CLINICAL STUDY PROTOCOL
AMENDMENT 7

A First-in-Human Phase 1/2 Trial to Determine the Safety and the Pharmacokinetic Profile of DSP-0509, a Synthetic Toll-Like Receptor 7 (TLR-7) Agonist, Administered as Monotherapy and in Combination with Pembrolizumab in Adult Patients with Advanced Solid Tumors

Protocol Number:	BBI-DSP-0509-101
EudraCT Number:	Not Applicable
Investigational Product:	DSP-0509
Phase:	Phase 1/2
Sponsor:	Sumitomo Dainippon Pharma Oncology, Inc 640 Memorial Drive Cambridge, MA 02139 US
Contract Research Organization:	Syneos Health 3201 Beechleaf Court, Suite 600 Raleigh, NC 27604-1547 US
Original Protocol (Version 1) Date:	06 Dec 2017
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Amendment 4 (Version 6):	30 Apr 2020
Amendment 5 (Version 7):	26 Mar 2021
Amendment 6 (Version 8):	04 May 2021
Amendment 7 (Version 9):	15 September 2021

Signature Page

Sponsor's Approval

The protocol has been approved by Sumitomo Dainippon Pharma Oncology, Inc.

Sponsor's Signatory:

[redacted]

Investigator's Agreement

I have received and read the Investigator's Brochure for DSP-0509. I have read the BBI-DSP-0509-101 protocol 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

1. CONTACT INFORMATION

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted]	640 Memorial Drive Cambridge, MA, 02139 US [redacted]
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Drug Safety Physician	[redacted]	640 Memorial Drive Cambridge, MA, 02139 US [redacted]
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2. SYNOPSIS

Name of Sponsor/Company:
Sumitomo Dainippon Pharma Oncology, Inc

Name of Investigational Product:
DSP-0509

Title of Study:
A First-in-Human Phase 1/2 Trial to Determine the Safety and the Pharmacokinetic Profile of DSP-0509, a Synthetic Toll-Like Receptor 7 (TLR-7) Agonist, Administered as Monotherapy and in Combination with Pembrolizumab in Adult Patients with Advanced Solid Tumors

Study Center(s):
The study will be conducted in approximately 5 to 15 centers in the US.

Phase of Development:
1/2

Indication:
As this is a first-in-human (FIH) study, a final indication has not been determined. However, DSP-0509 will be studied for the following indications:

- Monotherapy Arm A (Dose Escalation, Phase 1)
  - Advanced solid tumors that are metastatic or unresectable, and recurrent and/or refractory to available therapy
- Combination Arm B (Dose Escalation, Phase 1)
  - Advanced solid tumors that are (a) metastatic or unresectable and recurrent and/or refractory to available therapy, (b) a condition for which pembrolizumab is an approved treatment; and (c) in patients who have shown primary or acquired resistance to immune checkpoint inhibitors (ICIs)
- Combination Arm C (Dose Expansion, Phase 2)
  - Advanced Head and Neck Squamous Cell Carcinoma (HNSCC) tumors that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) in patients who have been treated with pembrolizumab or other programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors in monotherapy, and (c) who have subsequently shown primary or acquired resistance to ICIs

Objectives and Criteria for Evaluation (Endpoints):

Primary Objectives	Endpoints
Monotherapy Arm A - Dose Escalation (Phase 1):	
• To determine the safety, tolerability, and maximum tolerated dose (MTD) of DSP-0509 administered intravenously (IV) as a single agent in patients with advanced solid tumors • To identify a recommended Phase 2 dose (RP2D) of DSP-0509 monotherapy for patients with advanced solid tumors.	• Incidence of dose-limiting toxicities (DLTs) within the first 6 weeks of dosing • Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

	• Incidence of dose interruption, dose reduction, and dose intensity • Changes in clinical laboratory values (hematology, clinical chemistry, urinalysis), electrocardiogram (ECG) parameters, multigated acquisition (MUGA) scan/echocardiograms (ECHO) parameters
Combination Arm B - Dose Escalation (Phase 1):	
• To determine the safety, tolerability, and MTD of DSP-0509 administered IV in combination with pembrolizumab for patients with advanced solid tumors who have shown primary or acquired resistance to immune checkpoint inhibitors (ICIs) • To identify an RP2D of DSP-0509 when given in combination with pembrolizumab for such patients	• Incidence of DLTs within the first 6 weeks of dosing • Incidence and severity of TEAEs and SAEs using NCI CTCAE • Incidence of dose interruption, dose reduction, and dose intensity • Changes in clinical laboratory values (hematology, clinical chemistry, urinalysis), ECG parameters, MUGA scan/ECHO parameters
Combination Arm C – Dose Expansion (Phase 2):	
• To evaluate the preliminary antitumor activity of DSP-0509 in combination with pembrolizumab in patients with HNSCC who have shown primary or acquired resistance to ICIs	• Objective response rate (ORR), as assessed by Response Evaluation Criteria in Solid Tumors (RECIST), v1.1 and by Immune RECIST (iRECIST, modified RECIST for immunotherapy studies)

Study Design:

This is a Phase 1 dose-escalation study (with 2 treatment arms) with a Phase 2 dose expansion to evaluate the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of DSP-0509 given alone or in combination with pembrolizumab in patients with advanced solid tumors.

- Monotherapy Arm
  - Arm A: Dose escalation, Phase 1
- Combination Arms
  - Arm B: Dose escalation (patients with advanced solid tumor with primary or acquired resistance to ICIs), Phase 1
  - Arm C: Dose expansion (patients with HNSCC with primary or acquired resistance to ICIs), Phase 2

Monotherapy Arm A: The primary objective of Monotherapy Arm A is to determine the MTD or RP2D of DSP-0509 when administered as a single agent. Dose escalation uses a Bayesian logistic regression model (BLRM) approach. DSP-0509 will be administered on Day 1 and then every 2 weeks thereafter until discontinuation.

Combination Therapy Arm B: The primary objective of Combination Arm B is to determine the RP2D of DSP-0509 when administered in combination with pembrolizumab. Dose escalation is guided by the BLRM approach. Combination Arm B will enroll patients with advanced solid tumors that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) a condition for which pembrolizumab is an approved treatment, and (c) in patients who have shown either primary or

acquired resistance to an ICI. Dose escalation of DSP-0509 in combination with 400 mg pembrolizumab every 6 weeks (q6w) will start at the same dose of DSP-0509 as the highest (not exceeding the MTD) level tested in the combination regimen with 200 mg pembrolizumab every 3 weeks (q3w). Upon completion of the DLT evaluation period for the first DSP-0509 dose level tested in combination with 400 mg pembrolizumab q6w in newly enrolled patients, if this dose level is found not to exceed the MTD, any ongoing patients receiving DSP-0509 in combination with 200 mg pembrolizumab q3w will be allowed, at the investigator's discretion, to transition to the 400 mg pembrolizumab q6w regimen, while maintaining the originally assigned DSP-0509 dose level. **Combination Therapy Arm C:** The primary objective of Combination Arm C is to determine the ORR of DSP-0509 when administered in combination with pembrolizumab. Combination Arm C will enroll patients with HNSCC tumors that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) in patients who have been treated with pembrolizumab or other PD-1 or PD-L1 inhibitors in monotherapy, and (c) who have subsequently shown either primary or acquired resistance to ICIs. DSP-0509 will be administered on Day 1 and q2w thereafter until discontinued. Pembrolizumab will be administered on Day 1 and q6w thereafter until discontinued.
Number of Patients Planned: Dose escalation Monotherapy Arm A: approximately 21 to 30 patients Combination Arm B: approximately 21 to 30 patients Dose expansion Combination Arm C: approximately 20 to 40 patients
Inclusion Criteria: Each patient must meet the following criteria to be enrolled in this study: 1. Must have a histologically or cytologically confirmed advanced solid tumor that meets the following additional specifications for the Arm/Phase in which they are to be treated: • Monotherapy Arm A (Dose escalation, Phase 1) – Advanced solid tumors that are metastatic or unresectable, and recurrent and/or refractory to available therapy • Combination Arm B (Dose escalation, Phase 1) – Advanced solid tumors that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) a condition for which pembrolizumab is an approved treatment, and (c) in patients who have shown primary or acquired resistance to ICIs • Combination Arm C (Dose expansion, Phase 2) – Advanced HNSCC tumors of the oropharynx, oral cavity, hypopharynx, larynx, lip, or sinus that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) in patients who have been treated with pembrolizumab or other PD-1 or PD-L1 inhibitors in monotherapy, and (c) who have subsequently shown primary or acquired resistance to ICIs 2. Must be ≥18 years of age 3. Should have all side effects of any prior therapy or procedures for any medical condition recovered to CTCAE ≤Grade 1 (except alopecia) 4. Must have at least 1 measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.1 5. Must have a life expectancy ≥3 to 6 months

6. Female patients of childbearing age and women <12 months since the onset of menopause, except those who have been surgically sterilized (tubal ligation) or whose sexual partner(s) is surgically sterilized (vasectomy), must agree to use acceptable contraceptive methods for the duration of the study and for 9 months after the date of their last DSP-0509 infusion. If employing contraception, 2 of the following precautions must be used: birth control pill, vaginal diaphragm, intrauterine system or device, condom, or vaginal spermicide. Female patients who are postmenopausal are defined as those with an absence of menses for ≥12 consecutive months. Male patients must be surgically sterilized (vasectomy) or their female sexual partner(s) must be surgically sterilized (tubal ligation) to avoid using contraception. If they do not meet this criterion, male patients must agree to use a condom as well as one of the acceptable contraceptive methods listed above with their female partner(s), who meets the criterion of either being of childbearing age or <12 months since the onset of menopause. Male patients and their female partner(s) must agree to use acceptable contraception methods for the duration of time the male patient is on the study and for 9 months after the date of his last DSP-0509 infusion.
7. Females of childbearing potential must have a negative serum pregnancy test at Screening
8. Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
9. Must have adequate coagulation function at Screening as determined by:
   - Prothrombin international normalized ratio (INR) <1.5
   - Partial thromboplastin time (PTT) <1.5 times the upper limit of normal (ULN)
10. Must have adequate hematologic function at Screening as determined by:
    - White blood cell (WBC) count ≥3,000/microliter
    - Absolute neutrophil count (ANC) ≥1,500/microliter (patient may not use granulocyte-colony stimulating factor [G-CSF] or granulocyte-macrophage-colony stimulating factor [GM-CSF] to achieve these WBC and ANC levels)
    - Platelet count ≥100 × 10^3/microliter
    - Hemoglobin (Hgb) ≥9.0 g/dL (may not transfuse or use erythropoietin to obtain this Hgb level)
11. Must have adequate renal and hepatic function at Screening as determined by:
    - Serum creatinine <2.0 mg/dL or <1.5 times the ULN, whichever is lower
    - Total bilirubin ≤1.5 mg/dL or <1.5 times the ULN, whichever is lower (or ≤2.0 mg/dL for patients with known Gilbert syndrome)
    - Aspartate aminotransferase (AST) ≤2.5 times ULN (≤5 times ULN for patients with liver metastases)
    - Alanine aminotransferase (ALT) ≤2.5 times ULN (≤5 times ULN for patients with liver metastases)
12. Must be able to attend study visits as required by the protocol
13. Prior to the first DSP-0509 infusion, the patient must be able to provide tumor tissue for baseline studies as (a) a block of archival tissue sufficient to provide the required number of slides, (b) a sufficient number of fixed, unstained slides of archival tissue, or (c) consent to undergo tumor biopsy to acquire sufficient tumor tissue. Sites need to refer to the current version of the "NeoGenomics "BBI-DSP-0509-101 Tissue Sample Collection and Shipping Instructions" manual to determine how many slides are required for each patient, as the number varies based on (a) the study Arm/Phase in which the patient is enrolled, and (b) whether the patient consented to optional future testing.

Additional Inclusion Criteria for Combination Arm C Only:

In addition to the above criteria, patients must meet the following criteria to be eligible to enroll in Combination Arm C:

14. Have at least one accessible tumor for biopsy. This accessible lesion must be considered as non-measurable per RECIST criteria, v1.1.
15. Be platinum refractory, PD-1 or PD-L1 exposed, and have no more than 3 lines of prior therapy for advanced/metastatic disease
16. Have a known status of PD-L1 combined positive score (CPS)
17. Have a known human papilloma virus (HPV) status

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Has received prior therapy with a TLR agonist, excluding a topical TLR agonist
2. Has received anticancer chemotherapy (including molecular-targeted drugs), radiotherapy, immunotherapy (eg, vaccines or cytokines), or investigational agents within the 3 weeks before the first dose of DSP-0509. Local palliative radiotherapy is permitted.
3. Receives concurrent systemic (oral or IV) steroid therapy >10 mg prednisone daily or its equivalent
4. Not fully recovered from major surgery before the first dose of DSP-0509
5. Has central nervous system (CNS) metastases (including leptomeningeal or spinal metastases) or CNS primary tumors, eg, glioblastoma
6. Has a history of seizures other than isolated febrile seizure in childhood; has a history of a cerebrovascular accident or transient ischemic attack less than 6 months ago
7. Has effusions (pleural, pericardial, or ascites) requiring drainage
8. Has a neurodegenerative disease, eg, motor neuron disease, Parkinson disease, Alzheimer disease, Huntington disease
9. Has retinal detachment, ulcerative keratitis, uveitis, Vogt-Koyanagi-Harada syndrome, choroidal neovascularization, retinopathy/retinitis, thyroid-associated orbitopathy, idiopathic orbital inflammation, diabetic retinopathy, ischemic retinopathy (including glaucoma-associated retinopathy), retinal vein thrombosis, or a non-healing ocular or ophthalmic disease
10. Has a fever ≥38°C within 3 days before the first dose of study treatment
11. Has interstitial lung disease or active noninfectious pneumonitis
12. Has a history of active autoimmune or immunologic disorder requiring immunosuppression with steroids or other immunosuppressive agents (eg, azathioprine, cyclosporine A), that, after discussion between the investigator and the Medical Monitor is considered not acceptable for the study. If the autoimmune status is questionable, and the patient is not at risk, the investigator may discuss the patient's potential eligibility with the Medical Monitor.
13. Has a known hypersensitivity to a component of the protocol therapy, DSP-0509, or another pyrimidine
14. Has a history of another primary cancer within the 5 years before enrollment, except for the following: non-melanoma skin cancer, cervical carcinoma in situ, superficial bladder cancer, or other nonmetastatic carcinoma that has been in complete remission without treatment for more than 5 years

15. Has abnormal ECGs that are clinically significant, such as QT prolongation (corrected QT interval [QTc] >480 msec)
16. In the opinion of the treating investigator, has any concurrent conditions that could pose an undue medical hazard or interfere with interpretation of study results; these conditions include, but are not limited to, ongoing or active infection, clinically significant nonhealing or healing wounds, concurrent congestive heart failure (New York Heart Association Functional Classification Class II, III or IV), concurrent unstable angina, concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation), recent (within the prior 12 months) myocardial infarction or acute coronary syndrome, significant pulmonary disease (shortness of breath at rest or on mild exertion, eg, due to concurrent severe obstructive pulmonary disease), concurrent hypertension requiring more than 2 medications for adequate control, or diabetes mellitus with more than 2 episodes of ketoacidosis in the prior 12 months
17. Has an ejection fraction of 50% or less based on a MUGA scan or ECHO
18. Has the presence of a known, active, acute or chronic infection, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), as determined by fourth-generation (HIV antibody and antigen) assay, hepatitis B surface antigen (HBsAg), and hepatitis C serology, respectively
19. Has a cognitive, psychological, or psychosocial impediment that would impair the ability of the patient to receive therapy according to the protocol, or adversely affect the ability of the patient to comply with the informed consent process, protocol, or protocol-required visits and procedures
20. Receives concurrent strong inhibitors of cytochrome P450 2C8
21. Receives concurrent inhibitors of organic anion transporting peptide (OATP)1B1 and OATP1B3
22. Is pregnant or breastfeeding
23. Has active neurologic inflammatory or autoimmune disorders (eg, Guillain-Barre syndrome, amyotrophic lateral sclerosis)

The following exclusion applies only to enrollment in Combination Arms B and C:

24. Has a history of immune-related adverse events (irAEs) resulting in permanent discontinuation of prior ICI treatment

Duration of Study and Duration of Treatment

The duration of the study will be approximately 6 years.

Patients in each Arm (Monotherapy Arm A, Combination Arm B, Combination Arm C) will undergo a Screening period of up to 28 days; a treatment period of up to127 days (approximately 4.5 months) or as long as the patient is benefitting from treatment; and a 30-day safety follow-up. Survival follow-up, if applicable, will occur every 6 months, following the 30-day safety follow-up.

Treatment duration for each patient is unknown, as patients may continue therapy as long as they demonstrate clinical benefit.

Safety Assessments:

Adverse events (AEs) will be collected from the time the patient signs informed consent to the End-of-Study (EoS) visit scheduled for 30 days after last dose of study drug. AEs will be assessed according to NCI CTCAE v5.0. Additional safety assessments will include MUGA scans, ECHO, 12-lead ECGs, chest x-rays, vital signs, clinical laboratory tests, and ocular examinations (slit lamp, fundoscopy, visual field testing).

Efficacy Assessments:

The evaluation of efficacy will be based on the patient's disease status, assessed using RECIST and iRECIST. Of note, in immunotherapy studies, if progressive disease (PD) as defined by RECIST is observed, then, per iRECIST, an additional scan for confirmation of PD is required 4 to 8 weeks later.

The following additional efficacy variables will be evaluated:

- ORR: the proportion of patients who achieved complete response (CR)/partial response (PR) per RECIST, or immune complete response (iCR)/immune partial response (iPR) per iRECIST
- Time to Progression (TTP): the time from first day of treatment to the date of PD per RECIST, or immune unconfirmed progressive disease (iUPD) if immune confirmed progressive disease (iCPD) is subsequently confirmed per iRECIST
- Duration of Response (DoR): the time from first documentation of a response until the date of the first documented PD per RECIST, or iUPD if iCPD is subsequently confirmed per iRECIST
- Progression Free Survival (PFS): the time from first day of treatment to either (a) the date of PD per RECIST, or iUPD if iCPD is subsequently confirmed per iRECIST, or (b) in the absence of documented PD, the date of death by any cause

Pharmacokinetic Assessments:

Blood and urine samples will be collected for the determination of plasma concentration of DSP-0509. On the days when blood samples are taken, the precise infusion start and stop time (hours:minutes:seconds) must be documented. Infusion start and stop times and PK sample times are to be based on the same clock. Blood samples for PK assessments are to be drawn from the arm contralateral to the site of drug administration.

Note that urine samples to assess PK will be collected, but only in Monotherapy Arm A.

Biomarker Assessments:

The following samples will be collected for biomarker assessments:

- Plasma samples (eg, cytokine analysis)
- Peripheral blood mononuclear cells (PBMCs) (eg, lymphocyte immunophenotyping)
- Blood samples (eg, tumor-specific markers)
- Tumor tissue samples (eg, immune-related gene expression, CD8 immunohistochemistry (IHC), tumor-infiltrating lymphocytes (TIL) analysis, tumor mutational burden (TMB) analysis, PD-L1 IHC analysis [applicable only in the Combination Arms B and C])
- For patients who sign a separate consent, blood and tumor samples will be saved for future exploratory biomarker studies (this consent not required for study participation)

In exploratory analyses, blood and tumor biomarkers will be correlated, as appropriate, with PK, dose level, safety, and efficacy outcomes.

Statistical Methods:

Statistical analyses will be descriptive in nature. No formal sample size calculations will be performed for this study. Descriptive statistics (n, mean, standard deviation, median, and ranges for continuous variables; frequencies and percentages for categorical variables) will be provided by dose level and/or visit, if applicable. All data will be listed by patient, dose level, and visit where applicable. All summaries, statistical analyses, and individual patient data listings described below will be completed by using SAS v9.3 or later (SAS Institute, Inc, Cary, North Carolina, US).

All anti-tumor parameters, including RECIST and iRECIST response, will be summarized using descriptive statistics. Analyses for response based on RECIST and iRECIST also will be performed for patients in the per protocol population with evaluable data. Data listings and summaries may include

tumor markers, additional imaging, or other response data. Potential relationships between PK, pharmacodynamics, and other response data may be evaluated. Kaplan Meier estimates of PFS will be generated.

Adverse events will be assessed based on the safety population, coded using the Medical Dictionary for Regulatory Activities (MedDRA; version to be specified in the Statistical Analysis Plan [SAP]) and graded according to CTCAE v5.0. AEs will be analyzed by grade, relatedness to study drug, and coding, with listings and tabulated summaries of TEAEs generated for each Arm/Phase by dose level and for patients overall. Additionally, the number treated, number evaluable for dose escalation, and number with DLTs will be described for each dose level and for the study overall. Vital signs, laboratory data, and ECG data (stratified by dose level and overall) will be summarized for changes over time on-study and each post-baseline visit, together with the change from baseline.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions

λz	terminal elimination rate constant
A_e	cumulative amount of unchanged drug excreted into the urine
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	24-hour area under the concentration-time curve (daily exposure)
AUC_{inf}	area under the concentration-time curve from time 0 (dosing) extrapolated to infinity
AUC_t	area under the concentration-time curve from time 0 (dosing) to the time of the last measurable concentration
BLRM	Bayesian logistic regression model
BOR	best overall response
C_0	initial concentration of DSP-0509 (time = 0)
cGCP	current Good Clinical Practice
CL	clearance
CL_R	complete renal clearance from plasma
C_{max}	maximal plasma concentration
CNS	central nervous system
CPS	combined positive score
CR	complete response
CRC	colorectal carcinoma
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T-lymphocyte
CXCL10	chemokine C-X-C motif ligand 10
CYP	cytochrome P450 (enzyme)
DAMP	damage-associated molecular pattern
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group (performance status)
eCRF	electronic Case Report Form

EDC	electronic data capture
EoS	end of study
ES	Efficacy Set
EWOC	escalation with overdose control
FAS	Full Analysis Set
FDA	Food and Drug Administration
F_e(%)	percentage of the intravenously administered drug excreted into the urine
FIH	first in human
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte-macrophage-colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICI	immune checkpoint inhibitor
iCPD	immune confirmed progressive disease
iCR	immune complete response
iDCR	immune disease control rate
iDoR	immune duration of response
IEC	Independent Ethics Committee
IFN	interferon
IFNα	interferon alpha
IHC	immunohistochemistry
IL	interleukin
IL-1RA	interleukin 1 receptor antagonist
IL-6	interleukin 6
INR	International Normalized Ratio
iORR	immune objective response rate
IP-10	inducible protein 10
iPFS	immune progression-free survival
iPR	immune partial response
irAE	immune-related adverse event
IRB	Institutional Review Board

iRECIST	Immune Response Evaluation Criteria in Solid Tumors; modified RECIST for immunotherapy studies
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MEC	minimum effective concentration
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF-κB	nuclear factor kappa B
NSCLC	non-small cell lung cancer
OATP	organic anion transporting peptide
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
pDC	plasmacytoid dendritic cell
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PPS	Per-Protocol Set
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
q1w	once weekly
q2w	every 2 weeks
q3w	every 3 weeks
q6w	every 6 weeks
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease

SDV	source document/data verify(ied)
SEAP	secreted alkaline phosphatase
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
SoE	Schedule of Events
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
Th2	T helper 2
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocyte
TLR	Toll-like receptor
TMB	tumor mutational burden
TNFα	tumor necrosis factor alpha
TTP	time to progression
ULN	upper limit of normal
US	United States
V_c	initial volume of distribution (time 0)
V_z	volume of distribution at the terminal phase
WBC	white blood cell

Table 2: List of Definitions

Acceptable toxicity	dose level producing a DLT rate of approximately 16% to 33%
Acquired ICI resistance	previous treatment with ICIs (PD-1 or PD-L1 inhibitors) accompanied by objective clinical benefit (stable disease [SD] for at least 24 weeks, PR, or CR, according to RECIST criteria, v1.1, as the best clinical response to ICIs), followed by systemic progression of disease during or within 3 months after the last dose of ICI treatment. Resistance to treatment of PD-1/PD-L1 with CTLA4 also is considered.
End of Study	date of last visit of the patient
Excessive toxicity	probability of a DLT rate greater than 33% (determined while applying BLRM and the principle of escalation with overdose control [EWOC])
Extent of exposure	calculated as ([date last study treatment administered] - [date first study treatment administered] + 1)
Postmenopausal	females with spontaneous absence of menses for ≥12 consecutive months
Primary ICI resistance	previous treatment with ICIs with PD without prior objective clinical benefit, ie, without prior CR, PR, or SD (per RECIST criteria, v1.1) after 6 weeks or more of treatment.
Treated patients	patients who have received at least one dose of study drug

5. INTRODUCTION

5.1. Advanced Solid Tumors

In 2017, it was estimated that there would be more than 1.5 million persons diagnosed with advanced solid tumors, and more than half a million people with advanced solid tumors would die (American Cancer Society, 2017; Centers for Disease Control, 2017). Hence, there is an urgent unmet medical need for therapeutic innovations to treat advanced solid tumors. The primary goals of treatment of advanced solid tumors are to prolong survival and improve quality of life for patients. Although advanced solid tumors are generally not curable currently, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies. Especially important are those therapies that employ drugs with well-defined molecular targets that contribute to disease progression and chemotherapy resistance, and immuno-oncology drugs that boost the patient's own immune system against the tumor cells. The development of immunotherapeutic strategies, such as the development of agonists of Toll-like receptors (TLRs) has been a focus in clinical research efforts to address the challenges of chemotherapeutic resistance in advanced solid tumors.

