STATISTICAL ANALYSIS PLAN

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Based on Protocol Version:

Amendment 1, 21SEP2017
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Amendment 4, 01OCT2020
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Amendment 6, 22JUL2021

STUDY DRUG: Nelatimotide and Adegramotide (Ombipepimut-S) (hereafter referred to as DSP-7888) Dosing Emulsion

STUDY NUMBER: BBI-DSP-7888-102CI

STUDY TITLE:

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

Sponsor:

[redacted]

USA

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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AMENDMENTS FROM PREVIOUS VERSION(S)

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	24-Jun-2019	[redacted]	Initial Version
2.0	10-Aug-2021	[redacted]	1. Update the SMPO SAP template. 2. Incorporate updates from protocol amendment 6 ; 3. Update detailed definitions for Best Overall Responses, Progression Free Survival. 4. Update summary of Safety parameters. 5. Update biomarker analysis details.
3.0		[redacted]	As the study was terminated for phase 2 portion based on interim monitoring, the analysis strategy for final CSR has been changed to focus on the safety analysis. All the efficacy analysis and PD/Biomarker analysis is removed from final CSR.

LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
ADI	Actual Dose Intensity
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOR	Best Overall Response
CD8+	Cells containing Cellular Receptor, Cluster of Differentiation 8
CR	Complete Response
CS	Clinically Significant
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
DCR	Disease Control Rate
DDS	The Dose-Determining Set
DLT	Dose-limiting Toxicity
DOR	Duration of Response
DSP	Sumitomo Dainippon Pharma
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	Helper Peptide
DSP-7888-K	Cytotoxic T lymphocyte-inducing (Killer) Peptide
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (performance status)
eCRF	electronic Case Report Form
EOT	End of Treatment
ES	Efficacy Set
FT4	Free Thyroxine 4
GBM	Glioblastoma Multiforme
GCIG	Gynecological Cancer Intergroup
HCC	Hepatocellular carcinoma
HEENT	Head, Eyes, Ears, Nose, Throat
HLA	Human Leukocyte Antigen
HNSCC	Head and Neck Squamous Cell Carcinoma(s)
HPV	Human Papilloma Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	Immunohistochemistry
INN	International Nonproprietary Name
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors

Abbreviation or specialist term	Explanation
ISR	Injection Site Reaction
ITT	Intent to Treat
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MSI	Microsatellite Instability
MSI-H/dMMR	Microsatellite instability-high or mismatch repair deficient
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NCS	Not Clinically Significant
NSCLC	Non-Small Cell Lung Cancer
ODI	Overall Dose Intensity
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease/Disease Progression
PD-L1	Programmed Death Ligand 1
PD-1	Programmed Cell Death Protein 1
PET	Positron Emission Tomography
PFS	Progression-free Survival
PFSr	Progression-free Survival Ratio
PR	Partial Response
PROC	Platinum-resistant Ovarian Cancer
PT	Preferred Term
QTc	corrected QT
RCC	Renal Cell Carcinoma
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
[redacted]	[redacted]
SI	Standard International
SOC	System Organ Class
SS	Safety Set
Std Dev	Standard Deviation
TAA	Tumor-associated antigens
TEAE	Treatment-Emergent Adverse Event
TIL	Tumor Infiltrating Lymphocytes
TLF	Tables, Listings, and Figures
TSH	Thyroid-stimulating Hormone
ULN	Upper Limit of Normal

Abbreviation or specialist term	Explanation
WHO	World Health Organization
WT1	Wilms' Tumor 1

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Sumitomo Pharma Oncology Protocol DSP7888-102CI. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP has been developed using BBI-DSP7888-102CI_aCRF_21Jul2020 FINAL.pdf.

1.1. 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 previously administered 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, platinum-resistant ovarian cancer (PROC) patients will be enrolled in the Phase 2 part of the study and treated 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 activity in the subgroups of interest. However, the total sample size of Phase 2 part cannot exceed 60 patients.

1.2. Objectives and Endpoints

1.2.1. Phase 1b

A summary of objectives and endpoints of Phase 1b of the study is presented in Table 1 below.

Table 1: Objectives and Endpoints for 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	1. ORR, defined as proportion of patients who have achieved confirmed complete response (CR) or partial response (PR), evaluated using Response Evaluation

	Objectives	Endpoints
	in terms of ORR, disease control rate (DCR), duration of response (DOR), 6-month progression-free survival (PFS) Rate, overall survival (OS)	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 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
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

	Objectives	Endpoints
		6. Mutation status and tumor mutation burden (TMB) in tumor tissues
	To determine the PFS ratio as an evaluation of treatment benefit of DSP-7888 Dosing Emulsion administered with nivolumab or pembrolizumab	PFS ratio is defined as PFS/PFS (-1) ratio using RECIST (v.1.1) 1. PFS 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 Protocol Table 7 and Table 8.

1.2.1.1. Primary Endpoints:

Primary Endpoints include: Incidence of DLTs, except for those patients treated in the enrichment cohort, incidence and severity of AEs, serious AEs (SAEs), dose interruption, dose reduction, and dose intensity (Section 5.2.9).

1.2.1.1.1. 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).

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.

1.2.1.2. Secondary Endpoints:

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 disease progression.

1.2.1.2.1. Best Overall Reponses, Objective Response Rate and Disease Control Rate, and Duration of Response per RECIST (v1.1)

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 disease progression.

Best Overall Response (BOR) per RECIST (v1.1) is the best response recorded from first dose until disease progression or start of new anti-cancer therapy. Tumor scan assessment done after PD or after "new anti-cancer" treatment will not be considered in the evaluation of BOR. BOR is derived from the sequence of objective response determined by the following order:

- CR: One objective status of CR documented and confirmed (at least 4 weeks after) before progression or start of new anti-cancer therapy
- PR: One objective status of PR documented and confirmed (at least 4 weeks after) before progression or start of new anti-cancer therapy, but not qualifying as CR
- SD: At least 1 objective status of SD or better documented at least 1 nominal scan interval (6 weeks – 2 days window = 40 days) after first dose date and before progression and the start of new anti-cancer therapy, but not qualifying as CR or PR
- PD: Progression documented within 2 nominal scan intervals (or 12 weeks + 2 days window = 86) after first dose date and not qualifying as CR, PR, or SD
- NE: All other cases will be categorized as NE.

