CLINICAL STUDY PROTOCOL

Phase 2, Single-arm, Open-label Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer with Actionable Genomic Alterations and Progressed on or After Applicable Targeted Therapy and Platinum-based Chemotherapy (TROPION-Lung05)

(Phase 2 Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer with Actionable Genomic Alterations)

PROTOCOL NUMBER: DS1062-A-U202

IND Number 136626/
EudraCT Number 2020-002774-27

Version 5.0, 25 Sep 2023

Daiichi Sankyo, Inc.

211 Mt. Airy Road

Basking Ridge, NJ 07920, United States

INVESTIGATOR AGREEMENT

Phase 2, Single-arm, Open-label Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer with Actionable Genomic Alterations and Progressed on or After Applicable Targeted Therapy and Platinum-based Chemotherapy (TROPION-Lung05)

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation for Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6[R2]), which has its foundations in the Declaration of Helsinki, and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.

Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

DOCUMENT HISTORY

Version Number	Version Date
5.0	25 Sep 2023
4.0	17 May 2022
3.0	14 Jul 2021
2.0	23 Sep 2020
1.0	23 Jun 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 5.0 (dated 25 Sep 2023) vs. protocol Version 4.0 (dated 17 May 2022) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS1062-A-U202 clinical study protocol (Version 5.0) by section.

Amendment Rationale:

The main purpose of this amendment to Study DS1062-A-U202 is to update safety information based on a review of the emerging data across the Dato-DXd clinical development program. Additional changes are made to add clarity to the protocol language and to ensure consistency with other studies in the development program.

Conventions Used in This Summary of Changes

All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.

Minor edits, such as updates to language that do not alter original meaning, updates to version numbering, formatting, changes in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, changes in style, or changes in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Section 1.1. Protocol Synopsis Section 6.5. Guidelines for Dose Modification Section 9.5.2. Safety Analyses Section 10.5.5. Action Taken Regarding Study Drug Section 10.7. Appendix 7: Instructions Related to Coronavirus Disease 2019 (COVID-19)	Replaced the term “dose interruption” with “dose delay”; and added the term “infusion interruption.”	To clarify whether a subject had an interruption of an infused dose versus having an upcoming dose delayed.
Section 1.3. Schedules of Events Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period	Removed the text “For subjects with a positive ADA at the Follow-up visit, an additional plasma ADA sample must be collected every 3 months (±1 month) up to 1 year from the last dose of DS-1062a, or until the ADA becomes negative, or the ADA titer becomes less than baseline, or the subject starts another therapy for cancer, or the subject withdraws consent from the study, whichever occurs first.” and the “X” in the “Long-term Survival Follow-up (Every 3 Months)” column	Because of the updated understanding of ADA and for consistency with other studies of Dato-DXd.
Section 2.2. Study Rationale Section 2.3. Benefit and Risk	Added IRR to the list of identified risks and removed it from the list of important identified	To reflect the most recent safety information.

Section # and Title	Description of Change	Brief Rationale
Assessment Section 8.4.1.2. Adverse Events of Special Interest	risks.	
Section 1.3. Schedules of Events Table 1.1: Schedule of Events for Screening and Cycles 1 through 3 of the Treatment Period Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period Section 6.5. Guidelines for Dose Modification Table 6.3: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to DS-1062a	Added "It should be strongly recommended that subjects avoid the use of contact lenses starting on the day of the first DS-1062a dose and to use artificial tears (preferably preservative free) 4 times per day as a preventative measure and up to 8 times per day as clinically needed."	To reflect the most recent safety information.
Section 1.3. Schedules of Events Table 1.1: Schedule of Events for Screening and Cycles 1 through 3 of the Treatment Period Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period	Updated the following statement: "Subjects will be provided an oral care plan prior and during study treatment: **daily before dosing, throughout treatment, and up to the first follow-up visit**."	To reflect the most recent safety information.
	Added the following footnotes: "For prevention of oral mucositis/stomatitis, initiate a daily oral care plan (see Section 8.4.4). The importance of multiple daily mouth rinses during treatment (eg, prior to dosing) and up to the first follow-up visit should be emphasized. For prevention of ocular surface toxicity, it should be strongly recommended that subjects avoid the use of contact lenses starting on the day of the first DS-1062a dose and to use artificial tears (preferably preservative free) 4 times per day as a preventative measure and up to 8 times per day as clinically needed. Ophthalmologic assessments, including, but not limited to, visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining, will be performed at screening, as clinically indicated, and at the EOT visit by an ophthalmologist or, if unavailable, another licensed eye care	For added clarity.

Section # and Title	Description of Change	Brief Rationale
	provider."	
Section 1.1. Protocol Synopsis Section 6.5. Guidelines for Dose Modification Section 10.7. Appendix 7: Instructions Related to Coronavirus Disease 2019 (COVID-19)	Updated the following statement: "The dose may be ~~interrupted~~ **delayed** for up to ~~4~~ **9** weeks (~~28~~ **63** days) from the planned date of **the next cycle** administration **(ie, up to 12 weeks or 84 days from the last infusion)**. If a subject is assessed as requiring a dose ~~interruption~~ **delay** longer than ~~4~~ **12** weeks (~~28~~ **84** days) **from the last infusion**, the subject must ~~be withdrawn from the study~~ **discontinue study treatment**. ~~unless discussed with and agreed upon by the Sponsor's Medical Monitor~~."	The duration of a dose delay period was revised to allow subjects receiving clinical benefit but requiring more recovery time to continue to receive treatment without being discontinued. The requirement to discontinue the subject with an extended dose delay from the study was revised to the requirement to discontinue the subject from treatment while remaining in the study. The language regarding the discussion with the Medical Monitor was revised for readability.
Section 1.3. Schedules of Events Table 1.1: Schedule of Events for Screening and Cycles 1 through 3 of the Treatment Period Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period Section 6.1. Study Drug Description Table 6.1: Study Drug Dosing Information Section 6.2. Preparation, Handling, Storage, and Accountability for Study Drug Section 6.5. Guidelines for Dose Modification Table 6.3: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to DS-1062a Section 8.4.4. Other Safety	Added the following text: "If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle."	To shorten the 1-hour observation period after infusion, if appropriate.

Section # and Title	Description of Change	Brief Rationale
Section 1.3. Schedules of Events Table 1.1: Schedule of Events for Screening and Cycles 1 through 3 of the Treatment Period Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period Section 6.5. Guidelines for Dose Modification Table 6.3: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to DS-1062a Section 8.4.1.2. Adverse Events of Special Interest Section 8.4.4. Other Safety	For suspected ILD/pneumonitis events, made the following changes in evaluations: "For suspected ILD/pneumonitis, treatment with study drug should be ~~interrupted~~ **delayed** pending evaluation. Evaluations should include **the following**: • High-resolution CT • Pulmonologist consultation (infectious disease consultation as clinically indicated) • ~~Blood culture and complete blood count. Other blood tests could be considered as needed.~~ • ~~Consider~~ Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests **(including FVC and CO diffusing capacity)** and pulse oximetry (SpO_2) • ~~Arterial~~ **Clinical laboratory tests** (**arterial** blood gases if clinically indicated, **blood culture, blood cell count, differential white blood cell count, C-reactive protein, and a COVID-19 test**). • One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.	To reflect the most recent safety information.
Section 2.2. Study Rationale	Split the AESI of mucositis/stomatitis into 2 AESIs of oral mucositis/stomatitis and mucosal inflammation other than oral mucositis/stomatitis.	To reflect the most recent safety information.
Section 2.2. Study Rationale Section 8.4.1.2. Adverse Events of Special Interest	Added ocular surface toxicity to the list of AESIs.	To accurately reflect the safety information.
Section 2.3. Benefit and Risk Assessment	Removed the language "As of 04 Sep 2020," in the paragraph discussing the important identified risks and identified risks for the study drug.	For accuracy, because the changes to the list of identified risks were made after 04 Sep 2020.
Section 4.1.1. Design Overview Section 8.3. Efficacy Assessments	Added "To ensure accurate survival data are available at the time of any database lock, updated survival status may be requested during the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, the planned DCO and database lock for the primary analysis and final analysis. Upon Sponsor notification, all	To ensure survival data are accurately documented.

Section # and Title	Description of Change	Brief Rationale
	subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their survival status (excluding subjects who have discontinued from the entire study or with a previously reported death event)."	
Section 6.1. Study Drug Description Table 6.1: Study Drug Dosing Information Section 6.2. Preparation, Handling, Storage, and Accountability for Study Drug	Revised the following statement: "In case of IRR at any time during treatment, ~~subsequent doses will be infused over 90 minutes. Additional~~ **please refer to** details provided in Table 6.3."	For accuracy, as instructions for IRR may vary as indicated in Table 6.3: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to DS-1062a.
Section 6.2. Preparation, Handling, Storage, and Accountability for Study Drug	Added "For prevention of oral mucositis/stomatitis, subjects are advised to initiate a daily oral care plan (OCP; see Section 8.4.4 for details) before study intervention initiation and maintain it throughout the study. An OCP should include daily inert, bland mouth rinses (eg, with a nonalcoholic, bicarbonate-containing mouthwash 4 to 6 times a day), although other prophylaxis regimens (eg, dexamethasone oral solution 0.1 mg/mL 10 mL 3 to 4 times daily swish for 1 to 2 minutes then spit out, as well as cryotherapy throughout the infusion) advocated by institutional/local guidelines are permitted. An OCP should also include educating subjects on the importance of oral hygiene, tooth brushing, flossing, and hydration and lubrication of the oral mucosa, and on the benefits of adhering to their recommended OCP. Per the investigator's judgment, a professional dental evaluation before study drug initiation and dental treatment, if indicated, may reduce the risk of local and systemic infections from odontogenic sources."	For added clarity of instructions for oral care.
Section 6.5. Guidelines for Dose Modification	Added "If a subject cannot restart study treatment for other reasons (eg, intercurrent conditions not related to disease progression or toxicity), the case should be discussed with the Sponsor's Medical Monitor. Study treatment dose delay for conditions other than toxicity resolution should be kept as short as possible."	For added clarity.
Section 6.5. Guidelines for Dose Modification Table 6.3: Dose Modifications for	Removed the statement "If there are any signs or symptoms of a Grade 1 or Grade 2 IRR, the infusion of DS-1062a infusion must be either slowed down or interrupted based on the severity of the IRR. If the IRR is Grade 3 or	To reflect the most recent safety information.

Section # and Title	Description of Change	Brief Rationale
Non-hematologic and Hematologic Toxicity Related to DS-1062a	Grade 4 or if there are any signs of anaphylaxis, the infusion of DS-1062a must be discontinued"	
	For Grade 1 IRR, modified the guidelines as follows: "If IRR (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, **and Grade 1 or 2** hypotension) is observed during administration, the infusion rate should be reduced by 50% **of the initial infusion rate,** and subjects should be closely monitored. If no other reactions appear upon resumption of the study drug at the above reduced **infusion** ~~speed~~ **rate**, then the **infusion rate** for subsequent ~~infusion speed for next~~ treatment cycles may be resumed at the initial ~~planned speed~~ **infusion rate**."	
	For Grade 2 IRR, modified the guidelines as follows: "Administration of Dato-DXd should be interrupted ~~briefly~~. Symptomatic treatment **should be** started. ~~(eg, antihistamines, NSAIDs, narcotics, IV fluids).~~ • If the event resolves or improves to Grade 1, infusion can be restarted at a 50% reduced infusion rate **(ie, 180 minutes for a 90-minute infusion and 60 minutes for a 30-minute infusion).** • ~~Subsequent administrations should be conducted at the reduced rate.~~ **If an IRR recurs upon rechallenge of Dato-DXd while it is being infused at a reduced rate during the same cycle, then treat as Grade 3 and follow the Grade 3 toxicity management guideline (TMG).** **If there is no recurrence, the subsequent infusion should be administered at a reduced rate.** • **If there is no new IRR, then Dato-DXd can be administered at the initial planned infusion rate (90 or 30 minutes) for subsequent treatment cycles.**	
	For Grade 3 IRR, modified the guidelines as	

Section # and Title	Description of Change	Brief Rationale
	follows: "Administration of Dato-DXd should be stopped immediately for that cycle and initiate treatment of the IRR symptoms. • If the IRR does not resolve within the same day, recurrence of symptoms occurs following initial improvement, or hospitalization is necessary for clinical sequelae, then permanently discontinue Dato-DXd. • If the IRR resolves within the same day of Dato-DXd infusion, no recurrence of symptoms occurs following initial improvement, and no hospitalization is necessary for clinical sequelae, then for the next cycle, administer Dato-DXd at a 50% reduced infusion rate (ie, 180 minutes for a 90-minute infusion; 60 minutes for a 30-minute infusion). o If there is no new IRR, then for the subsequent cycle, administer Dato-DXd at the initial infusion rate (90 or 30 minutes). If the subject tolerates that initial infusion rate with no new IRR, then for the subsequent cycles, administer Dato-DXd at the same infusion rate (90 or 30 minutes). o If a new IRR occurs that is Grade 2 or greater with subsequent cycles, permanently discontinue Dato-DXd and initiate treatment of the IRR symptoms." ~~Administration of DS-1062a must be discontinued immediately and permanently.~~ ~~Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc, should be administered.~~ ~~IV antihistamines (H1 or H2 blocker), supplemental oxygenation, and volume resuscitation (IV fluid therapy) should also be considered as clinically indicated."~~	

Section # and Title	Description of Change	Brief Rationale
	For Grade 4 IRR, added the following guidelines: "Administration of DS-1062a must be discontinued immediately and permanently. Urgent intervention is indicated. Epinephrine, antihistamines, steroids, bronchodilators, vasopressors, IV fluid therapy, supplemental oxygen, etc. should be considered as clinically indicated."	
	For febrile neutropenia, added "Grade 3 and Grade 4: Discontinue subject from study treatment."	
	For Grade 1 pulmonary toxicity, added "b. Grade 0 refers to full resolution of ILD/pneumonitis, including the disappearance of radiological findings associated with active ILD/pneumonitis. Residual scarring or fibrosis following recovery of ILD/pneumonitis is not considered to be active disease."	
	For general considerations for ocular surface toxicity, added the following statement: "The following grading scale **replaces** the CTCAE 5.0 grades for triggering the toxicity management guidelines for cornea-related AEs: **Corneal Toxicity Severity Grading Scale** Normal = Clear cornea, no epithelial defects Grade 1 = Nonconfluent superficial keratitis Grade 2 = Confluent superficial keratitis, a cornea defect, or 3-line or more loss in best corrected distance visual acuity Grade 3 = Corneal ulcer or stromal opacity, or best corrected distance visual acuity 20/200 or worse Grade 4 = Corneal perforation"	
	For Grade 4, replaced "ophthalmological assessments" to "urgent ophthalmological assessments."	
	For gastrointestinal events, added "Grade 4 Vomiting: Discontinue subject from study treatment."	
	For oral mucositis/stomatitis, modified the guidelines as follows: "As soon as **oral pain, inflammation, and/or** ulceration develops, strongly consider	

Section # and Title	Description of Change	Brief Rationale
	steroid-containing mouth rinses (eg, dexamethasone 0.1 mg/mL, 10 mL ~~3 to~~ 4 times daily swish for 1 to 2 minutes then spit out, or local alternative). **May consider oral nystatin suspension or other topical antifungal agents at least 15 minutes after the steroid-containing mouthwash according to clinician preference based on institutional/local guidelines.**"	
	For Grade 3 diarrhea, modified the guidelines as follows: "If prophylaxis and supportive medications **per institutional guidelines** have NOT YET been optimized:"	
Section 6.7. Prior and Concomitant Medications	Added 2 bullet points in the Permitted Therapies/Products: • "Neurokinin-1 (NK1) receptor antagonists can be used, if needed. • Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (eg, albuterol) will be included in this study." Updated the following statement in the Permitted Therapies/Products: • "Based on the currently available clinical safety data, it is **highly** recommended that subjects receive prophylactic antiemetic agents prior to infusion of Dato-DXd and on subsequent days **as needed**. Antiemetics such as 5-hydroxytryptamine ~~receptor~~ 3 antagonists (5-HT3) ~~or neurokinin-1 receptor antagonists,~~ and steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines." Updated the following statement in the Prohibited Therapies/Products: • "Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications **>10 mg/day of prednisone or equivalent** except for managing AEs; inhaled steroids, intra-articular steroid injections, and other topical steroid formulations are permitted in this study. Corticosteroid mouthwash formulations are permitted to prevent and	To reflect the most recent safety information.

Section # and Title	Description of Change	Brief Rationale
	manage certain AEs. ~~Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study."~~	
Section 6.7. Prior and Concomitant Medications	Added "All concomitant medications administered during the study should be recorded in eCRF until the end of the Safety Follow-up Period. Concomitant medications administered as treatment for drug-related AESIs should be recorded until event resolution, end of study including any post-treatment follow-up (if applicable), study termination, withdrawal of consent, or subject death."	To reflect the most recent safety information.
Section 7.2. Subject Withdrawal/Discontinuation from the Study	Updated the following text: "If the subject ~~refuses~~ **declines** all of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. ~~If the subject continues to refuse~~ **If the subject declines routine follow-up, the Investigator should discuss with the subject if sparse survival follow-up by telephone or verification of medical records is permitted prior to database locks. If the subject continues to decline** all potential methods of follow-up, the investigator will document this as a withdrawal of consent (from the interventional portion and follow-up)."	To clarify the option of sparse contacts for survival follow-up only.
Section 7.2. Subject Withdrawal/Discontinuation from the Study Section 7.3. Lost to Follow-up	Added "Knowledge of the vital status at study end in all subjects is crucial for the integrity of the study."	To emphasize the necessity of accurate documentation of survival data.
Section 8.1. Eligibility Assessment	Added the following statements: "Informed consent should be obtained ≤28 days prior to initiation of treatment and before any protocol-specific procedures are performed, except scans that might be done prior to consent per SoC. Imaging studies (CT/MRI/bone scans) should be performed ≤28 days prior to initiation of treatment. If these scans are performed per SoC prior to consenting, as long as they are within 28 days of the planned dosing and from the same facility where follow-up scans during the study will be performed, they can be used as part of the screening assessments and do not need to	For added clarity.