5.2. Toll-Like Receptors as New Targets for Immunotherapy

Immuno-oncology drugs, including TLR agonists, have been designed to activate cancer-targeting immune responses (Khalil, 2016; Galluzzi, 2012). TLRs are a family of pattern-recognition receptors that recognize pathogen-associated molecular patterns to activate innate immunity (Rakoff-Nahoum, 2009; Kawai, 2011; Gay 2014). These receptors are highly conserved from *Drosophila* to humans and share structural and functional similarities. More than 10 types of TLRs have been identified (Kawai, 2011), and they are expressed on the cell surface or endosomal compartment. Toll-like receptors can be subdivided into 2 major categories, depending on their subcellular localization: (1) endosomal TLRs, including TLR-3, -7, -8, -9, and -10; and (2) plasma membrane-associated TLRs, including TLR-1, -2, -4, -5, and -6. Most endosomal and plasma membrane–associated human TLRs have been found to respond to conserved microbial products collectively known as microbe-associated molecular patterns, as well as to endogenous molecules collectively known as damage-associated molecular patterns (DAMPs) (Fucikova, 2015). Nonclinical and clinical evidence demonstrates that the release of TLR-activating DAMPs by dying cancer cells contributes to the elicitation of therapeutically relevant anticancer immune responses (Kroemer, 2013).

The bacillus Calmette–Guérin, an attenuated variant of *Mycobacterium bovis*, is the best known TLR agonist, and it is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of noninvasive transitional cell carcinomas of the bladder. Other approved TLR agonists for oncologic indications include (1) picibanil, a lyophilized preparation of *Streptococcus pyogenes* that is approved in Japan for the treatment of various carcinomas; (2) monophosphoryl lipid (MPL) A, a derivative of *Salmonella minnesota* lipopolysaccharide that is employed as an immunologic adjuvant in a peptide-based vaccine specific for cervical carcinoma–associated strains of human papillomavirus (HPV) (ie, HPV-16 and HPV-18), approved by FDA; and (3) imiquimod, an imidazoquinoline derivative that is used for the topical

treatment of actinic keratosis and superficial basal cell carcinoma, approved by FDA (Aranda, 2014; Hoffman, 2005).

5.2.1. Recent Clinical Experience With TLR-4, -5, -9 Agonists

Studies of TLR-4, -5, and -9 agonists, alone or in combination with other current treatments, are in progress on multiple cancer types (Merkel cell carcinoma [Bhatia, 2015]; colorectal [CRC] and non-small-cell lung [NSCLC] cancers [Bakhribah, 2015]; and relapsed and/or metastatic squamous cell carcinoma of the head and neck [HNSCC] [Machiels, 2013; Smith, 2014; Burtness, 2019; Chan, 2015]), with preliminary evidence of antitumor activity and generally acceptable safety profiles. An unacceptable safety profile, with multiple serious adverse events (SAEs), 50% of which were deemed product-related, including 1 death, was reported for the study of TLR-9 agonist IMO-2055 in combination with 5-fluorouracil, cisplatin, and cetuximab (PFE) in patients with relapsed and/or metastatic HNSCC, and the study was terminated early.

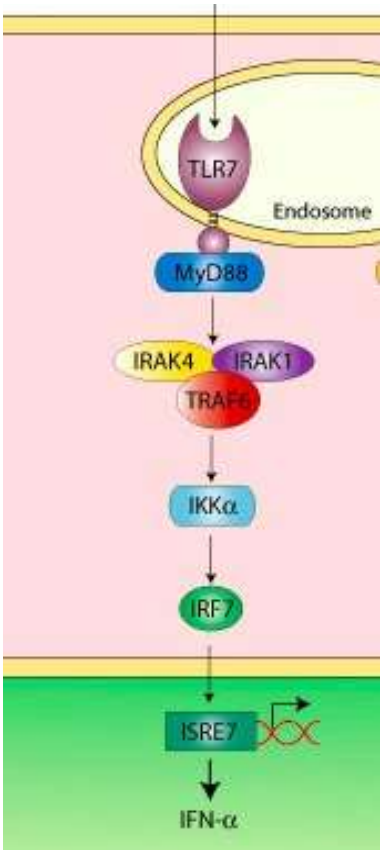
Additional studies of IMO-2055, in combination with a different set of therapies (erlotinib and bevacizumab; Smith, 2014) (folinic acid, 5-fluorouracil, irinotecan/cetuximab; Burtness, 2019; Chan, 2015) were conducted in advanced NSCLC and CRC, respectively, with limited antitumor activity and a mixed safety profile.

In a further TLR-9 agonist study in metastatic CRC (Schmoll, 2014), the study was stopped early since MGN1703 significantly improved progression-free survival (PFS), measured from the start of induction therapy versus placebo, and since all adverse events (AEs) were transient, mild, and limited to injection site reaction or immune system activity.

Additional achievement of preliminary antitumor and safety objectives was met in another study of MGN1703 (Weihrauch, 2015), with the majority of treatment-emergent AEs (TEAEs) less than Grade 2 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), and fatigue and activated partial thromboplastin time (aPTT) prolongation being the only 2 cases of drug-related Grade 3 AEs. Twenty-five percent of patients had stable disease (SD) after 6 weeks of treatment; 3 of those remained in SD after 12 weeks, and 4 patients were further treated in a compassionate-use program that showed long-term disease stabilization for up to 18 months.

5.2.2. Recent Clinical Experience With TLR-7 Agonists

Figure 1: Downstream Signal Transduction Cascade



Among the various TLRs, TLR-7 is primarily expressed on the endosomes of plasmacytoid dendritic cells (pDCs) and, to some extent, in B cells, monocytes, and macrophages. It recognizes guanosine and/or uridine-rich single-stranded RNA derived from viruses such as hepatitis C virus (HCV) or hepatitis B virus (HBV) (Rakoff-Nahoum, 2009; Kawai, 2011). TLR-7 activation in pDCs is responsible for the production of high levels of Type I interferon (IFN). TLR-7 agonists modulate T helper 2 (Th2) responses in vitro through the action of interferon alpha (IFNα) on T cells as well as through the upregulation of the costimulatory ligand DLL-4, and via the downregulation of the Th2 transcription factor, GATA-3, by IFNα. Ligand binding of TLR-7 induces myeloid differentiation primary response gene 88 recruitment to endosomes and triggers a downstream signal transduction cascade (Figure 1).

TLR-7 activation induces secretion of inflammatory cytokines, including IFNα or interleukin (IL)-12, through nuclear factor kappa B (NF-κB) and interferon regulatory factor-7 pathways, and enhances dendritic cell maturation and antigen presentation, which are recognized by cytotoxic T-lymphocyte (CTL) precursors (Rakoff-Nahoum, 2009; Kawai, 2011). Subsequently, CTL precursors are instructed to develop into CTLs. As described above, activating innate immunity by TLR-7 signaling results in adaptive immune activation. Because of their immunostimulatory ability, TLR-7 agonists are expected to exhibit antitumor effects. It is reported that systemic delivery of a TLR-7 agonist leads to the priming of systemic immune responses capable of reducing both primary and metastatic tumor burden in nonclinical models (Chi, 2017).

Recent Phase 1 studies of TLR-7 agonists have shown a mixed safety profile: limited, transient, mild to moderate TEAEs in a Glaxo-Smith-Kline study of GSK2245035 (Iribarren, 2016; Tsitoura, 2015); as well as a multiple ascending-dose study by AstraZeneca that was stopped after 2 healthy volunteers experienced severe influenza-like AEs. An additional study of a TLR-7 agonist (MEDI9197, administered to patients with solid tumors and reported under clinical trials.gov number NCT02556463) has been terminated and no study data are available.

5.2.3. DSP-0509

5.2.3.1. General Overview

Sumitomo Dainippon Pharma Oncology (SDP Oncology), Inc (formerly Boston Biomedical, Inc) is developing DSP-0509, a TLR-7 agonist, for the treatment of patients with advanced solid

tumors refractory to standard treatment, or patients who have contraindications to, are intolerant of, or have declined available therapy. DSP-0509 is a new molecular entity with TLR-7 agonist activity. The dosage form is a solution for intravenous (IV) administration.

DSP-0509 is designed to have high water solubility, is optimized for IV administration, and also is designed to achieve rapid elimination from the body, partially due to excretion via organic anion transporting peptide (OATP) transporters. It is anticipated that the rapid elimination, combined with the promising TLR-7–selective activity profile will provide the basis for a safe immunotherapy capable of prolonging the lives of patients with advanced solid tumors, either as monotherapy or in combination with other immunotherapeutic or chemotherapeutic agents.

This is the first clinical study with DSP-0509. Nonclinical toxicology and pharmacology studies have been conducted with DSP-0509, and the results from these studies support an acceptable safety profile for the initiation of the first-in-human (FIH) study of DSP-0509.

5.2.3.2. Summary of Nonclinical Toxicology Data

In accordance with its selective TLR-7–agonist activity, DSP-0509 did not exert any cytotoxicity, phospholipidosis, or mitochondrial toxicity in nonclinical studies. No genotoxic or phototoxic potential was found for DSP-0509 in vitro. A series of toxicology studies were performed to better understand the dose-effect relationships of the acute and subacute proinflammatory activity of DSP-0509. Rats and monkeys were selected as the principal species for toxicologic testing, consistent with literature reports of these 2 species being sensitive for TLR-7 agonists. Monkeys in repeated-dose studies received 5 once-weekly doses of DSP-0509, ranging from 2 mg/kg to 30 mg/kg. Animals were monitored during dosing and sacrificed at end-of-treatment (EoT; 1 week after last dose) or after recovery periods of 4 to 13 weeks. The pivotal toxicology studies were performed in full compliance with Good Laboratory Practice (GLP).

These studies are described in detail in the Investigator's Brochure (IB). A summary of clinical findings by System Organ Class (SOC) is presented below:

Cardiac disorders: Increased heart rate on electrocardiogram (ECG) and decrease in pO_2 blood analysis, myocardial degeneration, and necrosis were observed at doses ≥8 mg/kg in monkeys.

Eye disorders: Uveitis, retinal detachment, and retinal atrophy were noted in monkeys at 30 mg/kg. DSP-0509 caused histologically detectable inflammatory changes in multiple tissues, including the eyes, in both rats and monkeys.

Nervous system disorders: Histopathologic changes were observed in cynomolgus monkeys dosed at ≥15 mg/kg and were prevalent in animals dosed at 30 mg/kg. Histologic changes seen at EoT included mononuclear and inflammatory cell infiltrates in cerebrum (including choroid plexus), medulla, and pons; in some instances, the infiltrates were perivascular. Gliosis also was noted. Central nervous system (CNS) changes were persistent in recovery animals up to 13 weeks. Similar changes in other organs typically resolved during recovery.

Notable clinical findings included the following:

- Tremors were observed in monkeys dosed at ≥8 mg/kg and were present in the majority of animals dosed at 30 mg/kg.

- Seizures were observed in 2 monkeys dosed at 30 mg/kg:
  - A female (#30, study SBL 198-323) had seizures observed on Day 21 approximately 5 hours after dosing. The seizures were transitory; the animal completed treatment and was sacrificed as scheduled after a 4-week recovery period. Histopathologic changes included the inflammatory infiltrates noted above, with no additional findings.
  - A male (#26, study SBL 198-323) had continuous clonic convulsions on Day 5 accompanied by a decrease in pO_2 on blood gas analysis. The animal was euthanized and, at autopsy, CNS findings were notable for subarachnoid hemorrhages in cerebellum, cerebrum, and medulla; inflammatory changes were comparable to animals sacrificed after a course of 5 doses. The only notable finding outside the CNS was atrophy of mesenteric and mandibular lymph nodes and follicular atrophy in the spleen. In contrast, all males and females sacrificed after 5 doses had lymph node hyperplasia and moderate splenic hyperplasia.
- One other animal dosed at 30 mg/kg was euthanized during treatment:
  - A female (#14, study SBL 198-324) was euthanized on Day 25 for severe clinical deterioration, including failure to eat and decreased movement. At autopsy, CNS findings of inflammation were modestly increased compared to other 30 mg/kg animals. Hemorrhages were observed in pons and medulla, but not in the cerebellum or cerebrum. Of note, mesenteric and mandibular lymph nodes and spleen in this animal also showed atypical follicular atrophy.

Respiratory, thoracic, and mediastinal disorders: Inflammatory changes in the lung parenchyma and mediastinal lymph nodes were noted in rats at ≥10 mg/kg and in monkeys at ≥8 mg/kg. These changes were typically not found at the end of the recovery periods.

5.2.3.3. Summary of Nonclinical Safety Pharmacology Data

Numerous in vitro and in vivo studies were performed to provide insight on the mechanism of action, active concentration, and schedule dependencies of DSP-0509. In vitro safety pharmacology studies demonstrated no human ether-à go-go (hERG)-related gene inhibition. Additional detailed information can be found in the IB.

5.2.3.4. Summary of Nonclinical Pharmacodynamic Data

Pharmacodynamic studies investigating DSP-0509 tumoricidal activity in syngeneic mouse tumor models demonstrated promising single-agent activity and enhanced potency when combined with other treatment modalities (eg, radiation therapy, immune checkpoint inhibitor [ICI] therapy).

The TLR-7–specific agonist in vitro activity of DSP-0509 was evaluated using a reporter gene assay (ie, TLR-7/NF-κB/secreted alkaline phosphatase [SEAP]/human embryonic kidney 293 cells stably expressing human TLR-7 and a SEAP reporter gene under transcriptional control of an NF-κB response element) that demonstrated consistent and potent activation of human TLR-7 at nanomolar concentrations, with a mean negative logarithm of 50% effective concentration (pEC_{50}) of 6.5 ± 0.25 nM. Similar experience in cells expressing mouse, rat, or

cynomolgus monkey TLR-7 demonstrated activity at pEC_{50} concentrations of 7.5, 6.6, and 6.5 nM, respectively.

The minimum effective concentrations (MECs) of DSP-0509 that induced production of the inflammatory cytokines IFNα, chemokine C-X-C motif ligand 10 (CXCL10), and IL-1 receptor antagonist (IL-1RA) in plasma from healthy volunteers were determined to be 125, 63, and 125 nM, respectively. Similarly, the MECs of DSP-0509 required for production of IFNα2, IFNγ, IL-10, IL-12p40, IL-12p70, IL-1β, IL-1RA, IL-6, CXCL10, and tumor necrosis factor (TNF)α in healthy human plasma were 117, 234, 1,875, 1,875, 3,750, 234, 117, 117, 59, and 117 nM, respectively. In vivo, DSP-0509 MECs for induction of IFNα in mice, rats, and cynomolgus monkeys were 1, 0.3, and 0.3 mg/kg, respectively. See the IB for further details.

5.2.3.5. Summary of Nonclinical Data on Single-Agent In Vivo Antitumor Activity of DSP-0509 as Monotherapy and in Combination with Anti–Programmed Cell Death Protein 1 Antibody

The effects of DSP-0509 on tumor progression and lung metastasis were evaluated in LM8-bearing C3H/HeN mice. After mice were inoculated with LM8 cells, DSP-0509 (1 mg/kg) was administered IV once weekly (q1w) for 3 weeks. DSP-0509 significantly suppressed both tumor volume and lung metastasis compared with treatment with the vehicle. These results indicate that DSP-0509 monotherapy possesses antitumor activity not only in primary tumors but also in metastatic tumors. Antitumor activity of DSP-0509 in combination with anti-programmed cell death protein 1 (PD-1) antibody was evaluated in BALB/c mice bearing mouse colon carcinoma CT26 (CT26-bearing mice). DSP-0509 (5 mg/kg) or anti–PD-1 antibody (200 μg/animal) was administered to CT26-bearing mice once or twice weekly for 3 weeks, respectively, alone or in combination. DSP-0509 alone showed significant antitumor effect, and mouse anti–PD-1 antibody alone had little effect on tumor growth. On the other hand, combination therapy with DSP-0509 and anti–PD-1 antibody significantly suppressed tumor growth compared with treatment with the vehicle, DSP-0509 alone, or anti–PD-1 antibody alone. These results indicated that DSP-0509 has synergistic antitumor activity when combined with anti–PD-1 antibody.

5.2.4. Benefit/Risk Considerations

Immuno-oncology drugs, including TLR agonists, have been designed to activate cancer-targeting immune responses. Nonclinical and clinical evidence shows that the release of TLR-activating DAMPs by dying cancer cells contributes to the elicitation of therapeutically relevant anticancer immune responses.

SDP Oncology, Inc is developing DSP-0509, a TLR-7 agonist, for the treatment of patients with advanced solid tumors refractory to standard treatment or for whom no effective therapy exists. DSP-0509 is a new molecular entity with TLR-7 agonist activity.

Study BBI-DSP-0509-101 is a FIH study. In addition to the AEs observed to date, potential AEs that may be encountered with administration of DSP-0509 alone or in combination with ICIs include those previously observed with the administration of other TLR agonists and ICI (see IB for detailed presentation). Details of immune-related AEs (irAEs) and guidelines for monitoring and managing these potential events are described in Sections 7.8 and 7.9. In consideration of the

anticipated benefits of DSP-0509 administration and potential safety concerns, the benefit-risk profile of DSP-0509 in patients with advanced solid tumors is considered favorable.

5.2.5. Rationale for Choosing Head and Neck Squamous Cell Carcinoma in the Dose-expansion Combination Arm C

The decision to focus on patients with advanced and/or metastatic, recurrent and/or refractory HNSCC in the added dose-expansion Combination Arm C was made after careful review of the potential treatment space for such solid tumors. For newly diagnosed patients with relapsed/metastatic HNSCC, the standard of care consists of pembrolizumab alone or in combination with platinum-based chemotherapy (Burtness, 2019). Currently, different strategies to overcome resistance to ICIs are under investigation. The combination of DSP-0509 and pembrolizumab attempts to overcome resistance in patients with HNSCC after disease progression following previous therapy.

For patients with advanced HNSCC who have progressed to chemotherapy and pembrolizumab, the prognosis remains poor, with overall survival (OS) around 6 to 8 months (Burtness, 2019). Thus, there is a high unmet medical need for new treatment options for these patients.

The patient population selected for enrollment into Combination Arm C will have resistance to ICIs, either as a primary or acquired resistance, defined as:

- Primary resistance: patients who experience disease progression without clinical response to the ICI after 6 weeks or more of treatment
- Acquired resistance: patients who experience clinical response (complete response [CR], partial response [PR], and/or SD for at least 24 weeks on ICI therapy, but subsequently experience progressive disease (PD) during or within 3 months after the last dose of ICI treatment. Resistance to treatment of PD-1/PD-L1 with CTLA4 also is considered.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives and Endpoints

Primary Objectives	Endpoints
Monotherapy Arm A - Dose Escalation (Phase 1):	
• To determine the safety, tolerability, and maximum tolerated dose (MTD) of DSP-0509 administered IV) as a single agent in patients with advanced solid tumors • To identify a recommended Phase 2 dose (RP2D) of DSP-0509 monotherapy for patients with advanced solid tumors	• Incidence of dose-limiting toxicities (DLTs) within the first 6 weeks of dosing • Incidence and severity of TEAEs and SAEs using NCI CTCAE • Incidence of dose interruption, dose reduction, and dose intensity • Changes in clinical laboratory values (hematology, clinical chemistry, urinalysis), ECG parameters, multigated acquisition (MUGA) scan/electrocardiogram (ECHO) parameters
Combination Arm B - Dose Escalation (Phase 1):	
• To determine the safety, tolerability, and MTD of DSP-0509 administered IV in combination with pembrolizumab for patients with advanced solid tumors who have shown primary or acquired resistance to ICIs • To identify an RP2D of DSP-0509 when given in combination with pembrolizumab for such patients	• Incidence of DLTs within the first 6 weeks of dosing • Incidence and severity of TEAEs and SAEs using NCI CTCAE • Incidence of dose interruption, dose reduction, and dose intensity • Changes in clinical laboratory values (hematology, clinical chemistry, urinalysis), ECG parameters, MUGA scan/ECHO parameters
Combination Arm C – Dose Expansion (Phase 2):	
• To evaluate the preliminary antitumor activity of DSP-0509 in combination with pembrolizumab in patients with HNSCC who have shown primary or acquired resistance to ICIs	• Objective response rate (ORR), as assessed by Response Evaluation Criteria in Solid Tumors (RECIST), v1.1 and by Immune RECIST (iRECIST, modified RECIST for immunotherapy studies)

6.2. Secondary Objectives and Endpoints

Secondary Objectives	Endpoints
Monotherapy Arm A - Dose Escalation (Phase 1):	
• To evaluate pharmacokinetic (PK) parameters of DSP-0509 administered as a single agent in patients with advanced solid tumors	• Area under the concentration-time curve (AUC), maximal plasma concentration (C_{max}), and other parameters described in Table 18. Additional parameters may be added as needed.