Objective Response Rate (ORR) per RECIST (v.1.1) is defined as the proportion of patients who have achieved confirmed complete response (CR) or partial response (PR), evaluated using RECIST (v.1.1) by investigator assessment.

The patients will be considered as non-responders until proven otherwise. Thus, the patients who:
- Do not have CR or PR while on study; or
- Do not have a baseline or post-baseline tumor evaluation; or
- Do not have an adequate baseline tumor evaluation; or
- Receive new anti-cancer treatment other than the study medication prior to reaching a CR or PR; or
- Die, progress, or drop out for any reason prior to reaching a CR or PR

are considered non-responders.

Disease Control Rate (DCR) per RECIST (v.1.1) is defined as the percentage of patients with BOR of a documented complete response, partial response, and stable disease (CR + PR + SD), based on RECIST 1.1, by investigator assessment.

Duration of Response (DOR) per RECIST (v.1.1) is 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.

1.2.1.2.2. Best Overall Reponses, Objective Response Rate, Disease Control Rate and Duration of Response per iRECIST

Best Overall Response per iRECIST (iBOR) is the best response recorded from first dose until confirmed progression of disease (iCPD) or start of new anti-cancer therapy. In accordance with iRECIST, patients with stable disease (iSD) or better after an initial unconfirmed progression of disease (iUPD) are evaluated after iUPD for iCR (complete response)/iPR (partial response)/iSD(stable disease) in the determination of iBOR. Tumor scan assessment done after iCPD or after "new anti-cancer"

treatment will not be considered in the evaluation of iBOR. iBOR is derived from the sequence of objective response determined by the following order:

- iCR: One objective status of iCR documented before iCPD or start of new anti-cancer therapy
- iPR: One objective status of PR documented before iCPD or start of new anti-cancer therapy, but not qualifying as iCR
- iSD: At least 1 objective status of iSD or better documented within at least 1 nominal scan interval (6 weeks – 2 days window = 40 days) after first dose date or from previous adequate tumor assessment and before iCPD and the start of new anti-cancer therapy, but not qualifying as iCR or iPR
- iUPD (unconfirmed progression of disease): iUPD documented after first dose date and not qualifying as iCR, iPR, or iSD
- iCPD (confirmed progression of disease): iCPD documented and not qualifying as iCR, iPR, or iSD or iUPD
- NE: All other cases will be categorized as NE.

Objective Response Rate per iRECIST (immune **ORR, iORR**) is defined as the proportion of patients who have achieved confirmed immune complete response (iCR) or immune partial response (iPR), evaluated using iRECIST by investigator assessment.

The patients will be considered as non-responders until proven otherwise. Thus, the patients who:

- Do not have iCR or iPR while on study; or
- Do not have a baseline or post-baseline tumor evaluation; or
- Do not have an adequate baseline tumor evaluation; or
- Receive new anti-cancer treatment other than the study medication prior to reaching a iCR or iPR; or
- Die, progress, or drop out for any reason prior to reaching a iCR or iPR

are considered non-responders.

Disease Control Rate per iRECIST (immune DCR, iDCR) is defined as the percentage of patients with iBOR of a documented complete response, partial response, and stable disease (iCR + iPR + iSD), based on iRECIST, by investigator assessment.

Duration of Response per iRECIST (immune DOR, iDOR) is defined as the time from the first documentation of a response (iCR or iPR) until time of first documentation of disease progression by iRECIST or death by any cause. Patients with iUPD at their last assessment were assigned a date of progression at the earliest timepoint iUPD was consecutively determined for that patient (ie, sequential iUPD determinations without an intervening iSD, iPR, or iCR determination).

1.2.1.2.3. Progression Free Survival and 6 month PFS rate per RECIST (v1.1)

Progression-Free Survival (PFS) per RECIST (v1.1) is defined as the time from the date of the first dose of study treatment to the first objective documentation of disease progression by RECIST (v.1.1) or death by any cause, whichever comes first. If a patient has not progressed or died at the time of analysis (up to the date of data cutoff), PFS will be censored on the date of the last tumor assessment (up to the date of data cutoff).

PFS in months is calculated as (first event date/censored date – date of first dose +1)/30.4375.

Table 2 summarizes the censoring rules for the PFS analysis.

Table 2: PFS Definition: Events and Censoring Reasons and Hierarchy

Hierarchy Censoring	Situation	Date of Event or Censor	Event / Censor
1	**No baseline** radiological tumor assessment available	Date of first dose	Censor
5	**No post baseline** radiological tumor assessment available and no death reported within 2 scan intervals following the first dose date.	Date of first dose	Censor
	No post baseline radiological tumor assessment available but death reported within 2 scan intervals following the first dose date	Date of death	Event
6	**No tumor progression** (per RECIST 1.1) and no death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of last adequate radiological tumor assessment	Censor
	No tumor progression (per RECIST 1.1) but death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of death	Event
	Tumor progression (per RECIST 1.1) documented within 2 scan intervals following previous adequate radiological tumor assessment	Earliest of the target, non-target and new tumor assessment dates	Event
3	**Tumor progression** (per RECIST 1.1) documented after 2 scan intervals following previous adequate radiological tumor assessment	Date of previous adequate radiological assessment	Censor
2	**New anticancer treatment** started and no tumor progression	Date of previous adequate radiological assessment immediately prior to start of new therapy	Censor
4	**No tumor progression** (per RECIST 1.1) and patient lost to follow-up or withdrawal of consent	Date of last adequate radiological Assessment	Censor

Notes: (1) Symptomatic deteriorations (i.e. symptomatic progressions, which are not radiographically confirmed) will not be considered as progressions.
(2) If target, non-target, and new lesion assessments have different dates within a visit, then the earliest of those dates will be considered as the date of the tumor assessment if the assessment for that visit is progressive disease (PD); otherwise the latest date will be used.
(3) Adequate radiographical tumor assessment refers to an assessment with overall response of CR, PR, SD, non-CR/non-PD, or PD.