Section # and Title	Description of Change	Brief Rationale
	be repeated."	
Section 8.4.1. Adverse Event	Added "All ILD/pneumonitis events regardless of severity should be reported beyond the 28-day Safety Follow-up Period."	To reflect the most recent safety information.
Section 8.4.1. Adverse Event Section 8.4.1.2. Adverse Events of Special Interest	Added "All AESIs, regardless of severity or seriousness, must be followed until event resolution, end of study including any post-treatment follow-up (if applicable), study termination, withdrawal of consent, or subject's death."	To ensure all AESIs are followed to resolution.
Section 8.4.1.2. Adverse Events of Special Interest Section 8.4.4. Other Safety	Updated the following statement: "Ophthalmologic assessments, including, **but not limited to**, visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining, will be performed at screening, as clinically indicated, and at the EOT visit by an ophthalmologist or, if unavailable, another licensed eye care provider."	Because the ophthalmological assessment form is mandatory and all tests are recommended.
Section 8.4.1.3. Hepatic Events	Removed "within a 3-week interval or simultaneously at any time" for adverse event reporting requirements for hepatic events.	To reflect the most recent safety information.
Section 8.4.4. Other Safety	Updated the following statement: "Subjects should be advised to use artificial tears **4 times** daily **as a preventative measure and up to 8 times daily as clinically needed** and to avoid the use of contact lenses."	To reflect the most recent safety information.
Section 10.5.5. Action Taken Regarding Study Drug	Revised text as follows: • "~~Drug~~ Infusion Interrupted: The study drug **administration** was **started and then** temporarily stopped. • Dose Delayed: The study drug was **not administered at the next scheduled cycle/dosing visit but was administered at a later date**."	To clarify the meaning of the terms "dose delay" and "infusion interruption."

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
Phase 2, Single-arm, Open-label Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer with Actionable Genomic Alterations and Progressed on or After Applicable Targeted Therapy and Platinum-based Chemotherapy (TROPION-Lung05)
Protocol Short Title
Phase 2 Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer with Actionable Genomic Alterations
Protocol Number
DS1062-A-U202
Sponsor/Collaborators
Sponsor: Daiichi Sankyo, Inc.
Registry Identification(s)
EudraCT Number: 2020-002774-27
IND Number
IND Number 136626
Study Phase
Phase 2
Planned Geographical Coverage, Study Sites, and Locations
Global study at approximately 85 study sites located in North America, Europe, and Asia Pacific region.
Study Population
Subjects with advanced or metastatic non-small cell lung cancer (NSCLC) with actionable genomic alterations (ie, alterations in genes with approved therapies, such as epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], ROS proto-oncogene 1 [ROS1], neurotrophic tyrosine receptor kinase [NTRK], proto-oncogene B-raf [BRAF], mesenchymal-epithelial transition [MET] exon 14 skipping or rearranged during transfection [RET]) and who have progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study. Subjects whose tumors harbor KRAS mutations, in the absence of any of the genomic alterations specified above, will be excluded.
Study Objectives/Outcome Measures and Endpoints
The table below lists primary and secondary study objectives and endpoints that have outcome measures.

Objectives	**Outcome Measure**	**Endpoints**	**Category**
Primary			
To assess the efficacy of DS-1062a, as measured by the ORR, as a treatment for subjects with NSCLC with actionable genomic alterations	**Title:** ORR **Description:** ORR as assessed by BICR per RECIST v1.1. **Time frame:** Primary analysis: After	ORR is defined as the proportion of subjects who achieved a BOR of confirmed CR or confirmed PR.	Efficacy

that has progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study	all subjects have had either a minimum of 9 months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first.		
Secondary			
To further evaluate the efficacy of DS-1062a	**Title:** DoR **Description:** DoR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	DoR is defined as the time from the date of the first documentation of response (confirmed CR or confirmed PR) to the date of the first documentation of PD or death due to any cause, whichever occurs first.	Efficacy
	Title: Best percentage change in the SoD of measurable tumors **Description:** SoD as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	The best percentage change in the SoD of measurable tumors is defined as the percentage change in the smallest SoD from all post-baseline tumor assessments, taking as reference the baseline SoD.	Efficacy
	Title: DCR **Description:** DCR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	DCR is defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or SD.	Efficacy
	Title: CBR **Description:** CBR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	CBR is defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or an SD that lasts for at least 180 days.	Efficacy
	Title: PFS **Description:** PFS as assessed by	PFS is defined as the time from the start of study treatment to the	Efficacy

	BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	earlier of the dates of the first documentation of PD or death due to any cause.	
	Title: TTR **Description:** TTR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	TTR is defined as the time from the start of study treatment to the date of the first documentation of objective response (confirmed CR or confirmed PR) in responding subjects.	Efficacy
	Title: ORR **Description**: ORR as assessed by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	ORR is defined as the proportion of subjects who achieved a BOR of confirmed CR or confirmed PR.	Efficacy
	Title: OS **Description:** OS. **Time frame:** At the time of the primary analysis.	OS is defined as the time from the start of study treatment to the date of death due to any cause.	Efficacy
To further evaluate the safety of DS-1062a	**Title:** TEAEs and other safety parameters during the study* **Description:** Descriptive statistics of safety endpoints. **Time frame:** Continuous monitoring and reported at the time of the primary analysis. *Though this is a secondary objective, this is a primary outcome measure.	TEAEs, SAEs, AESIs, ECOG PS, vital sign measurements, standard clinical laboratory parameters (hematology, serum chemistry, and urinalysis), ECG parameters, ECHO/MUGA scan findings, and ophthalmologic findings. AEs will be coded using the most current version of MedDRA. AEs and laboratory test results will be graded using the NCI CTCAE v5.0.	Safety

To assess the PK of DS-1062a	**Title:** PK profile **Description:** Plasma concentrations and PK parameters of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a. **Time frame**: At the time of the primary analysis.	Plasma concentrations at each time point and PK parameters (Cmax, Tmax, AUClast, AUCtau. If data permit: AUCinf, t1/2, CL, Vss, Vz, and Kel) of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a (released drug) in the full PK sampling cohort.	PK
To assess the immunogenicity of DS-1062a	**Title:** Immunogenicity **Description:** Prevalence and incidence of ADA. **Time frame:** At the time of the primary analysis.	ADA prevalence: the proportion of subjects who are ADA positive at any point in time (including pre-existing ADA at baseline and treatment-emergent ADA). ADA incidence: the proportion of subjects having treatment-emergent ADA during the study period. Titer and neutralizing antibodies will be determined when ADA is positive.	Immunogenicity

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; AUCinf = area under the plasma concentration-time curve up to infinity; AUClast = area under the plasma concentration-time curve up to the last quantifiable time; AUCtau = area under the plasma concentration-time curve during dosing interval; BICR = blinded independent central review; BOR = best overall response; CBR = clinical benefit rate; CL = total body clearance; Cmax = maximum plasma concentration; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; Kel = elimination rate constant associated with the terminal phase; MAAA-1181a = released drug; MedDRA = Medical Dictionary for Regulatory Activities; MUGA = multigated acquisition; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; SoD = sum of diameters; t1/2 = terminal half-life; TEAE = treatment-emergent adverse event; Tmax = time to reach maximum plasma concentration; TROP2 = trophoblast cell surface protein 2; TTR = time to response; Vss = volume of distribution at steady-state; Vz = volume of distribution based on the terminal phase

Study Design

This is a global, multicenter, single-arm, open-label, Phase 2 study of the efficacy, pharmacokinetics (PK), and safety of DS-1062a in subjects with advanced or metastatic NSCLC with known actionable genomic alterations (ie, alterations in genes with approved therapies, such as EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, and RET) and that has progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study. Subjects whose tumors harbor KRAS

mutations, in the absence of any of the genomic alterations specified above, will be excluded. Subjects whose tumors harbor EGFR mutations should comprise approximately 50% of subjects enrolled in the study, among those, 80% should have received osimertinib (regardless of T790M status) as a prior line of therapy.

Eligible subjects will receive 6.0 mg/kg of DS-1062a.

The PK of DS-1062a will be evaluated in all subjects. Full PK sampling will be collected from the first approximately 30 subjects with adequate hepatic function and up to 9 subjects with moderate hepatic dysfunction. The remaining subjects will have sparse PK sampling.

The study will be divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period (which includes the Long-term Survival Follow-up [LTSFU]):

- The Screening Period will start on the day of signing the informed consent form (ICF) and will have a maximum duration of 28 days. Rescreening is permitted 1 time for any subject who did not meet reversible or transient eligibility criteria upon initial screening.
- Eligible subjects will enter the Treatment Period, which starts on Cycle 1 Day 1 and continues until a subject permanently discontinues DS-1062a. During the Treatment Period, eligible subjects will receive DS-1062a until they meet one of the discontinuation criteria. Subjects will undergo radiographic assessment of tumor response based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR) every 6 weeks (± 7 days) from the start of study treatment until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent. Subjects who discontinue treatment without radiographic disease progression or start new anticancer therapy without radiographic disease progression will continue to undergo tumor assessments every 6 weeks (±7 days) until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent. Subjects will continue to receive DS-1062a until radiographic disease progression, clinical progression, unacceptable toxicity, withdrawal of consent by subject, physician decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons. Note: Only protocol deviations that are deemed significant by the investigator, with or without consultation with the Sponsor, may lead to permanent study drug discontinuation.
- The Follow-up Period will start upon permanent discontinuation of DS-1062a. After discontinuing study drug, subjects who have not had radiographic disease progression will continue to be followed for tumor assessments every 6 weeks until radiographic disease progression by BICR. All subjects will be followed every 3 months for survival.

The **primary completion date** will occur when all subjects have had either a minimum of 9 months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first. This date is used as the data cutoff (DCO) date for the primary analysis. All subjects still on treatment and continuing to derive benefit from DS-1062a at the primary completion date will continue to follow the study Schedule of Events until the **overall end of study (EOS)** is reached. All subjects who have not had disease progression at the time of the primary completion date will continue to be followed for tumor assessments and survival. The subject's EOS is the date of their last study visit/contact. The overall EOS will occur after the last subject last visit has occurred; or after all subjects have discontinued treatment and discontinued from the study, or have died; or an alternative study becomes available for subjects continuing to derive benefit from treatment with DS-1062a where the drug is offered to these subjects; or the study is discontinued by the Sponsor for other reasons. A final analysis may be conducted after the overall EOS.

Study Duration

The study start date is the date when the first subject has signed an ICF. A subject is eligible to be enrolled into the study when the investigator or designee has obtained written informed consent, has confirmed all inclusion and exclusion criteria have been met by the subject, and all screening procedures have been completed.

Enrollment is planned to occur over approximately 19 months, with treatment and follow-up (28-day Safety Follow-up and LTSFU) projected to continue for approximately 24 months after the last subject is enrolled. The study will continue until the overall EOS is reached. The anticipated total duration of the study is approximately 43 months.

Key Eligibility Criteria

Key Inclusion Criteria:

Subjects eligible for inclusion in the study must meet all inclusion criteria for this study. Below is a list limited to the key inclusion criteria:

- Has pathologically documented NSCLC that
  - Is stage IIIB, IIIC or stage IV NSCLC disease at the time of enrollment (based on the American Joint Committee on Cancer, Eighth Edition).
  - Has 1 or more of the following documented activating genomic alterations*: EGFR**, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.

  * KRAS mutations in the absence of any of the genomic alterations specified above will be excluded.

  ** Overexpression of EGFR, in the absence of activating mutations, is **NOT** sufficient for enrollment. Subjects who have not received osimertinib should be evaluated for the presence of EGFR T790M mutation after relapse/progression on/after the most recent EGFR-tyrosine kinase inhibitor (TKI), unless the subject is already known to be positive with documented results for this mutation or unless osimertinib is not locally approved.
- Has documentation of radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.
- Subject must meet the following for advanced or metastatic NSCLC:
  - Has been treated with at least 1 but no more than 2 cytotoxic agent-containing therapy in the metastatic setting:
    - One platinum-containing regimen (either as monotherapy or combination therapy);
    - May have received up to one additional line of cytotoxic agent-containing therapy;
    - Those who received a platinum-containing regimen as adjuvant therapy for early stage disease must have relapsed or progressed while on the treatment or within 6 months of the last dose OR received at least one additional course of platinum-containing therapy (which may or may not be same as in the adjuvant setting) for relapsed/progressive disease;
  - May have received up to one checkpoint inhibitor (CPI)-containing regimen (may be in combination with a cytotoxic agent as part of a regimen described above or as an additional CPI regimen without a cytotoxic agent);
  - Has been treated with 1 or more lines of non-CPI targeted therapy that is locally approved for the subject's applicable genomic alteration at the time of screening; OR one or more of the agents specified in the table below;
    - Those who received a targeted agent for the applicable genomic alterations in the study as adjuvant therapy for early stage disease must have relapsed or progressed while on the treatment or within 6 months of the last dose OR received at least one additional course of targeted therapy for the same genomic alterations (which may or may not be same agent used in the adjuvant setting) for relapsed/progressive disease.
    - Subjects who have been treated with a prior TKI must receive additional targeted therapy, if clinically appropriate, for the genomic alterations that are considered amenable or the subject will not be allowed in the study.

Genomic Alterations	Applicable Targeted Agents
EGFR	erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib
EGFR exon20 insertion	amivantamab, mobocertinib
EGFR T790M	osimertinib
ALK fusion	crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib
ROS-1 fusion	entrectinib, lorlatinib, ceritinib, and crizotinib
NTRK fusion	entrectinib and larotrectinib
BRAF V600E	dabrafenib, alone or in combination with trametinib
MET exon 14 skipping	capmatinib and tepotinib
RET rearrangement	selpercatinib and pralsetinib

ALK = anaplastic lymphoma kinase; BRAF = proto-oncogene B-raf; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition; NTRK = neurotrophic tyrosine receptor kinase; RET = rearranged during transfection; ROS-1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

- Must undergo a mandatory pre-treatment tumor biopsy procedure.
  OR
  If available, a tumor biopsy that was recently collected (within 3 months of screening) after completion of the most recent anticancer treatment regimen and that has a minimum of 10 × 4 micron sections or a tissue block equivalent of 10 × 4 micron sections may be substituted for the mandatory biopsy collected during screening.
  Note: Results from this biopsy will not be used to determine eligibility for the study.
- Archival tumor tissue from initial diagnosis is required, to the extent that archival tumor tissue is available.
- Measurable disease based on local imaging assessment using RECIST v1.1.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 – 1 at screening.
- Within 7 days before Cycle 1 Day 1, has adequate bone marrow function defined as:
  - Platelet count ≥100,000/mm^3 (platelet transfusion is not allowed within 1 week prior to screening assessment).
  - Hemoglobin ≥9.0 g/dL (red blood cell/plasma transfusion is not allowed within 1 week prior to screening assessment).
  - Absolute neutrophil count ≥1500/mm^3 (granulocyte-colony stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment).

  (See Section 6.5 and Section 6.7 for use of G-CSF and erythropoietin)
- Within 7 days before Cycle 1 Day 1, has adequate organ function:
  - Adequate hepatic function defined as:
    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) or AST/ALT ≤5.0 × ULN if transferase elevation is due to liver metastases); AND
    - Total bilirubin (TBL) ≤1.5 × ULN (or <3.0 mg/dL in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia]).

  OR
  - Moderate hepatic dysfunction (a maximum of 9 subjects): TBL >1.5 × ULN and ≤3 × ULN and any AST.

  - Note: After a maximum of 9 subjects with moderate hepatic dysfunction have been enrolled, subsequent subjects with moderate hepatic dysfunction will be excluded.

- Within 7 days before Cycle 1 Day 1, has adequate renal function, including mild or moderate renal function, defined as:
  - Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation.
- Has a left ventricular ejection fraction (LVEF) ≥50% by either an echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan within 28 days before Cycle 1 Day 1.
- Has adequate blood clotting function defined as international normalized ratio/prothrombin time and either partial thromboplastin or activated partial thromboplastin time ≤1.5 × ULN within 7 days before enrollment.
- Has an adequate treatment washout period before Cycle 1 Day 1 defined as:

Treatment	Washout Period
Major surgery	≥3 weeks
Radiation therapy (curative) and palliative radiation to the chest	≥4 weeks ≥2 weeks (palliative radiation therapy to other areas [ie, limited field and 10 or fewer days or fractions] including whole brain radiotherapy)
Anticancer chemotherapy (immunotherapy [non-antibody-based therapy]), retinoid therapy	≥2 weeks or 5 times the t1/2 of the chemotherapeutic agent, whichever is longer; ≥6 weeks for nitrosoureas or mitomycin C, ≥1 week for TKIs approved for the treatment of NSCLC - baseline CT scan should be completed after discontinuation of TKI
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/Hydroxychloroquine	>14 days

CT = computed tomography; NSCLC = non-small cell lung cancer; t1/2; terminal elimination half-life; TKI = tyrosine kinase inhibitor

Key Exclusion Criteria:

Subjects meeting any exclusion criteria for this study will be excluded from this study. Below is a list limited to the key criteria:

- Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment. Note: A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain at baseline is required for all subjects. For those subjects in whom central nervous system (CNS) metastases are first discovered at the time of screening, the treating investigator should consider delay of study treatment to document stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, repeat of all screening activity may be required).
- Has leptomeningeal carcinomatosis.
- Had prior treatment with:
  - Any chemotherapeutic agent targeting topoisomerase I, including antibody-drug conjugate (ADC) containing such agent.
  - TROP2-targeted therapy.