• To evaluate the preliminary antitumor activity of DSP-0509 administered as a single agent in patients with advanced solid tumors	Using RECIST and iRECIST: • ORR • Time to progression (TTP) • 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 • Duration of response (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
• To assess DSP-0509–induced changes in plasma cytokine levels in patients with advanced solid tumors treated with DSP-0509 as a single agent	• Measurement of cytokines in plasma including but not limited to IFNα, inducible protein (IP) 10, interleukin 1 receptor agonist (IL-1RA), tumor necrosis factor alpha (TNFα), and interleukin 6 (IL-6)
Combination Arm B - Dose Escalation (Phase 1):	
• To evaluate PK parameters of DSP-0509 given in combination with pembrolizumab in patients with advanced solid tumors	• AUC, C_{max}, and other parameters described in Table 18. Additional parameters may be added as needed.
• To evaluate the preliminary antitumor activity of DSP-0509 in combination with pembrolizumab in patients with advanced solid tumors	Using RECIST and iRECIST: • ORR • TTP • PFS • DoR
• To assess changes in plasma cytokine levels induced by DSP-0509 in combination with pembrolizumab in patients with advanced solid tumors	• Measurement of cytokines in plasma, including but not limited to, IFNα, IP-10, IL-1RA, TNFα, and IL-6
Combination Arm C – Dose Expansion (Phase 2):	
• To evaluate the preliminary antitumor activity of DSP-0509 in combination with pembrolizumab in patients with HNSCC	• DoR • Disease control rate (DCR), defined as the percentage of patients who have achieved best overall response (BOR) of CR, PR, or SD, per RECIST v1.1 • PFS • 6-month PFS rate, defined as the proportion of patients who neither progress by RECIST v1.1 nor die before 6 months (24 weeks) from first study treatment • OS, defined as the time from date of first dose of study treatment to date of death by any cause

• To evaluate the preliminary antitumor activity of DSP-0509 in combination with pembrolizumab, in patients with HNSCC, using iRECIST criteria	• 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 • 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[a] 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
• To further evaluate the safety and tolerability of DSP-0509 administered with pembrolizumab	• Frequency and intensity of AEs/SAEs using NCI CTCAE v5.0
• To assess changes in plasma cytokine levels induced by DSP-0509 in combination with pembrolizumab in patients with advanced solid tumors	• Measurement of cytokines in plasma including, but not limited to, IFNα, IP-10, IL-1RA, TNFα, and IL-6

[a] The event date to be used for calculation of PFS should be the first date on 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

6.3. Exploratory Objectives and Endpoints

Exploratory Objectives	Endpoints
Monotherapy Arm A - Dose Escalation (Phase 1):	
• To evaluate the effect of DSP-0509 administered as a single agent on cardiac parameters in patients with advanced solid tumors	• Assessment of single agent QT interval/corrected QT interval (QTc) prolongation effect by continuous 25-hour ECG recording
• To profile potential metabolites of DSP-0509 in plasma and possibly in urine samples of patients treated with DSP-0509	• Detection of metabolites from DSP-0509 in pooled plasma and urine samples using liquid chromatography-tandem mass spectrometry
Monotherapy Arm A and Combination Arm B – Dose Escalation (Phase 1):	
• To evaluate biomarkers potentially predictive of the clinical efficacy, immune activation, and/or toxicity associated with DSP-0509	Examples include: • Immune-related gene expression • $CD8^+$ immunohistochemistry (IHC) • Lymphocyte immunophenotyping • Tumor infiltrating lymphocytes (TILs) • Human leukocyte antigen (HLA)-ABC (IHC)

	• Tumor mutational burden (TMB) • Programmed death ligand 1 (PD-L1$^+$) IHC (Combination Arms B and C only)
Combination Arm C – Dose Expansion (Phase 2):	

• To determine the PFS rate as an evaluation of treatment benefit of DSP-0509 administered with pembrolizumab	• PFS rate is defined as PFS1/PFS (-1) ratio using RECIST (v.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
	  • 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)

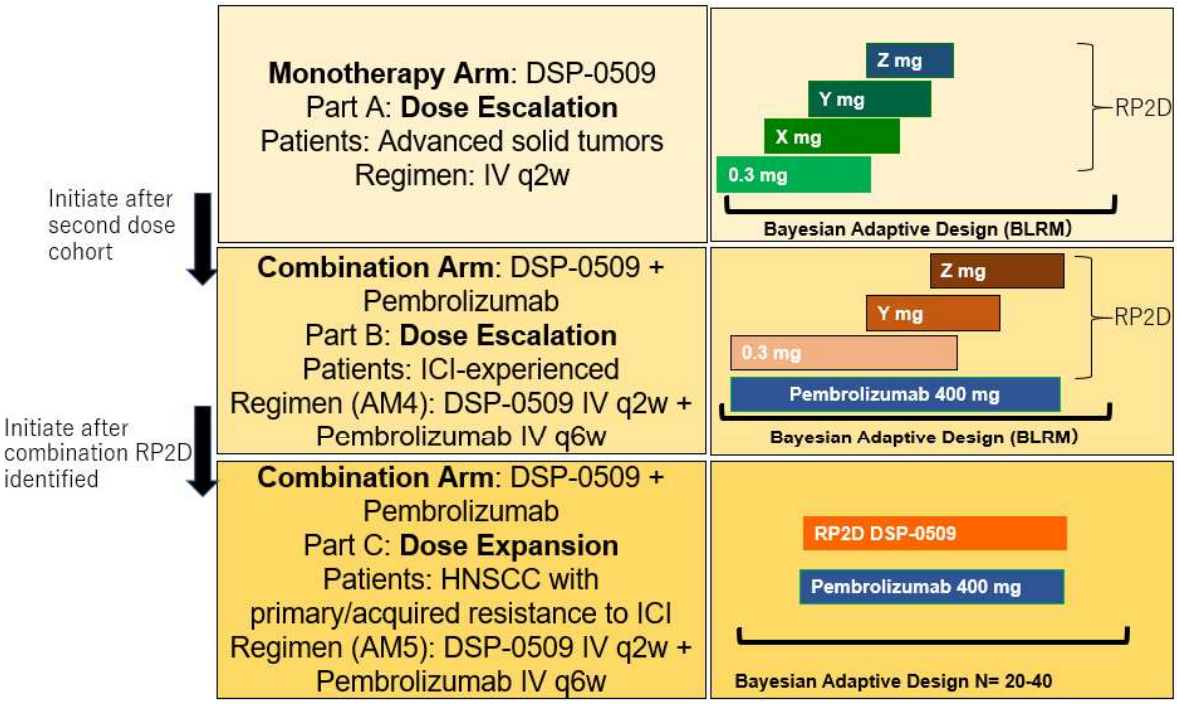
• To evaluate biomarkers potentially predictive of the clinical efficacy, immune activation, and/or toxicity associated with DSP-0509	Examples include: • Immune-related gene expression • CD8$^+$ IHC • Lymphocyte immunophenotyping • TILs • HLA-ABC (IHC) • TMB • PD-L1$^+$ IHC (Combination Arms B and C only)

7. INVESTIGATIONAL PLAN

7.1. Overview of Study Design

This is a multicenter, Phase 1/2 clinical study for patients with advanced solid tumors. The study has 3 parts: a dose-escalation monotherapy Arm A, a dose-escalation combination therapy Arm B, and a dose-expansion combination therapy Arm C. The study structure is summarized in Figure 2.

Figure 2: Study Design



See Section 7.4 and Appendix 18.4 for details regarding Bayesian Adaptive Design
Abbreviations: BLRM = Bayesian logistic regression model; DLT = dose-limiting toxicity; HNSCC = head and neck squamous cell carcinoma; ICI = immune checkpoint inhibitor; IV = intravenous; qXw = every X weeks (2 or 6); RP2D = recommended Phase 2 dose

7.1.1. Safety Monitoring in the Dose-escalation Cohorts

The guiding principles for dose escalation are to maximize patient safety and achieve precise dose selection. To accomplish this, the following provisions will be applied to all dose-escalation cohorts:

- Criteria for DLT events (see Section 7.7) include potential risks of immunotherapy, in general, and TLR agonists, in particular
- Dose escalation will be performed using a design based on Bayesian logistic regression model (BLRM) methods applied with the escalation with overdose control (EWOC) principle to limit the risk of exposing patients to excessive toxicity, defined as a DLT rate

greater than 33%. Based on this approach, a dose-escalation level is considered acceptable if the probability of excessive toxicity is ≤25%.

- After all patients in a newly escalated cohort have completed the DLT evaluation period (Days 1 through 42), the BLRM model will be updated and a recommendation for the next dose level will be provided.
- PK is monitored closely (ie, real time by cohort) for patients in the dose-escalation cohorts to assure correct application of a C_{max} cap; this cap specifies that dose escalation is contingent on the mean unbound Day 1 C_{max} for DSP-0509 for the prior cohort being <43.5 nM (22.3 ng/mL unbound, or 378.6 ng/mL total) (observed drug binding in human serum is 94.1%).
- A Safety Review Committee (SRC; Section 7.4.2) will review available clinical data and integrate that with PK data and guidance for dose escalation by the BLRM method. The SRC will make a recommendation for the next cohort in the study (Section 7.4.2).
- Within each cohort, enrollment will be staggered, ie, there will be at least 48 hours between initiation of treatment in successive patients.
- During the DLT period (Days 1 through 42), in the intervals that patients have no required study visits for infusions, a telephone safety check will be made to maintain close monitoring. These calls will be made (±1 day) on Days 8, 22, and 36 for both the Monotherapy Arm A and the Combination Therapy Arm B

Dose levels assessed as tolerated based on the SRC review may, with the approval of the SRC and Sponsor, be opened to enroll an additional 3 to 6 patients (referred to as enrichment cohorts).

7.1.2. Dose Escalation - Monotherapy Arm A

The primary objective of Monotherapy Arm A is to determine the MTD or RP2D of DSP-0509 when administered as a single agent. Approximately 21 to 30 patients with advanced solid tumors will be enrolled. Several provisional dose levels of DSP-0509, with approximately 3 to 6 patients at each level may be tested in patients with advanced solid tumors, with dose escalation contingent on the mean C_{max} for the prior cohort being below the C_{max} cap described in Section 7.1.1.

DSP-0509 will be administered as a single agent q2w beginning on Day 1. Within each cohort, patients will be entered in a staggered fashion as an additional safety measure. That is, treatment of a new patient will be delayed at least 48 hours after the first dose of the most recent patient entered within each cohort. See Figure 3 for details.

Figure 3: Dosing Schedule – Monotherapy Arm A

The provisional dose levels presented in Table 3 may be evaluated for both Arm A and Arm B. Intermediate dose levels may be added, or certain provisional dose levels may be skipped, based on the BLRM results. Every dose escalation will not be more than 100% higher than the previous dose in all dose levels above 3.0 mg. Enrollment of additional cohorts will be based on the dose -escalation procedures detailed in Section 7.4. Real-time DSP-0509 PK data (by dose cohort) will be obtained to support dose-escalation decisions.

Table 3: DSP-0509 Provisional Dose Levels in Arm A and Arm B

Provisional Dose Level	Dose of DSP-0509 (mg)
1	0.3
2	1.0
3	3.0
4	6.0
5	9.0
6	12.0
7	16.0
8	20.0
9	25.0
10	30.0

7.1.3. Dose Escalation - Combination Therapy Arm B

The primary objective of Combination Therapy Arm B is to determine the RP2D of DSP-0509 when administered in combination with pembrolizumab, using a BLRM approach. The combination arm will enroll approximately 21 to 30 patients with advanced solid tumors that are (a) metastatic or unresectable and recurrent, and/or refractory to available therapy, (b) a condition for which pembrolizumab is an approved treatment, and (c) in patients who have shown either primary or acquired resistance to an ICI. DSP-0509 will be administered on Day 1 and then every 2 weeks thereafter. Pembrolizumab will be initiated on Day 1 and administered at a dose of 400 mg IV every 6 weeks (q6w) (Merck and Co, 2020) (Figure 4).

To maximize patient safety, enrollment in the first combination-escalation cohort will begin at a dose level of 0.3 mg DSP-0509 after safety and tolerability of DSP-0509 monotherapy has been confirmed in patients receiving DSP-0509 at least 1 dose level higher. The provisional doses described in Section 7.1.2 also may be evaluated in Combination Therapy Arm B.

Figure 4: Dosing Schedule – Combination Arms B and C

7.1.4. Dose Expansion – Combination Therapy Arm C

The primary objective of Combination Therapy Arm C is to determine preliminary efficacy in the form of the ORR of DSP-0509 when administered in combination with pembrolizumab to an expansion cohort of patients with HNSCC, using a Bayesian Adaptive design approach. Combination Arm C will enroll approximately 20 to 40 patients with HNSCC tumors that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) in patients who have been treated with pembrolizumab or other PD-1 or PD-L1 inhibitors in monotherapy, and (c) who have subsequently shown either primary or acquired resistance to ICIs.

Dose escalation of DSP-0509 in combination with 400 mg pembrolizumab q6w will start at the same dose of DSP-0509 as the highest (not exceeding the MTD) level tested in the combination regimen with 200 mg pembrolizumab q3w. Upon completion of the DLT evaluation period for the first DSP-0509 dose level tested in combination with 400 mg pembrolizumab q6w in newly enrolled patients, if this dose level is found not to exceed the MTD, any ongoing patients receiving DSP-0509 in combination with pembrolizumab 200 mg q3w will be allowed, at the investigator's discretion, to transition to the 400 mg pembrolizumab q6w regimen, while maintaining the originally assigned DSP-0509 dose level. See Figure 4.

7.2. Rationale for Starting Dose

Data from nonclinical studies, together with the data from recent clinical studies with other TLR-7 agonists, have informed the Phase 1/2 study design.

The minimal anticipated biologic effective level, based on human whole blood cytokine induction activity, has been used to select a starting dose of 0.3 mg in Monotherapy Arm A. Based on nonclinical studies, the unbound C_{max} at the initial dose level in this FIH study is estimated to be in the range of 1.0 nM to 3.9 nM.

To maximize patient safety, the starting dose in Combination Arm B will be at least 1 dose level below that of the second dose level tested and tolerated in the Monotherapy Arm A.

7.3. Administration of Study Treatment

Each patient treated will receive DSP-0509 at the dose fixed for that Arm or Phase administered as a constant-rate IV infusion over 10 minutes using a syringe pump; see Appendix 18.1 for the detailed procedure.

Patients in Combination Arms B and C also will receive pembrolizumab administered as a 30-minute IV infusion. In both Arms B and C, pembrolizumab will be administered at a dose of 400 mg every 6 weeks, in accordance with the updated prescribing information (Merck and Co, 2020). On all occasions when patients are scheduled to receive both agents on the same day, the following procedures will apply:

- DSP-0509 will be administered first
- After 4 hours of observation, vital signs will be obtained
- After the investigator has assessed that the patient is clinically stable, including vital signs, infusion of pembrolizumab may be initiated
- Vital signs must be obtained 30 to 60 minutes after completion of the pembrolizumab infusion, just prior to discharge

7.4. Dose Escalation Procedures

7.4.1. Application of BLRM to Dose Escalation

As indicated in Section 7.1, dose-escalation procedures include BLRM models (Neuenschwander, 2008) that incorporate the EWOC principle (Babb , 1998). Details of statistical methodology and the specific BLRM models in this study are provided in Appendix 18.4.

The use of Bayesian adaptive models for Phase 1 dose-escalation studies has been advocated by the European Medicines Agency (EMA) in their guidelines on clinical studies in small populations (EMA, 2006). The BLRM method similarly provides guidance on the MTD and RP2D dose levels (see Section 7.5).

Intrapatient dose escalation is not allowed at any time in either of the dose-escalation treatment arms.

7.4.2. Safety Review Committee

The SRC will consist of the principal investigators (or delegates) and the Sponsor's Medical Monitor, Statistician, Pharmacovigilance Safety Lead, and PK Lead. The SRC will meet after all patients in a new cohort have completed the DLT evaluation period. The SRC may have unscheduled meetings on an as-needed basis to review results of routine signal detection efforts, unexpected toxicities, and/or other information that may be relevant to the conduct of this study or to patient safety.

At dose-escalation meetings, the SRC will review the following:

- Dose recommendation based on BLRM (treated as guidance and integrated into an overall clinical assessment)

- Available clinical and safety data, including assessments of AE severity/causality, action taken with study treatment, and action taken for AE management (including administration of systemic corticosteroids)
- Available PK and pharmacodynamics data

The SRC final recommendation may include, but is not limited to, the following:

- Dose escalation
- Dose de-escalation
- Enrollment of additional patients at the same dose level
- Proposal of the RP2D dose level, as detailed in Section 7.5

The SRC recommendation will be recorded in meeting minutes and reviewed by the Sponsor. SRC recommendations and the Sponsor's decision will be provided to investigators before dosing any new patients.

7.5. Determination of the MTD and RP2D

The RP2D is usually the highest dose with acceptable toxicity, generally defined as the dose level producing a DLT rate of approximately 16% to 33%.

In the current study, the unbound plasma C_{max} steady-state level or systemic exposure level (AUC) of DSP-0509 may be incorporated into the determination of the RP2D, especially if an association is found between toxicity and these PK parameters. The RP2D will be defined as the MTD, provided the MTD is not associated with a potentially toxic C_{max} or systemic exposure level of DSP-0509.

Determination of the RP2D will be performed in consultation with the SRC, based on safety and other data available at the time of the RP2D decision.

Dose escalation will continue until identification of the MTD or a suitable lower dose for expansion (the RP2D). This will occur when the following conditions are met:

- At least 6 patients have been treated at this dose
- This dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 21 patients already have been treated in the dose-escalation part of the study
- It is the dose recommended for patients, either per the model or by review of all available clinical data in the SRC meeting

Of note, dose escalation could be stopped earlier by a joint decision between the Sponsor and investigators during a dose-escalation meeting, by considering the model estimations and a global assessment of safety, PK, pharmacodynamics, and preliminary activity data.

7.6. Definition of Patients Evaluable for DLT

The DLT period for dose-escalation review is from Study Days 1 through 42. During this period, treated patients will be monitored closely for AEs in general and for DLTs in particular.

A patient will be considered evaluable for DLT if observed for 42 days following the first dose of DSP-0509 in monotherapy and with pembrolizumab in combination. Patients discontinued during the DLT period due to DLTs are considered as evaluable for DLT.

Patients who do not meet the above criteria will be considered nonevaluable for DLT and may be replaced to provide sufficient evaluable patients to fully assess a given dose level.

7.7. Definition of Dose-Limiting Toxicity

DLTs are defined below, including both irAEs and other AEs, grouped by SOC. Severity of the events will be graded based on NCI CTCAE version 5.0. Within each category, specific events not considered DLTs also will be indicated.

The TEAEs listed below will be considered DLTs if they meet all of the following criteria:

- Have onset from Days 1 through 42
- Are assessed as treatment-related, unless causality is determined to be related to pembrolizumab alone
- Meet criteria defined in Sections 7.7.1 through 7.7.4

7.7.1. Immune-related DLTs

- Any Grade 4 irAE (except immune-mediated endocrinopathies)
- Grade 3 pneumonitis and nephritis
- Grade 3 infusion-related reaction, except first occurrence without steroid prophylaxis and resolved within 6 hours with appropriate clinical management
- Recurrent Grade 2 pneumonitis
- Recurrent Grade 3 irAE
- Persistent Grade 2 or 3 irAE lasting ≥12 weeks after last dose

7.7.2. Hematologic DLTs

- Neutropenia Grade 4 (absolute neutrophil count [ANC] <500/mm^3) for ≥7 days
- Neutropenia Grade ≥3 (ANC <1000/mm^3) associated with infection **or** requiring granulocyte-colony stimulating factor (G-CSF)
- Febrile neutropenia (ANC <1000/mm^3 with a temperature of >38.3ºC once **or** ≥38ºC for 1 hour)
- Thrombocytopenia Grade 4 (platelet count <25,000/mm^3) for ≥7 days
- Thrombocytopenia Grade ≥3 (platelet count <50,000/mm^3) associated with bleeding **or** requiring platelet transfusion
- Anemia Grade 4 (requires urgent intervention)
- Anemia Grade 3 (hemoglobin [Hgb] <8 g/dL; requires blood transfusion)

The following hematologic event is NOT considered a DLT:

- Grade 3 or 4 lymphopenia (lymphocyte count <500/mm^3)

7.7.3. Liver-related DLTs

- Alanine aminotransferase (ALT) **or** aspartate aminotransferase (AST) >8 x the upper limit of normal (ULN)
- Total bilirubin >5 x ULN
- Cases that meet all 3 of the following criteria (ie, are consistent with Hy's law):
  - ALT **or** AST ≥3 x ULN
  - Serum total bilirubin >2 x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase)
  - Have no other reason identified to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury

The following liver-related events are NOT considered DLTs:

- Patients without liver metastases: isolated Grade 3 increases of ALT and/or AST (>5 x ULN) with recovery to Grade ≤1 (≤3 x ULN) within 10 days
- Patients with liver metastases: isolated Grade 3 increases of ALT and/or AST (>5 x baseline) with recovery to Grade ≤1 (≤3 x baseline) within 10 days

7.7.4. Other DLTs

- Any other ≥Grade 3 non-hematologic AE or ≥Grade 3 laboratory abnormality that either (a) leads to hospitalization, (b) persists for ≥7 days, or (c) requires medical intervention
- Any of the following eye-related AEs Grade ≥2: eye pain, retinal detachment, keratitis or uveitis, choroidal neovascularization, retinopathy/retinitis, thyroid-associated orbitopathy, idiopathic orbital inflammation
- Any seizure, regardless of the grade

The following events are NOT considered DLTs:

- Grade 4 vomiting that resolves to Grade ≤2 within 3 days with medical management
- Grade 3 nausea and/or vomiting
- Grade 3 hypertension that is controlled within 7 days with medical management
- Grade 3 fatigue that resolves to Grade ≤2 within 7 days
- Isolated Grade 3 electrolyte abnormalities that are (a) not associated with clinical signs or symptoms and (b) reversed within 3 days with medical intervention
- Isolated Grade 3 amylase or lipase abnormalities that are not associated with clinical signs or symptoms or with findings on imaging consistent with pancreatitis

7.8. Monitoring of Potential Adverse Events

The following materials are provided as guidance and reference for monitoring for potential events:

- National Comprehensive Cancer Network [NCCN, 2020] guidelines for monitoring immunotherapy-related toxicities and cytokine release syndrome, and assessing infusion-related- reactions (Appendix 18.3)
- Guidelines for monitoring potential AEs associated with DSP-0509 (Table 4)

Table 4: Monitoring of Potential Adverse Events

Potential AE	Monitoring	Ask Patients to Report Promptly
Postinfusion events associated with TLR-mediated cytokine induction	Monitor signs/symptoms post infusion for cytokine-related symptoms (eg, flulike symptoms, decreased blood pressure) Observe patients for 1 to 2 hours post infusion (at Day 1, then as needed)	Shortness of breath, chills or shaking, fever, wheezing, flushing, headache, itching, skin rash, dizziness, or feeling like passing out
Cardiac disorders	Monitor signs/symptoms of cardiac disorders; perform ECG monitoring, MUGA/ECHO monitoring; perform cardiodynamic assessments as scheduled	Pressure or tightness in the chest, chest pain, shortness of breath, sweating, fast heart rate, dizziness, cough, nausea and/or vomiting
Nervous system disorders	Monitor for signs/symptoms of nervous system disorders, eg, tremor, convulsions, mental status changes, encephalitis	Sudden, irregular/uncontrolled shaking of an arm or leg or of the body, involuntary contraction of muscles, stiffness, confusion, a sudden feeling of fear or panic, loss of consciousness
Eye disorders	Monitor signs/symptoms of eye disorders (eg, uveitis, retinal atrophy, retinal detachment); perform Slit Lamp exam, visual field testing, fundoscopy, as scheduled; ad hoc exams performed at investigator's discretion	Any visual changes
Pneumonitis	Monitor for signs and symptoms of pneumonitis; if suspected, perform appropriate evaluations	Shortness of breath, chest pain, new or worsening cough

Abbreviations: AE = adverse event(s); ECG = electrocardiogram; ECHO = echocardiogram; MUGA = multigated acquisition; TLR = Toll-like receptor

7.9. Guidance for Modifying or Discontinuing Study Treatment

For the clinical management of urgent or severe events (eg, acute infusion-related reactions, cardiopulmonary distress, seizures), investigators should follow applicable institutional standards, clinical practice guidelines, and their own judgement.

Refer to the latest NCCN guideline for management of immunotherapy-related toxicities in patients with irAEs and cytokine-release syndrome.

7.9.1. Guidance for Modifying or Discontinuing DSP-0509

DSP-0509 will be **withheld** for a given patient for:

- Any treatment-related Grade 3 or greater non-irAE: if recovered to Grade 2 or Grade 1 within 6 weeks after the last dose, treatment may be restarted at a lower dose

level (after discussion with Medical Monitor); if not recovered, permanently discontinue DSP-0509

- In case of treatment-related irAE, refer to withholding conditions listed in Table 5

DSP-0509 will be permanently **discontinued** for a given patient for:

- Use of a prohibited treatment for a concomitant illness or TEAE (exception: use of corticosteroids for an irAE)
- Toxicities meeting the DLT definition
- Any Grade 3 or higher allergic reaction or anaphylaxis
- Any symptomatic congestive heart failure, or decreased left ventricular ejection fraction of >10% from baseline, based on a MUGA scan or ECHO
- Corrected QT interval according to Fridericia's formula (QTcF) prolongation of greater than 500 msec

7.9.2. Guidance for Modifying or Discontinuing Pembrolizumab

Pembrolizumab will be withheld or permanently discontinued according to irAEs in Table 5. The dose of pembrolizumab cannot be modified.