Two scan intervals are 88 days (12 weeks+ 4 days) if previous assessment is within 124 days (18 weeks – 2 days) from the first dose date; or 130 days (18 weeks + 4 days) if previous assessment is after 124 days but prior to 146 (24 weeks – 2 day) days from the first dose date, or 172 days (24 weeks + 4 days) if previous assessment is after 146 days from the first dose date.

The 6-month PFS Rate per RECIST (v1.1) is defined as the proportion of patients who neither progressed by RECIST (v.1.1) nor died before 6 months from the first study treatment.

1.2.1.2.4. Progression Free Survival and 6 month PFS rate per iRECIST

Immune Progression-Free Survival (iPFS) is defined as the time from the date of the first dose of study treatment to the first objective documentation of disease progression by iRECIST or death by any cause, whichever comes first. If a patient has not progressed or died at the time of analysis (up to the date of data cutoff), iPFS will be censored on the date of the last tumor assessment (up to the date of data cutoff).

The event date to be used for calculation of iPFS 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. Patients with iUPD at their last assessment were assigned a date of progression at the earliest timepoint iUPD was consecutively determined for that patient (ie, sequential iUPD determinations without an intervening iSD, iPR, or iCR determination).

iPFS in months is calculated as (first event date/censored date – date of first dose +1)/30.4375.

As 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, the censoring rules for iPFS is defined different from PFS.

Table 3 summarizes the censoring rules for the iPFS analysis.

Table 3: iPFS Definition: Events and Censoring Reasons and Hierarchy

Hierarchy Censoring	Situation	Date of Event or Censor	Event / Censor
1	**No baseline** radiological tumor assessment available	Date of first dose	Censor
5	**No post baseline** radiological tumor assessment available and no death reported within 2 scan intervals following the first dose date	Date of first dose	Censor
	No post baseline radiological tumor assessment available but death reported within 2 scan intervals following the first dose date	Date of death	Event
6	**No tumor progression (**iUPD/iCPD) per iRECIST and no death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of last adequate radiological tumor assessment	Censor
	No tumor progression (iUPD/iCPD) per iRECIST but death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of death	Event
	Tumor progression (iCPD per iRECIST) documented.	Date of iCPD	Event
	Tumor progression (iUPD at their last assessment but sequential iUPD determinations without an intervening iSD, iPR, or iCR determination)	Date of the earliest iUPD date.	Event

Hierarchy Censoring	Situation	Date of Event or Censor	Event / Censor
3	**Tumor progression** (iUPD per iRECIST) but didn't confirmed later or intervening of iSD, iPR or iCR	Date of last adequate radiological assessment.	Censor
2	**New anticancer treatment** started and no tumor progression (iCPD or iUPD)	Date of previous adequate radiological assessment immediately prior to start of new therapy	Censor
4	**No tumor progression** (iUPD/iCPD) and patient lost to follow-up or withdrawal of consent	Date of last adequate radiological Assessment	Censor

Notes:

(1) If target, non-target, and new lesion assessments have different dates within a visit, then the earliest of those dates will be considered as the date of the tumor assessment if the assessment for that visit is progressive disease (iUPD or iCPD); otherwise the latest date will be used.

(2) Adequate radiographical tumor assessment refers to an assessment with overall response of iCR, iPR, iSD, iUPD, iCPD.

Two scan intervals are same as defined for PFS derivation.

The 6-month iPFS Rate per iRECIST is defined as the proportion of patients who neither progressed by iRECIST nor died before 6 months from the first study treatment.

1.2.1.2.5. Overall Survival

Overall Survival (OS) is defined as the time from the date of the first dose of study treatment to the date of death by any cause. Patients who are still alive at the time of the analysis data cutoff date, or who have become lost to follow-up will be censored at their last date known to be alive on or before the date of data cutoff.

OS in months is calculated as (date of death/last known to be alive – date of the first dose +1)/30.4375. Patients lacking any dates which support patients still alive beyond the first dose date will have their OS censored at the date of the first dose.

1.2.1.3. Exploratory Endpoints:

1.2.1.3.1. Pharmacodynamic (PD) and Biomarker Endpoints

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

1.2.1.3.1.1. WT1-specific CTL induction activity in blood samples

WT1 specific CTL induction activity will be measured every 2 cycles pre-dosing until dosing is discontinued (eg, Cycle 7, 9, 11, 13) for phase 1b, and at screening and, during treatment, prior to each dose Cycle 5, 7, 9 and subsequent assessments every 4 Cycle (Cycle 13, 17, 21 etc.) for phase 2 part.

Depending on the HLA types, WT1 -specific CTL Induction will be measured differently.

For patients with HLA-A*02:01 **NOT** HLA-A*02:06, below measurements will be measured and analyzed:

- %WT137-45 Tet+ in CD8+ (P7/P6),
- CD8+WT137-45 Tet+ (P7) Event #,

For patients with HLA-A*02:01/HLA-A*02:06, below measurements will be measured and analyzed:

- %WT137-45 Tet+ in CD8+ (P7/P6),
- %WT1126-134 Tet+ in CD8+ (P8/P6),
- CD8+WT137-45 Tet+ (P7) Event #,
- CD8+WT1126-135 Tet+ (P8) Event #

For patients with HLA-A*24:02, below measurements will be measured and analyzed:

- %WT1235-243 Tet+ in CD8+ (P9/P6),
- CD8+WT1235-243 Tet+ (P9) Event #

For patients with HLA-A*03:01 or HLA-B*15:01, below measurements will be measured and analyzed:

- %WT1126-134 Tet+ in CD8+,
- CD8+WT1126-134 Tet+ Event#

HLA-A*03:01 or HLA-B*15:01 will only be available for phase 2 not in phase 1b.

1.2.1.3.1.2. Other PD and Biomarker Endpoints

- WT1 expression level via chromogenic in situ hybridization (CISH) and PD-L1 expression level via immunohistochemistry (IHC)

WT1 expression level via chromogenic in situ hybridization (CISH) includes % Tumor cells WT1 positive; and WT1 Tumor H-score

- 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

1.2.1.3.2. Progression Free Survival Ratio

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).

PFS ratio is defined as PFS/PFS (-1) ratio using RECIST (v.1.1).

1.2.2. Phase 2

A summary of objectives, endpoints, and assessments of Phase II of the study is presented in Table 7 below.

