardize proprietary rights, the investigator agrees to give [redacted] the right to review all manuscripts, abstracts, and presentations related to this study prior to their submission for publication or presentation. [redacted] may use these data now and in the future for presentation or publication at [redacted] discretion or for submission to government regulatory agencies.

Authorship among Investigators generally will be based on the extent of significant contribution, including scientific and clinical, to the publication.

18. LIST OF REFERENCES

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19. APPENDICES

Performance Status Scores

Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1)

Immune Response Evaluation Criteria in Solid Tumors (iRECIST)

CA-125 Gynecologic Cancer Inter Group Criteria

Glucocorticoid Dose Equivalents

Common Terminology Criteria for Adverse Events (CTCAE) 4.03

Study Design Flow

Investigator Signature Page

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCORES

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

APPENDIX 2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), will be used by local site Investigators to assess tumor response and progression and make treatment decisions.

https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

Treatment decision

If a patients experiences objective disease progression according to RECIST (v 1.1) and is clinically stable, patients will continue on treatment with study drug until patients experiences immune confirmed PD (iCPD) per iRECIST.

Clinical Stability is defined as:
-No worsening of performance status
-No clinically relevant increase in disease-related symptoms
-No requirement for intensified management of disease-related symptoms (such as analgesics, radiation, or palliative care)

Patients who remain on study treatment following objective disease progression per RECIST (v.1.1) will continue to be evaluated for objective response to study treatment according to the SOA and evaluated according to iRECIST

Summary:

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances; and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

RECIST Response for Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	> 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	> 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once > 6 weeks from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
*See RECIST v1.1 publication for further details on what is evidence of a new lesion.
**Only for non-randomized trials with response as primary endpoint.
***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

RECIST Response for Patients with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease
*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

APPENDIX 3. IMMUNE-RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (IRECIST)

iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately. iRECIST criteria is applicable only after RECIST1.1 progression occurs.

Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in the table below, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New Lesion

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case report form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Time-Point (TP) Response

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non- iUPD	No	iPR	iPR
iPR	Non-iCR/Non- iUPD	No	iPR	iPR
iSD	Non-iCR/Non- iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥ 5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non- iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥ 5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥ 5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non- iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined in the table below (iRECIST Best Overall Response (iBOR) Time-Point).

iRECIST Best Overall Response (iBOR) Time-Point

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Table assumes a randomized study where confirmation of CR or PR is not required. This study requires confirmation of CR or PR same duration with RECIST criteria.

NE = not evaluable that cycle.

Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.

For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline) are met, taking as reference the smallest sum on study (including baseline).

APPENDIX 4. CA-125 GYNECOLOGIC CANCER INTER GROUP CRITERIA*

Definition of CA-125 response

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from latest baseline sample from C1D1. In addition, those patients who have a CA-125 response and whose CA-125 level falls to within the normal range can be classified as CA-125 complete responders. Patients can be evaluated according to CA-125 only if they have a baseline sample that is at least twice the upper limit of normal range within 28 days of C1D1. Patients who have an initial CA-125 which was less than twice the upper limit of the normal range will be evaluated for CA-125 progression only.

Definition of CA-125 progression

CA-125 progression is defined as the progressive serial elevation of serum CA-125, according to the following modified GCIG criteria:

- Patients with elevated CA-125 pre-treatment, must show evidence of CA-125 greater than, or equal to, two times the nadir value in the 28-day period before C1D1on two occasions at least one week apart,
- Patients with CA-125 in the normal range pre-treatment must show evidence of CA-125 greater than, or equal to,

Time to progression is determined by the first date of assessment which showed two times the ULN or nadir on two occasions at least one week apart.

Summary Table of CA-125 Assessment*

Response:	Definition:	Applies to:
CA-125 complete response	At least a 50% reduction in CA-125 levels from baseline and whose CA-125 level falls to within the normal range	Those patients who have a baseline sample that is at least twice the upper limit of normal range within 28 days of C1D1
CA-125 partial response	At least a 50% reduction in CA-125 levels from baseline, but not within normal range	
Non-PR/non-PD	Neither at least a 50% reduction in CA-125 levels from baseline nor progression	
Not PD	Not meet the criteria of progression (not evaluable population for CA-125 response)	Patients who have an initial CA-125 which was less than twice the upper limit of the normal range
Progression	2-fold increase from the baseline CA-125 (if above the ULN at	All patients

	baseline) or 2-fold greater than the ULN (if below the ULN at baseline)	

* Modified from original GCIG criteria for exploratory endpoint of this study

APPENDIX 5. GLUCOCORTICOID DOSE EQUIVALENTS

Equivalent Dose	Steroid
1.2 mg	Betamethasone (long acting)
1.5 mg	Dexamethasone (long acting)
8 mg	Methylprednisolone (intermediate-acting)
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)