- Uncontrolled or significant cardiovascular disease, including:
  - Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 milliseconds (msec) (based on the average of screening triplicate 12-lead electrocardiogram determinations).
  - History of myocardial infarction within 6 months prior to Cycle 1 Day 1.
  - History of uncontrolled angina pectoris within 6 months prior to Cycle 1 Day 1.
  - Symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV) at screening. Subjects with a history of Class II to IV CHF prior to screening must have returned to Class I CHF and have LVEF ≥50% (by either an ECHO or MUGA scan within 28 days of Cycle 1 Day 1) in order to be eligible.
  - History of serious cardiac arrhythmia requiring treatment.
  - LVEF <50% or institutional lower limit of normal by ECHO or MUGA scan.
  - Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).
- Has a history of non-infectious interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of Cycle 1 Day 1, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, etc.), or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc.), or prior pneumonectomy.
- Clinically significant corneal disease.
- Has other primary malignancies, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated, with no evidence of disease for ≥3 years.

Investigational Medicinal Product, Dose and Mode of Administration

DS-1062a drug product will be provided as sterile lyophilized-drug product (Lyo-DP) consisting of 100 mg of lyophilized powder in a single-use amber glass vial to be reconstituted with water for injection and further diluted with 5% dextrose injection prior to use.

DS-1062a will be administered as an intravenous (IV) infusion once every 3 weeks (Q3W) on Day 1 of 21-day cycles at a dose of 6.0 mg/kg. Premedication is required prior to any dose of DS-1062a that must include antihistamines and acetaminophen with or without glucocorticoids.

The dose may be delayed for up to 9 weeks (63 days) from the planned date of the next cycle administration (ie, up to 12 weeks or 84 days from the last infusion). If a subject is assessed as requiring a dose delay longer than 12 weeks (84 days) from the last infusion, the subject must discontinue study treatment.

Up to 3 dose reductions will be permitted for subjects, see Table 1. Once the dose of DS-1062a is reduced, no dose re-escalation will be permitted.

Table 1: Dose Reduction Levels for DS-1062a

Starting Dose	Dose Reduction 1	Dose Reduction 2	Dose Reduction 3
6.0 mg/kg	4.0 mg/kg	3.0 mg/kg	2.0 mg/kg

Active Ingredients/INN

DS-1062a/datopotamab deruxtecan

Planned Sample Size

A sample size of approximately 150 subjects, including approximately 50% (75 subjects) with EGFR genomic alterations, will provide sufficient statistical precision for the estimate of the objective response rate (ORR). The exact 95% confidence interval (CI) based on the Clopper-Pearson method at various ORRs is provided in Table 9.1. When the observed ORR is greater than or equal to 30%, the lower bound of the 95% CI is greater than 20% for all subjects and for the EGFR gene mutation subgroup, if there are 75 subjects with EGFR genomic alterations.[1,2] If there are 60 subjects with EGFR genomic alterations, then the lower bound of the 95% CI is greater than 20% when the observed ORR is greater than or equal to 32%.

Statistical Methodology

Primary and Final Analyses

- The primary analysis DCO will occur when all subjects have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study, whichever occurs first. The primary analysis will be included in the clinical study report.
- The final analysis will be performed after all subjects have discontinued from the study.

There is no interim analysis for this study.

Efficacy Analyses

The primary efficacy endpoint is ORR as assessed by BICR per RECIST v1.1. ORR is defined as the proportion of subjects who achieve a best overall response (BOR) of complete response (CR) or partial response (PR). CR/PR will be confirmed with a follow-up tumor assessment at least 4 weeks (28 days) apart. ORR as assessed by BICR will be summarized with the 2-sided 95% CI using the Clopper-Pearson method in the Full Analysis Set (FAS) (defined as all subjects who receive at least 1 dose of study drug). For the computation of ORR, subjects with BOR of "not evaluable (NE)" will be included in the FAS and will be considered non-responders.

Secondary efficacy endpoints include: duration of response (DoR), best percentage change in the sum of diameters (SoD) of measurable tumors, disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), and time to response (TTR), as assessed by BICR and by investigator per RECIST v1.1; ORR as assessed by investigator per RECIST v1.1; and overall survival (OS).

For DoR, PFS, and OS, the survival distribution of these endpoints will be summarized and presented graphically using the Kaplan-Meier method; median event times and their 2-sided 95% CI will be presented using Brookmeyer and Crowley methods. In addition, the event-free probability at different time points (eg, 3, 6, 9, 12 months) will be estimated with corresponding 2-sided 95% CIs using the Greenwood formula for variance derivation. TTR will be summarized descriptively.

Descriptive statistics for the best percent change from baseline in SoD of measurable tumors will be provided. A waterfall plot of the best percent change in SoD will be presented.

ORR, DCR, and CBR, as assessed by the investigator, will be analyzed in the same manner as the primary efficacy endpoint.

Safety Analyses

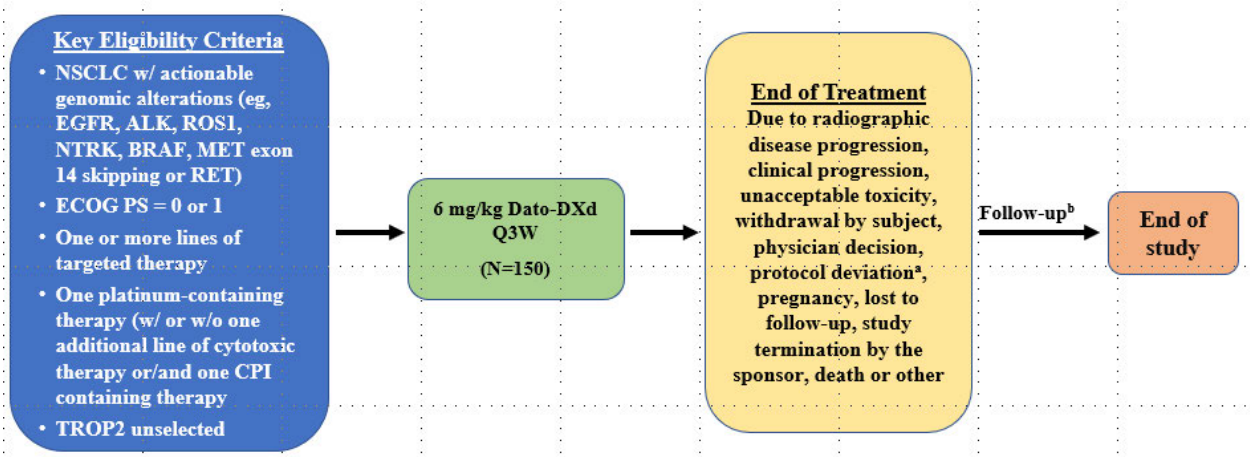
Safety analyses in general will be descriptive and will be presented in tabular format with summary statistics using the Safety Analysis Set (defined as all subjects who receive at least 1 dose of study drug).

Pharmacokinetic Analyses

Plasma concentrations for DS-1062a (ADC, total anti-TROP2 antibody, and MAAA-1181a) will be listed, plotted, and summarized using descriptive statistics. PK parameters will be listed and summarized using descriptive statistics.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



ALK = anaplastic lymphoma kinase; BICR = blinded independent central review; BRAF = proto-oncogene braf; CBR = clinical benefit rate; CPI = checkpoint inhibitor; Dato-DXd = datopotamab deruxtecan; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition; NSCLC = non-small cell lung cancer; NTRK = neurotrophic tyrosine receptor kinase; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RET = rearranged during transfection; ROS1 = ROS proto-oncogene 1; SoD = sum of diameters; TTR = time to response; TROP2 = trophoblast cell surface protein 2; w/ = with; w/o = without

[a] Only protocol deviations that are deemed significant by the investigator, with or without consultation with the Sponsor, may lead to permanent study drug discontinuation.

[b] Subjects who discontinue study treatment without radiographic disease progression will continue to undergo tumor assessments every 6 weeks (± 7 days) during follow-up until documented radiographic disease progression by BICR, death, lost to follow-up, or withdrawal of consent (regardless of discontinuing study treatment or starting new anticancer therapy).

Notes: Primary endpoint: ORR as assessed by BICR per RECIST v1.1
Secondary endpoints: DoR, SoD, DCR, CBR, PFS and TTR, each as assessed by BICR and investigator per RECIST v1.1; ORR as assessed by investigator per RECIST v1.1; OS; safety; PK; and immunogenicity.

The pharmacokinetics (PK) of DS-1062a will be evaluated in all subjects. Full PK sampling will be collected from the first approximately 30 subjects with adequate hepatic function and up to 9 subjects with moderate hepatic dysfunction. The remaining subjects will undergo sparse PK sampling (Section 8.5).

The overall end of study (EOS) will occur after the last treated subject's last visit has occurred; or after all subjects have discontinued treatment and discontinued from the study or have died; or an alternative study becomes available for subjects continuing to derive benefit from treatment with DS-1062a where the drug is offered to these subjects; or the study is discontinued by the Sponsor for other reasons.

The primary completion date will occur when all subjects have had either a minimum of 9 months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first.

1.3. Schedules of Events

Table 1.1: Schedule of Events for Screening and Cycles 1 through 3 of the Treatment Period

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
Informed Consent	ICF	X												A signed and dated ICF must be obtained before any study-specific procedures or assessments are initiated. See Section 8.1 and Section 10.1.2.
Demographics and Eligibility	Demographics	X												Includes: birth date, age at screening, sex, race, ethnicity, country.
	Medical History	X												
	NSCLC History	X												
	Inclusion/ Exclusion Criteria	X												See Section 5.1 and Section 5.2.
Safety	Vital Signs	X	X[b,c]	X					X[c]	X		X[c]	X	As clinically indicated. [b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a. See Section 8.4.4.
	Height	X												Measured in cm.
	Weight	X	X[b,c]						X[c]			X[c]		Recorded in kg. [b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
	SpO_2	X	X[b,c]	X					X[c]	X		X[c]	X	As clinically indicated. Measured by pulse oximeter and at the same time vital signs are measured. [b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a.
	Physical Exam and ECOG PS	X	X[b,c]						X[c]			X[c]		[b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a. See Section 8.4.4 and Section 10.3.3.
	Ophthalmologic Assessment	X	As clinically indicated											Includes but not limited to visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining. See Section 8.4.4.
	Oral Care Plan		Subjects will be provided an oral care plan prior and during study treatment: daily before dosing, throughout treatment, and up to the first follow-up visit.											See Section 8.4.4
	12-Lead ECG	X[d]	X[b,e]	X[f]										As clinically indicated (if ECG abnormality is detected, perform in triplicate). [b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [d] At screening only, ECG will be taken in triplicate in close succession, no more than approximately 5 min apart, and after at least 5 min of quiet rest in the supine position. Within 7 days before C1D1. [e] Single ECG only. Within 3 days BI of DS-1062a. [f] Single ECG only. Within 30 min after EOI. See Section 8.4.4.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
	ECHO or MUGA (LVEF)	X												Use the same test throughout the study. As clinically indicated. Within 28 days of C1D1. See Section 8.4.4.
Laboratory Assessments	Hematology	X[g]	X[b,c]						X[c]			X[c]		As clinically indicated. [b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a. [g] Screening labs for eligibility should be obtained within 7 days before C1D1. See Section 8.4.3 and Section 10.2.
	Clinical Chemistry	X[g]	X[b,c]						X[c]			X[c]		As clinically indicated. [b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a. [g] Screening labs for eligibility should be obtained within 7 days before C1D1. See Section 8.4.3 and Section 10.2.
	Coagulation	X												See Section 8.4.3 and Section 10.2.
	Urinalysis	X	As clinically indicated											See Section 8.4.3 and Section 10.2.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
	Pregnancy Test	X	X[b,c]						X[c]			X[c]		[b] Screening data may be used as C1D1 data if obtained within 3 days before administration of DS-1062a. [c] Within 3 days before administration of DS-1062a. A negative serum pregnancy test during screening is required (within 28 days prior to C1D1) for all female subjects of childbearing potential. Within 3 days before C1D1, pregnancy test (urine/serum per institutional guideline) must be done for all female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test. Repeat pregnancy tests (urine or serum test per institutional guideline) are done 3 days before infusion of each cycle, at EOT and at the 28-day Safety Follow-up visit. See Section 8.4.2.
	HIV Ab Test	X												If acceptable by local regulations or IRB/EC, subjects should be tested for HIV prior to C1D1. See exclusion criterion 9. Prior human immunodeficiency virus antibody test results can be used if performed within 120 days before enrollment. See Section 8.1.
	HBsAg, HCV Ab (if HCV Ab is positive, test HCV RNA)	X												Perform required hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) test (if HCV Ab is positive, test HCV RNA). Prior hepatitis B surface antigen and hepatitis C virus antibody test results can be used if performed within 120 days before enrollment. Refer to Section 5.2 for exclusion criterion regarding HBV and HCV infection.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
	COVID-19 Sample		X											Unless prohibited by local restrictions, if subject provides consent, serum samples should be collected prior to DS-1062a infusion. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Section 10.7.
Immunogenicity	ADA Sample		X[h]				X		X[h]					[h] Within 8 h BI of DS-1062a. See Section 8.6.6.
Prior/ Concomitant Therapies	Prior Medications, Non-drug Therapies, and Radiotherapy	X	X											See Section 6.7.
	Concomitant Medications, Non-drug Therapies, and Radiotherapy			X										See Section 6.7.
Biomarker Samples	Archived Tumor Sample	X												Archived tumor sample is defined as a tumor sample collected at the time of initial diagnosis. See Section 8.1 and Section 8.6.2.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
	Tumor Biopsy	X[i]									X[j]			Biopsies may be collected from a lesion that has been irradiated, provided that it can be documented that the lesion has increased/appeared since radiation occurred and that the biopsy is collected at least 3 months after radiation. [i] The subject must undergo a mandatory tumor biopsy procedure during screening OR if available, a tumor biopsy that was recently collected within 3 months and after completion of the most recent anticancer treatment regimen may be substituted for the mandatory pre-treatment biopsy procedure during screening. [j] On-treatment biopsy is optional if clinically feasible and not contraindicated. The sample can be obtained during C2D2 to C2D8. See Section 8.1 and Section 8.6.2.
	Pharmaco-genomics Blood Sample		X											Scheduled for C1D1 predose but may be collected at any time after the first dose of DS-1062a. See Section 8.6.5.
	Blood sample for cfDNA	X[k]							X[c]			X[c]		[c] Within 3 days before administration of DS-1062a. [k] Within 7 days before C1D1. See Section 8.6.1.
	Blood sample for predictive liquid biopsy	X												Within 7 days before C1D1. See Section 8.6.1.
	Blood sample for WES/WGS control		X											Scheduled for C1D1 predose but may be collected at any time after the first dose of study treatment. See Section 8.6.1.
	Plasma sample		X						X					Additional sample to be collected at time of suspected ILD.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
	Serum sample		X						X					Additional sample to be collected at time of suspected ILD.
Tumor Response and Lung Disease Assessment	CT/MRI of the chest, abdomen, and any other sites of disease	X[l,m]	Every 6 weeks (± 7 days) from C1D1 until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent (regardless of discontinuing study treatment or starting new anticancer therapy). For further instructions, refer to the Imaging Site Manual.											[l] Central reading will be performed for the screening tumor assessment. All baseline evaluations should NEVER be performed more than 28 days before C1D1. Additionally, all images including CT and MRI will be submitted to a central imaging CRO for independent review. [m] Baseline tumor assessment must be performed for measurable disease as assessed by the investigator. See Section 8.3 and Section 10.4.
	CT/MRI of Brain	X	CT/MRI of the brain at baseline is mandatory for all subjects. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated. Subjects with brain metastases at baseline should have brain MRI or CT scan performed every 6 weeks (± 7 days) from C1D1. Additional brain imaging may be performed as needed clinically.											
	Bone Scan (bone scintigraphy) or 18F FDG PET/CT	X	Follow-up bone imaging is required only if new bone metastases are suspected. When or disease progression in the bone or new lesion in the bone is suspected, 18F FDG PET/CT should be used to determine disease progression.											See Section 8.3 and Section 10.4.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
Study Drug	Administration of DS-1062a		X						X			X		Premedication is required prior to any dose of DS-1062a that must include antihistamines and acetaminophen with or without glucocorticoids. Subjects should remain at the site for at least 1-hour post infusion for close observation for possible allergic reaction. If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle. See Section 6.
PK Blood Samples	Full PK Sampling		X[h]	X[n]	X[o]	X	X	X	X[h]	X[p]		X[h]	X[p]	To be collected from the first approximately 30 subjects with adequate hepatic function and up to 9 subjects with moderate hepatic dysfunction. [h] Within 8 h BI of DS-1062a. [n] Within 30 min after EOI and 3, 5, and 7 h (± 15 min) after start of DS-1062a infusion. [o] 24 h (± 2 h) after the start of Day 1 infusion of DS-1062a. [p] Within 1 h after EOI of DS-1062a. See Section 8.5.
	Sparse PK Sampling		X[h]	X[q]	X	X	X		X[h]	X[p]				To be collected from the remaining subjects who do not undergo full PK sampling. [h] Within 8 h BI of DS-1062a. [p] Within 1 h after EOI of DS-1062a [q] Within 30 mins after EOI and 5 h (± 1 h) after start of infusion of DS-1062a. See Section 8.5.

Assessment		SCR[a]	Cycle 1						Cycle 2			Cycle 3		Comments
	Visit Day	-28 to Cycle 1 Day 1	1		2	4	8	15	1		2-8	1		[a] The duration of the screening period is up to 28 days, which starts on the day of the signing of the main informed consent form.
	Infusion		BI	EOI					BI	EOI		BI	EOI	
	Visit Window (Days)		±2			±1	±1	±1	±2			±2		
AEs	Non-serious AEs		X											See Section 8.4.1 and Section 10.5.
	SAEs	X	X											See Section 8.4.1 and Section 10.5.