Table 4: Summary of Objectives and Endpoints for 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

	Objectives	Endpoints
		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 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	PFS rate is defined as PFS1/PFS (-1) ratio using RECIST (v.1.1)

	Objectives	Endpoints
	DSP-7888 Dosing Emulsion administered with pembrolizumab	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 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 Protocol Amendment 6 Table 9.

1.2.2.1. Primary Endpoint:

Primary Endpoint of phase 2 part is ORR per RECIST (v.1.1) based on investigator assessment (refer to Section 1.2.1.2.1 for the definition.)

1.2.2.2. Secondary Endpoints:

Secondary endpoints include DOR, DCR, PFS, 6 – month PFS rate per RECIST (v1.1) (refer to for Section 1.2.1.2.1 Section 1.2.1.2.3 for definitions.) ; iORR, iDCR , iDOR and iPFS per iRECIST based on investigator assessment (refer to Section 1.2.1.2.2 Section 1.2.1.2.4 for definition) ; and OS (refer to Section 1.2.1.2.5 for definition).

Safety assessment of frequency and intensity of AEs assessed according to CTCAE v4.03. also included a secondary endpoint.

1.2.2.3. Exploratory Endpoints:

1.2.2.3.1. Progression Free Survival Ratio

PFS (-1) is defined as the date of initiation of the previous (penultimate) treatment regimen to the date of assessment of progression by RECIST (v1.1). PFS ratio is defined as PFS/PFS (-1) ratio using RECIST (v.1.1).

1.2.2.3.2. CA-125 and Time to progression with CA-125

For Phase 2, the CA-125 Response and time to CA-125 progression will be analyzed as exploratory endpoints using FAS as exploratory endpoints.

CA-125 response rate is defined as proportion of patients who have achieved response using the Gynecologic Cancer InterGroup (GCIG) CA-125 response definition. (see Appendix 1) . 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 (ULN) range within 28 days of C1D1. Patients who have an initial CA-125 that was less than twice the ULN range will be evaluated for CA-125 progression only.

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. (See Appendix 1) CA-125 progression is defined as the progressive serial elevation of serum CA-125, according to the following modified Gynecologic Cancer Inter-Group (GCIG) criteria (Appendix 1)

- Patients with elevated CA-125 pretreatment must show evidence of CA-125 greater than or equal to 2 times the nadir value in the 28-day period before C1D1 on 2 occasions at least 1 week apart,
- Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than, or equal to, the ULN.

Table 9: Summary 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 ULN range in CA-125 partial 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 meeting the criteria of progression (not evaluable population for CA-125 response)	Patients who have an initial CA-125 that was less than twice the ULN range
Progression	2-fold increase from the baseline CA-125 (if above the ULN at baseline) or 2-fold greater than the ULN (if below the ULN at baseline)	All patients

ULN = upper limit of normal
Time to progression is determined by the first date of the assessment that showed 2 times the ULN or nadir on 2 occasions at least 1 week apart, and will be calculated as:
Time to CA-125 Progression (months) = (Date of Progression / censor – Date of first dose + 1) / 30.4375.
Patients last known to be progression-free are censored at the date of the last overall assessment that verified lack of CA-125 progression (either scheduled or unscheduled visit).

1.2.2.3.3. Pharmacodynamic (PD) and Biomarker Endpoints

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

- WT1-specific CTL induction activity in blood samples (refer to Section 1.2.1.3.1.1)
- WT1 expression level 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
- HLA typing: potential include: HLA-A*02:01, HLA-A*02:06, HLA-A*24:02, HLA-A*03:01 and HLA-B*15:01.

2. HYPOTHESES AND DECISION RULES

2.1. Statistical Hypotheses

There is no formal hypothesis for this study including phase 1b and phase 2 part.

2.2. Statistical Decision Rules

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 [Protocol Amend 6, Section 4.3.1; Matulonis, 2019] 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 [Protocol Amend 6, Section 4.3.1; Matulonis, 2019] fand 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.

2.3. Sample Size Considerations and Power Calculation

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 20 to 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.

3. ANALYSIS POPULATIONS

3.1. 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).

3.2. 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 actual treatment if the patients took at least 1 dose of that treatment or the first treatment received if the assigned treatment was never received.

Safety analysis set will be used for all safety related analyses such as AE, concomitant medication, laboratory tests, and vital signs and drug exposure evaluation.

3.3. Treatment Allocation

Phase 1b (a dose search part and an enrichment part) of this study, there will be 2 arms: Arm 1 and Arm 2:

- Arm 1: DSP-7888 Dosing Emulsion + nivolumab combination:
- Arm 2: DSP-7888 + pembrolizumab combination:

Phase 1b patients who get at least one dose of DSP-7888 and nivolumab will belong to Arm 1; and who at least one dose of DSP-7888 and pembrolizumab will belong to Arm 2.

Phase 2 part of the study, patients will be treated with DSP-7888 Dosing Emulsion in combination with pembrolizumab.

4. DATA HANDLING CONVENTIONS

4.1. Data Presentation Conventions

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

4.2. Baseline Definition

Baseline is defined as the most recent, non-missing value prior to or on the first study drug dose date within 28 days from first dose.

4.3. Derived and Transformed Data

4.3.1. Baseline Age

The reference date for age is the date of Screening informed consent. Age is calculated as the (reference date – date of birth +1)/365.25 round down to the nearest integer.

4.3.2. Study Day

Study day 1 is defined as the treatment start date. Study day is calculated as:

- Date of interest – treatment start date + 1, if the assessment was performed on or after the treatment start date;
- Date of interest – treatment start date, if the assessment was performed prior to the treatment start date.

There is no safety study Day 0.

4.3.3. Duration:

- Duration in days: (End Date – Start Date + 1)
- Duration in weeks: (End Date – Start Date + 1) / 7
- Duration in months: (End Date – Start Date + 1) / 30.4375; Average days in months = average number of days in a year /12
- Duration in years: (End Date – Start Date + 1) / 365.25; Average days in a year = 365.25, reflecting the Julian Year of 3 years with 365 days each and 1 leap year of 366 days.

4.3.4. Change from Baseline

Change from baseline is calculated as (visit value – baseline value).