Table 5: Modifications for Immune-related Adverse Events

Adverse Reaction	Severity	Dose Modification
Immune-mediated pneumonitis	Grade 2	Withhold[a]
	Recurrent Grade 2 Grade 3 or 4	Permanently discontinue
Immune-mediated colitis	Grades 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Immune-mediated hepatitis in patients without hepatocellular carcinoma (HCC)	AST or ALT 3 to 5 x ULN or Total bilirubin 1.5 to 3 x ULN	Withhold[a]
Immune-mediated hepatitis in patients with HCC	AST or ALT ≥5 x ULN if baseline <2 x ULN AST or ALT >3 times baseline if baseline ≥2 x ULN Total bilirubin >2.0 mg/dL if baseline <1.5 mg/dL; or Total bilirubin >3.0 mg/dL, regardless of baseline levels	Withhold[b]
	ALT or AST >10 x ULN or Child-Pugh score ≥9 points Gastrointestinal bleeding suggestive of portal hypertension or new onset of clinically detectable ascites or encephalopathy	Permanently discontinue
Immune-mediated endocrinopathies	Grades 3 or 4	Withhold until clinically stable
Immune-mediated nephritis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Immune-mediated skin adverse reactions	Grade 3 or suspected Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)	Withhold[a]
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Grades 2 or 3 based on severity and type of reaction	Withhold[a]
	Grade 3 based on severity and type of reaction, or Grade 4	Permanently discontinue
Recurrent immune-mediated adverse reactions	Recurrent Grade 3 or 4 Recurrent Grade 2 pneumonitis	Permanently discontinue
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion[c]

Adverse Reaction	Severity	Dose Modification
	Grade 3 or 4	Permanently discontinue
Inability to taper corticosteroid	Requires ≥10 mg/day prednisone or equivalent for >12 weeks after last dose of study drug	Permanently discontinue
Persistent Grade 2 or 3 AE (excluding endocrinopathy)	Lasting ≥12 weeks after last dose	Permanently discontinue

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; SJS = Stevens-Johnson Syndrome; TEN = Toxic Epidermal Necrolysis; ULN = upper limit of normal
Guidelines based on approved pembrolizumab label with minimal modifications for patients eligible for this study
[a] Resume when AE recovers to Grade ≤1 after corticosteroid taper
[b] Resume in HCC patients when AST or ALT and total bilirubin recover to Grade ≤1 or baseline
[c] If symptoms resolve within one hour of stopping drug infusion, infusion may be restarted at 50% of original infusion rate; otherwise, dosing will be held until symptoms resolve. Patient should be premedicated for the next scheduled dose.

If DSP-0509 is discontinued permanently, dosing with pembrolizumab may continue, provided the investigator considers it to be safe and potentially beneficial for the patient. If pembrolizumab is discontinued permanently, dosing with DSP-0509 may continue, provided the investigator considers it to be safe and potentially beneficial for the patient.

7.9.3. Study Discontinuation

Patients must be **discontinued** from this study if any of the following occurs:

- Patient withdraws consent
- Investigator decision to withdraw patient from treatment
- Pregnancy in a female patient
- Confirmed PD per iRECIST criteria (Appendix 18.2): initial PD should be confirmed within 4 to 8 weeks. Study treatment may continue after confirmed progression if there is potential benefit for the patient, following discussion between the investigator and the Medical Monitor.
- Loss to follow-up
- Unacceptable toxicities, described in Section 7.9, or other toxicities according to investigator
- Noncompliance with study treatment or procedures
- Initiation of other anticancer therapy
- Sponsor terminates the study

In the event of premature discontinuation, the patient should return to the study site within 30 days (±7 days) after last dose of study treatment to have the end-of-study (EoS) assessments performed.

7.10. Study Duration

The duration of the study will be approximately 6 years.

Patients in each Arm (Monotherapy Arm A, Combination Arm B, Combination Arm C) will undergo a Screening period of up to 28 days; a treatment period of up to 127 days (approximately 4.5 months) or as long as the patient is benefitting from treatment; and a 30-day safety follow-up. Survival follow-up, if applicable, will occur every 6 months, following the 30-day safety follow-up.

Treatment duration for each patient is unknown, as patients may continue therapy as long as they demonstrate clinical benefit.

7.11. Selection of Study Population

7.11.1. Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Must have a histologically or cytologically confirmed advanced solid tumor that meets the following additional specifications for the Arm/Phase in which they are to be treated:
   a. Monotherapy Arm A (Dose Escalation), Phase 1 – Advanced solid tumors that are metastatic or unresectable, and recurrent and/or refractory to available therapy
   b. Combination Arm B (Dose Escalation), Phase 1 – Advanced solid tumors that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) a condition for which pembrolizumab is an approved treatment, and (c) in patients who have shown either primary or acquired resistance to ICIs
   c. Combination Arm C (Dose Expansion), Phase 2 – Advanced HNSCC tumors of the oropharynx, oral cavity, hypopharynx, larynx, lip, or sinus that are (a) metastatic or unresectable, and recurrent and/or refractory to available therapy, (b) in patients who have been treated with pembrolizumab or other PD-1 or PD-L1 inhibitors in monotherapy, and (c) who have subsequently shown primary or acquired resistance to ICIs
2. Must be ≥18 years of age
3. Should have all side effects of any prior therapy or procedures for any medical condition recovered to CTCAE ≤Grade 1 (except alopecia)
4. Must have at least 1 measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.1
5. Must have a life expectancy ≥3 to 6 months
6. Female patients of childbearing age and women <12 months since the onset of menopause, except those who have been surgically sterilized (tubal ligation) or whose sexual partner(s) is surgically sterilized (vasectomy), must agree to use acceptable contraceptive methods for the duration of the study and for 9 months after the date of their last DSP-0509 infusion. If employing contraception, 2 of the following precautions must be used: birth control pill, vaginal diaphragm, intrauterine system or device, condom, or vaginal spermicide. Female

patients who are postmenopausal are defined as those with an absence of menses for ≥12 consecutive months. Male patients must be surgically sterilized (vasectomy) or their female sexual partner(s) must be surgically sterilized (tubal ligation) to avoid using contraception. If they do not meet this criterion, male patients must agree to use a condom as well as one of the acceptable contraceptive methods listed above with their female partner(s) who meets the criterion of either being of childbearing age or <12 months since the onset of menopause. Male patients and their female partner(s) must agree to use acceptable contraception methods for the duration of time the male patient is on the study and for 9 months after the date of his last DSP-0509 infusion.

7. Females of childbearing potential must have a negative serum pregnancy test at Screening
8. Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
9. Must have adequate coagulation function at Screening as determined by:
    a. Prothrombin time (PT) international normalized ratio (INR) <1.5
    b. Partial thromboplastin time (PTT) <1.5 times the ULN
10. Must have adequate hematologic function at Screening as determined by:
    a. White blood cell (WBC) count ≥3,000/microliter
    b. ANC ≥1,500/microliter (patient may not use G-CSF or GM-CSF to achieve these WBC and ANC levels)
    c. Platelet count ≥100 × 10^3/microliter
    d. Hgb ≥9.0 g/dL (may not transfuse or use erythropoietin to obtain this Hgb level)
11. Must have adequate renal and hepatic function at Screening as determined by:
    a. Serum creatinine <2.0 mg/dL or <1.5 times the ULN, whichever is lower
    b. Total bilirubin ≤1.5 mg/dL or <1.5 times the ULN, whichever is lower (or ≤2.0 mg/dL for patients with known Gilbert syndrome)
    c. AST ≤2.5 times ULN (≤5 times ULN for patients with liver metastases)
    d. ALT ≤2.5 times ULN (≤5 times ULN for patients with liver metastases)
12. Must be able to attend study visits as required by the protocol
13. Prior to the first DSP-0509 infusion, the patient must be able to provide tumor tissue for baseline studies as (a) a block of archival tissue sufficient to provide the required number of slides; (b) a sufficient number of fixed, unstained slides of archival tissues; or (c) consent to undergo tumor biopsy to acquire sufficient tumor tissue. (Sites need to refer to the current version of the "Sample Collection & Shipment Instructions" manual to determine how many slides are required for each patient, as the number varies based on (a) the study Arm/Phase in which the patient is enrolled, and (b) whether the patient consented to optional future testing)

Additional Inclusion Criteria for Combination Arm C Only:

In addition to the above criteria, patients must meet the following criteria to be eligible to enroll in Combination Arm C:

14. Have at least one accessible tumor for biopsy. This accessible lesion must be considered as nonmeasurable per RECIST criteria, v1.1.
15. Be platinum refractory, PD-1 or PD-L1 exposed, and have no more than 3 lines of prior therapy for advanced/metastatic disease
16. Have a known status of PD-L1 combined positive score (CPS)
17. Have a known HPV status

7.11.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Has received prior therapy with a TLR agonist, excluding a topical TLR agonist
2. Has received anticancer chemotherapy (including molecular-targeted drugs), radiotherapy, immunotherapy (eg, vaccines or cytokines), or investigational agents within the 3 weeks before the first dose of DSP-0509. Local palliative radiotherapy is permitted
3. Receives concurrent systemic (oral or IV) steroid therapy >10 mg prednisone daily or its equivalent
4. Not fully recovered from major surgery before the first dose of DSP-0509
5. Has CNS metastases (including leptomeningeal or spinal metastases) or CNS primary tumors, eg, glioblastoma
6. Has a history of seizures other than isolated febrile seizure in childhood; has a history of a cerebrovascular accident or transient ischemic attack less than 6 months ago
7. Has effusions (pleural, pericardial, or ascites) requiring drainage
8. Has a neurodegenerative disease, eg, motor neuron disease, Parkinson disease, Alzheimer disease, Huntington disease
9. Has retinal detachment, ulcerative keratitis, uveitis, Vogt-Koyanagi-Harada syndrome, choroidal neovascularization, retinopathy/retinitis, thyroid-associated orbitopathy, idiopathic orbital inflammation, diabetic retinopathy, ischemic retinopathy (including glaucoma-associated retinopathy), retinal vein thrombosis, or a non-healing ocular or ophthalmic disease
10. Has a fever ≥38°C within 3 days before the first dose of study treatment
11. Has interstitial lung disease or active noninfectious pneumonitis
12. Has a history of active autoimmune or immunologic disorder requiring immunosuppression with steroids or other immunosuppressive agents (eg, azathioprine, cyclosporine A), that, after discussion between the investigator and the Medical Monitor is considered not acceptable for the study. If the autoimmune status is questionable, and the patient is not at risk, the investigator may discuss the patient's potential eligibility with the Medical Monitor.

13. Has a known hypersensitivity to a component of the protocol therapy, DSP-0509, or another pyrimidine
14. Has a history of another primary cancer within the 5 years before enrollment except for the following: non-melanoma skin cancer, cervical carcinoma in situ, superficial bladder cancer, or other nonmetastatic carcinoma that has been in complete remission without treatment for more than 5 years
15. Has abnormal ECGs that are clinically significant, such as QT prolongation (QTc >480 msec)
16. In the opinion of the treating investigator, has any concurrent conditions that could pose an undue medical hazard or interfere with interpretation of study results; these conditions include, but are not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, concurrent congestive heart failure (New York Heart Association Functional Classification Class II, III or IV), concurrent unstable angina, concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation), recent (within the prior 12 months) myocardial infarction or acute coronary syndrome, significant pulmonary disease (shortness of breath at rest or on mild exertion, eg, due to concurrent severe obstructive pulmonary disease), concurrent hypertension requiring more than 2 medications for adequate control, or diabetes mellitus with more than 2 episodes of ketoacidosis in the prior 12 months
17. Has an ejection fraction of 50% or less based on a MUGA scan or ECHO
18. Has the presence of a known, active, acute or chronic infection, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), as determined by fourth-generation (HIV antibody and antigen) assay, hepatitis B surface antigen (HBsAg), and hepatitis C serology, respectively
19. Has a cognitive, psychological, or psychosocial impediment that would impair the ability of the patient to receive therapy according to the protocol, or adversely affect the ability of the patient to comply with the informed consent process, protocol, or protocol-required visits and procedures
20. Receives concurrent strong inhibitors of cytochrome P450 (CYP)2C8 (see Section 7.13.2)
21. Receives concurrent inhibitors of OATP1B1 and OATP1B3 (see Section 7.13.2)
22. Is pregnant or breastfeeding
23. Has active neurologic or inflammatory or auto immune disorders (eg, Guillain-Barre syndrome, amyotrophic lateral sclerosis)

The following exclusion applies only to enrollment in Combination Arms B and C:

24. Has a history of irAEs resulting in permanent discontinuation of prior ICI treatment

7.12. Investigational Product

7.12.1. Identity of the Investigational Product DSP-0509

The investigational product is formulated as a sterile solution for injection. Each vial contains 8.5 mL of DSP-0509 at the concentration of 0.3 mg/mL. The assigned fixed dose of DSP-0509 will be administered as an IV constant-rate infusion over 10 minutes using a syringe pump; see Appendix 18.1 for a detailed description of the procedure. For patients who have indwelling ports, it is acceptable to use this access for DSP-0509 administration. For full information about drug storage, preparation, and handling, please refer to the Pharmacy Manual.

7.12.2. Combination Therapy – Pembrolizumab

In Combination Therapy Arms B and C, pembrolizumab will be administered in the clinic at 400 mg IV q6w over 30 minutes, in accordance with pembrolizumab labeling, unless otherwise specified. See Section 7.3 for details related to administration of both pembrolizumab and DSP-0509 on the same day.

7.13. Prior and Concomitant Therapy

7.13.1. Allowed Concomitant Medications

Patients may receive concomitant medications, including supportive care drugs, during treatment for all intercurrent medical conditions or TEAEs (whether assessed as related or not related to study treatment) at the discretion of the investigator, in conformance with community or institutional medical standards. Use of megestrol acetate for treatment of loss of appetite and weight loss due to disease is allowed.

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.

7.13.2. Prohibited Medication/Therapy

- There are no scheduled premedications.
  - Patients in the dose-escalation cohorts may not, during the DLT period, receive prophylactic medications aimed at preventing TEAEs, unless it is required as per Table 4
  - After the DLT period, prophylactic treatments, including antiemetics, may be given with the approval of the Medical Monitor
- During the study, patients may not receive any other anticancer therapy, including therapeutic radiotherapy
  - Local palliative radiotherapy is permitted but, if to a target lesion, that lesion must be excluded from tumor response assessments
  - Therapy with denosumab and bisphosphonates for bone metastases may continue if a patient is taking this medication before starting study treatment
- Patients may not receive immunosuppressive agents, including systemic corticosteroids with the following exceptions:

  - Intranasal corticosteroids at a physiologic dose not to exceed 10 mg/day of prednisone or equivalent
  - A course of systemic corticosteroids given for the treatment of an irAE. Note that if the response is not adequate to permit tapering of the steroids within the time indicated, the patient must be discontinued from study treatment (see Table 5)
- Patients should not receive live vaccines (eg, FluMist®); vaccines containing killed organisms or purified products are permitted.
- Herbal preparations/medications are prohibited including, but not limited to, dehydroepiandrosterone, ephedra (ma huang), gingko biloba, ginseng, kava, saw palmetto, St. John's wort, and yohimbe
- Patients with renal cell carcinoma being considered for combination therapy must discontinue axitinib before starting study treatment due to increased risks of hepatic toxicity in combinations with pembrolizumab
- The strong inhibitors of CYP2C8 and of OATP1B1 and OATP1B3 transporters indicated in Table 6 are prohibited:

Table 6: Prohibited Strong Inhibitors of CYP2C8 and OATP1B1/B3

Target	Prohibited Strong Inhibitors[a]
CYP2C8	clopidogrel gemfibrozil
OATP1B1 and OATP1B3	clarithromycin erythromycin rifampin gemfibrozil cyclosporine

[a] Additional strong inhibitors of OATP1B1 and OATP1B3 transporters include atazanavir, lopinavir, ritonavir, and simeprevir. These are antiviral agents for the treatment of HIV and HBV. However, patients with HIV or HBV (whether previously known or found at Screening) are excluded from the study. Patients diagnosed with those infections while on study treatment should be discontinued.

8. STUDY PROCEDURES

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

8.1. Schedule of Events

The planned schedules of events (SoE), including treatment, procedures, and assessments, for the Monotherapy Arm A and for Combination Therapy Arms B and C are presented in Table 7 through Table 16.

- For each part, events during Screening and the DLT period (Days 1 through 42) and during ongoing treatment (Day 43 to EoS) are presented separately by study day
- Additional detailed tables are provided for events that have hourly schedules, including collection of blood and urine samples for PK, cytokines, and cardiodynamic assessments

Following the SoEs, a detailed description of each study procedure and assessment to be performed is provided (Section 8.2).

Table 7: Schedule of Events – Screening and DLT Period - Monotherapy Part A

Tests and Procedures	Screening		DLT Period					
Day	**-28 to -1**	**-7 to -1**	1	8	**15**	**22**	**29**	**36**
Window			**–**	**± 1 d**	**± 1 d**	**± 1 d**	**± 1 d**	**±1 d**
Informed Consent[a]	X							
Assess Eligibility	X							
Demographics	X							
Medical and Cancer History	X							
Hospitalization[b]			X					
DSP-0509 Infusion			X		X		X	
Telephone Safety Call[c]				X		X		X
Physical Examination	X		X		X		X	
Pregnancy Test, *if Necessary*	X							
ECOG Performance Status		X	X		X		X	
Vital Signs		X	X		X		X	
Body Weight		X	X		X		X	
Height		X						
Hematology Tests		X	X[d]		X		X	
Chemistry Tests		X	X[d]		X		X	
Coagulation Tests (PT & PTT only)		X						
Urinalysis		X	X[d]		X		X	
Serum Virology (HBV, HCV, HIV)[e]	X							
Chest X-ray	X							
MRI scan of brain[f]	X							
Bone scan (if indicated)[g]	X							
MUGA Scan or ECHO	X						X	
Eye Examination by an Ophthalmologist[h]	X						X	
12-Lead Safety ECGs[i]	X		X				X	
Cardiodynamic Assessment by Holter Monitor[j]			X					
Pharmacokinetics[k]			X		X		X	
Plasma for Cytokines[k]			X		X		X	
Blood for PBMC Lymphocyte Markers	X							
Blood for Tumor Markers[l]	X							
Blood for Future Biomarker Analysis[m]	X							
Tumor Samples for TMB Analysis	X							
Tumor Samples for Immune-Related Biomarkers	X							
Tumor Samples for Future Biomarker Analysis[m]	X							
Objective Disease Assessment[n]	X							
Concomitant Medications	<---------- Continuously from Consent to EoS --------->							
Adverse Events	<---------- Continuously from Consent to EoS --------->							

d = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hr = hour; IFNα = interferon alpha; IHC = immunohistochemistry; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; min = minutes; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PR = partial response; PT = Prothrombin time; PTT = Partial thromboplastin time; SOI = start of infusion

[a] Informed consent is to be obtained before performing any study-specific procedures; begin AE collection after informed consent is obtained.

[b] Hospitalization extends into Day 2 to at least 24 hours post infusion to allow completion of the events in Table 8.

[c] On Days 8, 22, and 36 (±1 day) during the dose-limiting toxicity (DLT) period, when there are no required visits, telephone calls will be made to maintain close safety monitoring of patients.

[d] Day 1 laboratory assessments do not need to be repeated if done within the previous 3 days.

[e] Viral serology tests include HbsAg, anti-HCV, and HIV Ag and Ab screening tests (ie, fourth-generation)

[f] A brain MRI will be performed at baseline to rule out brain metastases, and at subsequent time points if clinically indicated

[g] A bone scan will be conducted when clinically indicated

[h] Eye exam includes slit lamp exam, visual field testing, and fundoscopy

[i] Manual 12-lead ECGs are to be performed after 10 minutes rest, in triplicate, at least 5 minutes apart at Screening, predose on Day 1, at 24 hours postdose on Day 2, and predose on Day 29

[j] Cardiodynamic assessments: On Day 1, a Holter monitor will be placed on the patient 1 hour prior to start of DSP-0509 infusion and will remain in place until 24 hours (Day 2) after the end of infusion. On Day 1, patients should be supine and at rest from at least 10 minutes before to 5 minutes after (a) the interval from start of infusion (SOI) to 30 minutes post-SOI; and (b) for similar periods around each subsequent timepoint shown in Table 8. Concurrent PK samples should be obtained on time, and the exact times for the SOI and the start and end of the rest periods recorded to permit ECG extraction by the Holter vendor.

[k] See Table 8 for a detailed schedule of collection times for blood and urine for PK and cytokines

[l] Tumor markers in blood will be assessed as appropriate for those cancers for which markers are known to exist, eg, CA-125, PSA, AFP, CA19-9, CEA

[m] An additional separate informed consent is needed at the prestudy evaluation to permit collection and storage of blood and tumor tissues (archival and/or fresh biopsy) for future exploratory biomarker analyses

[n] Objective disease assessment (tumor imaging) pretreatment represents the baseline study for the patient's response to treatment evaluated using RECIST and iRECIST. The same imaging modality must be used throughout the study for an individual patient. See Table 9 for timepoints of subsequent post-treatment evaluations.

Table 8: Schedule of Cardiodynamics, PK, and Cytokine Samples – Monotherapy Arm A

Day	**Day 1**													**Day 2**	**Day 15 and Day 29**				
Time After Start of Infusion	Predose	0	8 min	11 min	15 min	20 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr	Predose	0	1 hr	4 hr	6 hr
Acceptable Range for Blood Sampling	-2 hr to -2 min	-	± 0.5 min	± 0.5 min	± 1 min	± 1 min	± 1 min	± 3 min	± 5 min	± 10 min	± 15 min	± 20 min	± 20 min	± 1 hr	-2 hr to -2 min	NA	±3 min	±10 min	±15 min
DSP-0509 Infusion		X														X			
Plasma for Cytokines	X							X	X	X	X		X	X	X		X	X	X[c]
Plasma for PK	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X[c]
Cardiodynamic Assessment, Holter Monitor[a]	X		X	X	X	X	X	X	X	X	X	X	X	X					
Urine Collection[b]	X	<---------- 0 to 4 hr ---------->								4 to 8hr			8–12 hr	12–24 hr					

[a] Cardiodynamic assessments: On Day 1, a Holter monitor will be placed on the patient 1 hour prior to start of DSP-0509 infusion and will remain in place until 24 hours (Day 2) after the end of infusion. On Day 1, patients should be supine and at rest from at least 10 minutes before to 5 minutes after (a) the interval from start of infusion (SOI) to 30 minutes post-SOI; and (b) for similar periods around each subsequent timepoint shown in Table 9. Concurrent PK samples should be obtained on time, and the exact times for the SOI and the start and end of the rest periods recorded to permit ECG extraction by the Holter vendor.

[b] Urine collections for PK: Predose urine samples may be collected any time on Day 1 prior to DSP-0509 dosing (ie, they are not limited to be within 2 hours before treatment). After start of infusion of DSP-0509, urine should be collected during the following intervals: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, and 12 to 24 hours (ie, into Day 2).