18F FDG = 18F fluorodeoxyglucose; ab = antibody; ADA = antidrug antibody; AE = adverse event; BI = before infusion; C= Cycle; cfDNA = cell-free deoxyribonucleic acid; COVID-19 = coronavirus disease 2019; CRO = contract research organization; CT = computed tomography; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOT = end of treatment; h = hour; HBV = hepatitis B virus; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; ICF = informed consent form; ILD = interstitial lung disease; IRB/EC = Institutional Review Board/Ethics Committee; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PK = pharmacokinetics; RNA = ribonucleic acid; SAE = serious adverse event; SCR = Screening; SpO_2 = peripheral oxygen saturation; WES = whole exome sequencing; WGS = whole genome sequencing

Notes: For suspected ILD/pneumonitis, treatment with study drug should be delayed pending evaluation.

Evaluations should include the following:

- High-resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests (including force vital capacity and CO diffusing capacity) and pulse oximetry (SpO_2)
- Clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, C-reactive protein, and a COVID-19 test).
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible

Other tests can be considered, as needed.

For prevention of oral mucositis/stomatitis, initiate a daily oral care plan (see Section 8.4.4). The importance of multiple daily mouth rinses during treatment (eg, prior to dosing) and up to the first follow-up visit should be emphasized.

For prevention of ocular surface toxicity, it should be strongly recommended that subjects avoid the use of contact lenses starting on the day of the first DS-1062a dose and to use artificial tears (preferably preservative free) 4 times per day as a preventative measure and up to 8 times per day as clinically needed.

Ophthalmologic assessments, including, but not limited to, visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining, will be performed at screening, as clinically indicated, and at the EOT visit by an ophthalmologist or, if unavailable, another licensed eye care provider.

Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
					28-day Safety Follow-up[a]	Long-term Survival Follow-up (Every 3 Months)		[a] 28 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the day of discontinuation is over 35 days from last study drug administration, follow-up assessment is not needed
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		-3, +7	+7	±14		
Safety	Vital Signs	X[a]	X	X	X			As clinically indicated. [a] Within 3 days BI of DS-1062a. See Section 8.4.4.
	Weight	X[a]		X	X			Recorded in kg. [a] Within 3 days BI of DS-1062a.
	SpO2	X[a]	X	X	X			As clinically indicated. Measured by pulse oximeter and at the same time vital signs are measured. [a] Within 3 days BI of DS-1062a.
	Physical Exam and ECOG PS	X[a]		X	X			[a] Within 3 days BI of DS-1062a. See Section 8.4.4 Section 10.3.3.
	Ophthalmologic Assessment	As clinically indicated		X				Includes but not limited to visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining. See Section 8.4.4.
	Oral Care Plan	Subjects will be provided an oral care plan prior and during study treatment: daily before dosing, throughout treatment, and up to the first follow-up visit.						See Section 8.4.4
	12-Lead ECG	X[a,b]		X	X			Single ECG only. As clinically indicated (if ECG abnormality is detected, perform in triplicate). [a] Within 3 days BI of DS-1062a.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
					28-day Safety Follow-up[a]	Long-term Survival Follow-up (Every 3 Months)		[a] 28 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the day of discontinuation is over 35 days from last study drug administration, follow-up assessment is not needed
	Visit Day	1						
	Infusion	**BI**	**EOI**					
	Visit Window (Days)	±2		-3, +7	+7	±14		
								[b] Every 4 cycles only. See Section 8.4.4.
	ECHO/MUGA (LVEF)			X				Use the same test throughout the study. As clinically indicated. See Section 8.4.4.
Laboratory Assessments	Hematology	X[a]		X	X			As clinically indicated. [a] Within 3 days BI of DS-1062a. See Section 8.4.3 and Section 10.2.
	Clinical Chemistry	X[a]		X	X			As clinically indicated. [a] Within 3 days BI of DS-1062a. See Section 8.4.3 and Section 10.2
	Urinalysis	As clinically indicated						See Section 8.4.3 and Section 10.2
	Pregnancy Test	X		X	X			Repeat pregnancy tests (urine or serum test per institutional guideline) are done 3 days before infusion of each cycle, at EOT and at the 28-day Safety Follow-up visit. See Section 8.4.2
	COVID-19 Sample	X		X				Unless prohibited by local restrictions, starting at C5D1 and every 4 cycles thereafter. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Section 10.7.
Immunogenicity	ADA Sample	X[c,d]		X	X			[c] Within 8 h BI of DS-1062a. [d] Every 2 cycles from C4 to C8 (ie, C4, C6, and C8) then every 4 cycles from C8 to EOT (ie, C8, C12, C16, etc.). See Section 8.6.6.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
	Visit Day	1			28-day Safety Follow-up[a]	Long-term Survival Follow-up (Every 3 Months)		[a] 28 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the day of discontinuation is over 35 days from last study drug administration, follow-up assessment is not needed
	Infusion	BI	EOI					
	Visit Window (Days)	±2		-3, +7	+7	±14		
Concomitant Therapies	Concomitant Medications, Non-drug Therapies, and Radiotherapy	X						See Section 6.7.
Biomarker Samples	Tumor Biopsy			X[e]				Biopsies may be collected from a lesion that has been irradiated, provided that it can be documented that the lesion has increased/appeared since radiation occurred and that the biopsy is collected at least 3 months after radiation. [e] Optional. The EOT biopsy can be performed from EOT to the Follow-up visit prior to starting new treatment See Section 8.6.2.
	Blood sample for cfDNA	X[f]		X				[f] Within 3 days before administration of DS-1062a at C6D1 and C9D1 only. See Section 8.6.1.
	Plasma sample	Sample to be collected at the time of suspected ILD						
	Serum sample	Sample to be collected at the time of suspected ILD						
Tumor Response and Lung Disease Assessment[h]	CT/MRI of the chest, abdomen, and any other sites of disease	Every 6 weeks (±7 days) from C1D1 until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent (regardless of discontinuing study treatment or starting new anticancer therapy) For further instructions, refer to the Imaging Site Manual.				X[g]		[g] Subjects who discontinued treatment without radiographic disease progression as assessed by BICR will continue to undergo tumor assessments every 6 weeks (± 7 days) until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent. In addition, all subjects who have not had disease progression at the time of the primary completion date will continue to be followed for tumor assessments and survival. See Section 8.3 and Section 10.4.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
					28-day Safety Follow-up[a]	Long-term Survival Follow-up (Every 3 Months)		[a] 28 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the day of discontinuation is over 35 days from last study drug administration, follow-up assessment is not needed
	Visit Day	1						
	Infusion	**BI**	**EOI**					
	Visit Window (Days)	±2		-3, +7	+7	±14		
								h. All images including CT and MRI will be submitted to a central imaging CRO for independent review.
	CT/MRI of brain	Subjects with brain metastases at baseline should have brain MRI or CT scan performed every 6 weeks (±7 days) from C1D1. Additional brain imaging may be performed as needed clinically.				X[i]		[i] Subjects with brain metastases at baseline who discontinued treatment without radiographic disease progression as assessed by BICR will continue to undergo brain MRI or CT scans every 6 weeks (±7 days) until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent. In addition, all subjects with brain metastases at baseline who have not had disease progression at the time of the primary completion date will continue to be followed for brain MRI or CT scans and survival.
	Bone Scan (bone scintigraphy) or 18F FDG PET/CT	Follow-up bone imaging is required only if new bone metastases are suspected. When or disease progression in the bone or new lesion in the bone is suspected, 18F FDG PET/CT should be used to determine disease progression.						See Section 8.3 and Section 10.4.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
					28-day Safety Follow-up[a]	Long-term Survival Follow-up (Every 3 Months)		[a] 28 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the day of discontinuation is over 35 days from last study drug administration, follow-up assessment is not needed
	Visit Day	1						
	Infusion	**BI**	**EOI**					
	Visit Window (Days)	±2		-3, +7	+7	±14		
Study Drug	Administration of DS-1062a	X						Premedication is required prior to any dose of DS-1062a that must include antihistamines and acetaminophen with or without glucocorticoids. Subject should remain at the site for at least 1 h post-infusion for close observation for possible allergic reactions. If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle. See Section 6.
PK Blood Samples	Full PK Sampling	X[c,j]	X[j,k]					To be collected from the first approximately 30 subjects with adequate hepatic function and up to 9 subjects with moderate hepatic dysfunction. [c] Within 8 h BI of DS-1062a. [j] C4, C6, and C8 only. No PK sampling after C8. [k] Within 1 h after EOI of DS-1062a. See Section 8.5
	Sparse PK Sampling	X[c,j]	X[j,k]					To be collected from the remaining subjects who do not undergo full PK sampling. [c] Within 8 h BI of DS-1062a. [j] C4, C6, and C8 only. No PK sampling after C8. [k] Within 1 h after EOI of DS-1062a. See Section 8.5.
	Non-serious AEs	X						See Section 8.4.1 and Section 10.5

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
					28-day Safety Follow-up[a]	Long-term Survival Follow-up (Every 3 Months)		[a] 28 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the day of discontinuation is over 35 days from last study drug administration, follow-up assessment is not needed
	Visit Day	1						
	Infusion	**BI**	**EOI**					
	Visit Window (Days)	±2		-3, +7	+7	±14		
AEs	SAEs	X				X[1]		[1] Only SAEs considered related by the investigator should be reported during LTSFU. See Section 8.4.1 and Section 10.5
OS	Survival FU					X		See Section 8.3
Reason for Treatment Discontinuation				X				See Section 7
Reason for Study Discontinuation							X	

18F FDG = 18F fluorodeoxyglucose; ADA = antidrug antibody; AE = adverse event; BI = before infusion; BICR = blinded independent central review; C = cycle; COVID-19 = coronavirus disease 2019; D = Day 1; cfDNA = cell-free deoxyribonucleic acid; CRO = contract research organization; CT = computed tomography; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOS = end of study; EOT = end of treatment; FU = follow-up; h = hour; ILD = interstitial lung disease; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; OS = overall survival; PET = positron emission tomography; PK = pharmacokinetics; SAE = serious adverse event; SpO_2 = peripheral oxygen saturation

Notes: For suspected ILD/pneumonitis, treatment with study drug should be delayed pending evaluation.

Evaluations should include the following:

- High-resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests (including force vital capacity and CO diffusing capacity) and pulse oximetry (SpO_2)
- Clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, C-reactive protein, and a COVID-19 test)
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible

Other tests can be considered, as needed.

For prevention of oral mucositis/stomatitis, initiate a daily oral care plan (see Section 8.4.4). The importance of multiple daily mouth rinses during treatment (eg, prior to dosing) and up to the first follow-up visit should be emphasized.

For prevention of ocular surface toxicity, it should be strongly recommended that subjects avoid the use of contact lenses starting on the day of the first DS-1062a dose and to use artificial tears (preferably preservative free) 4 times per day as a preventative measure and up to 8 times per day as clinically needed.

Ophthalmologic assessments, including, but not limited to, visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining, will be performed at screening, as clinically indicated, and at the EOT visit by an ophthalmologist or, if unavailable, another licensed eye care provider.

2. INTRODUCTION

2.1. Background

2.1.1. Non-small Cell Lung Cancer

Lung cancer is the most common cancer and the leading cause of cancer-related mortality worldwide, with an estimated 2.1 million new cases of lung cancer in 2018 (11.6% of all new cases) and 1.8 million deaths (18.4% of all cancer deaths) globally based on GLOBOCAN data.[3] Advances in early detection of lung cancer have been slow, and more than half of lung cancers are still diagnosed at an advanced stage.[4] Only 18% of all patients with lung cancer are alive 5 years or more after diagnosis.[5] Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers.[6]

The introduction of targeted therapies and checkpoint inhibitors in recent years has improved the treatment landscape and patients with metastatic NSCLC are now surviving longer.[7,8] A number of genomic alterations have been identified in NSCLC that have an impact on therapy selection and molecular testing is part of the standard of care (SoC) in the evaluation of NSCLC.[8] These genomic alterations include epidermal growth factor receptor (EGFR) gene mutations, which are associated with responsiveness to EGFR-tyrosine kinase inhibitors (TKIs); anaplastic lymphoma kinase (ALK) gene rearrangements, associated with response to ALK TKIs; and more rarely, ROS proto-oncogene 1 (ROS1) gene rearrangements (associated with responsiveness to ROS1 TKIs), neurotrophic tyrosine receptor kinase (NTRK) gene fusions (associated with responsiveness to NTRK inhibitors), and proto-oncogene B-raf (BRAF) point mutations (associated with responsiveness to combined therapy with inhibitors of BRAF and MEK).[8] Targeted therapies (eg, EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, or RET kinase inhibitors) are recommended during the course of treatment as systemic treatments for a subset of patients with NSCLC whose tumors have driver genomic alterations. However, once subjects have developed acquired resistance to the various kinase inhibitors, there are limited treatment options. Hence, there is a significant unmet medical need for patients with advanced or metastatic NSCLC with actionable genomic alterations.

2.1.2. DS-1062a

Trophoblast cell surface protein 2 (TROP2), also known as tumor-associated calcium signal transducer 2, is a 36-kDa single-pass transmembrane protein expressed primarily in a variety of epithelial cells. TROP2 has several binding partners, including claudin 1, claudin 7, cyclin D1, protein kinase C, phosphatidylinositol 4,5-biphosphate, and insulin-like growth factor 1. TROP2 is highly expressed in various epithelial tumors, including NSCLC.[9]

DS-1062a (datopotamab deruxtecan; Dato-DXd) is an antibody-drug conjugate (ADC) that comprises a recombinant humanized anti-TROP2 immunoglobulin 1 (IgG1) monoclonal antibody (mAb), MAAP-9001a, that is covalently conjugated to a drug linker, MAAA-1162a, via thioether bonds. The released drug, MAAA-1181a, inhibits deoxyribonucleic acid (DNA) topoisomerase I and leads to apoptosis of the target cells.

2.2. Study Rationale

DS-1062a is a TROP2-targeted antibody and topoisomerase I inhibitor conjugate. High expression levels of TROP2 have been reported in NSCLC[10,11] and other solid tumors.[12] TROP2 high expression in tumors has been shown to be indicative of poor prognosis.[9]

DS-1062a showed antitumor activity in both in vitro and in vivo nonclinical studies. The mean terminal half-life (t1/2) of DS-1062a is 4.62 days (6.0 mg/kg) in humans, which allows a once every 3-week (Q3W) dosing schedule.[11]

Clinical data are available from the ongoing Phase 1 first-in-human (FIH) study, DS1062-A-J101, evaluating escalating doses of DS-1062a (0.27 mg/kg to 10.0 mg/kg) in unselected subjects with unresectable advanced NSCLC relapsed or refractory to SoC therapy. As described in the Investigator's Brochure (IB),[13] DLTs occurred in 3 subjects: 2 subjects at 10.0 mg/kg (1 subject with Grade 3 stomatitis and 1 subject with Grade 3 mucosal inflammation) and 1 subject at 6.0 mg/kg (Grade 3 maculopapular rash). The maximum tolerated dose (MTD) was determined at 8.0 mg/kg.[13]

As of the data cutoff (DCO) date of 04 Sep 2020, data are available for 208 subjects (204 NSCLC, 1 large-cell neuroendocrine carcinoma, and 3 breast cancer subjects) treated with DS-1062a in the 0.27 mg/kg to 10.0 mg/kg Q3W cohorts, including 50 subjects treated at 4.0 mg/kg, 46 subjects at 6.0 mg/kg, and 82 subjects at 8.0 mg/kg doses.[13] The median duration of treatment was 2.76 months (range: 0.7 to 20.0) across all doses; 2.09 months (range: 0.7 to 20.0) in the 4.0 mg/kg dose group; 2.07 months (range: 0.7 to 19.7 months) in the 6.0 mg/kg dose group; and 3.19 months (range: 0.7 to 13.5 months) in the 8.0 mg/kg dose group. As of the DCO, study treatment was ongoing in 72 subjects at the 4 mg/kg, 6 mg/kg, and 8 mg/kg dose levels.

As of the DCO date of 04 Sep 2020, 189 subjects were evaluable for tumor assessments, defined as subjects who received at least 1 dose of DS-1062a and had pre-treatment and at least 1 post-treatment tumor assessment or discontinued from study treatment.[13] The ORR by blinded independent central review (BICR) was 17.5% (7 partial responses [PRs] in 40 subjects) in the 4 mg/kg dose group, 15.4% (6 PRs in 39 subjects) in the 6 mg/kg dose group, and 23.8% (19 PRs in 80 subjects) in the 8 mg/kg dose group. The DCR was 72.5% (7 PRs and 21 stable diseases [SDs] in 40 subjects) in the 4 mg/kg dose group, 66.7% (6 PRs and 18 SDs in 39 subjects) in the 6 mg/kg dose group, and 80.0% (19 PRs and 43 SDs in 80 subjects) in the 8 mg/kg dose group.

As of 04 Sep 2020, treatment-emergent adverse events (TEAEs) regardless of causality were reported in 199 (95.7%) of 208 subjects, including 48 (96.0%) of 50 subjects in the 4 mg/kg dose group, 42 (91.3%) of 46 subjects in the 6 mg/kg dose group, and 81 (98.8%) of 82 subjects in the 8 mg/kg dose group.[13] The most frequent (≥20% of subjects) TEAEs across all doses, all grades, regardless of dose and causality were nausea (46.6%), stomatitis (38.9%), fatigue (34.1%), alopecia (33.7%), decreased appetite (24.5%), vomiting (23.1%), and constipation (20.7%).

A total of 89 (42.8%) of 208 subjects experienced at least 1 ≥Grade 3 TEAE regardless of causality including 11 (22.0%) of 50 subjects in the 4 mg/kg dose group, 17 (37.0%) of 46 subjects in the 6 mg/kg dose group, and 46 (56.1%) of 82 subjects in the 8 mg/kg dose group. The frequency of ≥Grade 3 TEAEs appears to be dose-related.