Percent change from baseline is calculated as (change from baseline/baseline value) x 100 when baseline value is not 0.

Post / pre ratio is calculated as Visit value / baseline value when baseline value is not 0.

If either the baseline value or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

Schedule and unscheduled visits post baseline: unless otherwise specified, for the summary by visit post baseline, only scheduled visits will be included; for summary of the maximum or maximum changes post baseline, all scheduled visits and unscheduled visits will be included. All records (scheduled/unscheduled) regardless post baseline reporting period or not will be listed in the data listings.

4.4. Handling of Missing Data

For the patient data listings, no imputation of incomplete dates will be applied. The listings will present the incomplete dates without any change.

4.4.1. Missing or Partial Death Dates

When the death is missing or is partial, it will be imputed based on the last contact date.

- If the entire date is missing, the death date will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, the death date will be imputed to the maximum date among the following dates:

  1 day after the date of last contact;

  1st day of the month and year of death, if day of death is missing OR

  January 1st of the year of death, if both the day and month of death are missing.

4.4.2. Missing or Partial Dates in Adverse Events

Every effort will be made to avoid missing/partial adverse event dates in on-study data.

Adverse events with start date that is completely or partially missing will be imputed as follows:

- If the start date has month and year but day is missing, the first day of the month will be imputed;
  - If this date is earlier than the first dose date, then the first dose date will be used instead;
  - If this date is later than the stop date (possibly imputed), then the stop date will be used instead.
- If the start date has year, but day and month are missing, the 15th of June will be imputed:
  - If this date is earlier than the first dose date, then the first dose date will be used instead;
  - If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date of an event is completely missing, then it is imputed with the first dose date.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If the stop date has month and year but day is missing, the last day of the month will be imputed;
- If the stop date has year, but day and month are missing, the 31th of December will be imputed.

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

4.4.3. Missing or Partial Dates in Concomitant Medications

Every effort will be made to avoid missing/partial concomitant medication dates in on-study data. Concomitant medication with start dates that are completely or partially missing will be analyzed as follows to be included as Concomitant Medications summary tables :

- If the start date has month and year but day is missing, the medication will be included in the summary table if the month and year of the start date of the event are:
  - On or after the month and year of the date of the first dose of study drug and
  - On or before the month and year of the date of the last dose of study drug plus 30 days.
- If the start date has year, but day and month are missing, the therapy will be included in the summary table if the year of the start date of the event is:
  - On or after the year of the date of the first dose of study drug and
  - On or before the year of the date of the last dose of study drug plus 30 days.

If the start date of an event is completely missing, then the therapy will be included in the summary table.

4.4.4. Missing or Partial New Anti-Cancer Therapy Start Date

Post treatment anti-cancer therapy and radiotherapy start dates may be imputed to determine date of new anti-cancer therapy.

Incomplete dates for start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below;
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy;
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.
- For patients who have not discontinued study drug at the analysis cutoff date, last dose of study drug is set to the analysis cutoff date is the imputations below
- *If the* start date of new anti-cancer therapy *is completely or partially missing, the imputed start date of new anti-cancer therapy is:*

  *= 31DECYYYY, if only Year is available and Year < Year of min [max(*PD date + 1, last dose of study drug + 1), end date of new anti-cancer therapy*]*

  = Last day of the month, if both Year and Month are available and

  *Year = Year of min [max(*PD date + 1, last dose of study drug + 1), end date of new anti-cancer therapy*]*

  *Month < Month of min [max(*PD date + 1 day, last dose of study drug + 1 day), end date of new anti-cancer therapy*]*

  *= min [max(*PD date + 1, last dose of study drug + 1), end date of new anti-cancer therapy*], for all other cases.*

5. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

As the study was terminated for phase 2 portion due to the interim monitoring for efficacy. The final CSR will focus on the safety updates for the study as a synoptic CSR. As a result, the analyses strategy will focus on the safety portion. No analysis for efficacy and PD/biomarker are included for the final CSR.

Whilst every effort has been made to pre-specify all analyses in this statistical analysis plan, if any additional exploratory analyses be found to be necessary, the analyses and the reasons for them will be detailed in the clinical study report (CSR).

5.1. General Statistical Methods

5.1.1. Analysis for Continuous Data

Descriptive statistics, including the mean, standard deviation, median, minimum and maximum values will be provided for continuous endpoints.

5.1.2. Analysis for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables. Change from baseline for Categorical data will be evaluated by shift table if appropriate.

5.2. Standard Analysis

5.2.1. Subjects Disposition

All patients who signed pre-screened and screened informed consent will be summarized. The number and percentage of study patients will be tabulated for different analysis sets (Section 3) and by different phases and treatment information below.

Phase 1b: Arm 1, Arm 2; Overall,

Phase 2: CPS < 10, CPS >= 10, Overall

The number and percentage of patients reaching end of treatment, and end of study, along with the discontinuation reasons will be summarized as treatment assignment in phase 1b and CPS subgroups and overall in phase 2.

Listing for analysis sets and end of treatment and end of study reasons will be provided.

5.2.2. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

- Age, Age group (< 65 years and >= 65 years), sex, race, ethnicity, ECOG status, and smoking history, HLA type, CPS score, and CA-125 (for phase 2 only).
- Weight (kg), height (cm), body mass index (BMI).

Demographic and baseline characteristics will also be listed for each patient.

5.2.3. Disease Characteristics, Cancer History and Prior Cancer treatment

Disease characteristics including, but not limited to, cancer type, cancer history, prior cancer therapy, baseline tumor burden will be summarized:

- Cancer type
- Duration of Last Cancer Therapy in weeks: calculated by (end date - start date + 1) / 7 from last cancer therapy, Status of patient entering study in regarding to the last therapy.
- Number of prior therapy (1,2, >=3).
- Prior Bevacizumab (only for phase 2 part):
- Prior cancer system medication (Yes vs No); the number and percentage of patients with each preferred base, best response from prior cancer system medication will be summarized. If multiple best responses are reported, the best one is reported.
- Prior Radiotherapy: prior radiotherapy (Yes, No), time (months) since Stop Date of Radiation Therapy to the first dose date(Computed as [(first dose date) – (stop date of radiation therapy) + 1]/30.4375), Number of Fractions and Total Dose (Gy) per person, best response from prior cancer radiotherapy will be summarized. If multiple best responses are reported, the best one is reported.
- Prior Cancer Surgery (Yes , No) and by SOC and Preferred Terms of Medical Dictionary for Regulatory Activities (MedDRA 20.0).
- Tumor Burden: Sum of Product of Diameters of Target Lesion (mm2), Site of Target Lesion

5.2.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded to ATC (Anatomical Therapeutic Chemical) classification and Drug Name using WHODrug Dictionary (WHO-DD-B2) version June 2017.