[c] Optional blood collection for cytokine and PK is at 6 hours

Table 9: Schedule of Events – Day 43 to End of Study – Monotherapy Arm A

Tests and Procedures	Ongoing Treatment								End of Study
Day	43	57	71	85	99	113	127	Subse-quent[a]	30 days after last dose of DSP-0509
Window	± 3 d	± 3 d	± 3 d	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	+ 7 d
Hospitalization	X								
DSP-0509 Infusion	X	X	X	X	X	X	X	q2w	
Physical Examination	X	X	X	X	X	X	X	q2w	X
Pregnancy Test[b]									X
ECOG Performance Status	X	X	X	X	X	X	X	q2w	X
Vital Signs	X	X	X	X	X	X	X	q2w	X
Body Weight	X	X	X	X	X	X	X	q2w	X
Hematology Tests	X	X	X	X	X	X	X	q2w	X
Clinical Chemistry Tests	X	X	X	X	X	X	X	q2w	X
Urinalysis[c]	X	X	X	X	X	X	X	q4w	X
MUGA Scan or ECHO									X
Eye Exam by an Ophthalmologist[d]		X		X			X	q6w	X
12-Lead Safety ECG[e]									X
Pharmacokinetics[f]	X								
Plasma for Cytokines [f]	X			X					
Blood for PBMC Lymphocyte Markers[g]	X						X		
Blood for Tumor Markers[h]	X			X			X	X[i]	X
Blood for Future Biomarker Analysis[g, j]	X			X			X		X
Tumor Samples for Immune-Related Biomarkers[j, k]				X					X
Tumor Samples for Future Biomarker Analysis[j, k]				X					X
Objective Disease Assessment[l]	X			X			X	X	X
Concomitant Medications	<---------- Continuously from Consent to EoS ---------->								
Adverse Events	<---------- Continuously from Consent to EoS ---------->								

[a] Entries in the "Subsequent" column indicate the interval at which procedures need to be repeated after Day 127, **if** the patient remains on treatment. For additional details, see the specific footnote for the procedure
[b] A pregnancy test (serum) is to be performed on all females of child-bearing potential at Screening and at the End-of-Study visit as scheduled, and at other times as judged appropriate by the investigator
[c] After the Day 127 visit, urinalysis will be performed every 4 weeks (ie, every other visit)
[d] Eye exam includes slit lamp exam, visual field testing, and fundoscopy
[e] Manual 12-lead ECGs are to be performed after 10 minutes rest, in triplicate, at least 5 minutes apart at the End-of-Study visit
[f] See Table 10 for a detailed schedule of blood sampling for cytokines on Days 43, 44, and 85, and of blood and urine sampling for PK on Days 43 and 44
[g] Blood sampling for PBMC lymphocyte markers and future biomarkers will be performed as shown. (Note: the schedule for each item is different.). Samples to be collected will include whole blood (for PBMCs), whole blood and plasma (see Laboratory Manual for details)
[h] Tumor markers in blood will be assessed as appropriate for those cancers for which markers are known to exist, eg, CA-125, PSA, AFP, CA19-9, CEA
[i] Subsequent samples are to be collected on Day 169 and then every 12 weeks to coincide with objective evaluation (radiologic imaging; see footnote “l”)
[j] An additional separate informed consent is needed at the pre-study evaluation to collect and store blood and archival and/or fresh biopsy tumor tissues for future exploratory biomarker analyses
[k] Optional tumor sample collections if medically feasible. See Section 8.2.15.2 for further details
[l] Objective disease assessments by tumor imaging are used to assess the patient's response to treatment according to RECIST and iRECIST. The same modality for tumor imaging must be used throughout the study for an individual patient. Post-treatment imaging will be performed every 6 weeks through Day 127 (18 weeks), as shown, also on **Day 169, and subsequently**, **every 12 weeks** until PD is observed. Imaging should be performed at the end of study unless it has been done in the previous 8 weeks

Table 10: Schedule for Sampling for PK, Cytokines– Monotherapy Arm A

Day	**Day 43**													**Day 44**	**Day 85**					
Time After Start of Infusion	Predose	0	8 min	11 min	15 min	20 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr	Predose	0	1 hr	2 hr	4 hr	6 hr
Acceptable Range for Blood Sampling	-2 hr to -2 min	-	± 0.5 min	± 0.5 1min	± 1 min	± 1 min	± 1 min	± 3 min	± 5 min	± 10 min	± 15 min	± 20 min	± 20 min	± 1 hr	-2 hr to -2 min	NA	±3 min	±5 min	±10 min	±15 min
DSP-0509 Infusion		X														X				
Plasma for Cytokines	X							X	X	X	X		X	X	X		X	X	X	X
Plasma for PK	X		X	X	X	X	X	X	X	X	X	X	X	X						
Urine Collection[a]	X	<---------- 0 to 4 hr ---------->								4 to 8 hr			8–12 hr	12– 24 hr						

CR = complete response; d = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hr = hour; IFNα = interferon alpha; IHC = immunohistochemistry; IL-1RA = interleukin 1 receptor antagonist; IL-6 = interleukin 6; IP-10 = inducible protein 10; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; min = minutes; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetics; PR = partial response; PT = Prothrombin time; PTT = Partial thromboplastin time; SD = stable disease; TIL = tumor infiltrating lymphocyte; TMB = tumor mutational burden; TNFα = tumor necrosis factor alpha

[a] Urine collections for PK: Predose urine samples may be collected any time on Day 43 prior to DSP-0509 administration (ie, they are not limited to be within 2 hours before treatment.) After start of infusion of DSP0509, urine should be collected for the following intervals: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, and 12 to 24 hours (ie, into Day 44)

Table 11: Schedule of Events – Screening and DLT Period – Combination Arm B

Tests and Procedures	Screening		DLT Period					
Day	-28 to -1	-7 to -1	1	8	15	22	29	36
Window			_	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d
Informed Consent[a]	X							
Assess Eligibility	X							
Demographics	X							
Medical and Cancer History	X							
Hospitalization			X					
Telephone Safety Call[b]				X		X		X
DSP-0509 Infusion			X		X		X	
Pembrolizumab Infusion[c, d]			X[c,d]					
Physical Examination	X		X		X		X	
Pregnancy Test[e]	X							
ECOG Performance Status		X	X		X		X	
Vital Signs		X	X[d]		X		X	
Body Weight		X	X		X		X	
Height		X						
Hematology Tests		X	X[f]		X		X	
Clinical Chemistry Tests		X	X[f]		X		X	
Coagulation Tests (PT & PTT only)		X						
Urinalysis		X	X[f]		X		X	
Serum Virology (HBV, HCV, HIV)[g]	X							
Chest X-ray	X							
MRI scan of brain[h]	X							
Bone scan (if indicated)[i]	X							
MUGA Scan or ECHO	X						X	
Eye Examination by an Ophthalmologist[j]	X						X	
12-Lead Safety ECGs[k]	X		X				X	
Pharmacokinetics[l]			X		X		X	
Plasma for Cytokines[l]			X		X		X	
Blood for PBMC Lymphocyte Biomarkers	X							
Blood for Tumor Markers[m]	X							
Blood for Future Biomarker Analysis[n]	X							
Tumor Samples for TMB Analysis[o]	X							
Tumor Samples for Immune-related Biomarkers[o]	X							
Tumor Samples for Future Biomarker Analysis[n]	X							
Objective Disease Assessment[p]	X							
Concomitant Medications	<------ Continuously from Consent to EoS ------->							
Adverse Events	<-------- Continuously from Consent to EoS ------->							

CR = complete response; d = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hr = hour; IFNα = interferon alpha; IHC = immunohistochemistry; IL-1RA = interleukin 1 receptor antagonist; IL-6 = interleukin 6; IP-10 = inducible protein 10; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; IV = intravenous; min = minutes; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetics; PR = partial response; PT = prothrombin time; PTT = partial thromboplastin time; SD = stable disease; TIL = tumor infiltrating lymphocyte; TMB = tumor mutational burden; TNFα = tumor necrosis factor alpha

[a] Informed consent is to be obtained before performing any study-specific procedures; begin collection of AEs after consent is obtained
[b] On Days 8, 22, and 36 (±1 day) during the DLT period when there are no required visits, sites will make a telephone call to the patients to ensure ongoing close safety monitoring of patients
[c] Pembrolizumab treatment (400 mg intravenous [IV]) will start on Day 1 and thereafter will be administered every 6 weeks as detailed in Section 7.3, in accordance with the US Package Insert
[d] On days when both DSP-0509 and pembrolizumab are administered, vital signs will be taken (a) prior to DSP-0509 infusion; (b) 4 hours after DSP-0509 infusion and, if assessed as stable by the investigator, then pembrolizumab will be infused; and (c) 30 to 60 minutes after the end of the pembrolizumab infusion, prior to discharge from the site
[e] A pregnancy test (serum) is to be performed on all females of child-bearing potential at Screening and at the End-of-Study visit as scheduled, and at other times as judged appropriate by the investigator
[f] Day 1 laboratory assessments do not need to be repeated if done within the previous 3 days
[g] Viral serology tests include HBsAg, anti-HCV, and HIV Ag & Ab screening test
[h] A brain MRI will be performed at baseline to rule out brain metastases, and at subsequent time points if clinically indicated
[i] A bone scan will be conducted when clinically indicated
[j] Eye exam includes slit lamp exam, visual field testing, and fundoscopy
[k] Manual 12-lead ECGs are to be performed after 10 minutes rest, in triplicate, at least 5 minutes apart, at Screening, predose on Day 1, at 24 hours postdose on Day 2, and predose on Day 29
[l] See Table 12 for a detailed schedule of blood sampling for PK and for cytokines
[m] Tumor markers in blood will be assessed as appropriate for those cancers for which markers are known to exist, eg, CA-125, PSA, AFP, CA19-9, CEA
[n] An additional separate informed consent is needed at the prestudy evaluation to permit collection and storage of blood and tumor tissues (archival and/or fresh biopsy) for future exploratory biomarker analyses
[o] Tumor samples are required at the Screening evaluation; either archival tissue samples or fresh biopsy samples are acceptable
[p] Objective disease assessment (tumor imaging) pretreatment represents the baseline study for the patient's response to treatment evaluated using RECIST and iRECIST. The same imaging modality must be used throughout the study for an individual patient. See Table 13 for timepoints of subsequent evaluations

Table 12: Schedule for Sampling for PK and Cytokines – Combination Arm B

Day	**Day 1**											**Day 2**	**Day 15**					**Day 29**										
Time After Start of Infusion	Predose	0	8 min	11 min	15 min	20 min	30 min	1 hr	2 hr	4 hr	6 hr	24 hr	Predose	0	1 hr	4 hr	6 hr	Predose	0	8 min	11 min	15 min	20 min	30 min	1 hr	2 hr	4 hr	6 hr
Acceptable Range for Blood Sampling	-2 hr to -2 min		± 0.5 min	± 0.5 min	± 1 min	± 1 min	± 1 min	± 3 min	± 5 min	± 10 min	± 15 min	± 1 hr	-2 hr to -2 min		±3 min	±10 min	±15 min		-2 hr to -2 min		±0.5 min	±0.5 min	±1 min	±1 min	±1 min	±3 min	±5 min	±10 min	±15 min
DSP-0509 Infusion		X												X					X									
Plasma for PK	X		X	X	X	X	X	X	X	X	X	X	X			X	X	X		X	X	X	X	X	X	X	X	X
Plasma for Cytokines	X							X	X	X	X	X	X		X	X	X[a]	X							X	X	X	X

[a] Optional blood collection for cytokine and PK is at 6 hours

Table 13: Schedule of Events – Day 43 to End of Study – Combination Arm B

Tests and Procedures	**Day 43 and Ongoing**								**End of Study**
Day	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**Subsequent[a]**	**30 Days After Last Dose of DSP-0509**
Window	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**+ 7 d**
DSP-0509 Infusion	X	X	X	X	X	X	X	q2w	
Pembrolizumab Infusion[b, c]	X			X			X	q6w[c]	
Physical Examination	X	X	X	X	X	X	X	q2w	X
Pregnancy Test[d]									X
ECOG Performance Status	X	X	X	X	X	X	X	q2w	X
Vital Signs	X[c]	X	X	X[c]	X	X	X[c]	q2w	X
Body Weight	X	X	X	X	X	X	X	q2w	X
Hematology Tests	X	X	X	X	X	X	X	q2w	X
Clinical Chemistry Tests	X	X	X	X	X	X	X	q2w	X
Urinalysis	X	X	X	X	X	X	X	q4w	X
MUGA Scan or ECHO									X
Eye Exam by Ophthalmologist[e]		X		X			X	q6w	X
12-Lead Safety ECG[f]									X
Pharmacokinetics[g]	X								
Plasma for Cytokines[g]	X			X					
Blood for PBMC Lymphocyte Markers[h]	X						X		
Blood for Tumor Markers[i]	X			X			X	X[j]	X
Blood for Future Biomarker Analysis[h, k]	X			X			X		X
Tumor Samples for Immune-related Biomarkers[l]				X					X
Tumor Samples for Future Biomarker Analysis[l, k]				X					X
Objective disease Assessment[m]	X			X			X	X	X
Concomitant Medications	<------ Continuously from Consent to EoS ------->								
Adverse Events	<------ Continuously from Consent to EoS ------->								

ECG = electrocardiogram; ECHO = echocardiogram; HLA = human leukocyte antigen; IHC = immunohistochemistry; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; TIL = tumor infiltrating lymphocyte

[a] Entries in the "Subsequent" column indicate the interval at which procedures need to be repeated after Day 127, **if** the patient remains on treatment. For additional details, see the specific footnote for the procedure

[b] Pembrolizumab treatment (400 mg IV) will start on Day 1 and thereafter will be administered every 6 weeks as detailed in Section 7.3 in accordance with the US Package Insert

[c] On days when both DSP-0509 and pembrolizumab are administered, vital signs will be taken (a) prior o DSP-0509 infusion, (b) 4 hours after DSP-0509 infusion and, if assessed as stable by the investigator, pembrolizumab will be infused, and (c) 30 to 60 minutes after the end of the pembrolizumab infusion, prior to discharge from the site
[d] A pregnancy test (serum) is to be performed on all females of child-bearing potential at Screening and at the End-of-Study visit as scheduled, and at other times as judged appropriate by the investigator
[e] Eye exam includes slit lamp exam, visual field testing, and fundoscopy
[f] Manual 12-lead ECGs are to be performed after 10 minutes rest, in triplicate, at least 5 minutes apart at the End-of-Study visit
[g] See Table 14 for detailed schedule of blood sampling for cytokines on Days 43 and 85, and of blood sampling for PK on Day 43
[h] Blood sampling for PBMC lymphocyte markers and future biomarkers will be performed as shown. (Note: the schedule for each item is different.). Samples to be collected will include whole blood (for PBMCs), whole blood and plasma (see Laboratory Manual for details)
[i] Tumor markers in blood will be assessed as appropriate for those cancers for which markers are known to exist, eg, CA-125, PSA, AFP, CA19-9, CEA
[j] Subsequent samples are to be collected on Day 169 and then every 12 weeks to coincide with objective evaluation (radiologic imaging; see footnote "l")
[k] An additional separate informed consent is needed at the prestudy evaluation to collect and store blood and archival and/or fresh biopsy tumor tissues for future exploratory biomarker analyses
[l] Optional tumor sample collections if medically feasible. See Section 8.2.15.2 for further details
[m] Objective disease assessments by tumor imaging are used to assess the patient's response to treatment according to RECIST and iRECIST. The same modality for tumor imaging must be used throughout the study for an individual patient. Post-treatment imaging will be performed every 6 weeks through Day 127 (18 weeks), as shown, also on **Day 169, and subsequently**, **every 12 weeks** until PD is observed. Imaging should be performed at the end of study unless it has been done in the previous 8 weeks

Table 14: Schedule for Sampling for PK and Cytokines – Combination Arm B

Day	**Day 43**					**Day 85**					
Time After End of Infusion	Predose	0	1 hr	4 hr	6 hr	Predose	0	1 hr	2 hr	4 hr	6 hr
Acceptable Range for Blood Sampling	-2 hr to -2 min		± 3 min	± 10 min	± 15 min	-2 hr to -2 min		± 3 min	± 5 min	± 10 min	± 15 min
DSP-0509 Infusion		X					X				
Plasma for Cytokines	X		X	X	X[a]	X		X	X	X	X
Plasma for PK	X			X							

[a] Optional blood collection for cytokine at 6 hours

Table 15: Schedule of Events – Screening and Treatment Periods - Combination Arm C

Tests and Procedures	Screening		Dose-expansion Treatment Period											End of Study	
Day	**-28 to -1**	**-7 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**Subsequent**	**EoS 30 days after last DSP-0509 infusion**	**Survival Follow-up every 6 months**
Window			**–**	**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**+7 d**	**±7 d**
													(DSP-0509 q2w) (Pembro q6w)		
Informed Consent[a]	X														
Assess Eligibility	X														
Demographics	X														
Medical and Cancer History	X														
Hospitalization			X												
DSP-0509 Infusion			X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Infusion[b, c]			X[c]			X[c]			X[c]			X[c]	X[c]		
Physical Examination	X		X	X	X	X	X	X	X	X	X	X	q2w	X	
Pregnancy Test[d]	X													X	
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	q2w	X	
Vital Signs[c]		X	X[c]	X	X	X[c]	X	X	X[c]	X	X	X[c]	q2w[c]	X	
Body Weight		X	X	X	X	X	X	X	X	X	X	X	q2w		
Height		X													
Hematology		X	X[e]	X	X	X	X	X	X	X	X	X	q2w	X	

Tests and Procedures	Screening		Dose-expansion Treatment Period											End of Study	
Day	**-28 to -1**	**-7 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**Subsequent**	**EoS 30 days after last DSP-0509 infusion**	**Survival Follow-up every 6 months**
Window			**–**	**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**+7 d**	**±7 d**
Clinical Chemistry		X	X[e]	X	X	X	X	X	X	X	X	X	q2w	X	
Coagulation (PT and PTT only)		X													
Urinalysis		X	X[e]	X	X	X	X	X	X	X	X	X	q4w	X	
Serum Virology (HBV, HCV, HIV)[f]	X														
Chest X-ray	X														
MRI of brain[g]	X														
Bone scan (if indicated)[h]	X														
MUGA or ECHO	X				X									X	
Eye Exam by Ophthalmologist[i]	X				X		X		X			X	q6w	X	
12-Lead Safety ECG[j]	X		X		X									X	
PK[k]			X		X	X									
Plasma for Cytokines[k]			X		X	X			X						
Blood for PBMC Lymphocyte Biomarkers	X			X	X	X			X						
Blood for Tumor Markers[l]	X					X			X			X	X	X	
Blood for Future Biomarker Analysis[m]	X					X			X			X		X	

Tests and Procedures	Screening		Dose-expansion Treatment Period											End of Study	
Day	**-28 to -1**	**-7 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**Subsequent**	**EoS 30 days after last DSP-0509 infusion**	**Survival Follow-up every 6 months**
Window			**–**	**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**+7 d**	**±7 d**
Blood for ctDNA Analysis	X														
Tumor Samples for TMB Analysis[n]	X														
Tumor Samples for Immune-related Biomarkers[n]	X					X								X	
Tumor Samples for Future Biomarker Analysis[m,n]	X					X								X	
Objective Disease Assessment[o]	X					X			X			X	X	X	
Survival Follow-up															X[p]
Concomitant Medications	---------- Continuously from Consent to EoS ----------														
Adverse Events	---------- Continuously from Consent to EoS ----------														

CR = complete response; d = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hr = hour; IFNα = interferon alpha; IHC = immunohistochemistry; IL-1RA = interleukin 1 receptor antagonist; IL-6 = interleukin 6; IP-10 = inducible protein 10; iRECIST = Immune Response Evaluation Criteria in Solid Tumors; min = minutes; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetics; PR = partial response; PT = prothrombin time; PTT = partial thromboplastin time; q2wk = every 2 weeks; q3wk = every 3 weeks; q4wk = every 4 weeks; q6wk = every 6 weeks; SD = stable disease; TIL = tumor infiltrating lymphocyte; TMB = tumor mutational burden; TNFα = tumor necrosis factor alpha.

[a] Informed consent is to be obtained before performing any study-specific procedures; begin collection of AEs after consent is obtained

[b] Pembrolizumab treatment (400 mg IV) will start on Day 1 and thereafter will be administered every 6 weeks as detailed in Section 7.3, in accordance with the US Package Insert

[c] On days when both DSP-0509 and pembrolizumab are administered, vital signs will be taken (a) prior to DSP-0509 infusion, (b) 4 hours after DSP-0509 infusion and, if assessed as stable by the investigator, pembrolizumab will be infused, and (c) 30 to 60 minutes after the end of the pembrolizumab infusion, prior to discharge from the site

[d] A pregnancy test (serum) is to be performed on all females of child-bearing potential at Screening and at EoS visit as scheduled, and at other times as judged appropriate by the Investigator
[e] Day 1 laboratory assessments do not need to be repeated if done within the previous 3 days
[f] Viral serology tests include HBsAg, anti-HCV, and HIV Ag & Ab screening test
[g] A brain MRI will be performed at baseline to rule out brain metastases, and at subsequent time points if clinically indicated
[h] A bone scan will be conducted when clinically indicated.
[i] Eye exam includes slit lamp exam, visual field testing, and fundoscopy.
[j] Manual 12-lead ECGs are to be performed after 10 min rest, in triplicate, at least 5 min apart, at Screening, predose on Day 1, at 24 hours postdose on Day 2, and predose on Day 29.
[k] See Table 16 for detailed schedule of blood sampling for pharmacokinetics and for cytokines
[l] Tumor markers in blood will be assessed as appropriate for those cancers for which markers are known to exist, eg, CA-125, PSA, AFP, CA19-9, CEA
[m] An additional, separate informed consent is needed at the prestudy evaluation to permit collection and storage of blood and tumor tissues (archival and/or fresh biopsy) for future exploratory biomarker analyses
[n] Tumor samples are required at the Screening evaluation; either archival tissue samples or fresh biopsy samples are acceptable. See Section 8.2.15 for further details.
[o] Objective disease assessment by tumor imaging are used to assess the patient's response to treatment evaluated using RECIST and iRECIST. The same modality for tumor imaging must be used throughout the study for an individual patient. Post-treatment imaging will be performed every 6 weeks up to the Day 547 visit (18 months), and subsequently every 12 weeks until PD is observed. Imaging should be performed at the End-of-Study visit unless it has been done in the previous 6 weeks for patients coming off study prior to or on Day 547, or in the previous 12 weeks for patients who come off study after the Day 547 visit.
[p] A phone call to the last phone numbers provided by the patient will be made every 6 months (±7 days) starting from the date of the final dose of DSP-0509, to determine overall survival (OS) until the patient is known to be no longer alive or withdraws consent. A date of death should be obtained, and any anticancer treatments, whether systemic, surgical, or radiation, also should be collected and reported on the Survival Follow-up eCRF.

Table 16: Schedule for Sampling for PK and Cytokines – Combination Arm C

Day	**Day 1**							**Day 29**							**Day 43**							**Day 85**						
Time After Start of Infusion	Predose	0	8 min	11 min	30 min	2 hr	4 hr	Predose	0	8 min	11 min	30 min	2 hr	4 hr	Predose	0	8 min	11 min	30 min	2 hr	4 hr	Predose	0	8 min	11 min	30 min	2 hr	4 hr
Acceptable Range for Blood Sampling	-2 hr to -2 min		±0.5 min	±0.5 min	±1 min	±5 min	±10 min	-2 hr to -2 min		±0.5 min	±0.5 min	±1 min	±5 min	±10 min	-2 hr to -2 min		±0.5 min	±0.5 min	±1 min	±5 min	±10 min	-2 hr to -2 min		±0.5 min	±0.5 min	±1 min	±5 min	±10 min
DSP-0509 Infusion		X							X							X							X					
Plasma for PK	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X							
Plasma for Cytokines	X					X	X	X					X	X	X					X	X	X					X	X

8.2. Description of Study Procedures

Please see the SoEs for study visits when the procedures are to be performed in the individual study Arms and Phases.

8.2.1. Telephone Contacts

Patients will be asked to provide telephone numbers for both themselves and a close family member or caregiver. This primary purpose for this information is for use in the following contexts:

- Follow-up of an AE reported by the patient at a visit
- A clinically significant abnormal test result or finding is returned after a visit
- The patient misses a scheduled visit without informing the site
- During the DLT period (Days 1 through 42), a telephone safety check will be done on the following days (±1) when there is no clinic visit scheduled for infusion:
  - Monotherapy Arm A: Days 8, 22, and 36
  - Combination Therapy Arm B: Days 8, 22, and 36
- To determine OS via phone call every 6 months, starting from the date of the final dose of DSP-0509, until the patient is known to no longer be alive or withdraws consent. A date of death should be obtained, and any anticancer treatments, whether systemic, surgical, or radiation, also should be collected and reported on the Survival Follow-up electronic Case Report Form (eCRF).

8.2.2. Medical and Cancer History

The medical history will include all pertinent aspects of the patient's past health, as well as aspects of the underlying tumor, including date of diagnosis, extent of surgery, dose of radiotherapy administered, duration of chemotherapy, and date of recurrence or progression.

8.2.3. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status (Table 17) is a scale used to assess the progress of a patient's disease, evaluate how the disease affects the patient's daily living abilities, and determine appropriate treatment and prognosis.

Table 17: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity; fully active; able to carry on all predisease 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 out any self-care; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

8.2.4. Clinical Laboratory Evaluation

The hematology, coagulation parameters (only required at Screening visit; prothrombin time (PT) and partial PTT needed for inclusion criteria), and clinical chemistry laboratory analyses will be performed at a local laboratory. Reference ranges will be supplied and used by the investigator to assess the laboratory data for clinical significance and pathological changes. Day 1 laboratory assessments do not need to be repeated if done within the previous 3 days.

8.2.4.1. Hematology

A complete blood count will include red blood cell (RBC) count, Hgb, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, WBC count with differential, absolute and percent neutrophils, absolute and percent lymphocytes, absolute and percent monocytes, absolute and percent eosinophils, and absolute and percent basophils; and platelet count.

8.2.4.2. Coagulation

Coagulation parameters (PT and PTT) will be collected at Screening for eligibility purposes.

8.2.4.3. Clinical Chemistry

Serum chemistry tests will include measurements of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, lactate dehydrogenase, amylase, gamma glutamyl transpeptidase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, uric acid, total protein, albumin, globulin, creatinine kinase, cholesterol, triglycerides, calcium, magnesium, and phosphate; also C-reactive protein (CRP), thyroid stimulating hormone (TSH), and free thyroxine (free T4).

8.2.4.4. Urinalysis

A urinalysis will include measurements of pH, specific gravity, and dipstick determinations of protein, nitrite, glucose, ketones, RBCs, WBCs, 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.

8.2.4.5. Pregnancy Testing

Pregnancy testing in women of childbearing potential may be obtained with a serum beta human chorionic gonadotropin test at Screening. A pregnancy test also will be performed by serum at the EoS visit, and if clinically indicated per the investigator's judgment.