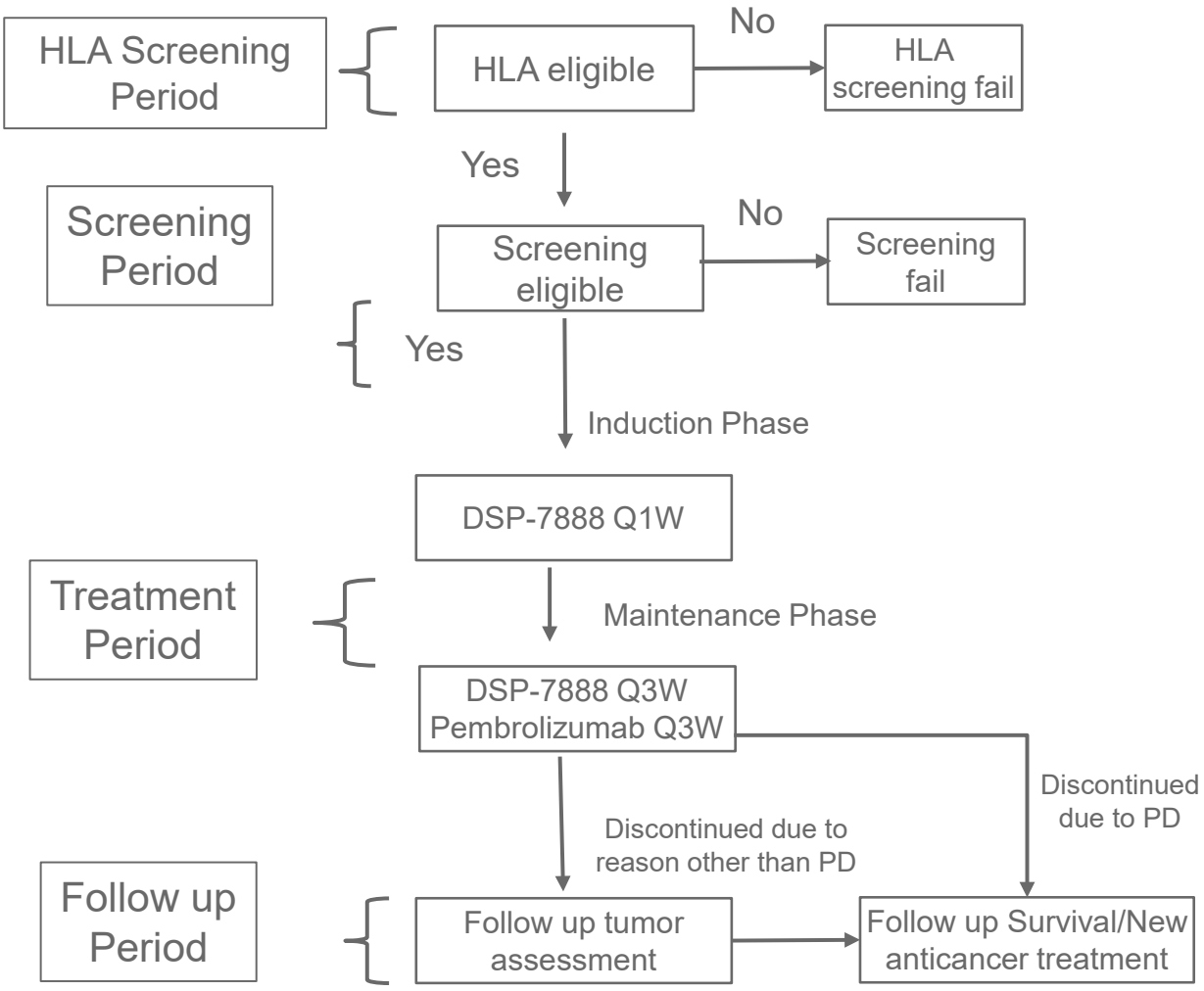
Source: http://emedicine.medscape.com/article/2172042-overview

APPENDIX 6. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The link below is for the Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE, v4.03):

https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

APPENDIX 7. PHASE 2 STUDY DESIGN FLOW



APPENDIX 8. LEGACY PHASE 1 TREATMENT SCHEDULE

Table 12: Legacy Phase 1* DSP-7888 Dosing Emulsion, Nivolumab, and Pembrolizumab Treatment Dose and Schedule

DSP-7888 Dosing Emulsion					Treatment Schedule DSP-7888 Dosing Emulsion, Nivolumab, Pembrolizumab	
Dose Level	**Dose Intensity**	**Number of Injection* Sites**	**Amount Per Injection* Site (mL)**	**Total Amount to Administer Per Dosing Day (mL)**	**Nivolumab Arm** (Arm 1)	**Pembrolizumab Arm** (Arm 2) of Phase 1b and Phase 2
DSP-7888 Dosing Emulsion Dose Level I	10.5 mg	6	0.1	0.6	**DSP-7888 Dosing Emulsion** induction phase: weekly for 4 weeks then maintenance phase: every 2 weeks **nivolumab 240 mg** administered IV over 30 (±5) minutes every 14 days (2 weeks)	**DSP-7888 Dosing Emulsion** induction phase: weekly for 6 weeks then maintenance phase: every 3 weeks **pembrolizumab 200 mg/8mL** administered IV over 30 (±5) minutes every 21 days (3 weeks)
DSP-7888 Dosing Emulsion Dose Level II	3.5 mg	2	0.1	0.2		
DSP-7888 Dosing Emulsion Dose Level III (only used for dose reduction)	1.75 mg	1	0.1	0.1		

Abbreviations: IV – intravenous(ly)
*Legacy schedule refers to that which was followed prior to Amendment 5.

Figure 5: Schematic of Legacy Study Conduct