Medications that start and stop prior to the date of first treatment administration (either DSP-7888 or checkpoint inhibitor (CPI) whichever is administrated first) will be classified as ‘prior’ medications. If a medication starts on or after the date of first treatment administration, then the medication will be classified as ‘concomitant’. If a medication starts before the date of first treatment administration and stops on or after the date of first treatment administration, then the medication will be categorized as both a ‘prior’ and ‘concomitant’ medication.

Prior and concomintant medications will be listed for the safety analysis set.

5.2.5. Medical History

Medical history will be coded using MedDRA v20.0. Medical history will be listed.

5.2.6. Extent of Exposure

Dose Schedule for phase 1b part is summarized as below:

Table 5: 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 6: 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.

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 10.

Table 7: 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

The dose schedules for the study have been changed under different protocol amendment. Below is a summary of the different dosing schedule:

Table 8: Planned Dose Intensity

Treatment Group	Dose Level	During Induction Phase	During Maintenance Phase
DSP-7888 Dosing Emulsion + nivolumab	Level I (10.5 mg)	10.5 mg / week	5.25 mg / week
	Level II (3.5 mg)	3.5 mg / week	1.75 mg / week
	Level III (1.75 mg)	1.75 mg / week	0.875 mg / week
DSP-7888 Dosing Emulsion + pembrolizumab	Level I (10.5 mg)	10.5 mg / week	3.5 mg / week
	Level II (3.5 mg)	3.5 mg / week	1.17 mg / week
	Level III (1.75 mg)	1.75 mg / week	0.58 mg / week

In Phase 2, the dose of DSP-7888 Dosing Emulsion will be the recommended dose, as determined in the Phase 1b Arm 2 part (DSP-7888 + pembrolizumab) of the study

Figure 1: Dose Schedule Summary.

	induction				maintenance											
102CI-NIV	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106
DSP7888	x	x	x	x	x		x		x		x		x		x	
NIVO	x		x		x		x		x		x		x		x	

102CI-NIV	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106
DSP7888	x	x	x	x	x		x		x		x		x		x	
NIVO					x		x		x		x		x		x	

102CI-PEM	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106
DSP7888	x	x	x	x	x	x	x			x			x			x
PEM	x			x			x			x			x			x

102CI-PEM	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106
DSP7888	x	x	x	x			x			x			x			x
PEM				x			x			x			x			x

Duration of exposure (i.e., weeks on study drug) will be calculated as the number of weeks from first to last dose date, (last exposure date - first exposure date + 1)/7.

The number of patients with a dose reduction or dose interruption in each dose group or treatment group will also be summarized.

5.2.6.1. Exposure of DSP7888

Dose exposure of DSP7888 will be summarized as below:

- Intended Treatment Duration (weeks) = ((last dose date of DSP7888 + intended timing) OR (last dose of checkpoint inhibitors (CPI) + intended timing) which comes later– (first dose date of DSP7888 or CPI which comes first))/7. Intended timing is 7 days for induction phase, and 14 days for maintenance phase for combination with nivolumab and 21 days for maintenance phase for combination with pembrolizumab.
- Actual Cumulative Dose (mg) = Sum of all administered dose of DSP7888 (mg)
- Actual Dose Intensity (mg/week), ADI = Actual Cumulative Dose (mg) / Intended Treatment Duration (weeks)
- Cumulative Planned Dose = Sum of all protocol-defined planned doses (mg) during the intended treatment duration period
- Planned Dose Intensity (mg/week), PDI = Cumulative planned dose (mg) / Intended Treatment Duration (weeks)
- Relative Dose Intensity (%), RDI = 100 * ADI (mg/week) / PDI (mg/week)

Dose exposure of DSP7888 will also be summarized by phase: Induction Phase and Maintenance Phase.

For the induction phase:

- Intended Treatment Duration (weeks) in the induction phase = (first dose date of DSP7888 in the maintenance phase - first dose date of DSP7888 in the induction phase)/7 or (last dose date of DSP7888 in the induction phase - first dose date of DSP7888 in the induction phase + 7) /7 if patients didn't enter the maintenance phase
- Actual Cumulative Dose (mg) in the induction phase = Sum of all administered doses of DSP7888 (mg) in the induction phase
- Actual Dose Intensity (mg/week), ADI in the induction phase = Actual Cumulative Dose (mg) / Intended Treatment Duration (weeks) in the induction phase
- Relative Dose Intensity (%), RDI in the induction phase = 100* ADI (mg/week) / Planned Dose Intensity (Table 11)

For the maintenance phase:

- Intended Treatment Duration (weeks) in the maintenance phase = (last dose date of DSP7888 in the maintenance phase - first dose date of DSP7888 in the maintenance phase + intended timing) /7. Intended timing is 14 days in combination with nivolumab and 21 days in combination with pembrolizumab.
- Actual Cumulative Dose (mg) in the maintenance phase = Sum of all administered doses of DSP7888 (mg) in the maintenance phase
- Actual Dose Intensity (mg/week), ADI in the maintenance phase = Actual Cumulative Dose (mg) /Intended Treatment Duration (weeks) in the maintenance phase
- Relative Dose Intensity (%), RDI in the maintenance phase = 100* ADI (mg/week) / Planned Dose Intensity (Table 11)

5.2.6.2. Exposure of Nivolumab

Nivolumab is planned to provide as 240 mg administered intravenously (IV) over 30 minutes (±5)* every 14 days (2 weeks/cycle). The exposure of nivolumab is summarized as below:

- Intended Treatment Duration (weeks) = (last dose date of nivolumab – first dose date of nivolumab + 14 days)/7.
- Actual Cumulative Dose (mg) = Sum of all administered dose of nivolumab
- Actual Dose Intensity (mg/week), ADI = Actual Cumulative Dose (mg) / Intended Treatment Duration (weeks)
- Relative Dose Intensity (%), RDI = 100 * ADI (mg/week) / (120 mg / week)

5.2.6.3. Exposure of Pembrolizumab

Pembrolizumab is provided as 200 mg/8 mL administered through IV infusion over 30 (±5) minutes every 21 days. The exposure of pembrolizumab is summarized as below:

- Intended Treatment Duration (weeks) = (last dose date of pembrolizumab – first dose date of pembrolizumab + 21 days)/7.
- Actual Cumulative Dose (mg) = Sum of all administered dose of pembrolizumab

- Actual Dose Intensity (mg/week), ADI = Actual Cumulative Dose (mg) / Intended Treatment Duration (weeks)
- Relative Dose Intensity (%), RDI = 100 * ADI (mg/week) / (200 / 3 (mg / week))

5.3. Statistical Methodology

Phase 1b

Determination of Recommended Dose of DSP-7888 Dosing Emulsion with nivolumab or pembrolizumab (Only Phase 1b)

Determination of a 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 7.4 of protocol). 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 out of 6 patients at the starting dose level experience a DLT, then the dose level is eligible for consideration as the recommended dose of DSP-7888.

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

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 dosing cycles.

Phase 2

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 or 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 until 40 evaluable patients have been accrued.

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

5.4. Safety Analyses

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 until 30 days after last dose date.

5.4.1. Adverse Events

Treatment-Emergent Adverse Events

An AE will be regarded as treatment-emergent, if

- it occurs for the first time on or after the first dose date of either DSP-7888 or CPI up to 30 days after the last dose of study drug; or
- it occurs up to any time if serious and considered related to study drug.

The emphasis for AE analysis will be based on treatment-emergent AE (TEAE), however all AEs will be listed.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 20.0) and summarized by MedDRA System Organ Class and Preferred Term. The severity of all AEs will be graded by the Investigator using NCI CTCAE version 4.0.

An overview of treatment-emergent adverse events (TEAEs) will be provided. The number and percentage of subjects with following will be summarized for phase 1b, Arm 1 and Arm2 overall, phase 2: CPS < 10, CPS > = 10 and Overall.

- Subjects with any TEAE
- Subjects with TEAE of CTCAE grade 3 or higher
- Subjects with serious adverse events (all causality and related)
- TEAEs related to study drug
- TEAEs related to study drug with CTCAE grade 3 or higher
- Subjects with TEAE leading to study drug discontinuation (all causality and related)
- Subjects with TEAE leading to study drug dose reduction(all causality and related)
- Subjects with TEAE leading to study drug dose interruption (all causality and related)

Summary of AEs by SOC and Preferred Term

The number and percentage of subjects with TEAEs by SOC, PT and maximum CTCAE grade will be summarized. A summary of TEAEs of CTCAE grade 3 or higher (Grade 3, 4, 5) will be presented by SOC and PT and maximum CTCAE grade (All Grade, ≥Grade 3).

The number and percentage of patients who experience any TEAE will be summarized by SOC and PT (All Grade, ≥Grade 3). A summary of TEAEs by PT and maximum CTCAE grade will be presented. The most commonly reported TEAEs using a different cutoff (e.g. 2% or 10% or more of patients in either arm) may also be summarized by PT as needed.

TEAEs associated with permanent discontinuation /dose reduction/drug interruption of either DSP7888 and/or CPI will be summarized by SOC and PT and maximum CTCAE Grade (taking into consideration the action taken from CRF AE page).

Treatment Related Adverse Events

Treatment-related TEAEs are those judged by the investigator to be at least possibly related to the study drugs (DSP7888 and/or CPI) or for which relatedness is recorded as "unknown" by the investigator. Treatment related will include "possible", "probable" or "definite" causality assessments. Missing relationship will be considered as "Related" to all drugs received by the patient. Similar summaries as noted for all causality TEAEs will be provided for treatment related TEAEs.

Serious Adverse Events and Death

Treatment-emergent SAEs and Treatment-related SAEs will be summarized by MedDRA SOC and PT and maximum CTCAE grade.

TEAE leading to death will be summarized by MedDRA SOC and Preferred Term.

Deaths will be summarized by on study and on treatment (within 30 days of last dose of study medication). The number and percentage of patients who died on study and on treatment, as well as primary cause of death will be summarized. Deaths may also be categorized according to time of occurrence after first dose.

A listing of death data will also be provided and will include all deaths that occurred from the signing of the informed consent to the end of the follow up period. The listing will include primary cause of death and the number of days relative to the administration of first and last dose.

Adverse Events of COVID-19

Preferred Terms corona virus infection and coronavirus test positive will be used to identified COVID-19 positive cases in adverse event.

Injection Site Reaction (ISR)

The predominant adverse effect observed with DSP-7888 is injection site reaction. The Preferred Terms of TEAEs within the High Level Group Term of "Administration Site Reaction" (MedDRA version 20.0) will be used to identify events of injection site reaction.

Below analysis will be provided for ISR:

- ISR by SOC, PT, and maximum CTCAE Grade
- Onset time of first ISR for patients with at least one ISR: Time to onset is analyzed for patients with at least one ISR from the first dose of the DSP-7888 to the first occurrence of ISR regardless of CTCAE grade.
- Onset time of first ISR: Time to first ISR is defined as the time from the first dose of the DSP-7888 to the first occurrence of ISR . For patients with no ISR, the onset time will be censored as data cutoff date,

end of study date, death date, or safety follow-up completion date (end of treatment date + 30 days) whichever is shorter.

- Onset time of the first Grade 3 or higher ISR for patients with at least one Grade 3 or higher ISR: Time to onset is analyzed for patients with at least one Grade 3 or higher ISR from the first dose of DSP-7888 to the first occurrence of the Grade 3 or higher ISR.

- Onset time of the first Grade 3 or higher ISR: Time to first Grade 3 or higher ISR is defined as the time from the first dose of DSP-7888 to the first occurrence of the Grade 3 or higher ISR. For patients with no Grade 3 or higher ISR, the onset time will be censored as data cutoff date, end of study date, death date, or safety follow-up completion date (end of treatment date + 30 days) whichever is shorter.