8.2.4.6. Serology Testing

Testing for HBsAg, HCV antibody, and HIV.

8.2.5. Vital Signs

Vital signs will include systolic and diastolic blood pressures, pulse, respiratory rate, temperature, and weight. Height is assessed at Screening only. Blood pressure and heart rate will be recorded after the patient has rested in the sitting position for at least 5 minutes.

8.2.6. Physical Examination

A physical examination will include examination of the skin; head, eyes, ears, nose, and throat; and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

8.2.7. Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded from Screening through the EoS visit. See Section 7.13.2 for a list of medications and therapies that are prohibited during the study.

8.2.8. Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted from signing of the informed consent form through 30 days after last dose of investigational therapy. Refer to Section 11 for details regarding definitions, documentation, reporting, and follow-up of AEs and SAEs, including information on Adverse Events of Special Interest (AESIs), such as COVID-19.

8.2.9. Objective Disease Assessments

Tumor lesions will be evaluated radiologically by CT or MRI scans while on study so that response to treatment can be assessed according to RECIST and iRECIST. At the EoS visit, CT/MRI scans will be performed according to the SoE. The same modality must be used throughout the study for an individual patient. PET-CT scans may be used for patients with non-small-cell lung cancer (NSCLC), breast cancer, HNSCC, renal cancer, and melanoma, but only if this imaging procedure is approved by the health insurance company of the patient.

An MRI scan of the brain will be done primarily to rule out brain metastases.

8.2.10. Cardiac Assessments

8.2.10.1. 12-lead Safety ECGs

A 12-lead ECG will be obtained in triplicate with the patient having rested in a supine position for at least 10 minutes before the first recording, and with at least 5-minute intervals between recordings. The following intervals should be determined for each recording either by the machine used or manually: PR interval, QRS complex duration, QT interval, and QTcF. If any results outside normal ranges are deemed clinically significant by the investigator or appropriately qualified designee, these should be recorded as AEs.

8.2.10.2. Cardiodynamic Assessment

The 12-lead Holter and associated laptop computer equipment will be supplied to the study sites. Holter devices will be required only for Day 1 of the Monotherapy Arm A.

On Day 1, a Holter monitor will be placed on the patient 1 hour prior to start of DSP-0509 infusion and remain in place until 24 hours (Day 2) after the end of infusion. On Day 1, patients should be supine and at rest from at least 10 minutes before to 5 minutes after (a) the interval from start of infusion to 30 minutes post-start of infusion; and (b) for similar periods around each subsequent timepoint shown in Table 8. Concurrent PK samples should be obtained on time, and the exact times for the start of infusion and the start and end of the rest periods recorded to permit ECG extraction by the Holter vendor.

The continuous 12-lead digital ECG data are stored on memory cards in the device. After the Holter is removed, the memory card is collected, placed in the laptop provided, the data is transferred via internet to the central vendor and analyzed as follows: up to 13 triplicate 12-lead ECGs will be extracted at the nominal time points detailed in Table 7 using the precisely recorded times indicating the start of infusion and the start of the rest interval. The procedures for ECG extraction, interval measurements, and statistical analysis will be provided separately.

8.2.10.3. MUGA Scan and ECHO Assessments

Either MUGA scan or ECHO may be used to perform cardiac assessments, which should include left ventricular ejection fraction (%), presence or absence of pericardial effusion and, if done by ECHO, interventricular septum thickness. Additionally, any abnormalities will be noted, as well as their clinical significance.

8.2.11. Chest X-rays

Chest x-rays will be performed at Screening to assess for pulmonary disorders and patient eligibility. Any clinically significant findings will be noted in history.

After consent, chest x-rays can be performed at the investigator's discretion on an as-needed basis. Clinically significant changes (new or worsening) will be recorded as AEs.

8.2.12. Ocular Examinations

Ocular examinations, including Slit Lamp examinations, visual field testing, and fundoscopy, will be performed as indicated on the SoE by a qualified ophthalmologist to monitor for potential ophthalmologic toxicity.

Should any ocular symptoms occur between scheduled exams, the patient should be referred immediately to an ophthalmologist for diagnostic work-up, and the Medical Monitor is to be notified. Symptoms may include, but are not limited to, sudden appearance of floaters, flashes of light in one or both eyes (photopsia), blurred or distorted vision, gradually reduced peripheral vision, a curtain-like shadow over visual field, and/or lost vision.

Ocular examinations will note any abnormalities and, if present, whether the abnormalities are new, the same as noted at baseline, or worsening.

8.2.13. Pharmacokinetic Testing

Blood and urine samples will be collected for the determination of plasma concentration of DSP-0509. On the days when blood samples are taken, the morning dose of DSP-0509 must be administered at the site, and the precise infusion start and stop times (hours:minutes:seconds) must be documented. Infusion start and stop times and PK sample times are to be based on the same clock.

Blood samples for PK assessments are to be drawn from the arm contralateral to the site of drug administration.

Note that urine samples to assess PK will be collected, but only in Monotherapy Arm A.

8.2.13.1. Infusion Procedure on PK Sampling Days

The procedure for administering DSP-0509 as a 10-minute infusion by syringe infusion pump is detailed in Appendix 18.1. On days when PK samples are to be collected, it is essential that the procedure be followed exactly as described to avoid artifactual levels.

- **Of critical importance**: At the end of infusion, solution remaining in the catheter connecting the syringe in the pump to the patient **must not be manually** flushed into the patient.

8.2.13.2. Collection of PK Blood Samples

Please note the following items regarding timing of collection of all PK samples. DSP-0509 is to be administered as a 10-minute infusion using a syringe infusion pump (see Appendix 18.1 for full details)

- Time zero (t=0) is defined as the infusion **start** time.
- PK collection times are specified as time relative to the start of infusion, eg,:
  - 8-minute sample occurs 8 minutes after start of infusion, ie, 2 ± 0.5 minutes before end of infusion
  - 11-minute sample occurs 11 minutes after start of infusion, ie, 1 ± 0.5 minutes after end of infusion
- Collection times (and windows) for all PK blood samples are detailed in the SoE

Critical elements of the procedure for collecting valid PK samples are the following:

- PK blood samples must be collected from the arm contralateral to DSP-0509 infusion
- Immediately prior to collecting each PK sample, a volume of blood equal to or slightly greater than the void volume of the sampling catheter must be drawn and discarded to

assure no dilution of the sample by fluid in the sampling catheter. (The latter assumes the PK sampling catheter remains in the patient's vein between PK samples.)
- Please refer to the Study Laboratory manual for required sample blood volumes, collection tube specifications, sample processing, specimen storage, and other details of the procedures for collecting PK blood samples.

Please refer to the Study Laboratory manual for further details and guidance on obtaining PK samples in an indwelling line.

8.2.13.3. Collection of PK Urine Sample

The times for collection of a urine sample for PK analysis on Day 1 and Day 43 of Monotherapy Arm A are detailed on the SoE for those days. On the day of dosing, the predose urine sample is collected as convenient before the start of infusion of DSP-0509 and the time recorded. The time of the last void before the start of infusion also should be recorded. For each of the collection intervals, the volume of urine collected and the times of the first and last voids within each collection interval will be recorded.

8.2.14. Blood Samples for Tumor Markers, Lymphocyte Phenotype, and Cytokines

Blood samples for serum, plasma, and peripheral blood mononuclear cells (PBMCs) will be collected to assess the following:

- Tumor markers for those cancers for which markers have been established, eg, CA-125, PSA, AFP, CA19-9, CEA
- Lymphocyte immunophenotype, eg, activated lymphocytes, effector memory cells, myeloid cells, T cell proliferation
- Cytokines, eg, IFNα, IP-10, IL-1RA, TNFα, and IL-6
- ctDNA (in Combination Arm C, dose-expansion patients only)

8.2.15. Tumor Tissue Samples

8.2.15.1. Tumor Tissue Samples to be Provided at Screening

Prior to initiation of study treatment, tumor tissue samples are required of all patients and may be obtained in one of the 3 forms described below. Please refer to the NeoGenomics "BBI-DSP-0509-101 Tissue Sample Collection and Shipping Instructions" manual for requirements relating to each form (eg, size of the tissue block; number of fixed, unstained slides; handling of fresh biopsy tissue) as well as details regarding handling and shipping.

- Preferred archival material is a block of formalin-fixed tumor tissue embedded in paraffin. The block of tissue must be of sufficient size to provide the required number of slides needed for baseline assessments. The remaining part of the tumor block will be returned to the site upon request.
- As an alternative to a block of tumor tissue, required number of slides may be provided as fixed, unstained archival tumor tissue mounted on positively charged glass slides.
- If archival tumor tissue is unavailable, an attempt should be made to obtain a fresh biopsy of tumor tissue.

8.2.15.2. Tumor Tissue Obtained On- or Post-Treatment

After start of treatment, obtaining fresh tumor tissue requires a biopsy procedure, which is optional, and should be performed only if medically feasible. The timepoints and conditions at which tumor tissue should be obtained are:

- EoS, if the patient discontinues study treatment before Day 43 (Combination Arm C patients) or before Day 85 (Monotherapy Arm A or Combination Arm B patients)
  - Should be obtained as soon as feasible after study treatment is discontinued
- Day 43 (Combination Arm C patients) or Day 85 (Monotherapy Arm A or Combination Arm B patients) unless the patient has achieved CR (whichever comes first)
- After Day 43 or Day 85 under the following conditions:
  - Patients with SD at Day 43 or Day 85 who show PR in subsequent disease assessment; biopsy will be performed when PR is confirmed (= iPR according to iRECIST)
  - Patients with suspected pseudo-progression at Day 43 or Day 85 who show PR or SD in subsequent disease assessment; biopsy will be performed when PR or SD is confirmed (= iPR or iSD according to iRECIST)

Details of sample collection, processing, shipping, and storage are described in the "Sample Collection and Shipping Instructions" manual.

8.2.16. Analysis of Tumor Samples

Tumor tissue samples obtained before study drug treatment (archival or fresh) may be analyzed for immune-related gene expression and additional biomarkers, eg, CD8 (by IHC), TMB, TIL, and HLA-ABC (by IHC). Biopsies from patients in the Combination Arms B and C also may be analyzed for PD-L1.

8.2.17. Specimen Sampling for Future Exploratory Biomarker Analysis

If consent is given, both blood samples and tumor tissue may be collected and stored long-term for future analysis of as-yet unidentified exploratory biomarkers (eg, protein and gene expression analysis) that may be important to the understanding of DSP-0509 mechanism of action. Providing informed consent for storage of samples for this purpose is optional and is not a requirement for participation in the study.

9. EFFICACY ASSESSMENTS

9.1. Efficacy Assessment

The evaluation of efficacy will be based on the patient's measurable disease, using RECIST and iRECIST. If PD is determined by RECIST, an additional scan for confirmation of PD is required (per iRECIST) 4 to 8 weeks later.

Additional efficacy variables include the following:

- ORR – the proportion of patients who achieve CR/PR per RECIST or iCR/ iPR per iRECIST
- TTP – time from date of enrollment to date of first documented PD per RECIST, or iUPD if iCPD is subsequently confirmed per iRECIST
- DOR – time from first documentation of response until time of first documentation of PD per RECIST, or iUPD if iCPD is subsequently confirmed per iRECIST
- PFS – time from first day of treatment to either (a) date of PD per RECIST, or iUPD if iCPD is subsequently confirmed per iRECIST, or (b) in the absence of documented PD, the date of death by any cause

9.2. Biomarker Assessments

Plasma cytokines will be correlated with dose level and safety outcomes.

Blood and tumor exploratory biomarkers will be correlated with efficacy outcomes.

10. PHARMACOKINETIC ASSESSMENTS

The pharmacokinetics of DSP-0509 will be evaluated in this study and will include those parameters described in Table 18, data permitting. Additional parameters may be added. PK data may be analyzed in conjunction with data from other studies (for example, for population PK analyses).

Table 18: Pharmacokinetic Parameters to be Assessed in DSP-0509

λz	terminal elimination rate constant
A_e	cumulative amount of unchanged drug excreted in urine
AUC_t	area under the concentration-time curve from time 0 (dosing) to the time of the last measurable concentration
AUC_{24}	area under the concentration-time curve from time 0 (dosing) through 24 hours post-dosing (ie, daily exposure)
AUC_{inf}	area under the concentration-time curve from time 0 (dosing) extrapolated to infinity
CL	clearance
CL_R	complete renal clearance from plasma
C_{max}	maximal plasma concentration
C_0	initial concentration of DSP-0509 at time 0 (dosing)
F_e (%)	Percentage of the intravenously administered drug excreted into the urine
$t_{1/2}$	terminal elimination half-life
V_c	initial volume of distribution (time 0)
V_z	volume of distribution at the terminal phase

11. SAFETY ASSESSMENTS

Safety will be evaluated using scheduled assessments, reported AEs, and unscheduled assessments performed to evaluate AEs.

- Scheduled assessments include physical examinations, vital signs, clinical laboratory tests, ECGs, imaging studies (MUGA scans, ECHO, chest x-ray, CT/MRI) and ocular examinations (slit lamp, fundoscopy, visual field testing)
- Patients will be asked about AEs at all scheduled and unscheduled contacts. Events will be collected from the time the patient signs his or her informed consent through 30 days after the last dose of study treatment. As detailed in Section 12.4.2, all events will be reported in data listings; treatment-emergent AEs (TEAEs), defined as events with onset after start of the first infusion of investigational agent, also will be summarized in tables.

11.1. Adverse Events and Serious Adverse Events

11.1.1. Adverse Events: Definition

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 investigational agent, 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 11.2.4.5 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 study, the investigator must notify the Sponsor according to the procedures provided in Section 11.2.5.1.

11.1.2. Adverse Reactions and Suspected Adverse Reactions: Definition

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 also may 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.

11.1.3. Serious Adverse Events: Definition

A serious adverse event (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 preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form (ICF) (as documented as medical history on the eCRF)
- 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.

11.2. Procedures for Eliciting, Recording, and Reporting 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 through 30 days after the last dose of the investigational agent will be recorded in the eCRF

An AE will be followed until it is either resolved, has returned to baseline status, 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 the Sponsor or designee, as outlined in Section 11.2.5.1.

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 nonserious.

11.2.1. Relationship to Investigational Agent

A medically qualified investigator must assess the relationship of any AE to the use of the investigational agent as not related, unlikely related, possibly related, probably related, or definitely 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 to the Study Drug

- 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 the AE cannot be excluded with complete confidence

Related to the Study Drug

- 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 also could have been produced by other factors)
- Probably Related: suggests that a reasonable temporal sequence of the event with the investigational agent administration exists, and that the likely causal association of the event with the investigational agent exists as well. This will be based upon the known pharmacologic 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 the event, which corresponds with the known pharmaceutical profile, improvement on discontinuation, or reappearance upon rechallenge.

11.2.2. Adverse Event Severity

The severity of AEs will be assessed according to NCI CTCAE, version 5.0. For events not specifically found in CTCAE, the following definitions will be used to estimate the 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 used often 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 11.1.3), 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.

11.2.3. Assessment of Expectedness

The Reference Safety Information (RSI) for assessing the expectedness of an AE in this study is to be the section identified as the RSI in the most recent DSP-0509 Investigator's Brochure (IB). The RSI for assessing the expectedness of an AE for a co-suspect drug in this study is to be the US full prescribing information for pembrolizumab.

11.2.4. Specific Instructions for Recording Adverse Events on the eCRF

11.2.4.1. 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 the elevated transaminases, bilirubin, or jaundice). However, if a constellation of signs and/or symptoms cannot be characterized medically as a single diagnosis or syndrome, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is established subsequently, it should be reported as follow-up and should replace the individual signs and/or symptoms with the event term on the eCRF.

11.2.4.2. 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).

11.2.4.3. Medication Errors, Misuse, and Abuse of Investigational Agent

Overdose, medication error, misuse, off-label use, abuse, and occupational exposure are defined as follows:

- Overdose: refers to the administration of a quantity of investigational agent given per administration or cumulative that is above the maximum dose according to the protocol. Clinical judgement always should 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 used intentionally for medical purpose not in accordance with the protocol
- Misuse: refers to situations where the investigational agent is used intentionally and inappropriately not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional, excessive use of the investigational agent that is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to exposure to the investigational agent as a result of one's professional or nonprofessional occupation

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

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

11.2.4.4. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should be recorded only once on the SAE Report form and/or the AE eCRF. If a persistent AE increases 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.

11.2.4.5. 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 to be additional information that must be collected 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 AE 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 AEs 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

11.2.4.6. New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least 1 of the seriousness criteria (Section 11.1.3). New primary cancers are those that are not the primary reason for administration of study treatment and have developed after inclusion of the patient in 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 AEs/SAEs unless fatal.

11.2.4.7. 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.

11.2.4.8. Death

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 the Sponsor or its designee as an SAE and recorded on the AE eCRF.

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

11.2.5.1. Immediate Reporting of Serious Adverse Events or Pregnancy by the Investigator to the Sponsor

All SAEs from the time of signing informed consent through 30 days of receiving the last dose of investigational agent, including SAEs from screen failure patients, 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:

Sumitomo Dainippon Pharma Oncology, Inc
Pharmacovigilance Department Contact Information:
Email: BBISafety@bostonbiomedical.com
Fax: +1.617.674.8660

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 a hospital discharge summary) must be documented on a follow-up form. All follow-up information must be reported in the same timelines as the 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.

11.2.5.2. Immediate Reporting of Adverse Events of Special Interest, Occupational Exposure, Overdose, or New Cancers

Any occupational exposure or exposure of an individual not enrolled in the study to the investigational agent 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 of the investigational agent must be reported to the Sponsor or designee **within 24 hours** of the investigator's first knowledge of the event. Overdose should be communicated on the SAE Report form, as described above for SAEs.

Any new cancer 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. New cancers should be communicated on the SAE Report form, as described above for SAEs.

11.2.5.3. 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 11.2.5.1.

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 11.2.5.1.

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.

11.2.5.4. Reporting Pregnancies

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

If not all information on the Pregnancy Report 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 is completed. The pregnancy outcome and the status of the newborn (if applicable) will be reported on the Pregnancy Report form within 24 hours of becoming aware. SAEs associated with the pregnancy, including fetal death, miscarriage, or congenital anomalies must be reported as SAEs, according to Section 11.2.5.1.

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).

11.2.5.5. 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 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), in accordance with local laws and regulations.

11.2.5.6. 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 into the Investigator's Regulatory Binder, in accordance with local regulations.

12. STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor/designee.

12.1. Statistical Methods

- Statistical analyses will be descriptive in nature. No formal sample size calculations will be performed for this study.
- All antitumor parameters including response will be evaluated on the per-protocol population, as defined in Section 12.2, and summarized using descriptive statistics. Patient response will be assessed based on RECIST or iRECIST; Kaplan-Meier estimates of PFS will be generated. Data listings and summaries may include tumor markers, additional imaging, or other response data. Potential relationships between PK, pharmacodynamics, and other response data may be evaluated.
- Adverse events will be assessed based on the safety population, as defined in Section 12.2, according to CTCAE v 5.0 when appropriate, and will be evaluated by grade and SOC. Adverse event listings and tabulated summaries of categorized TEAEs will be generated for each dose level and for patients overall. Additionally, the number treated, number evaluable for dose escalation, and number with DLTs will be described for each dose level and for the study overall. Vital signs, laboratory data, and ECG data (stratified by dose level and overall) will be summarized for changes over time on study and each postbaseline visit together with the change from baseline.
- Descriptive statistics (n, mean, standard deviation, median, and ranges for continuous variables; frequencies and percentages for categorical variables) will be provided by dose level and/or visit, if applicable. All data will be listed by patient, dose level, and visit where applicable. All summaries, statistical analyses, and individual patient data listings described below will be completed by using SAS v9.3 or later (SAS Institute, Inc, Cary, North Carolina, USA).

12.2. Definition of Study Populations

The Full Analysis Set (FAS) in this study consists of all patients who entered the study and received one dose of study treatment (DSP-0509 or pembrolizumab).

The safety population is the same as the FAS.

The DLT population will consist of all patients who met the prespecified criteria for being evaluable for DLT detailed in Section 7.6.

The Per-protocol Set (PPS) will consist of patients who meet all the following criteria:

- Received at least 2 consecutive doses of DSP-0509 as scheduled
- Had a baseline (Screening) tumor assessment
- After initiation of therapy, had at least 1 objective disease assessment according to RECIST or iRECIST

The determination of the PPS will be finalized following a complete data review by both Syneos Health and/or the Sponsor representatives before the database lock.

The PK Set (PKS) will be all treated patients with at least 1 measurable PK value.

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 the treatment for 6 months or more without regard to tumor response status.

12.3. Determination of Sample Size

The study is exploratory in nature; there is no hypothesis test and thus no power calculation has been performed.

12.3.1. Dose Escalation and Dose Expansion

Dose Escalation (Phase 1)
The exact number of patients to be enrolled in each dose-escalation cohort cannot be specified in advance because of the dynamic features of BLRM (see Section 7.4.1). The actual sample size may vary depending on the incidence of DLT events and the number of dose levels studied.

It is envisaged that approximately 21 to 30 patients will be enrolled (aimed to complete treatment and assessments) in each dose-escalation Arm (A or B), for a total of 42 to 60 patients.

Dose Expansion (Phase 2)
Approximately 20 to 40 patients will be enrolled in the dose-expansion Combination Arm C, for a total of 62 to 100 patients overall. This is considered clinically adequate for the preliminary assessment of PK, pharmacodynamics, and efficacy data.

A Bayesian approach will be used to continuously assess the posterior probability of the ORR.

If the probability of the posterior probability in the target ORR range (≥target ORR, eg, ≥15%) is <10% (stopping zone), enrollment may be stopped and the final actual sample size may be less than 40, depending on the enrollment rate. If the probability of the posterior probability in the target ORR range is ≥10%, enrollment may continue until all 40 patients have been enrolled.

With 20 patients enrolled who meet the ES criteria, and the true ORR is 15%, there will be an 82% probability to observe a minimum of 2 objective responders.

12.4. Planned Analyses

All safety analyses will be performed on the safety population, and all efficacy analyses will be based on the PPS. Efficacy analyses also may be conducted in all patients who receive at least 1 dose of study drug (DSP-0509 or pembrolizumab), ie, FAS.

12.4.1. Demographic and Other Baseline Characteristics

All demographic and baseline characteristics information will be summarized using the FAS and the PPS.

12.4.2. Safety Endpoints

Safety evaluation will include assessments of TEAEs, DLTs, serum chemistry tests, hematology values, urinalysis, pregnancy, performance status (ECOG score) evaluations, study drug exposure, vital signs, physical examinations, ECGs, MUGA/ECHO scans, xrays, and eye tests.

Patient incidence rates of all TEAEs/DLTs will be tabulated by SOC and preferred term. Tables and/or narratives of on-study deaths and serious and significant TEAEs, including early withdrawals due to TEAEs, also will be provided. The extent of study exposure also will be summarized descriptively.

12.4.3. Efficacy Endpoints Analysis

The efficacy endpoints are PFS, DoR, TTP, OS, DCR, and ORR. The Kaplan-Meier method will be used to estimate and visualize the distribution of PFS. For the calculation of PFS, progressions assessed by CT or MRI will be used as events. The calculation approach for PFS considering the various situations for censoring will follow the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 (Center for Drug Evaluation and Research, 2007). Further details for the analysis of the PFS will be provided in the SAP.

For the dose-expansion Combination Arm C, the ORR will be monitored and used to adjust the patient enrollment as follows:
•After 10 evaluable patients, assess posterior probability ORR:
—If posterior prob ($\Theta \geq 0.15$) <0.10, consider stopping for futility
—If posterior prob ($\Theta \geq 0.15$) ≥0.80, consider stopping for early efficacy*
—At 40 patients, if posterior prob ($\Theta \geq 0.15$) ≥0.50, consider declaring efficacy*
* Consider proceeding to dose expansion or Phase 2 for that patient set (either HNSCC with primary or acquired resistance or both).

12.4.4. Pharmacokinetic Analyses (Secondary Endpoints)

The PK concentrations and parameters will be derived for DSP-0509, and the relationship of PK parameters with dose (dose-proportionality) will be evaluated by statistical methods.

The following standard PK parameters will be analyzed: AUC_t, AUC_{24h}, AUC_{inf}, C_{max}, accumulation ratios (R_{acc}) for C_{max} and AUC, C_0, λz, $t_{1/2}$, V_C, V_z, CL, A_e, F_e (%), and CL_R. Additional parameters may be added as needed.