Forty two (20.2%) of 208 subjects experienced ≥Grade 3 TEAEs assessed by the investigator as study drug-related, including 5 (10.0%) of 50 subjects in the 4 mg/kg dose group, 7 (15.2%) of 46 subjects in the 6 mg/kg dose group, and 27 (32.9%) of 82 subjects in the 8 mg/kg dose group.[13] The most frequently reported ≥Grade 3 TEAE (≥5 subjects) assessed by the investigator as study drug-related across all doses was mucosal inflammation (6 subjects [2.9%]).

Numerically higher rates of drug-related TEAEs, TEAEs ≥Grade 3, drug-related TEAEs ≥Grade 3, serious TEAEs, drug-related serious TEAEs, TEAEs associated with drug discontinuation, drug-related TEAEs associated with study drug discontinuation, TEAEs associated with dose reduction, and TEAEs associated with death were observed in the 8 mg/kg cohort compared to the 4 mg/kg and/or 6 mg/kg cohorts. A total of 20 (9.6%) of 208 subjects experienced TEAEs associated with study drug withdrawal, including 4 (8.0%) of 50 subjects in the 4 mg/kg dose group, 4 (8.7%) of 46 subjects in the 6 mg/kg dose group, and 12 (14.6%) of 82 subjects in the 8 mg/kg dose group. The most frequent TEAE across all doses leading to study drug withdrawal was pneumonitis (8 subjects [3.8%]). A total of 35 (16.8%) of 208 subjects experienced TEAEs associated with dose reduction, including 1 (2.0%) of 50 subjects in the 4 mg/kg dose group, 4 (8.7%) of 46 subjects in the 6 mg/kg dose group, and 25 (30.5%) of 82 subjects in the 8 mg/kg dose group. The most frequent (≥5 subjects) TEAEs associated with dose reduction across all doses were stomatitis (12 subjects [5.8%]) and mucosal inflammation (7 subjects [3.4%]). A total of 28 (13.5%) of 208 subjects experienced TEAEs associated with dose interruption, including 2 (4.0%) of 50 subjects in the 4 mg/kg dose group, 9 (19.6%) of 46 subjects in the 6 mg/kg dose group, and 16 (19.5%) of 82 subjects in the 8 mg/kg dose group. The most frequent (≥4 subjects) TEAEs across all doses associated with dose interruption were lung infection and pneumonitis (4 subjects [1.9%] each).

As of 04 Sep 2020 across all doses, there were 14 subjects (6.7%) with interstitial lung disease (ILD)/pneumonitis events that were independently adjudicated as drug-related: 12 subjects (14.6%) on 8.0 mg/kg, 1 subject (2.2%) on 6.0 mg/kg, and 1 subject (2.0%) on 4.0 mg/kg. Of the 14 subjects with events adjudicated as drug-related ILD, 3 (1.4%) subjects experienced Grade 5 events; these 3 subjects were in the 8.0 mg/kg dose group.

Across all doses, 40 (19.2%) of 208 subjects treated have experienced TEAEs of infusion-related reaction (IRR).[13] All events of IRR were Grade 1 or Grade 2 except for 2 Grade 3 events (1 at 4 mg/kg and 1 at 6 mg/kg). All occurred during Cycle 1 or 2 of study treatment and were manageable.

ILD/pneumonitis is an important identified risk for DS-1062a. Other identified risks include IRR, fatigue, anemia, stomatitis/mucosal inflammation, diarrhea, nausea, decreased appetite, alopecia, vomiting, dry eye, and rash/maculopapular rash. Potential risks include keratitis, skin pigmentation, AST increased, ALT increased, and constipation. Adverse events of special interest (AESIs) include ILD/pneumonitis, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, ocular surface toxicity, and IRR. Established treatment guidelines are in place to manage these and other toxicities associated with DS-1062a.

Refer to the most recent IB for additional information.[13]

There is a significant unmet medical need for patients with advanced or metastatic NSCLC with actionable genomic alterations after having received kinase inhibitors and platinum-based chemotherapy. DS-1062a has the potential to offer a treatment option for patients with advanced

or metastatic NSCLC with genomic alterations. This study will further evaluate the efficacy and safety of DS-1062a at a dose of 6.0 mg/kg in this population.

2.3. Benefit and Risk Assessment

DS-1062a is being developed for the treatment of TROP2-expressing malignant tumors.

Nonclinical studies have demonstrated the antitumor activity of DS-1062a in TROP2 tumor-bearing mouse models. Thus, DS-1062a is expected to demonstrate efficacy in treating TROP2-expressing tumors in patients.

In nonclinical toxicology studies, lung toxicity, corneal toxicity, skin toxicity, intestinal toxicity, lymphatic/hematopoietic system toxicity, reproductive and accessory organ toxicities, hepatic toxicity, renal toxicity, and joint cartilage toxicity were found in association with the administration of DS-1062a. As with any therapeutic antibodies, there is a possibility of IRRs and immune responses causing allergic or anaphylactic reactions to DS-1062a.

In vitro studies indicate that DS-1062a exhibits TROP2 expression-dependent cell growth inhibitory activity, and in vivo studies using a tumor-bearing mouse model indicate that administration of DS-1062a results in the regression of TROP2-expressing tumors.

As of the DCO date of 04 Sep 2020, a total of 208 subjects have been treated with DS-1062a in the ongoing DS1062-A-J101 Phase 1 study.[13] Data from this study show antitumor activity across dose groups with tumor responses observed at starting doses of 4.0, 6.0, and 8.0 mg/kg with an acceptable and manageable toxicity profile. As of the DCO date of 04 Sep 2020, DS-1062a has demonstrated response rates across these 3 dose cohorts with confirmed and durable responses as described in Section 2.2.

Based on cumulative review, an important identified risk for DS-1062a is ILD/pneumonitis. Other identified risks include IRR, fatigue, anemia, stomatitis/mucosal inflammation, diarrhea, nausea, decreased appetite, alopecia, vomiting, dry eye, and rash/ rash maculopapular. The potential risks include keratitis, skin pigmentation, AST increased, ALT increased, and constipation. DS-1062a exhibits an acceptable and generally manageable safety profile with adequate mitigation measures for the important identified risks and other risks mentioned above.

In summary, aggregate safety and efficacy data from the DCO date of 04 Sep 2020 suggest a more favorable benefit/risk profile for 6 mg/kg relative to those of the 8 mg/kg and 4 mg/kg doses supporting the selection of 6 mg/kg for further development of DS-1062a.

For additional information on justification for dose selected in this study, see Section 4.3.

2.3.1. Benefit and Risk with Regard to COVID-19

With the emergence of coronavirus disease 2019 (COVID-19), there is a potential safety risk due to the impact of COVID-19 on the lung. The Sponsor has developed a monitoring plan to limit and manage the potential risk of COVID-19 to DS-1062a study subjects. For details regarding the assessment and management of confirmed or suspected COVID-19, see Section 10.7.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

The objectives, definitions of associated endpoints, and applicable outcome measures are described in Table 3.1. Further requirements for the endpoint analyses and censoring rules, where applicable, can be found in Section 9.5.1 (efficacy assessments), Section 9.5.2 (safety assessments), and Section 9.5.3 (other assessments).

Table 3.1: Description of Objectives, Outcome Measures, and Endpoints

Objectives	Outcome Measures	Endpoints	Category
Primary			
To assess the efficacy of DS-1062a, as measured by the ORR, as a treatment for subjects with NSCLC with actionable genomic alterations that has progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study	**Title:** ORR **Description:** ORR as assessed by BICR per RECIST v1.1. **Time frame:** Primary analysis: After all subjects have had a minimum of 9 months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first.	ORR is defined as the proportion of subjects who achieved a BOR of confirmed CR or confirmed PR.	Efficacy
Secondary			
To further evaluate the efficacy of DS-1062a	**Title:** DoR **Description:** DoR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	DoR is defined as the time from the date of the first documentation of response (confirmed CR or confirmed PR) to the date of the first documentation of PD or death due to any cause, whichever occurs first.	Efficacy
	Title: Best percentage change in the SoD of measurable tumors **Description:** SoD as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	The best percentage change in the SoD of measurable tumors is defined as the percentage change in the smallest SoD from all post-baseline tumor assessments, taking as reference the baseline SoD.	Efficacy
	Title: DCR **Description:** DCR as assessed by	DCR is defined as the proportion of subjects who achieved a BOR of	Efficacy

Objectives	Outcome Measures	Endpoints	Category
	BICR and investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	confirmed CR, confirmed PR, or SD.	
	Title: CBR **Description:** CBR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	CBR is defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or an SD that lasts for at least 180 days.	Efficacy
	Title: PFS **Description:** PFS as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	PFS is defined as the time from the start of study treatment to the earlier of the dates of the first documentation of PD or death due to any cause.	Efficacy
	Title: TTR **Description:** TTR as assessed by BICR and by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	TTR is defined as the time from the start of study treatment to the date of the first documentation of objective response (confirmed CR or confirmed PR) in responding subjects.	Efficacy
	Title: ORR **Description**: ORR as assessed by investigator per RECIST v1.1. **Time frame:** At the time of the primary analysis.	ORR is defined as the proportion of subjects who achieved a BOR of confirmed CR or confirmed PR.	Efficacy
	Title: OS **Description:** OS. **Time frame:** At the time of the primary analysis.	OS is defined as the time from the start of study treatment to the date of death due to any cause.	Efficacy

Objectives	Outcome Measures	Endpoints	Category
To further evaluate the safety of DS-1062a.	**Title:** TEAEs and other safety parameters during the study* **Description:** Descriptive statistics of safety endpoints. **Time frame:** Continuous monitoring and reported at the time of the primary analysis. *Though this is a secondary objective, this is a primary outcome measure.	TEAEs, SAEs, AESIs, ECOG PS, vital sign measurements, standard clinical laboratory parameters (hematology, serum chemistry, and urinalysis), ECG parameters, ECHO/MUGA scan findings, and ophthalmologic findings. AEs will be coded using the most current version of MedDRA. AEs and laboratory test results will be graded using the NCI CTCAE v5.0.	Safety
To assess the PK of DS-1062a.	**Title:** PK profile **Description:** Plasma concentrations and PK parameters of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a. **Time frame**: At the time of the primary analysis.	Plasma concentrations at each time point and PK parameters (Cmax, Tmax, AUClast, AUCtau. If data permit: AUCinf, t1/2, CL, Vss, Vz, and Kel) of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a (released drug) in the full PK sampling cohort.	PK
To assess the immunogenicity of DS-1062a.	**Title:** Immunogenicity **Description:** Prevalence and incidence of ADA. **Time frame:** At the time of the primary analysis.	ADA prevalence: the proportion of subjects who are ADA positive at any point in time (including pre-existing ADA at baseline and treatment-emergent ADA). ADA incidence: the proportion of subjects having treatment-emergent ADA. Titer and neutralizing antibodies will be determined when ADA is positive.	Immunogenicity

Objectives	Outcome Measures	Endpoints	Category
Exploratory			
To evaluate biomarkers that may associate with the clinical benefit from DS-1062a used to treat NSCLC.	Not applicable.	Tumor TROP2 expression by IHC (central laboratory analysis). Other biomarkers including genomic alterations, gene expression, and protein expression will be measured in tumor and blood samples.	Biomarkers and pharmacogenomics
To explore how changes in biomarkers may relate to exposure and clinical outcomes.	Not applicable.	Biomarkers (tumor and/or blood gene expression, genomic alteration, gene expression signatures, TROP2 expression) assessed pre- and post-treatment.	Biomarkers
To evaluate pre-treatment tumor biopsy samples and archival tumor samples for key biomarkers that correlate with the clinical benefit from DS-1062a.	Not applicable.	The expression of key biomarkers in pre-treatment tumor biopsy samples will be compared with the expression in archival tumor samples using validated assays for IHC and/or gene expression.	Biomarkers
To evaluate exposure-response relationships for efficacy and safety endpoints.	Not applicable.	Characterization of population PK and its relationship with efficacy and safety endpoints.	PK

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; AUCinf = area under the plasma concentration-time curve up to infinity; AUClast = area under the plasma concentration-time curve up to the last quantifiable time; AUCtau = area under the plasma concentration-time curve during dosing interval; BICR = blinded independent central review; BOR = best overall response; CBR = clinical benefit rate; CL = total body clearance; Cmax = maximum plasma concentration; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; Kel = elimination rate constant associated with the terminal phase; MAAA-1181a = released drug; MedDRA = Medical Dictionary for Regulatory Activities; MUGA = multigated acquisition; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST v1.1= Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; SoD = sum of diameters; t1/2 = terminal half-life; TEAE = treatment-emergent adverse event; Tmax = time to reach maximum plasma concentration; TROP2 = trophoblast cell surface protein 2; TTR = time to response; Vss = volume of distribution at steady-state; Vz = volume of distribution based on the terminal phase

3.1. Rationale for Selection of Primary and Secondary Endpoints

The primary efficacy endpoint of the study will be the ORR, defined as the proportion of subjects who achieve a confirmed best overall response (BOR) of confirmed CR or PR as assessed by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The ORR is a direct measure of the drug antitumor activity. Because ORR is directly attributable to drug effect, it is an appropriate measure of efficacy in studies without comparator.[14]

Duration of response in subjects with confirmed response of CR or PR is an important secondary endpoint of the study. A durable response is clinically meaningful in subjects with advanced or metastatic NSCLC who have received 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study, in which there remains an unmet medical need.

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, single-arm, open-label, Phase 2 study designed to evaluate the efficacy, PK, and safety of DS-1062a in subjects with advanced or metastatic NSCLC with actionable genomic alterations specified in Section 5.1 and who have been previously been treated with 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study. The study population is described in Section 5.

The study will be conducted at approximately 85 study sites located in North America, Europe, and the Asia Pacific region.

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the study when the investigator or designee has obtained written consent, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed.

4.1.1. Design Overview

This study will enroll approximately 150 subjects with advanced or metastatic NSCLC with known genomic alterations in EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET who had previously received treatment with progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study. Patients with tumors expressing mutations in KRAS are not eligible for this study. The rationale for this exclusion is that KRAS mutations are rarely found in conjunction with the genomic alterations listed above and as such do not typically receive targeted kinase inhibitors. In addition, and in contrast to patients with the above listed genomic alterations, patients with KRAS mutant tumors respond to treatment with checkpoint inhibitors, and thus represent a population distinct from the kinase mutant populations included in this study.

Subjects whose tumors harbor EGFR mutations should comprise approximately 50% of subjects enrolled in the study, among those, 80% should have received osimertinib (regardless of T790M status) as a prior line of therapy. Subjects who meet these prior therapy requirements for advanced or metastatic NSCLC are eligible. See the washout period for prior treatments in Section 5.1.

The PK of DS-1062a will be evaluated in all subjects; see Section 8.5. Full PK sampling will be collected from the first approximately 30 subjects with adequate hepatic function and up to 9 subjects with moderate hepatic dysfunction. The remaining subjects will have sparse PK sampling.

Up to 9 subjects with moderate hepatic dysfunction, as defined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG),[15] will be allowed in the study. After a maximum of 9 subjects with moderate hepatic dysfunction have been enrolled, subsequent subjects with moderate hepatic dysfunction will be excluded.

The schedules of events are presented in Table 1.1 (Screening and Cycles 1 through 3 of the Treatment Period) and Table 1.2 (Cycle 4 onwards, End of Treatment [EOT], and the Follow-up Period).

The study will be divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period (which includes the Long-term Survival Follow-up [LTSFU]):

- The Screening Period will start on the day of signing the informed consent form (ICF) and will have a maximum duration of 28 days. Rescreening is permitted 1 time for any subject who did not meet reversible or transient eligibility criteria upon initial screening. During the 28-day Screening Period, subjects' eligibility will be confirmed. Subjects will undergo medical history evaluation, physical examination, vital signs determination, laboratory tests, electrocardiogram (ECG), echocardiogram (ECHO) or multigated acquisition (MUGA) scan, ophthalmologic assessment, and tumor biopsy procedure. A tumor biopsy previously obtained within 3 months of signing the ICF, and with no anticancer treatment administered in the 3 months, may be substituted for the mandatory pre-treatment biopsy procedure during screening. Biopsies may be collected from a lesion that has been irradiated, provided that it can be documented that the lesion has increased/appeared since radiation occurred and that the biopsy is collected at least 3 months after radiation. Documented results for genomic alterations in EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET must be obtained for inclusion in the study and the previously known tumor genomic alteration status will be used.
- Eligible subjects will enter the Treatment Period. The Treatment Period starts on Cycle 1 Day 1 and continues until a subject permanently discontinues DS-1062a. During the Treatment Period, eligible subjects will receive DS-1062a until they meet one of the discontinuation criteria (see Section 7.1). Subjects will undergo radiographic assessment of tumor response based on RECIST v1.1 every 6 weeks (±7 days) from Cycle 1 Day 1 until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent, regardless of treatment discontinuation or start of new anticancer therapy (tumor assessment is not restricted to Treatment Period). Subjects who experience clinical benefit will continue to receive DS-1062a until radiographic disease progression, clinical progression, unacceptable toxicity, withdrawal of consent by subject, physician decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons (see Section 7.1).
- The Follow-up Period will start upon permanent discontinuation of DS-1062a. During the Follow-up Period, subjects will be followed for 28 days (+7 days) for safety. After discontinuation of study drug, subjects will then enter the LTSFU Period, during which they will be followed every 3 months for collection of information on subsequent anticancer treatment and survival, including the cause and date of death. During the Follow-up Period, subjects who discontinued treatment without radiographic disease progression as assessed by BICR will continue to undergo tumor assessments every 6 weeks (± 7 days) until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent.

To ensure accurate survival data are available at the time of any database lock, updated survival status may be requested during the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, the planned data cut and database lock for the primary analysis and final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their survival status (excluding subjects who have discontinued from the entire study or with

a previously reported death event). A potential companion diagnostic (CDx) assay to analyze TROP2 expression may be developed as part of the DS-1062 program. Depending on the results of biomarker association with clinical benefit, a CDx may be developed in the course of this study.

The primary analysis of ORR by BICR will be conducted after all subjects either have been followed for at least 9 months after the start of study treatment or have discontinued from the study, whichever occurs first. The final analysis will occur after all subjects have discontinued from the study (see definition of overall EOS in Section 4.1.2).