- Duration of ISR and Duration of Grade 3 or higher ISR and may be analyzed in the CSR. The duration is defined as (end date – start date + 1), and for ongoing ISR/ or ongoing Grade 3 or higher ISR, the ISR end date is truncated as the minimum of {by data cutoff date, end of study date, death date, last known to be alive date, or safety follow-up completion date (end of treatment date + 30 days)} whichever is shorter.

A listing of ISR will also be provided.

5.4.2. Clinical Laboratory Evaluations

All samples will be analyzed at a central laboratory and collected per Schedule of Assessments in the protocol. Local laboratories may be used as deemed necessary by the Investigator in order to make treatment related decisions.

The results of laboratory parameters will be graded according to NCI CTCAE v4.03 for below parameters (Table 12). For patients with both baseline and post baseline assessments, a summary of shift from baseline CTCAE grade to maximum postbaseline CTCAE grade will be provided. All records on or after the first dose (scheduled and unscheduled) until 30 days following the last dose of study drug will be considered as post baseline. Additional parameters may be added for the shift tables. Both scheduled and unscheduled laboratory test results will be included in the shift tables.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Table 9: CTCAE Lab Grading Parameters.

	↓	↑
HEMATOLOGY	Anemia	
HEMATOLOGY	White blood cell decreased	
HEMATOLOGY	Lymphocyte count decreased	
HEMATOLOGY	Neutrophil count decreased	
HEMATOLOGY	Platelet count decreased	
CHEMISTRY		Alanine aminotransferase increased

CHEMISTRY	Hypoalbuminemia	
CHEMISTRY		Alkaline phosphatase increased
CHEMISTRY		Aspartate aminotransferase increased
CHEMISTRY		Blood bilirubin increased
CHEMISTRY		Blood Urea Nitrogen Increased
CHEMISTRY	Hypocalcemia	Hypercalcemia
CHEMISTRY		Creatinine increased
CHEMISTRY	Hypoglycemia	Hyperglycemia
CHEMISTRY	Hypomagnesemia	Hypermagnesemia
CHEMISTRY	Hypophosphatemia	
CHEMISTRY	Hypokalemia	Hyperkalemia
CHEMISTRY	Hyponatremia	Hypernatremia

Blood Urea Nitrogen Increased is not in CTCAE grading, SDPO will define as grade 1 is 23 – 26 mg/dL, grade 2 is 27-31 mg/dL, grade 3, >31 mg/dL.

Listings of hematology and biochemistry, urinalysis and coagulation will be provided, including the test result, units, normal range, change from baseline, and CTCAE grade if available.

5.4.3. Electrocardiograms

A 12-lead Electrocardiogram (ECG) with categorical results (normal; abnormal, not clinically significant; abnormal, clinically significant) will be summarized in the shift summary from baseline to worst post baseline. Post baseline includes non-missing records collected (scheduled and unscheduled) after the first dose of study treatment until 30 days following the last dose of study treatment. QT measurements corrected by heart rate will be used for the data analysis and interpretation. QTc interval will be calculated using Fridericia's correction. The formula is:

Fridericia's correction: $\mathrm{QT_cF} = \mathrm{QT} / \mathrm{RR}^{0.33}$

where unit of QT is milliseconds (msec) and unit of RR is second (sec). The number and percentage of patients in QT and QTcF (QT and QTcF interval: ≤ 450 msec, > 450 - ≤ 480 msec, > 480 - ≤ 500 msec, and > 500 msec) will be summarized at baseline and maximum post baseline. Categories of maximum changes from baseline (≤ 30 msec, > 30 - ≤ 60 msec, > 60 msec) will be summarized as well.

An ECG result listing that including PR interval, RR interval, QT, QTc, QRS duration and Heart Rate will also be provided.

5.4.4. Vital Signs

Body temperature will be summarized in °C. If body temperature is recorded as °F, then temperature will be converted to °C using:

Temperature (°C) = 5/9 (Temperature [°F]-32).

Summaries of post baseline markedly abnormal vital signs, including systolic blood pressure, diastolic blood pressure, pulse rate, weight change, and temperature will be presented. Markedly abnormal ranges for vital signs parameters are given in Table 13 . Post baseline includes non-missing records from both scheduled and unscheduled visits after the first dose of study drug until 30 days following the last dose of study treatment.

Table 10: Markedly Abnormal Ranges for Vital Signs

Parameter	Markedly Abnormal (Low)	Markedly Abnormal (High)
Systolic Blood Pressure	• Absolute value ≤ 90 mmHg for post baseline, or • a decrease from baseline ≥20 mmHg for change from baseline	• Absolute value ≥ 180 mmHg for post baseline, or • an increase from baseline ≥20 mmHg for change from baseline
Diastolic Blood Pressure	• Absolute value ≤ 50 mmHg for post baseline, or • a decrease from baseline ≥15 mmHg for change from baseline	• Absolute value ≥ 105 mmHg for post baseline, or • an increase from baseline ≥ 15 mmHg for change from baseline
Pulse	• Absolute value ≤ 50 bpm for post baseline, or • a decrease from baseline ≥ 15 bpm for change from baseline	• Absolute value ≥ 120 bpm for post baseline, or • an increase from baseline ≥ 15bpm for change from baseline
Weight Change	Weight loss from baseline ≥ 20%	Weight gain from baseline ≥ 20%
Temperature	≤ 35°C post baseline only	≥ 40°C post baseline only

A listing of vital signs results will also be presented using the Safety Set.

5.5. Efficacy Analyses

As the study was terminated for phase 2 portion due to the interim monitoring for efficacy. The final CSR will focus on the safety updates for the study as a synoptic CSR. As a result, there will no analysis included for efficacy portion. The timepoint overall response evaluation, BOR, ORR, DCR and DOR based on RECIST 1.1 will be listed.

5.6. Pharmacodynamic and Biomarker Analysis

As the study was terminated for phase 2 portion due to the interim monitoring for efficacy. The final CSR will focus on the safety updates for the study as a synoptic CSR. As a result, there will no analysis included for PD and Biomarker portion.

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APPENDIX 1. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

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	
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