PK concentration at 4 hours postdose on Days 15, 29, and 43, and trough PK concentrations on Days 15, 29, and 43 will be used to evaluate the attainment of steady state. The R_{acc} will be calculated for C_{max} and AUC and compared between Day 1 and the next DSP-0509 infusion for which dense PK sampling is available.

Descriptive statistics will be provided for the PK parameters and concentrations. Dose-proportionality, attainment of steady state, and R_{acc} will be assessed. Correlation of exposure with response, and correlation with pharmacodynamics parameters such as response and survival, may be conducted. PK data may be analyzed in conjunction with data from other studies (for example, for population PK analyses). Each of the above PK analyses will be conducted where data permits.

The details of statistical analyses and presentation of the PK data will be discussed in the SAP.

12.4.5. Pharmacodynamic Analyses (Secondary Endpoints)

Descriptive statistics will be provided for actual measured data in tumors at Screening. The results of the testing of plasma cytokine levels will be presented in listings and summarized by tumor type and cohort. The relationship between the baseline and on-treatment cytokines levels and efficacy results will be evaluated as prognostic factors by statistical methods as the data allow. Graphical presentations will also support preliminary inferential analyses. The pharmacodynamics summaries and exploratory analyses will be described in the SAP in greater detail.

12.4.6. ECG Analysis

The analysis of ECG results will be based on patients in the safety analysis set and will follow the ICH E14 guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (Thomson, 2018).

Exploratory analysis may be conducted to assess the relationship between DSP-0509 plasma concentration and QT interval length from the Holter ECG data using a PK/pharmacodynamics modeling approach. The intensive ECGs from the Holter recordings will be analyzed by an ECG core laboratory, and details of the analyses will be provided in a separate SAP and/or report.

12.4.7. Subgroup Analyses

Details of subgroup analyses as appropriate will be presented in the SAP.

12.4.8. Protocol Deviations

All deviations related to study inclusion or exclusion criteria, 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 clinical study report.

Major and minor protocol deviation criteria will be defined prospectively before study analysis. Major deviations are those considered likely to affect the reliability of the results of the study or the safety of the patient. Minor deviations are those considered to be unlikely to have an impact on the reliability of the results, but which still contribute significant deviations from this protocol.

13. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

13.1. Study Monitoring

During the study, a monitor from the Sponsor or its designee will have regular contact with the investigational site, to:

- Provide information and support to the investigator and study staff
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that DSP-0509/pembrolizumab accountability checks are being performed
- Perform source data verification (SDV). This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. SDV will require direct access to all original records for each patient (eg, clinic charts, ECHOs)
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm that any AEs, SAEs, and AESIs have been properly documented on eCRFs, and confirm that any SAEs have been forwarded to the Sponsor, and that those SAEs that met criteria for reporting have been forwarded to the IRB/IEC

The monitor will be available between visits if the investigator(s) or other staff need information or guidance.

During the COVID-19 public health emergency, traditional on-site monitoring might be difficult for the following reasons:

(1) sites may not be able to accommodate monitoring visits (eg, due to staffing limitations or site closures)

(2) monitors may not be able to travel to study sites. When planned on-site monitoring visits are not possible, the reason should be documented and available for review by the Sponsor and during FDA inspections

13.2. Audits and Inspections

Authorized representatives of the Sponsor, any regulatory authority having an interest in this study, or the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may visit the site to perform audits or inspections. The purpose of audit or inspection by the Sponsor is to examine all study-related activities and documents systematically and independently, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if notified by a regulatory agency about an inspection.

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 informed consent form (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 ASSURANCE AND QUALITY CONTROL

14.1. Audit and Inspection

Study sites and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. This would include routine clinical audits or directed or for-cause audits. In addition, inspections may be conducted by regulatory authorities at their discretion.

14.2. Monitoring

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF.

In accordance with current GCP and ICH guidelines, the study monitor will carry out SDV at regular intervals to ensure that the data collected in the eCRF 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 the data contained in the eCRFs.

14.3. Data Management and Coding

The Sponsor or Syneos Health will be responsible for the activities associated with 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 from this clinical study will be handled according to the relevant standard operating procedures of the Data Management and Biostatistics Departments of Syneos Health.

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

14.4. Data Collection/Electronic Data Capture

The Sponsor/Syneos Health will provide eCRFs. Results from Screening and data collected during the study (except clinical laboratory test results) will be recorded in the patient's eCRF.

Study sites will use an electronic data capture (EDC) system that is compliant with relevant FDA regulatory requirements per title 21 Code of Federal Regulations Part 11. Password-protected access to the EDC system will be enabled via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed eCRFs must be reviewed and electronically signed and dated by the Investigator.

The database will be locked after completion of the study, when all data have been checked for plausibility and corrected to the extent possible, and all coding and assessments have been completed.

14.5. Records and Supplies

14.5.1. Drug Accountability

On receipt of study drug, the investigator (or designee) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study site and return the original receipt to the study monitor. The study monitor may check the study supplies at each study site at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or designee) has documented correctly the amount of study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study site at all times. The study monitor also will perform an inventory of study drug at the close-out visit to the study site. All discrepancies must be accounted for and documented.

14.6. Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between Syneos Health and the Sponsor.

14.7. Compensation

The patient will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the ICF and the site clinical trial agreement (CTA).

15. ETHICS

15.1. Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study site, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB, together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of patients or conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB, as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

15.2. Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of participating countries, according to local/national requirements, for review and approval before beginning the study. On completion of the study, regulatory authorities will be notified that the study has ended.

15.3. Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence with the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and applicable national and local laws and regulatory requirements.

15.4. Informed Consent

The process of obtaining informed consent must be performed in accordance with applicable regulatory requirement(s) and must adhere to ICH GCP.

The investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study.

The investigator or designated personnel will inform each patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the patient's ICF will be provided to the patient or the patient's legally authorized representative.

A patient may refuse to enter the study or to withdraw from the study at any time, without consequences for further care or penalty or loss of benefits to which the patient is otherwise

entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to a patient's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). Study patients will be informed about this new information and reconsent will be obtained.

15.5. Patient Confidentiality

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 regulatory agency(ies), will be granted direct access to the study patient's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patient to the extent permitted by laws and regulations. In any presentation of the results of this study or in publications, the patient's 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 the confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act and applicable national and/or local laws and regulations regarding personal data protection.

16. REPORTING AND PUBLICATION, INCLUDING ARCHIVING

The complete publication policy for the study will be described in detail in the clinical study agreement. To avoid disclosures that could jeopardize proprietary rights, the investigator agrees to give the Sponsor the right to review all publications, including, but not limited to, manuscripts, abstracts, and presentations related to this study, with adequate time prior to their submission for publication or presentation. The Sponsor may use these data now and in the future for all purposes, including presentation or publication at the Sponsor's discretion, for submission to government regulatory agencies, or for purposes of inclusion in patent-related filings and submissions. Publication authorship among investigators will be based on the extent of significant contribution, including scientific and clinical.

17. REFERENCES

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18. APPENDICES

18.1. DSP-0509 Infusion Procedure

DSP-0509 is to be given IV as a 10-minute infusion administered using an infusion pump.

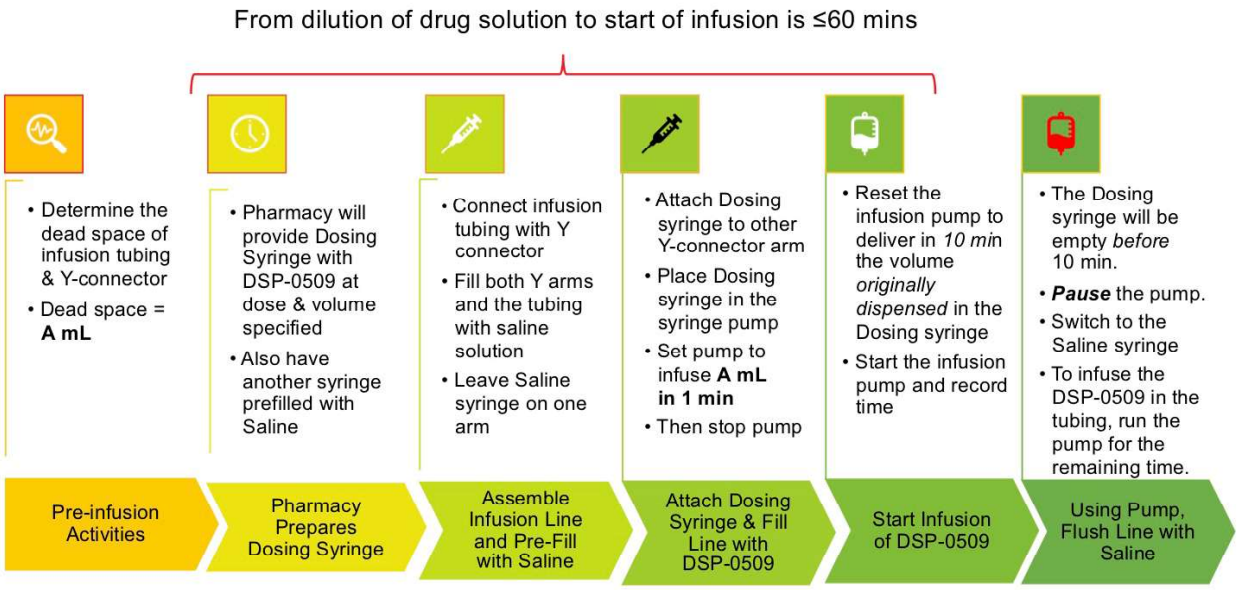
- This procedure is designed to assure the entire volume of dosing solution is delivered over 10 minutes at as constant a rate as possible. This is particularly critical to have valid monitoring of C_{max}, which is required for this investigational product and is determined by dense PK sampling on Days 1 and 43 for all patients in dose-escalation cohorts.
- This procedure has been developed based on extensive conversations with site clinical and pharmacy personnel. Individual sites may have preferences, experience, and/or equipment that could require modifications to the procedure. To accommodate this, sites may discuss those modifications with the Medical Monitor and may then submit a formal description of the proposed procedure. If approved, the modified procedure will be filed in the site's Trial Master File and the site will document that all personnel administering DSP-0509 have been trained in that procedure.

Definitions of Key Materials Needed

- "Dosing syringe" – provided by the pharmacy and containing the assigned dose of DSP-0509 in the volume specified below
- "Saline syringe" – with approximately10 mL normal saline for injection (may be provided by the pharmacy or prepared by site personnel). Will be used (a) to prime the IV tubing before start of infusion, and (b) to administer the dosing solution remaining in the tubing after the dosing syringe is empty
- IV tubing – to run from the Y-connector (see below) to the IV in the patient
- Y-connector – will connect to the IV tubing just before the infusion pump; the two arms of the Y-connecter will go to (a) the dosing syringe and (b) the saline syringe
  Note: The following plastic materials used in syringes and tubing have been evaluated and confirmed as compatible with the dosing solution: polypropylene, polycarbonate, polybutadiene, acrylonitrile-butadiene-styrene copolymer
- An accurate timepiece (eg, watch, clock) – to be available from start of the infusion for at least the next 4 hours, and during that period to be used as the source of the times recorded for all events associated with both the infusion and PK sample collection

Preinfusion Activities

- In advance of the infusion, get a reliable estimate of the total dead space (volume) of the tubing and the Y-connector
  - Typically, this volume should be ≤2 mL. If the volume of the proposed tubing at the site exceeds that, please discuss with the Medical Monitor.
- **Note:** The simplest way to determine the total dead space is to assemble the items, attach a syringe with a known volume of saline and see how much saline must be injected to fill the tubing. Obviously, the actual components used for this purpose must be discarded, but the *exact* same make/model of tubing and connector *products* must be used for *all* infusions.



Preparation of Dosing Syringe in Pharmacy

The pharmacy will prepare the Dosing syringe as described below.

- *The infusion should begin within one (1) hour after the syringe is prepared.*
- The DSP-0509 dosing solution provided is 0.3 mg/mL. At dose levels of ≥1.5 mg the dose volume is ≥5 mL which is sufficient for the procedure described.
- At dose levels of 0.3 and 1 mg, the pharmacy will add saline (as indicated in the table below) to the dose volume as provided so the Dosing syringe contains at least 5 mL.

Dose per infusion (mg)	Dose volume (mL) as provided	Volume (mL) of saline to be added	Final volume (mL) in Dosing syringe
0.3	1	4	5
1	3.33	1.67	5

- If the SRC recommends dose levels <1.5 mg not shown, the Sponsor will indicate the saline volume needed for that dose level.

Assemble Tubing and Y-connector and Prefill with Saline

- Identify the end of the tubing that will go into the patient's IV line.
- Connect the *opposite* end of the tubing (the pump end) to the "base" of the Y-connector.
- Connect the Saline syringe to one arm of the Y-connector.
- Fill just that arm and clamp it.
- Transfer the Saline syringe to the other arm of the Y-connector.
- Fill that arm *and* the entire tubing.
- Cap the "patient" end of the tubing.
- Then, leaving the Saline syringe attached, clamp that arm of the Y-connector.

Attach Dosing Syringe and Fill Tubing with DSP-0509 Solution

- Attach the available arm of the Y-connector to the Dosing syringe.

- Place the Dosing syringe in the syringe pump
- Set the syringe pump to deliver *in 1 min*
  - ***only*** the dead space volume of the connector and the tubing
- Start the infusion pump.
- When the infusion pump stops, reset the infusion pump to deliver *in 10 min*
  - the volume *originally dispensed* in the Dosing syringe (see table above)

Infusion of DSP-0509

- The delegated site personnel must remain at the infusion pump the entire procedure.
- Start the infusion pump. Record the exact time as *Start of Infusion*.
- **Note:** The Dosing syringe will be empty *before* the end of the 10 min infusion time.
  - The *approximate* time the Dosing syringe should be empty is

$$10\ \text{min} \times \left(\frac{\text{The volume in the Dosing syringe } as\ received - \text{The dead space volume}}{\text{The volume in the Dosing syringe } as\ received}\right)$$

- **Note:** On PK days, there are blood draws scheduled at
  - 8 (±0.5) min post-start of infusion, i.e., 2 (±0.5) min *before* end of infusion
  - 11 (±0.5) min post-start of infusion, i.e., 1 (±0.5) min *after* the end of infusion
  - It should be anticipated that an additional person will be needed to help collect these samples at the required timepoints.

Using the Infusion Pump, Flush Tubing with Saline

- When the dosing syringe is empty, there will still be time remaining on the pump. ***Pause*** the infusion pump. Do ***not*** cancel the program.
- *Do not administer the Dosing solution in the tubing by* **manual** *flushing of the line.*
- *The remaining dosing solution must be administered using the following procedure.* **Please proceed as smoothly and quickly as possible***:*
  - Clamp the arm of the Y-connector attached to the Dosing syringe
  - Remove the Dosing syringe from the syringe pump
  - Place the Saline syringe in the syringe pump
  - Unclamp the Connector arm attached to the Saline syringe
  - Restart the syringe pump to complete the programmed 10 min infusion
- At the end of the programmed 10 minutes, the pump should stop the infusion. Record the exact time the pump stopped as the *End of Infusion*.
- Disconnect the tubing from the patient's IV line.
- Attach the patient to Normal Saline; follow institutional KVO (keep vein open) procedure
- Proceed with PK blood draws, if scheduled on that day.
- Discard the Dosing syringe, Saline syringe, tubing, and Y-connector per institutional procedure.

18.2. RECIST 1.1 and iRECIST

Table 19: Comparison of RECIST 1.1 vs. iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1: Comparison of RECIST 1.1 and iRECIST

Table 20: Assignment of Timepoint Response using iRECIST

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 2: Assignment of timepoint response using iRECIST

18.3. Extracts from NCCN Guidelines for irAEs

The tables below are from the NCCN monograph "Management of Immune Checkpoint Inhibitor-Related Toxicities" (NCCN, 2020).

Table 21: Principles of Routine Monitoring for Immune-Checkpoint Inhibitors

Pre-Therapy Assessment[a]	Monitoring Frequency[b]
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening as indicated	Clinical exam at each visit with adverse event (AE) symptom assessment
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated
General bloodwork • CBC with differential • Comprehensive metabolic panel	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms
Pancreatic (ICI_ENDO-1) • Baseline testing is not required.	No routine monitoring needed if asymptomatic
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)[c]	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated
Adrenal/Pituitary (ICI_ENDO-4) • Adrenal: Serum cortisol (morning preferred)[c] • Pituitary: TSH, free thyroxine (T4)[c]	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6–12 weeks
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs) for high-risk patients	Repeat oxygen saturation tests based on symptoms
Cardiovascular (ICI_CARDIO-1) • Consider baseline EKG • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B).
[b] Closer monitoring may be required for patients with combination immunotherapy regimens.
[c] After first four doses of immunotherapy, only as clinically indicated.

Table 22: Assessment and Grading of Infusion-Related Reactions

Adverse Event	Assessment	Grading
Infusion-related reactions [a]	Physical Exam Vital Signs Pulse Oximetry ECG (if chest pain or sustained tachycardia)	Grade 1: Mild, transient Grade 2: Moderate [b] Grade 3: Severe [c]

[a] Symptoms include: Fever/chills/rigors, urticaria/pruritus, angioedema, flushing/headache, hypertension, hypotension, shortness of breath, cough/wheezing, hypoxemia, dizziness/syncope, sweating, and arthralgia/myalgia. Refer to prescribing information for each individual immunotherapy agent for recommendations for premedication to prevent infusion reactions

[b] Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, acetaminophen, NSAIDs, narcotics, intravenous [IV] fluids); prophylactic medications indicated for less than or equal to 24 hours.

[c] Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement. Hospitalization indicated; life-threatening consequences; urgent intervention

18.4. Bayesian Logistic Regression Model

Operating Characteristics of the BLRM for Monotherapy Arm A

Introduction

In the dose-escalation part of the study, an adaptive BLRM with EWOC will be used to guide dose escalation and estimate the MTD(s) based on occurrence of DLT during Cycle 1.

This appendix provides details on the statistical model, prior definitions, and operating characteristics in order to illustrate the performance of the design in estimating the MTD under various dose-toxicity relationships through simulations. Finally, hypothetical dose-escalation scenarios will be presented to illustrate the dose allocation in the first cohorts of the study.

Dose Escalation Method

Statistical Model

The dose-DLT relationship in the dose-escalation part of the study with a q1w schedule is described by a 2-parameter model (logistic model):

$$logit\left(\pi_{(d)}\right) = \log(\alpha) + \beta \log(d/d^*), \alpha > 0, \beta > 0$$

where $logit\left(\pi_{(d)}\right) = \log\left(\frac{\pi_{(d)}}{1-\pi_{(d)}}\right)$, $\pi_{(d)}$ is the probability of a DLT at dose d. Doses are rescaled as d/d^* with reference dose $d^* = 2.4\ mg$ of DSP-0509. As a consequence, α is equal to the odds of toxicity at d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

The MTD is the highest drug dosage that is unlikely (<25% posterior probability) to cause DLT in more than 33% of the treated patients in the first cycle of DSP-0509 treatment.

Provisional Doses Level

This study currently plans to conduct dose escalation with the provisional dose levels shown in Table 3. However, it is possible that intermediate dose levels may be added, that certain provisional dose levels may be skipped, or that certain provisional dose levels may not be tested during the course of the study.

Notes:

- The dose level as well as the reference dose level input into the BLRM can be expressed either as the individual administered dose level or the total planned doses to be administered in the DLT period (first 42 days)
- If a new dosing schedule for DSP-0509 in the DLT period is added (eg, q2w), a new BLRM model with a similar form can be set up. The posterior distributions from the BLRM of the previous dosing schedule (eg, q1w) with available DLT data up to the new dosing schedule cohort start will be used to define the priors distribution for the new BLRM model.

Prior Specifications

The bivariate normal prior for the BLRM parameters with a reference dose level of 2.4 mg is obtained as follows:

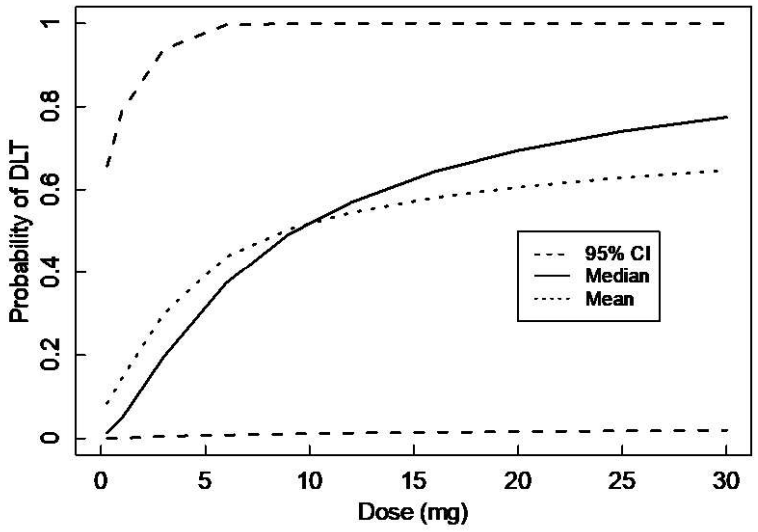
The following noninformative prior for $(\log(\alpha), \log(\beta))$ was used:

- The median DLT rate at the DSP-0509 reference dose (2.4 mg) was assumed to be 15%, ie, $\text{mean}(\log(\alpha)) = \log(0.15/0.85)$.
- A doubling in dose was assumed to double odds of a DLT, ie, $\text{mean}(\log(\beta)) = 0$.
- The standard deviation of $\log(\alpha)$ was set to 2, and the standard deviation of $\log(\beta)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha)$ and $\log(\beta)$ was set to 0.

Table 23: Prior Parameters for Bivariate Normal Distribution of Model Parameters

Parameters	Means	Standard deviations	Correlation
$\log(\alpha), \log(\beta)$	(-1.7346, 0.000)	(2.000, 1.000)	0

Figure 5: Prior Distribution of DLT Rates



Abbreviations: CI = confidence interval; DLT = dose-limiting toxicity.

Table 24: Prior Distribution Summaries Derived from Priors in Table 23

DSP-0509 Dose (mg)	Prior Probabilities That Pr(DLT) is in Interval			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]			2.5%	50%	97.5%
0.3*	0.8424	0.0773	0.0803	0.0841	0.1645	0	0.0129	0.6576
1	0.723	0.1277	0.1493	0.1446	0.2104	0.0001	0.0479	0.7889
3	**0.4591**	**0.178**	**0.3629**	**0.2992**	**0.2867**	**0.0046**	**0.1953**	**0.9376**
6	**0.3063**	**0.1592**	**0.5345**	**0.4383**	**0.3382**	**0.0078**	**0.3733**	**0.9968**
9	**0.2537**	**0.1391**	**0.6072**	**0.5045**	**0.3503**	**0.0102**	**0.4926**	**0.9997**
12	**0.2221**	**0.1288**	**0.6491**	**0.5452**	**0.3539**	**0.0124**	**0.5694**	**1**
16	**0.1966**	**0.1196**	**0.6838**	**0.5812**	**0.3545**	**0.0142**	**0.6438**	**1**
20	**0.1794**	**0.1116**	**0.709**	**0.6063**	**0.3534**	**0.0159**	**0.6943**	**1**
25	**0.1646**	**0.1048**	**0.7306**	**0.6293**	**0.3513**	**0.0175**	**0.7409**	**1**
30	**0.1525**	**0.1015**	**0.746**	**0.6467**	**0.3491**	**0.0191**	**0.7745**	**1**

Abbreviations: DLT = dose-limiting toxicity; SD = standard deviation
Bold values – doses not meeting the overdose criterion (>25% chance of excessive toxicity) with prior information only.
* Starting dose.
Note: This updated table includes the additional provisional dose levels from 6 mg to 30 mg, while keeping the same prior distribution of the DLT rate as in the original BLRM setup. Therefore, it shows high toxicity levels at the higher provisional dose levels. The DLT posterior from the BLRM will be mostly driven by the clinical study data after a few patients complete the DLT evaluation with minimum impact from the initial prior.

Dose Recommended by the BLRM Method

The dose allocation will start at the dose of 0.3mg. Patients will be included by cohort of 3 to 6 patients.

After each cohort of patients is completed, the dose recommendation by the model will be based on posterior summaries including the mean, median, standard deviation, 95% credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0, 16%) under dosing
- [16%, 33%) targeted toxicity
- [33%, 100%] excessive toxicity

Following the principle of EWOC, after each cohort of patients, the recommended dose by the model is the one with the highest posterior probability of the DLT rate falling in the targeted

interval (16%, 33%) among the admissible doses fulfilling EWOC, ie, it is unlikely (<25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval.