The study population is described in Section 5. A study level flow diagram is presented in Figure 1.1.

4.1.2. End of Study

The **primary completion date** will occur when all subjects have had either a minimum of 9 months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first. This date is used as the DCO date for the primary analysis. All subjects still on treatment and continuing to derive benefit from DS-1062a at the primary completion date will continue to follow the study Schedule of Events (SoE) until the **overall EOS** is reached. All subjects who have not had disease progression at the time of the primary completion date will continue to be followed for tumor assessments and survival.

The subject's EOS is the date of their last study visit/contact.

The overall EOS will occur after the last subject last visit has occurred; or after all subjects have discontinued treatment and discontinued from the study, or have died; or an alternative study becomes available for subjects continuing to derive benefit from treatment with DS-1062a where the drug is offered to these subjects; or the study is discontinued by the Sponsor for other reasons.

4.1.3. Dose Regimen

DS-1062a will be administered as an intravenous (IV) infusion at a dose of 6.0 mg/kg Q3W on Day 1 of each 21-day cycle. The study will use the DS-1062a drug product (lyophilized-drug product [Lyo-DP]).

Subjects who experience clinical benefit will continue to receive DS-1062a until radiographic disease progression, clinical progression, death, pregnancy, withdrawal of subject consent, the subject becomes lost to follow-up, study termination by the Sponsor, physician decision, adverse event (AE), protocol deviation, or other reasons (see Section 7.1). See Table 6.1 for complete details on dose regimen.

Up to 3 dose reductions will be permitted for subjects. The adjustment for reduced dosing of DS-1062a is shown in Table 6.2. Once the dose of DS-1062a is reduced, no dose escalation is permitted.

4.1.4. Duration

Study duration is inclusive of 3 periods: Screening Period, Treatment Period, and Follow-up Period (which includes the LTSFU) as shown in Figure 1.1.

Duration of Treatment and Subject Participation

Subjects who experience clinical benefit will continue to receive DS-1062a until radiographic disease progression, clinical progression, unacceptable toxicity, withdrawal of consent by subject, physician decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons (see details in Section 7.1).

Note: Only protocol deviations that are deemed significant by the investigator, with or without consultation with the Sponsor, may lead to permanent study drug discontinuation.

In the event of early termination of the study, the Sponsor will consider providing DS-1062a to subjects who benefit from treatment according to legal regulations in the corresponding countries. Alternatively, these subjects may also be treated with SoC per investigator's decision.

Overall Study Duration

Enrollment is planned to occur over a period of approximately 19 months, with treatment and follow-up (28-day Safety Follow-up and Long-term Survival Follow-up) projected to continue for approximately 24 months after the last subject receives the first dose of DS-1062a. The study will continue until the overall EOS is reached. Thus, the anticipated total duration of the study is approximately 43 months.

See Section 4.1 for the definition of study start and Section 4.1.2 for the definition of the overall EOS.

Study Drug Continuation After the End of Study

Not applicable.

4.2. Rationale for Study Design

There is significant unmet medical need for patients with advanced or metastatic NSCLC with actionable genomic alterations after they have received platinum-based chemotherapy. This Phase 2 study is to further evaluate the efficacy, PK, and safety of 6.0 mg/kg DS-1062a as monotherapy.

The primary efficacy endpoint, ORR, will be based on BICR and represents an additional measure to minimize bias in the assessment of the efficacy endpoints in the study.

The rationale for dose selection is presented in Section 4.3 and the rationale for selection of the primary efficacy endpoint is presented in Section 3.1.

4.3. Justification for Dose

The 6.0-mg/kg dose of DS-1062a was selected based on preliminary results of the ongoing FIH Phase 1 study DS1062-A-J101, which enrolled 208 subjects with NSCLC across a DS-1062a dose range of 0.27 mg/kg to 10 mg/kg. In this study, DS-1062a has shown a generally tolerable safety profile in subjects with NSCLC across a DS-1062a dose range of 0.27 mg/kg to 8.0 mg/kg. The non-tolerated dose for DS-1062a was 10.0 mg/kg, at which 2 subjects had Grade 3 DLTs of mucosal inflammation and stomatitis. In addition, 1 subject at 6.0 mg/kg had a dose-limiting toxicity of Grade 3 maculopapular rash. The MTD was reached at 8.0 mg/kg. Enrollment was expanded to include 50, 50, and 80 subjects at doses of 4.0, 6.0, and 8.0 mg/kg,

respectively, to enrich the data for the part of the dose-response relationship where benefit-risk balance is most delicate.

As noted in Section 2.2, the ORR was 17.5% (7 PRs in 40 subjects) in the 4 mg/kg dose group, 15.4% (6 PRs in 39 subjects) in the 6 mg/kg dose group, and 23.8% (19 PRs in 80 subjects) in the 8 mg/kg dose group. Numerically higher rates of drug-related TEAEs, TEAEs ≥Grade 3, drug-related TEAEs ≥Grade 3, serious TEAEs, drug-related serious TEAEs, TEAEs associated with drug discontinuation, drug-related TEAEs associated with study drug discontinuation, TEAEs associated with dose reduction, and TEAEs associated with death were observed in the 8 mg/kg cohort compared to the 4 mg/kg and/or 6 mg/kg cohorts (Section 2.2). DS-1062a was less tolerated at 8.0 mg/kg compared to 4.0 mg/kg and 6.0 mg/kg, and based on overall safety and efficacy data, 8.0 mg/kg was not considered an optimal dose for further evaluation.

The Phase 1 study DS1062-A-J101 is ongoing, and data are continually emerging. Barring any substantial changes in the efficacy and safety profiles of the 4.0-mg/kg and 6.0-mg/kg doses with more mature data, 6.0 mg/kg is considered to be the optimal dose for DS-1062a monotherapy studies in NSCLC.

With respect to the dosing schedule, the mean terminal half-life of DS-1062a is 4.62 days at the 6.0-mg/kg dose in clinical studies, thus supporting a Q3W dosing schedule.

5. STUDY POPULATION

The study population includes adult subjects with a diagnosis of advanced or metastatic NSCLC with actionable genomic alterations specified below that have progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study.

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment into the study:

1. Sign and date the ICF prior to the start of any study-specific qualification procedures.
1. Adults ≥18 years (if the legal age of consent is >18 years old, then follow local regulatory requirements).[16]
2. Has pathologically documented NSCLC that
    a. Is stage IIIB, IIIC or stage IV NSCLC disease at the time of enrollment (based on the American Joint Committee on Cancer, Eighth Edition).
    b. Has 1 or more of the following documented activating tumor genomic alterations*: EGFR**, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.

        * Those whose tumors harbor KRAS mutations, in the absence of any of the genomic alterations specified above, will be excluded.

        ** Overexpression of EGFR, in the absence of activating mutations, is **NOT** sufficient for enrollment. Subjects who have not received osimertinib should be evaluated for presence of EGFR T790M mutation after relapse/progression on/after most recent EGFR TKI, unless the subject is already known to be positive with documented results for this mutation or unless osimertinib is not locally approved.
3. Has documentation of radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.
4. Subject must meet the following for advanced or metastatic NSCLC:
    a. Has been treated with at least 1 but no more than 2 cytotoxic agent-containing therapy in the metastatic setting:
        i. One platinum-containing regimen (either as monotherapy or combination therapy);
        ii. May have received up to one additional line of cytotoxic agent-containing therapy;
        iii. Those who received a platinum-containing regimen as adjuvant therapy for early-stage disease must have relapsed or progressed while on the treatment or within 6 months of the last dose OR received at least one additional course of platinum-containing therapy (which may or may not be same as in the adjuvant setting) for relapsed/progressive disease;

b. May have received up to one checkpoint inhibitor (CPI)-containing regimen (may be in combination with a cytotoxic agent as part of a regimen described in 5a above or as an additional CPI regimen without a cytotoxic agent);

c. Has been treated with one or more lines of non-CPI targeted therapy that is locally approved for the subject's applicable genomic alteration at the time of screening; OR one or more of the agents specified in the table below;

   i. Those who received a targeted agent as adjuvant therapy for early stage disease must have relapsed or progressed while on the treatment or within 6 months of the last dose OR received at least one additional course of targeted therapy for the same genomic alterations (which may or may not be same agent used in the adjuvant setting) for relapsed/progressive disease.

   ii. Subjects who have been treated with a prior TKI must receive additional targeted therapy, if clinically appropriate, for the applicable genomic alterations, or the subject will not be allowed in the study.

Genomic Alterations	Applicable Targeted Agents
EGFR	erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib
EGFR exon20 insertion	amivantamab, mobocertinib
EGFR T790M	osimertinib
ALK fusion	crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib
ROS-1 fusion	entrectinib, lorlatinib, ceritinib, and crizotinib
NTRK fusion	entrectinib and larotrectinib
BRAF V600E	dabrafenib, alone or in combination with trametinib
MET exon 14 skipping	capmatinib and tepotinib
RET rearrangement	selpercatinib and pralsetinib

ALK = anaplastic lymphoma kinase; BRAF = proto-oncogene B-raf; EGFR = epidermal growth factor receptor; MET = mesenchymal-epithelial transition; NTRK = neurotrophic tyrosine receptor kinase; RET = rearranged during transfection; ROS-1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

5. Must undergo a mandatory pre-treatment tumor biopsy procedure.

   OR

   If available, a tumor biopsy that was recently collected (within 3 months of screening) after completion of the most recent anticancer treatment regimen and that has a minimum of 10 × 4 micron sections or a tissue block equivalent of 10 × 4 micron sections may be substituted for the mandatory biopsy collected during screening.
   Note: Results from this biopsy will not be used to determine eligibility for the study.

6. Archival tumor tissue from initial diagnosis is required, to the extent that archival tumor tissue is available.

7. Has measurable disease based on local imaging assessment using RECIST v1.1 (see criteria in Section 10.4).

8. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at screening (see criteria in Section 10.3.3).

9. Within 7 days before Cycle 1 Day 1, has adequate bone marrow function defined as:
   a. Platelet count ≥100,000/mm^3 (platelet transfusion is not allowed within 1 week prior to screening assessment).
   b. Hemoglobin ≥9.0 g/dL (red blood cell/plasma transfusion is not allowed within 1 week prior to screening assessment).
   c. Absolute neutrophil count ≥1500/mm^3 (granulocyte-colony stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment).

   (See Section 6.5 and Section 6.7 for use of G-CSF and erythropoietin)
10. Within 7 days before Cycle 1 Day 1, has
    - Adequate hepatic function, defined as:
      - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) or AST/ALT ≤5.0 × ULN if transferase elevation is due to liver metastases) AND
      - Total bilirubin (TBL) ≤1.5 × ULN or (<3.0 mg/dL in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia]).

    OR
    - Moderate hepatic dysfunction (a maximum of 9 subjects): TBL >1.5 × ULN and ≤3 × ULN and any AST.
      - Note: After a maximum of 9 subjects with moderate hepatic dysfunction have been enrolled, subsequent subjects with moderate hepatic dysfunction will be excluded.
11. Within 7 days before Cycle 1 Day 1, has adequate renal function, including mild or moderate renal function, defined as:
    – Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation (see Section 10.3.1).
12. Has a left ventricular ejection fraction (LVEF) ≥50% by either an ECHO or MUGA scan within 28 days before Cycle 1 Day 1.
13. Has adequate blood clotting function defined as international normalized ratio/prothrombin time and either partial thromboplastin or activated partial thromboplastin ≤1.5 × ULN within 7 days before enrollment.
14. Has an adequate treatment washout period before Cycle 1 Day 1 defined as:

Treatment	Washout Period
Major surgery	≥3 weeks
Radiation therapy (curative) and palliative radiation to the chest	≥4 weeks ≥2 weeks (palliative radiation therapy to other areas [ie, limited field and 10 or fewer days or fractions] including whole brain radiotherapy)
Anticancer chemotherapy (immunotherapy [non-antibody-based therapy]), retinoid therapy	≥2 weeks or 5 times the t1/2 of the chemotherapeutic agent, whichever is longer; ≥6 weeks for nitrosoureas or mitomycin C, ≥1 week for TKIs approved for the treatment of NSCLC - baseline CT scan should be completed after discontinuation of TKI
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/Hydroxychloroquine	>14 days

CT = computed tomography; NSCLC = non-small cell lung cancer; t1/2; terminal elimination half-life; TKI = tyrosine kinase inhibitor

15. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at screening and must be willing to use highly effective birth control (as detailed in Section 10.3.4) upon enrollment, during the Treatment Period, and for 7 months following the last dose of study drug. Females of non-childbearing potential are defined as pre-menopausal females with a documented tubal ligation or hysterectomy, or postmenopausal (defined as 12 months of spontaneous amenorrhea [in questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH) >40 mIU/mL and estradiol <40 pg/mL/147 pmol/L is confirmatory]). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the contraception methods outlined for women of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.
16. If male, the subject must be surgically sterile or must use a condom in addition to highly effective birth control (as detailed in Section 10.3.4) if their partners are of reproductive potential upon enrollment, during the Treatment Period, and for 4 months after the final dose of study drug administration.
17. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered before enrollment in the study.
18. Female subjects must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration. Preservation of ova should be considered prior to enrollment in the study.
19. Be willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
20. Has a life expectancy ≥3 months based on investigator's opinion.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of

whole brain radiotherapy and study enrollment. Note: A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain at baseline is required for all subjects. For those subjects in whom central nervous system (CNS) metastases are first discovered at the time of screening, the treating investigator should consider delay of study treatment to document stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, repeat of all screening activity may be required).

2. Has leptomeningeal carcinomatosis.
3. Prior treatment with:
    a. Any chemotherapeutic agent targeting topoisomerase I, including ADC containing such agent.
    b. TROP2-targeted therapy.
4. Uncontrolled or significant cardiovascular disease, including:
    a. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 milliseconds (msec) (based on the average of screening triplicate 12-lead ECG determinations).
    b. History of myocardial infarction within 6 months prior to Cycle 1 Day 1.
    c. History of uncontrolled angina pectoris within 6 months prior to Cycle 1 Day 1.
    d. Symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV) at screening. Subjects with a history of Class II to IV CHF prior to screening must have returned to Class I CHF and have LVEF ≥50% (by either an ECHO or MUGA scan within 28 days of Cycle 1 Day 1) in order to be eligible (see criteria in Section 10.3.2).
    e. History of serious cardiac arrhythmia requiring treatment.
    f. LVEF <50% by ECHO or MUGA scan within 28 days before Cycle 1 Day 1.
    g. Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) within 28 days before Cycle 1 Day 1.
5. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
6. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of the study Cycle 1 Day 1, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion, etc.), or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc.), or prior pneumonectomy.
7. Clinically significant corneal disease.
8. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals. Note: Subjects with localized fungal infections of skin or nails are eligible.
9. Has known HIV infection that is not well controlled. All of the following criteria are required to define an HIV infection that is well controlled: undetectable viral RNA load,

CD4+ counts/levels >250, no history of AIDs-defining opportunistic infection within the past 12 months, and stable for at least 4 weeks on same anti-HIV retroviral medications. If an HIV infection meets the above criteria, monitoring of the subjects' viral RNA load as well as the CD4+ count levels would be important. Subjects should be tested for HIV prior to Cycle 1 Day 1 if acceptable by local regulations or Institutional Review Board (IRB)/Ethics Committee (EC).

10. Has an active or uncontrolled hepatitis B and/or hepatitis C infection, is positive for hepatitis B or C virus based on the evaluation of results of tests for hepatitis B (hepatitis B surface antigen [HBsAg], anti-hepatitis B surface antigen [anti-HBs], anti-hepatitis B core antibody [anti-HBc], or hepatitis B virus [HBV] DNA) and/or hepatitis C infection (as per HCV RNA) within 28 days of Cycle 1 Day 1.

    Subjects are eligible if:

    a. Subjects have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis.
    b. Subjects who are HBsAg+, with HBV infection for more than 6 months (ie, chronic HBV infection) must meet the following conditions:
        i. HBV DNA viral load <2000 IU/mL.
        ii. Have normal transaminase values, or, if liver metastases are present, abnormal transaminases with a result of AST/ALT <3 × ULN which are not attributable to HBV infection.
        iii. Start or maintain antiviral treatment if clinically indicated as per the investigator.
    c. Subjects have been curatively treated for hepatitis C infection as demonstrated clinically and by viral serology.

11. Has other primary malignancies, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated, with no evidence of disease for ≥3 years.

12. Concomitant medical condition that would increase the risk of toxicity in the opinion of the investigator.

13. Toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet improved to NCI CTCAE version 5.0 Grade ≤1 or baseline.

    Note: Subjects may be enrolled with chronic, stable Grade 2 toxicities (defined as no worsening to >Grade 2 for at least 3 months prior to Cycle 1 Day 1 and managed with SoC treatment) that the investigator deems related to previous anticancer therapy, comprised of (including, but not limited to):

    a. Chemotherapy-induced neuropathy
    b. Fatigue
    c. Residual toxicities from prior immunotherapy treatment: Grade 1 or Grade 2 endocrinopathies, which may include:
        - Hypothyroidism/hyperthyroidism
        - Type I diabetes

- Hyperglycemia
- Adrenal insufficiency
- Adrenalitis
- Skin hypopigmentation (vitiligo)

14. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients (including but not limited to polysorbate 80).
15. History of severe hypersensitivity reactions to other monoclonal antibodies.
16. Is pregnant or breastfeeding or planning to become pregnant.
17. Has substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
18. Psychological, social, familial, or geographical factors that would prevent regular follow-up. Adults under guardianship, curatorship, safeguard of justice, or family empowerment measure are not eligible.
19. Otherwise considered inappropriate for the study by the investigator.

5.3. Screening Failures, Rescreening, and Subject Replacement

For subjects who do not meet the criteria for participation in the study (screen failures), the reason for screen failure must be recorded in the Screening Log.

Subjects who have dropped out will not be replaced.

Rescreening is permitted 1 time for any subject who did not meet reversible or transient eligibility criteria upon initial screening. The Screening Period for subjects who are rescreened is 28 days. A new subject identification number must be provided at the time of rescreening.

6. STUDY TREATMENT

See Figure 1.1 for treatment sequence.

6.1. Study Drug Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of DS-1062a.

Table 6.1: Study Drug Dosing Information

Study Drug Name	DS-1062a (Datopotamab Deruxtecan; Dato-DXd)
Dosage Formulation	DS-1062a DP will be provided as sterile lyophilized-DP consisting of 100 mg of lyophilized powder in a single-use amber glass vial to be reconstituted with water for injection and further diluted with 5% dextrose injection prior to use.
Dosage Level	6.0 mg/kg
Route of Administration	IV
Dosing Instructions/Regimen	One IV infusion every 3 weeks on Day 1 of each 21-day cycle. Premedication is required prior to any dose of DS-1062a that must include antihistamines and acetaminophen with or without glucocorticoids. Subjects should remain at the site for at least 1-h post-infusion of every dose of DS-1062a for close observation for possible allergic reaction. If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle.
Duration	The initial dose will be infused over approximately 90 min on Cycle 1 Day 1. In the absence of an IRR, the subsequent doses will be infused over approximately 30 min. In case of IRR at any time during treatment, please refer to details provided in Table 6.3.
Packaging	DS-1062a will be supplied by the Sponsor. The packaging will be clearly labeled "For Clinical Study Use Only," and will show the display name of the study drug, the lot number, storage condition, protocol number and other required information in accordance with local regulations.
Labeling	DS-1062a glass vials will be labeled as required per local regulatory requirement.

DP = drug product; IRR = infusion-related reaction; IV = intravenous

6.2. Preparation, Handling, Storage, and Accountability for Study Drug

Preparation, Handling, and Disposal

The preparation of study drug will be conducted in accordance with the Pharmacy Manual provided by the Sponsor. The drug for IV infusion is prepared by dilution of the required volume of the DP calculated based on the subject's baseline body weight, defined as the last

measurement on or before the first dose. Prepared medicinal solutions should be used immediately. Refer to the Pharmacy Manual for detailed information about preparation and administration of DS-1062a.

Procedures for proper handling and disposal should be followed in compliance with the standard operating procedures (SOPs) or other institutional guidelines of the site.

Administration

DS-1062a will be administered as a 6.0 mg/kg IV infusion Q3W on Day 1 of each 21-day cycle. Premedication is required prior to any dose of DS-1062a that must include antihistamines and acetaminophen with or without glucocorticoids.

The initial dose of DS-1062a will be infused over approximately 90 minutes. If there is no IRR after the initial dose, the next dose of DS-1062a will be infused over approximately 30 minutes. In case of IRR at any time during treatment, refer to details provided in Table 6.3. Subjects should remain at the site for at least 1-hour post-infusion of every DS-1062a dose for close observation for possible allergic reaction. If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle.

For prevention of oral mucositis/stomatitis, subjects are advised to initiate a daily oral care plan (OCP; see Section 8.4.4 for details) before study intervention initiation and maintain it throughout the study. An OCP should include daily inert, bland mouth rinses (eg, with a nonalcoholic, bicarbonate-containing mouthwash 4 to 6 times a day), although other prophylaxis regimens (eg, dexamethasone oral solution 0.1 mg/mL 10 mL 3 to 4 times daily swish for 1 to 2 minutes then spit out, as well as cryotherapy throughout the infusion) advocated by institutional/local guidelines are permitted. An OCP should also include educating subjects on the importance of oral hygiene, tooth brushing, flossing, and hydration and lubrication of the oral mucosa, and on the benefits of adhering to their recommended OCP. Per the investigator's judgment, a professional dental evaluation before study drug initiation and dental treatment, if indicated, may reduce the risk of local and systemic infections from odontogenic sources.

The subject's weight at baseline (ie, the last weight measurement taken prior to the first dose) will be used to calculate the initial dose. If during the treatment the subject's weight changes by ± 10% of the baseline weight, the subject's dose must be recalculated based on the subject's updated weight. After the recalculation, the updated subject's weight will be used as the new baseline weight. The site may follow local institutional policy for recalculating dose based on weight changes less than 10%.

The drug formulation used in this study will be Lyo-DP.

Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions as noted on the label: Lyo-DP should be stored between 2°C and 8°C, protected from light.

If storage conditions are not maintained per specified requirements, then the Sponsor or contract research organization (CRO) should be contacted. See the Pharmacy Manual for additional information on storage conditions of study drug/storage conditions of the infusion solution.

Drug Accountability

When a drug shipment is received, the pharmacist or designee will check the amount and condition of the drug against the shipping documentation. The pharmacist or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

The Receipt of Shipment Form should be faxed as instructed on the form unless receipt is controlled by IRT. The original will be retained at the study site.

The pharmacist is responsible for study drug accountability, reconciliation and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

At the end of the study, all unused DS-1062a will be returned or destroyed as per local laws or site policy and only after the CRO's study monitor has completed a final inventory. As applicable, the study site must file a copy of the appropriate institution policy within their investigator site file and provide a copy to the Sponsor. See the Pharmacy Manual for details.

6.3. Measure to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Treatment Compliance

DS-1062a will be administered as an IV infusion to subjects under the supervision of study site personnel. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for administration of study drug. Start and stop date/time of infusion must be recorded in the electronic case report form (eCRF).

6.5. Guidelines for Dose Modification

All dose modifications (ie, infusion interruptions, dose delays, dose reduction, and/or treatment discontinuation) should be based on the worst preceding toxicity (NCI CTCAE v5.0). Possible exceptions to the dose modification criteria may be allowed on a case-by-case basis after discussion and agreement between the investigator and Sponsor. The agreement must be documented. Dose modification decisions may be based on local laboratory results.

All infusion interruptions, dose delays, or other modifications must be recorded in the eCRF. If study drug is delayed, missed doses will not be made up.

In the event of an infusion interruption or a dose delay occurring prior to completion of a PK/pharmacodynamic blood sampling in the study, investigators should contact the Sponsor's Medical Monitor for guidance regarding scheduling of these procedures.

Dose Reduction Guidelines

Up to 3 dose reductions will be permitted for subjects (Table 6.2). If toxicity continues after the permitted dose reductions, the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

Once the dose of DS-1062a has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. Once the dose of DS-1062a is reduced, no escalation is permitted.

Table 6.2: Dose Reduction Levels for DS-1062a

Starting Dose	Dose Reduction 1	Dose Reduction 2	Dose Reduction 3
6.0 mg/kg	4.0 mg/kg	3.0 mg/kg	2.0 mg/kg

Dose Modification – Toxicity Management Guidelines

Dose modification criteria for subjects with suspected or confirmed COVID-19 are presented in Section 10.7.

Specific criteria for DS-1062a infusion interruption, dose delay, dose reduction, and/or discontinuation in case of TEAEs that are considered related to the use of DS-1062a by the investigator are presented in Table 6.3, which is applicable only to TEAEs that are assessed as related to use of DS-1062a by the investigator(s). For non-drug-related TEAEs or if nothing is noted in Table 6.3, standard practice should be followed. Appropriate experts should be consulted as deemed necessary. The investigator may consider infusion interruption, dose delay, or study treatment discontinuation based on other events not listed in Table 6.3 according to the subject's condition.

There will be no dose modifications for Grade 1 or Grade 2 TEAEs unless specified in Table 6.3. For Grade 3 or Grade 4 events, monitoring (including local laboratory tests when appropriate) should be performed frequently and at an interval no greater than 7 days. The dose may be delayed for up to 9 weeks (63 days) from the planned date of the next cycle administration (ie, up to 12 weeks or 84 days from the last infusion). If a subject is assessed as requiring a dose delay longer than 12 weeks (84 days) from the last infusion, the subject must discontinue study treatment. Study treatment dose delay for conditions other than toxicity resolution should be kept as short as possible.

If a subject cannot restart study treatment for other reasons (eg, intercurrent conditions not related to disease progression or toxicity), the case should be discussed with the Sponsor's Medical Monitor.

A subject for whom DS-1062a dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last DS-1062a dose.

Table 6.3: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to DS-1062a

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	Management Guidelines for DS-1062a
Infusion-related Reaction	
Premedication is required prior to any dose of Dato-DXd that must include antihistamines and acetaminophen with or without glucocorticoids. Subjects should remain at the site for at least 1-hour post-infusion of every dose of Dato-DXd for close observation for possible allergic reaction. If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle.	
Grade 1	If IRR (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, and Grade 1 or 2 hypotension) is observed during administration, the infusion rate should be reduced by 50% of the initial infusion rate, and subjects should be closely monitored. If no other reactions appear upon resumption of the study drug at the above reduced infusion rate, then the infusion rate for subsequent treatment cycles may be resumed at the initial infusion rate.
Grade 2	Administration of Dato-DXd should be interrupted. Symptomatic treatment should be started. • If the event resolves or improves to Grade 1, infusion can be restarted at a 50% reduced infusion rate (ie, 180 minutes for a 90-minute infusion and 60 minutes for a 30-minute infusion). • If an IRR recurs upon rechallenge of Dato-DXd while it is being infused at a reduced rate during the same cycle, then treat as Grade 3 and follow the Grade 3 TMG. If there is no recurrence, the subsequent infusion should be administered at a reduced rate. • If there is no new IRR, then Dato-DXd can be administered at the initial planned infusion rate (90 or 30 minutes) for subsequent treatment cycles.
Grade 3	Administration of Dato-DXd should be stopped immediately for that cycle and initiate treatment of the IRR symptoms. • If the IRR does not resolve within the same day, recurrence of symptoms occurs following initial improvement, or hospitalization is necessary for clinical sequelae, then permanently discontinue Dato-DXd. • If the IRR resolves within the same day of Dato-DXd infusion, no recurrence of symptoms occurs following initial improvement, and no hospitalization is necessary for clinical sequelae, then for the next cycle, administer Dato-DXd at a 50% reduced infusion rate (ie, 180 minutes for a 90-minute infusion; 60 minutes for a 30-minute infusion). o If there is no new IRR, then for the subsequent cycle, administer Dato-DXd at the initial infusion rate (90 or 30 minutes). If the subject tolerates that initial infusion rate with no new IRR, then for the subsequent cycles, administer Dato-DXd at the same infusion rate

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	Management Guidelines for DS-1062a
	(90 or 30 minutes). o If a new IRR occurs that is Grade 2 or greater with subsequent cycles, permanently discontinue Dato-DXd and initiate treatment of the IRR symptoms.
Grade 4	Administration of Dato-DXd must be discontinued immediately and permanently. Urgent intervention is indicated. Epinephrine, antihistamines, steroids, bronchodilators, vasopressors, IV fluid therapy, supplemental oxygen, etc. should be considered as clinically indicated.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3 (ANC defined as <1.0-0.5 × 10^9/L; WBC defined as <2.0-1.0 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then maintain dose
Grade 4 (ANC defined as <0.5 × 10^9/L; WBC defined as <1.0 × 10^9/L)	Delay dose until resolved to ≤Grade 2: – If resolved in ≤14 days from day of onset, maintain dose. – If resolved in >14 days from day of onset, reduce dose by 1 level.
Febrile neutropenia	
Grade 3 (ANC <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38 °C for more than 1 hour)	Delay dose until resolved, then reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment.
Lymphocyte Count Decreased	
Grade 4 (<0.2 × 109/L)	Delay dose until resolved to ≤Grade 2: – If resolved in ≤14 days from day of onset, maintain dose. – If resolved in >14 days from day of onset, reduce dose by 1 level.
Anemia	
Grade 3 (Hb <8.0 g/dL; transfusion indicated)	Delay dose until resolved to ≤Grade 2, then maintain dose.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay dose until resolved to ≤Grade 2, then reduce dose by 1 level.
Platelet Count Decreased	
Grade 3 (platelets <50 – 25 × 109/L)	Delay dose until resolved to ≤Grade 1: – If resolved in ≤7 days from day of onset, maintain dose. – If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4 (platelets <25 × 109/L)	Delay dose until resolved to ≤Grade 1, then reduce dose by 1 level.
Non-hematologic Toxicities	
Pulmonary Toxicity	
If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis.	

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	**Management Guidelines for DS-1062a**
If the AE is confirmed to have an etiology other than treatment related ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with DS-1062a should be delayed pending further evaluations. Evaluations should include the following: • High-resolution CT • Pulmonologist consultation (infectious disease consultation, as clinically indicated) • Bronchoscopy and BAL if clinically indicated and feasible • Pulmonary function tests (including force vital capacity and CO diffusing capacity) and pulse oximetry (SpO_2) • Clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, C-reactive protein, and a COVID-19 test) • One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered, as needed. If the AE is confirmed to be ILD/pneumonitis as per the above evaluations, follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness must be followed until resolution including after Dato-DXd discontinuation.	
Grade 1	The administration of Dato-DXd must be delayed for any ILD/pneumonitis events regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry (SpO_2) • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If the event worsens despite initiation of corticosteroids, then follow Grade 2 guidelines[a]. For Grade 1 events, Dato-DXd can be restarted only if the event is fully resolved to Grade 0:[b] – If resolved in ≤28 days from day of onset, maintain dose – If resolved in >28 days from day of onset, reduce dose by 1 level However, if the Grade 1 ILD/pneumonitis has not resolved within 84 days from the last infusion, the drug should be permanently discontinued. a. If the subject is asymptomatic, then the subject should still be considered as Grade 1 even if steroid treatment is given. b. Grade 0 refers to full resolution of ILD/pneumonitis, including the disappearance of radiological findings associated with active ILD/pneumonitis. Residual scarring or fibrosis following recovery of ILD/pneumonitis is not considered to be active disease.
Grade 2	Permanently discontinue subject from study treatment.

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	**Management Guidelines for DS-1062a**
	• Promptly start and treat with systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone). – Re-consider additional workup for alternative etiologies as described above. – Escalate care as clinically indicated.
Grade 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, – Re-consider additional workup for alternative etiologies as described above. – Consider other immuno-suppressants and/or treat per local practice.
Ocular Surface Toxicity (eg, dry eye, decreased or blurred vision, photophobia, keratitis, corneal ulcer)	
General considerations	Consider obtaining an ophthalmological assessment to ensure accurate diagnosis, event grading, appropriate treatment, and event resolution, as appropriate. It should be strongly recommended that subjects avoid the use of contact lenses starting on the day of the first DS-1062a dose and to use artificial tears (preferably preservative free) 4 times per day as a preventative measure and up to 8 times per day as clinically needed. Use of eye medications (eg, topical corticosteroids) other than artificial tears should be at the discretion of an ophthalmologist or if unavailable, another licensed eye care provider. The following grading scale **replaces** the CTCAE 5.0 grades for triggering the TMGs for cornea-related AEs: **Corneal Toxicity Severity Grading Scale** Normal = Clear cornea, no epithelial defects Grade 1 = Nonconfluent superficial keratitis Grade 2 = Confluent superficial keratitis, a cornea defect, or 3-line or

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	Management Guidelines for DS-1062a
	more loss in best corrected distance visual acuity Grade 3 = Corneal ulcer or stromal opacity, or best corrected distance visual acuity 20/200 or worse Grade 4 = Corneal perforation
Grade 1	Consider obtaining an ophthalmological assessment.
Grade 2	Obtain an ophthalmological assessment. Delay dose until resolved to ≤Grade 1, then maintain dose.
Grade 3	Obtain an ophthalmological assessment. Delay dose until resolved to ≤Grade 1, then reduce dose by 1 level.
Grade 4	Obtain an urgent ophthalmological assessment. Discontinue subject from study treatment.
Hepatic Toxicity	
AST or ALT with simultaneous TBL increased	
AST/ALT >3.0 × ULN with simultaneous TBL >2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.
AST or ALT	
Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT.
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤Grade 1 if baseline ≤3 × ULN, otherwise delay dose until resolved to ≤baseline, then: – If resolved in ≤7 days from day of onset, maintain dose. – If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 3: (>8.0 - 20.0 × ULN if baseline was normal; >8.0 - 20.0 × baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was >3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤baseline level, then: – If resolved in ≤7 days from day of onset, maintain dose. – If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment.
TBL	
Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤Grade 1: – If resolved in ≤7 days from day of onset, maintain dose. – If resolved in >7 days from day of onset, reduce dose by 1 level. If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment.