Final Recommendation and Stopping Rules

Dose escalation will continue until identification of the MTD(s) or suitable lower dose for recommended dose(s) for expansion. This will occur when the following conditions are met:

- At least 6 patients have been treated at this dose
- This dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 21 patients have already been treated on the study
- It is the dose recommended for patients, by review of all clinical data by participants of the end of cohort meeting

Of note, the dose-escalation part could be stopped earlier by a joint decision from the Sponsor and the Investigators during a dose escalation meeting, by considering the model estimations and a global assessment of the safety, PK, pharmacodynamics, and preliminary activity data.

Operating Characteristics

Introduction

This section presents the operating characteristics illustrating the precision of the design in estimating the MTD under various assumed true dose-toxicity relationships.

True Dose-DLT Scenarios

Multiple simulations for true dose-toxicity relationships were performed with MTD located at none, late, middle, or early, or lowest (all) of the provisional dose levels as shown in Table 24.

Table 25: True Underlying DLT Probabilities

True Dose-DLT Scenario	DSP-0509 Dose Level (mg)									
	0.3	**1**	**3**	**6**	**9**	**12**	**16**	**20**	**25**	**30**
A	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
B	0.05	0.07	0.09	0.11	0.13	0.15	0.17	0.19	0.21	0.23
C	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
D	0.2	0.25	0.3	0.35	0.4	0.45	0.45	0.45	0.45	0.45
E	0.36	0.4	0.45	0.45	0.45	0.45	0.5	0.55	0.6	0.65

Abbreviation: DLT = dose-limiting toxicity.
Gray shading indicates doses with true DLT probability within the targeted toxicity interval (16%, 33%).

Simulation Parameters

For each dose-DLT scenario, 1000 clinical study replications were generated using R software version 3.4.4 on a x86-64 architecture on a Windows OS. The Markov chain Monte Carlo

(MCMC) estimation is obtained using Rjags R package with 5000 burn-in and 10,000 iterations on 2 chains (5000 each). The seed used for data generation is 123456789, and the seed used for MCMC estimation is 1 for chain 1 and 2 for chain 2.

The following study simulation parameters were used:

- Cohort size: 3
- Maximum number of patients: 30

The dose allocation rule used in the simulations is identical to the rule presented above, ie, dose having the highest posterior probability of the DLT rate falling in the targeted interval (16%, 33%) among the admissible doses fulfilling EWOC.

Evaluation Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance of the design under each true dose-DLT relationship. The following metrics were:

- Probability of recommending as the MTD:
  - An undertoxic dose level, ie, a dose with true probability of DLT in the under-dosing toxicity interval [0%, 16%) (Sponsor risk)
  - A targeted dose level, ie, a dose with true probability of DLT in the targeted toxicity interval [16%, 33%] (correct final decision)
  - An overtoxic dose level, ie, a dose with true probability of DLT in the excessive toxicity interval [33%, 100%] (patient risk)
- Average number of patients per study exposed at:
  - An undertoxic dose level, as defined above
  - A targeted dose level, as defined above
  - An overtoxic dose level, as defined above
- Summary of the total number of patients per study (average, first quartile, median, third quartile)
- Average total number of DLTs observed per study

Operating Characteristics of the Design

Operating characteristics of the final design are reviewed to investigate performance of the model under each true dose-DLT scenario. Table 26 summarizes the results from the simulations performed.

Table 26: Summary Metrics of the Simulations Performed

True Dose-DLT Scenario	Probability of Recommending a Dose With True P(DLT)			No MTD Recom-mendation	Average Number of Patients Per Trial Receiving a Dose With True P(DLT)			Average Number of Patients	
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]		[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Per Trial	Experiencing a DLT per Trial
A	97.3	0	0	2.7	29.1	0	0	29.2	1.4
B	68.4	27.5	0	4.1	26.5	1.8	0	28.6	2.7
C	59.9	32.1	4.8	3.2	21.5	5.8	0.3	27.9	3.7
D	0	60.9	2.7	36.4	0	16.3	0.5	19.2	4.4
E	0	0	16.8	83.2	0	0	4	9.7	3.6

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NA = not applicable.

The BLRM method with the specified prior performs well, with a high probability of correctly identifying a targeted dose level (60.9%) and a low probability of excessive toxicity (2.7%) under Scenario D, which is considered to be the most likely dose-toxicity scenario. The method performs reasonably well under the unlikely scenarios (Scenarios A and E).

In general, the probability of selecting a targeted dose level is sufficiently high across the scenarios (except for Scenarios A and E), and the average number of patients treated at excessively toxic doses is low. In Scenario E, where all provisional doses are considered too toxic, the simulations show that the study will terminate early with the average of 9.7 treated patients, and MTD will not be determined more than 80% of the time.

Hypothetical Dose Allocation Scenarios in Early Cohorts

Aside from the overall operating characteristics studied above, the design should make reasonable decisions during a study based on the observed DLTs. After completion of a given cohort, the dose allocation for the subsequent cohort will depend on the recommendation of the model and medical review of all available data.

Some scenarios to illustrate on-study dose allocation are presented in Table 27. These scenarios assume that each cohort has 3 evaluable patients, and the next recommended dose is based on the rule defined above, with the provisional doses as specified. However, during the study it may be possible to include 3 to 6 patients by cohort and to add new provisional dose levels.

Table 27: Hypothetical Dose Allocation Scenarios in Early Cohorts

Cohort [Scenario] Prior DLTs	Dose (mg)	Number of DLT(s) / Number of Patients	Next Dose Level (NDL) Proposed (mg)	Decision †	P(Target) NDL	P(Overtox) NDL	Median DLT Rate at NDL
1	0.3	0/3	1.8	E	0.162	0.136	0.071
		1/3	0.3	S	0.288	0.230	0.168
		2/3	--*	--*	--*	--*	--*
		3/3	--*	--*	--*	--*	--*
2a 0/3 DLT in Cohort 1	1.8	0/3	3	E	0.190	0.148	0.089
		1/3	1.8	S	0.338	0.236	0.191
		2/3	0.6	D	0.270	0.154	0.129
		3/3	0.3	D	0.214	0.144	0.095
2b 1/3 DLT in Cohort 1	0.3	0/3	0.6	E	0.311	0.160	0.149
		1/3	--*	--*	--*	--*	--*
		2/3	--*	--*	--*	--*	--*
		3/3	--*	--*	--*	--*	--*
3a 0/3 DLT in Cohort 1 and Cohort 2	3	0/3	3	S	0.122	0.030	0.049
		1/3	3	S	0.335	0.225	0.183
		2/3	1.8	D	0.314	0.127	0.140
		3/3	1.8	D	0.262	0.205	0.144
3b 0/3 DLT in Cohort 1, 1/3 DLT in Cohort 2	1.8	0/3	1.8	S	0.287	0.074	0.118
		1/3	1	D	0.299	0.081	0.124
		2/3	1	D	0.400	0.228	0.208
		3/3	0.6	D	0.330	0.219	0.181
3c 1/3 DLT in Cohort 1, 0/3 DLT in Cohort 2	0.6	0/3	1	E	0.310	0.126	0.138
		1/3	0.6	S	0.439	0.216	0.208
		2/3	0.3	D	0.465	0.245	0.227
		3/3	--*	--*	--*	--*	--*
3d 1/3 DLT in Cohort 1, 1/3 DLT in Cohort 2	**	0/3	1.8	E	0.162	0.136	0.071
		1/3	0.3	S	0.288	0.230	0.168
		2/3	--*	--*	--*	--*	--*
		3/3	--*	--*	--*	--*	--*

Abbreviations: DLT = dose-limiting toxicity; EWOC = escalation with overdose control.
† Decision E = escalate, S = stay, D = de-escalate.

P(Target) NDL: posterior probability that the true DLT rate for the next recommended dose lies in the targeted interval (16%, 33%).
P(Overtox) NDL: posterior probability that the true DLT rate for the next recommended dose lies in the excessive toxicity interval (33%, 100%).
* No doses are considered safe according to the EWOC condition.
** No provisional dose level meeting EWOC criteria

In general, when no DLTs are observed in 3 patients at a dose level, the decision is made to increase the dose. When 1 DLT is observed in 3 patients, the decision is to stay at the current dose level or to escalate to the higher provisional dose level. When more than 1 DLT is observed in a 3-patient cohort, the decision is made to decrease the dose level or to stay at the current level.

Operating Characteristics of the BLRM For Combination Arm B

Introduction

This document defines the key elements of a dose-escalation design for a combination therapy based on Agent 1 (DSP-0509) and Agent 2 (pembrolizumab) using a BLRM approach.

General Considerations

A dose-escalation design for combination therapies based on a BLRM approach (Neuenschwander, 2008) will be used in this study to examine the number of DLTs in the individual patient cohorts and determine the MTD. The BLRM method will be applied along with the EWOC principle (Babb , 1998; Rogatko, 2007) to control the risk of exposing patients to toxic doses.

BLRM Model

A BLRM model that allows for an interaction between the 2 agents will be used in this study. The model has 3 components, namely, the marginal models for each agent and an interaction model.

The marginal model for Agent 1 is given by

$$\text{logit}(\pi_1) = \log(\alpha_1) + \beta_1 \log(x_1).$$

Here π_1 is the probability of a DLT as a function of the dose d_1. Also, x_1 is a standardized dose with respect to a predefined reference dose, eg, x_1 is equal to d_1/d_1^*, where d_1^* is the reference dose for Agent 1, ie, 2.4 mg.

The marginal model for Agent 2 is given by

$$\text{logit}(\pi_2) = \log(\alpha_2) + \beta_2 \log(x_2).$$

As above, π_2 is the probability of a DLT as a function of the dose d_2 and x_2 is a standardized dose with respect to a predefined reference dose for Agent 2, ie, 200 mg.

Finally, the interaction model is expressed in terms of the odds of a DLT. Let φ_{12} denote the odds of a DLT at the combination dose (x_1, x_2). Similarly, let φ_1 and φ_2 denote the odds of a

DLT for Agent 1 at the dose x_1 and for Agent 2 at the dose x_2, respectively. The interaction model is given by

$$\varphi_{12} = (\varphi_1 + \varphi_1 + \varphi_1\varphi_2)\, g(\eta, x_1, x_2),$$

where η is the interaction parameter, and the interaction multiplier is defined as follows:

$$g(\eta, x_1, x_2) = \exp(\eta x_1 x_2).$$

To enable Bayesian inferences, the following prior distributions will be used. The logistic model parameters for each agent are assumed to follow a bivariate normal distribution, and the interaction parameter η is assumed to be normally distributed.

Selection of Prior Distributions

The prior distributions for the logistic model parameters $\log(\alpha_1)$ and $\log(\beta_1)$ corresponding to Agent 1 will be selected from the posterior distributions derived from the dose-toxicity data collected in the monotherapy portion of the study.

To illustrate the process, consider weakly informative priors for $\log(\alpha_1)$ and $\log(\beta_1)$ and assume that DLT outcomes from 2 cohorts (0/3 DLTs at 0.3 mg and 1/4 DLTs at 1 mg in the monotherapy study) are available to compute the posterior distributions of the model parameters. The resulting posterior distribution for Agent 1 computed from the 2 cohorts in the monotherapy study are presented in Table 28.

Table 28: Parameters of the Prior and Posterior Distributions for Agent 1

Distribution	Mean		Standard Deviation		Correlation
	$\log(\alpha_1)$	**$\log(\beta_1)$**	**$\log(\alpha_1)$**	**$\log(\beta_1)$**	
Prior distribution	-1.7346	0	2	1	0
Posterior distribution	-1.0944	-0.1677	1.2700	0.5653	0.5397

Continuing to Agent 2, weakly informative priors will be selected for the logistic model parameters $\log(\alpha_2)$ and $\log(\beta_2)$ (Neuenschwander, 2008). The weakly informative priors are defined as follows:

- The median DLT rate at the reference dose is set to 0.5 and thus the mean of $\log(\alpha_2)$ is equal to $\log(0.05/0.95)$.
- A doubling of the dose is assumed to double the odds of a DLT; ie, the mean of $\log(\beta_2)$ is set to 0.
- The standard deviation of $\log(\alpha_2)$ is set to 2 and the standard deviation of $\log(\beta_2)$ is set to 1. These choices indicate considerable prior uncertainty for the dose-toxicity profile.
- The correlation between the 2 logistic model parameters is set to 0.

The resulting parameters of the prior distribution for Agent 2 are shown in Table 29.

Table 29: Parameters of the Prior Distribution for Agent 2

Distribution	Mean		Standard Deviation		Correlation
	$\log(\alpha_2)$	$\log(\beta_2)$	$\log(\alpha_2)$	$\log(\beta_2)$	
Prior distribution	-2.9444	0	2	1	0

A general rule for selecting the prior of the interaction parameter η is to set its mean to 0 and select its standard deviation based on a predefined characteristic of the interaction multiplier:

$$g(\eta, x_1, x_2).$$

Specifically, the standard deviation of η is chosen to ensure that the 97.5% percentile of the interaction multiplier's distribution at the reference doses $x_1 = 1$ and $x_2 = 1$ ranges between 3 and 9. The lower limit of this interval (3) corresponds to the case of moderate uncertainty, and the upper limit of this interval (9) indicates a considerable amount of uncertainty for the interaction parameter. In this study, the 97.5% percentile is set to 9, which means that η is normally distributed with mean = 0 and standard deviation 1.12.

The dose level, as well as the reference dose level input into the BLRM can be expressed as either the individual administered dose level or the total planned doses to be administered in the DLT period (first 42 days).

If a new dosing schedule for DSP-0509 in the DLT period is added (eg, q2w), a new BLRM model with a similar form can be set up. The posterior distributions from the BLRM of the previous dosing schedule (eg, q1w) with available DLT data up to the new dosing schedule cohort start will be used to define the priors distributions for the new BLRM model. For pembrolizumab, the 2 planned dosing schedules, eg, 200 mg q3w or 400 mg q6w results in the same total dose of 400 mg administered during the DLT period (first 42 days). For this reason, the dosing schedules will be considered equivalent when the BLRM model is fitted to the DLT data.

Decision Rules

Key components of the study design and decision rules are defined below.

Toxicity Intervals

The toxicity intervals will be defined in the study as follows:

- Underdosing interval: DLT probability is less than 16%
- Targeted toxicity interval: DLT probability is between 16% and 33%
- Excessive toxicity interval: DLT probability is greater than 33%

Overdose Control (EWOC) Criterion

A combination dose is considered safe if the probability of the excessive toxicity interval is no greater than 25%.

Dose Selection

Patients will be enrolled in cohorts of 3 to 6 patients. After each cohort, the dose recommendation by the BLRM model will be based on posterior summaries including the mean, median, standard deviation, and credible interval for the true DLT rates across the dose combinations. In addition, the probability that the true DLT rate for each dose combination is within each of the toxicity intervals (underdosing interval, targeted toxicity interval, excessive toxicity interval) will be computed. Following the EWOC principle, the recommended dose combination will be the combination with the highest posterior probability of the DLT rate falling in the targeted toxicity interval among the admissible doses that meet the EWOC criterion. The following restriction will be imposed for the purpose of evaluating the operating characteristics of the dose-escalation design:

- Only 1 agent can be escalated at a time

Stopping Rules

Dose escalation will continue until an MTD or a suitable lower dose for expansion is identified. This will occur when the following conditions are met:

- At least 6 patients have been treated at the selected dose/combination dose
- This dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 21 patients have already been treated in the dose escalation part of this study
- It is the dose/combination dose recommended for patients, either per the model or by review of all available clinical data in the joint SRC/dose escalation meeting

Clinical Study Simulations

Extensive clinical study simulations will be performed to evaluate the operating characteristics of the dose-escalation design.

The prior distributions defined in Table 28 and Table 29 will be used in the simulations. Other simulation parameters include:

- Agent 1 doses: 0.3, 1, 3, 6, 9, 12, 16, 20, 25, and 30 mg
- Agent 2: 200 mg
- Patients/Cohort: 3 each in the first two cohorts; 4 each in the remaining cohorts
- Maximum number of patients: 30 patients

Simulations will be performed under the dose-toxicity scenarios (true DLT probabilities for each combination dose) shown in Table 32. These DLT probabilities are derived from the agent-specific dose-toxicity scenarios defined in Table 30 and Table 31 under the assumption of no interaction between the 2 agents.

Table 30: Dose-Toxicity Scenarios (True DLT Probability at Each Dose) for Agent 1

Scenario	DSP-0509 Dose Level (mg)									
	0.3	1	3	6	9	12	16	20	25	30
1A	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
1B	0.05	0.07	0.09	0.11	0.13	0.15	0.17	0.19	0.21	0.23
1C	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
1D	0.2	0.25	0.3	0.35	0.4	0.45	0.45	0.45	0.45	0.45
1E	0.36	0.4	0.45	0.45	0.45	0.45	0.5	0.55	0.6	0.65

Abbreviation: DLT = dose-limiting toxicity.
Note: Gray shading = doses and scenarios with true DLT probability within the targeted toxicity interval (16%, 33%).

Table 31: Dose-Toxicity Scenarios (True DLT Probability) for Agent 2

Scenario	Pembrolizumab*
2A	0.05
2B	0.20

Abbreviation: DLT = dose-limiting toxicity.
Note: Gray shading indicates scenarios with true DLT probability within the targeted toxicity interval (16%, 33%).
* Dosing regimen (per US labeling) = 200 mg IV every 3 weeks

Table 32: Dose-Toxicity Scenarios (True DLT Probability) for Agents 1 & 2 Combined

Scenario for Agent 1	Scenario for Agent 2	Scenario	Dose Level DSP-0509 (mg) / Pembrolizumab (mg)									
			0.3 / 200	**1.0 / 200**	**3 / 200**	**6 / 200**	**9 / 200**	**12 / 200**	**16 / 200**	**20 / 200**	**25 / 200**	**30 / 200**
1A	2A	1	0.098	0.098	0.098	0.098	0.098	0.098	0.098	0.098	0.098	0.098
	2B	2	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24
1B	2A	3	0.098	0.117	0.136	0.155	0.174	0.192	0.212	0.231	0.25	0.269
	2B	4	0.24	0.256	0.272	0.288	0.304	0.32	0.336	0.352	0.368	0.384
1C	2A	5	0.098	0.145	0.192	0.24	0.288	0.335	0.383	0.43	0.478	0.525
	2B	6	0.24	0.28	0.32	0.36	0.4	0.44	0.48	0.52	0.56	0.6
1D	2A	7	0.24	0.288	0.335	0.383	0.43	0.478	0.478	0.478	0.478	0.478
	2B	8	0.36	0.4	0.44	0.48	0.52	0.56	0.56	0.56	0.56	0.56
1E	2A	9	0.392	0.43	0.478	0.478	0.478	0.478	0.525	0.572	0.62	0.668
	2B	10	0.488	0.52	0.56	0.56	0.56	0.56	0.6	0.64	0.68	0.72

Abbreviation: DLT = dose-limiting toxicity.
* Dosing regimens: DSP-0509 every 2 weeks
Pembrolizumab (per US labeling) = 200 mg IV every 3 weeks

Operating Characteristics of the Design

Operating characteristics of the dose-escalation design in the combination therapy study were evaluated under each of the 16 true dose-toxicity scenarios defined above using the assumed DLT outcomes from 2 cohorts in the monotherapy study (0/3 DLTs at 0.3 mg and 1/4 DLTs at 1 mg). Table 33 summarizes the results from the simulation study.

Table 33: Summary Metrics of the Simulations Performed

True Dose-DLT Scenario	Probability of Recommending a Dose With True P(DLT)			No MTD Recom-mendation	Average Number of Patients Per Trial Receiving a Dose With True P(DLT)			Average Number of Patients	
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]		[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Per Trial	Experiencing a DLT per Trial
1	0.952	0	0	0.048	27.4	0	0	27.4	2.6
2	0	0.629	0	0.371	0	15.8	0	15.8	3.1
3	0.953	0.014	0	0.033	27.1	0.2	0	27.3	3
4	0	0.628	0	0.372	0	15.6	0	15.6	3.2
5	0.64	0.32	0	0.04	21.1	5.2	0	26.3	3.6
6	0	0.314	0	0.686	0	15.5	0	15.5	3.4
7	0	0.569	0.024	0.407	0	14	0.5	14.5	3.1
8	0	0	0.223	0.777	0	0	5.2	5.2	1.4
9	0	0	0.154	0.846	0	0	3.5	3.5	0.9
10	0	0	0.023	0.977	0	0	0.5	0.5	0.2

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

The simulation results presented in Table 33 indicate that the BLRM method performs well in the combination therapy setting. A targeted dose level is identified with a high probability (over 60%) under Scenarios 2 and 4 that correspond to the most likely dose-toxicity scenarios. When the less likely or very unlikely scenarios are considered, eg, Scenarios 8, 9, and 10, under these scenarios, all provisional dose levels are overly toxic, eg, they range between 36% and 72%, and the probability of identifying an MTD is 22.3%, 15.4%, and 2.3%, respectively. The table also shows that the average number of patients exposed to excessively toxic doses is low. The highest number of patients treated at excessively toxic doses is achieved under Scenario 8, which is considered very unlikely, since all provisional doses are expected to be too toxic. Under the scenarios with very high toxicity levels, eg, Scenarios 8, 9, and 10, the method stops without determining the MTD about 80% or over 80% of the time.

Hypothetical Dose Allocation Scenarios in Early Cohorts

The dose-escalation rules in the combination therapy study are further illustrated by considering 32 hypothetical scenarios in the first 3 cohorts (Table 34) using these assumptions:

- The dose recommended for each subsequent cohort depends only on the model
- There are 3 patients each in the first two cohorts and 4 patients in the third cohort. During the actual study, there could be 3 to 6 patients per cohort and new provisional dose levels

Table 34: Hypothetical Dose Allocation Scenarios in Early Cohorts

Scenario	Cohort	DLT in Cohort 1 (0.3 mg)	DLT in Cohort 2 (1 mg)	Dose of Agent 1 (mg)	DLT outcomes	NDL for Agent 1	P(Target) NDL	P(Over-dosing) NDL
1	1	–	–	0.3	0/3	1	0.328	0.168

2		–	–	0.3	1/3	0.3	0.359	0.229
3		–	–	0.3	2/3	NA	NA	NA
4		–	–	0.3	3/3	NA	NA	NA
5	2A	0	–	1	0/3	1.8	0.294	0.191
6		0	–	1	1/3	1	0.437	0.218
7		0	–	1	2/3	0.3	0.375	0.135
8		0	–	1	3/3	NA	NA	NA
9	2B	1	–	0.3	0/3	0.6	0.415	0.148
10		1	–	0.3	1/3	NA	NA	NA
11		1	–	0.3	2/3	NA	NA	NA
12		1	–	0.3	3/3	NA	NA	NA
13	3A	0	0	1.8	0/4	1.8	0.208	0.037
14		0	0	1.8	1/4	1.8	0.409	0.178
15		0	0	1.8	2/4	1	0.506	0.121
16		0	0	1.8	3/4	0.6	0.435	0.092
17		0	0	1.8	4/4	0.6	0.467	0.166
18	3B	0	1	1	0/4	1	0.371	0.063
19		0	1	1	1/4	1	0.514	0.194
20		0	1	1	2/4	0.6	0.545	0.178
21		0	1	1	3/4	0.3	0.444	0.166
22		0	1	1	4/4	NA	NA	NA
23	3C	0	2	0.3	0/4	0.6	0.481	0.122
24		0	2	0.3	1/4	0.3	0.46	0.128
25		0	2	0.3	2/4	NA	NA	NA
26		0	2	0.3	3/4	NA	NA	NA
27		0	2	0.3	4/4	NA	NA	NA
28	3D	1	0	0.6	0/4	1	0.363	0.069
29		1	0	0.6	1/4	1	0.49	0.196
30		1	0	0.6	2/4	0.3	0.491	0.178
31		1	0	0.6	3/4	NA	NA	NA
32		1	0	0.6	4/4	NA	NA	NA

DLT = dose-limiting toxicity; NDL = next dose level; P(Target) NDL = posterior probability that the true DLT rate for the next recommended dose lies in the targeted interval (16%, 33%); P(Overdosing) NDL = posterior

probability that the true DLT rate for the next recommended dose lies in excessive toxicity interval (33%, 100%)