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	**Management Guidelines for DS-1062a**
Grade 3 (>3.0 - 10.0 × ULN if baseline was normal; >3.0 - 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 1: – If resolved in ≤7 days from day of onset, reduce dose by 1 level. – If resolved in >7 days from day of onset, discontinue DS-1062a. If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to <Grade 2: – If resolved in ≤7 days from day of onset, reduce dose by 1 level. – If resolved in >7 days from day of onset, discontinue Dato-DXd.
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment.
Gastrointestinal	
Nausea/Vomiting	
Grade 3	If prophylaxis and supportive medications have NOT YET been optimized: - Delay dose until resolved to ≤Grade 1 or baseline, optimize medications, and then maintain dose. If prophylaxis and supportive medications have ALREADY been optimized: - Delay dose until resolved to ≤Grade 1 or baseline, and then reduce dose by 1 level.
Grade 4 Vomiting	Discontinue subject from study treatment
Oral Mucositis/Stomatitis	
General considerations	Increase the frequency of bland mouth rinses up to every hour, if necessary, and applicable. Provide adequate pain management (eg, doxepin 0.5%, viscous lidocaine 2%). As soon as oral pain, inflammation, and/or ulceration develops, strongly consider steroid-containing mouth rinses (eg, dexamethasone 0.1 mg/mL, 10 mL 4 times daily swish for 1 to 2 minutes then spit out, or local alternative). May consider oral nystatin suspension or other topical antifungal agents at least 15 minutes after the steroid-containing mouthwash according to clinician preference based on institutional/local guidelines. Consider cryotherapy (ice chips or ice water held in the mouth) throughout the infusion. For severe and/or persistent events, consider referral to a dentist or oral surgeon.
Grade 1	Maintain dose. Optimize prophylactic and supportive medications.
Grade 2	Optimize prophylactic and supportive medications. Consider a dose delay or reduction if clinically indicated.
Grade 3	If prophylaxis and supportive medications have NOT YET been optimized:

Worst NCI CTCAE v5.0 Grade Toxicity (unless otherwise specified)	Management Guidelines for DS-1062a
	- Delay dose until resolved to ≤Grade 1 or baseline, optimize medications, and then maintain dose. If prophylaxis and supportive medications have ALREADY been optimized: - Delay dose until resolved to ≤Grade 1 or baseline, then reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment
Diarrhoea	
Grade 3	If prophylaxis and supportive medications per institutional guidelines have NOT YET been optimized: - Delay dose until resolved to ≤Grade 1 or baseline, optimize medications, and then maintain dose. If prophylaxis and supportive medications have ALREADY been optimized: - Delay dose until resolved to ≤Grade 1 or baseline, then reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment.
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤Grade 1 or baseline level, if determined by the investigator to be clinically significant.
Grade 4	Discontinue subject from study treatment.
Other Non-Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤Grade 1 or baseline level, if determined by the investigator to be clinically significant
Grade 4	Discontinue subject from study treatment.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; CHF = congestive heart failure; COVID-19 = coronavirus disease 2019; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; Dato-DXd = datopotamab deruxtecan; Hb = hemoglobin; ILD = interstitial lung disease; IRR = infusion-related reaction; IV = intravenous; LVEF = left ventricular ejection fraction; NCI = National Cancer Institute; PK = pharmacokinetic; TBL = total bilirubin; TMG = toxicity management guideline; ULN = upper limit of normal; WBC = white blood cell.
All dose modifications should be based on the worst preceding toxicity.

6.6. Emergency Unblinding

Not applicable.

6.7. Prior and Concomitant Medications

Therapies used from the time the subject signs the ICF for study participation to the 28-Day Follow-up Visit (+ 7 days) after the last administration of DS-1062a will be recorded in the eCRF. Prophylactic therapies (including any required premedication), prior therapies, and all concomitant therapies will be recorded in the eCRF.

All therapies received by subjects within 28 days prior to the first dose of DS-1062a will be recorded as prior therapies. Concomitant therapies include all prescription, over-the-counter, and herbal remedies.

All concomitant medications administered during the study should be recorded in eCRF until the end of the Safety Follow-up Period. Concomitant medications administered as treatment for drug-related AESIs should be recorded until event resolution, end of study including any post-treatment follow-up (if applicable), study termination, withdrawal of consent, or subject death.

Prohibited Therapies/Products

With the exception of medications that are under investigation in the study (eg, SoC, comparators, or combination therapies), the following medications, treatment and procedures will be prohibited during the treatment period. The Sponsor must be notified if a subject receives any of these during the study:

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, transplant, or anticancer hormonal treatment (concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and HRT] is acceptable).
- Live vaccines.
- Other investigational therapeutic agents.
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or delay treatment for more than the maximum time specified in the dose modification section [see Section 6.5]).
- Radiotherapy to the thorax.
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications >10 mg/day of prednisone or equivalent except for managing AEs; inhaled steroids, intra-articular steroid injections, and other topical steroid formulations are permitted in this study. Corticosteroid mouthwash formulations are permitted to prevent and manage certain AEs.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If chloroquine or hydroxychloroquine is administered per local clinical practice and regulations, then a washout period of no less than 14 days is required before resumption of DS-1062a.

Restricted Therapies/Products

- The use of tobacco products, e-cigarettes, and vaping is strongly discouraged but not prohibited.
- Subjects should be closely monitored when DS-1062a is concomitantly used with drugs that inhibit CYP3A, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 2-K, P-glycoprotein, breast cancer resistance protein, and multidrug resistance-associated protein (MRP) 1. For a list of inhibitor drugs, refer to the United States (US) Food and Drug Administration (FDA) Table of Substrates, Inhibitors and Inducers[17] or locally available sources.

Permitted Therapies/Products

- Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the investigator.
- Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged, but not prohibited.
- Prophylactic or supportive treatment of study drug-induced AEs will be otherwise as per investigator's discretion and institutional guidelines.
- Based on the currently available clinical safety data, it is highly recommended that subjects receive prophylactic antiemetic agents prior to infusion of Dato-DXd and on subsequent days as needed. Antiemetics such as 5-hydroxytryptamine 3 antagonists (5-HT3) and steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.
- Inhaled intranasal, intraocular, intra-articular or topical steroids, and adrenal replacement steroid doses are permitted in the absence of active autoimmune disease.
- Neurokinin-1 (NK1) receptor antagonists can be used, if needed.
- Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (eg, albuterol) will be included in this study.
- The use of approved bone-modifying agents (eg, bisphosphonates or receptor activator of nuclear factor kappa B ligand [RANKL] targeting agents) to treat or control bone disease is allowed on study if a subject had initiated treatment with such agents at least 4 weeks prior to baseline tumor assessment. Subjects who started the study without receiving bisphosphonates or RANKL targeted agents are not allowed to begin treatment with those medications while receiving study treatment unless otherwise allowed by the protocol to be used for the treatment of AEs or SAEs.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

The primary reason for the permanent discontinuation of DS-1062a treatment administration must be recorded. Reasons for treatment discontinuation include:

- Death
- AE
- Disease progression
- Clinical progression
- Withdrawal by subject (**to discontinue study drug**)
    - Note: This section only refers to withdrawal from treatment with study drug, which is NOT the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments, including survival follow-up).
- Physician decision
- Lost to follow-up (see Section 7.3 for details on when a subject is considered Lost to Follow-up)
- Pregnancy
- Protocol deviation (Note: Only protocol deviations that are deemed significant by the investigator, with or without consultation with the Sponsor, may lead to permanent study drug discontinuation)
- Study termination by the Sponsor
- Other

After study drug is permanently discontinued for any reason other than death or lost to follow-up, the subject will be treated as clinically indicated by the investigator or referring physician.

The investigator must discuss with the subject that their decision to permanently discontinue the study drug means the subject may still agree to continue into the Follow-up Period for onsite or modified follow-up visits. Subjects will be followed for disease progression, if applicable, and survival at regularly scheduled intervals (see Table 1.2).

Subjects who discontinue study treatment for reasons other than disease progression as assessed by BICR, including clinical progression or the initiation of new anticancer treatment, will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent.

Procedures for Discontinuation from Study Drug

The subject should be instructed to contact the investigator or study site staff before or at the time study drug is discontinued.

If a subject is discontinued from the study drug:

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF.
- Due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.
- An EOT evaluation should be performed as described in the SoE (Table 1.2).
- A safety follow-up evaluation should be performed approximately 28 days (+7 days) after the last dose of study drug as described in the SoE (Table 1.2).
- If subject has discontinued without disease progression, continue tumor assessments until disease progression, if applicable, and survival as described in the SoE (Table 1.2).
- LTSFU evaluations will be performed to assess survival as described in the SoE (Table 1.2).

The investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of last dose. All procedures and tumor assessments specified for the EOT visit will be conducted. See Table 1.2 for specific EOT procedures.

If a subject does not agree to continue to come to the study site, then a modified follow-up must be arranged to ensure the continued collection of endpoints and safety information. Options for modified follow-up are noted below.

Modified Follow-up Options

The following modified follow-up options can be offered to the subject who does not agree to study visits at the study site. If a subject does not come back to the study site, every effort should be made to contact the subject to gain required information, such as the approaches listed below.

- Study personnel contacting the subject by telephone (may be quarterly, bi-annually, annually, or only at EOS).
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician or other healthcare provider).
- Study personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes, hospital records).

Dates of the modified follow-up contact(s) should be recorded. See Section 7.2 for definition of withdrawal by subject from the study (ie, withdrawal of consent).

7.2. Subject Withdrawal/Discontinuation From the Study

Subjects may discontinue from the study for any of the following reasons:

- Death
- Withdrawal by subject (**from the study**)
    - NOTE: This indicates that the subject withdraws consent and decides to not undergo any further study procedures or be followed for long-term survival.
- Lost to follow-up (see Section 7.3 for details on when a subject is considered lost to follow-up).
- Study termination by Sponsor.
- Other.

Reason for study discontinuation and date of last contact will be recorded on the eCRF.

If the reason for study discontinuation is the death of the subject, the options for categorizing the primary cause of death are progressive disease or an AE. If the reason of death is unknown, every effort should be made to obtain the primary cause of death. Only 1 AE will be recognized as the primary cause of death.

Only subjects who decline all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol.
- Study personnel contacting the subject by telephone.
- Study personnel contacting an alternative person.
- Study personnel accessing and reviewing the subject's medical information from alternative sources.

If the subject declines all of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject declines routine follow-up, the investigator should discuss with the subject if sparse survival follow-up by telephone or verification of medical records is permitted prior to database locks. If the subject continues to decline all potential methods of follow-up, the investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

Withdrawal Procedures

If a subject is withdrawn from both the interventional and follow-up portions of the study:

- The investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last dose, date of last contact, and the reason for withdrawal.
- Any disclosure of future information is also withdrawn; the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- The subject may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- Study site personnel may use local, regional, and national public records (in accordance with local law) to monitor vital status. Knowledge of the vital status at study end in all subjects is crucial for the integrity of the study.

See SoE (Table 1.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he/she does not return for 2 consecutive scheduled visits per the Schedules of Events and is unable to be contacted by the study site staff. Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls, texts, or emails, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented.

If direct contact with the subject is not possible the site must make every effort to collect survival status from public records (eg, obituaries, death certificates, etc.) in accordance with local laws. Knowledge of the vital status at study end in all subjects is crucial for the integrity of the study.

8. STUDY PROCEDURES

See SoE in Table 1.1 for study procedures during the Screening Period and the first 3 cycles of the Treatment Period, and Table 1.2 for study procedures during Cycle 4 and the subsequent cycles of the Treatment Period, EOT, and the Follow-up Period.

8.1. Eligibility Assessment

Review the subject's demographics, medical and NSCLC history, prior medications, non-drug therapies and radiotherapy, vital signs, and results of tests (physical examination, height, weight, peripheral oxygen saturation (SpO_2), ECOG PS, ophthalmologic assessment, 12-lead ECG in triplicate, ECHO/MUGA scan, laboratory assessments) and compare against the eligibility criteria (Section 5.1 and Section 5.2). See Section 5.3 for rescreening/subject replacement.

Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive responses to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

Informed consent should be obtained ≤28 days prior to initiation of treatment and before any protocol-specific procedures are performed, except scans that might be done prior to consent per SoC. Imaging studies (CT/MRI/bone scans) should be performed ≤28 days prior to initiation of treatment. If these scans are performed per SoC prior to consenting, as long as they are within 28 days of the planned dosing and from the same facility where follow-up scans during the study will be performed, they can be used as part of the screening assessments and do not need to be repeated.

See Section 10.1.2 for additional details.

Qualifying Tumor Tissue Specimen

A baseline biopsy procedure to collect fresh tumor tissue from the primary or metastatic lesions performed after termination of the most recent anticancer treatment is mandatory for all subjects. If available, a tumor biopsy that was recently collected (within 3 months of screening) and after the most recent anticancer treatment regimen and that has a minimum of 10 × 4 micron sections or a tissue block equivalent of 10 × 4 micron sections may be substituted for the mandatory pre-treatment biopsy procedure during screening. Results from the TROP2 testing of the pre-treatment tumor biopsy will not be used to determine eligibility for the study. Although baseline fresh biopsies taken from metastatic lesions prior to the date of ICF are acceptable, collection during the Screening Period using Sponsor-provided neutral-buffered formalin in kits is preferred to standardize tissue fixation for subsequent analysis. On-treatment biopsy is optional at Cycle 2 Days 2 to 8 (if clinically feasible and not contraindicated). Biopsies may be collected from a lesion that has been irradiated, provided that it can be documented that the lesion has increased/appeared since radiation occurred and that the biopsy is collected at least

3 months after radiation. Any SAE directly related to the new biopsy should be reported as outlined in Section 8.4.1.1. It is recommended, if possible, that the optional Cycle 2 biopsy be taken from a lesion in the same anatomical location as the pre-treatment biopsy and fixed in Sponsor-provided neutral buffered formalin.

Additionally, archival tumor tissue samples from the initial diagnosis are required, to the extent that the archival tumor tissue is available, for measurement of TROP2 expression level or for the assessment of other biomarkers. Archived tissue samples from surgery, endoscopy, or core needle biopsy already collected and formalin-fixed paraffin-embedded (FFPE) will be used. Archival samples can be FFPE tissue block(s), prepared by the standard procedure at the study site. Additional information on tumor tissue collection, processing and immediate shipping procedures is included in the Study Laboratory Manual.

Non-Small Cell Lung Cancer History

Subject's NSCLC history will be obtained by the investigator or a qualified designee.

Actionable Mutation Status

Subjects must have documented results for genomic alterations in EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET to be enrolled in the study.

General Medical History and Baseline Conditions

Subject's medical history will be obtained by the investigator or a qualified designee.

Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of NSCLC/vital signs that are out of range) that were diagnosed or known to exist prior to signing the ICF will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF. Record the start date of any medical occurrence that started after the ICF was signed and is ongoing at the time of the first dose of DS-1062a on the General Medical History and Baseline Conditions eCRF.

Demographics

Review the subject's demographics against the eligibility criteria.

Human Immunodeficiency Virus Antibody Test

Perform an HIV antibody test as acceptable by local regulations or independent IRB/EC.

Hepatitis Screening

Hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) must be performed prior to enrollment (if HCV Ab is positive, test HCV RNA). Subjects with known active hepatitis or uncontrolled hepatitis B and/or hepatitis C infection, is positive for hepatitis B or C virus based on the evaluation of results of tests for hepatitis B (HBsAg, anti-HBs, anti-HBc, or HBV DNA) and/or hepatitis C infection (as per HCV RNA) will be excluded except those meeting certain conditions specified under exclusion criterion 10 (Section 5.2).

8.2. Randomization

Not applicable.

8.3. Efficacy Assessments

Radiographic Tumor Assessments

Radiographic tumor assessments will include all known or suspected sites of disease, as per RECIST v1.1 (Section 10.4). Imaging must include CT or MRI scans of the chest, abdomen, and any other sites of disease; as well as brain CT or MRI scan at baseline (screening) for all subjects. Subjects with brain metastases at baseline should have brain MRI or CT scan performed every 6 weeks (± 7 days) from Cycle 1 Day 1. Additional brain imaging may be performed as needed clinically.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons; follow the local label/package insert/Summary of Product Characteristics or institutional guidelines for allergic reactions to contrast agents.

Baseline tumor assessment must be performed within 28 days of Cycle 1 Day 1. A tumor assessment performed for the assessment of disease progression on the prior therapy will be acceptable as baseline if performed within 28 days of Cycle 1 Day 1.

A complete set of the scans is required in this study (see Section 8.3). All scans during the subjects' participation in the study must be sent to BICR. Perform radiographic tumor assessments using spiral CT or MRI with ≤5 mm cuts unless another modality of disease assessment is necessary for the lesions.

Antitumor activity will be assessed at baseline (screening), and every 6 weeks (± 7 days) from Cycle 1 Day 1, independent of treatment cycle, until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent regardless of discontinuation of study treatment or initiation of new anticancer therapy (Table 1.1 and Table 1.2). Subjects who discontinue study treatment for reasons other than disease progression per BICR will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent. Imaging timing should follow calendar days. In addition, radiographic tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 6 weeks). Tumor measurements will be performed as per RECIST v1.1 (see Section 10.4).

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the subsequent tumor assessments.

Bone scan (bone scintigraphy) or 18F-fluorodeoxyglucose-positron emission tomography (PET)/CT is required at baseline and follow-up bone imaging is required only if new bone metastases are suspected. When disease progression in the bone or new lesion (NL) in the bone is suspected, 18F FDG PET/CT should be used to determine disease progression.

When tumor assessments at a visit are performed over multiple days, the date of response (CR, PR, SD, Non-CR/Non-PD [subjects with non-target lesions {NTL} only] or not evaluable [NE]) should be recorded as the date of the last radiographic evaluation included in the series for that assessment, and the date of progression should be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions (TLs) unless increase in size has been observed after completion of radiation therapy.

Response Assessment

Assessment of response will be made by BICR based on RECIST v1.1 (Section 10.4). Assessment of response will also be made by the investigator based on RECIST v1.1. Objective responses (CR or PR) must be confirmed at the next tumor assessment time point at least 4 weeks (28 days) apart. Tumor assessments will continue until disease progression is confirmed by BICR. The results of BICR assessment of the subject scans will not be shared with the site or investigator. The investigator will manage the subject and make treatment decisions based solely on investigator/local assessment and will be completely independent of BICR.

Subsequent Anticancer Treatments

Subsequent anticancer treatments, radiation therapy received, and surgeries performed since the EOT must be monitored and recorded in the eCRF until the end of the study.

Disease Progression

Subjects who discontinue study treatment for reasons other than disease progression as assessed by BICR, including clinical progression, or subjects who start new anticancer treatment will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent.

The date of disease progression on subsequent therapies will be recorded in the eCRF regardless of subsequent anti-NSCLC treatments.

Survival Follow-up

All subjects should be followed for survival at least every 3 months after discontinuing study drug (see Table 1.2). Survival monitoring will continue until the end of the study.

To ensure accurate survival data are available at the time of any database lock, updated survival status may be requested during the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, the planned data cut and database lock for the primary analysis and final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their survival status (excluding subjects who have discontinued from the entire study or with a previously reported death event).

8.4. Safety Assessments

8.4.1. Adverse Event

Method to Detect Adverse Events

The definitions of an AE or SAE can be found in Section 10.5. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue DS-1062a.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, lead to dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

Time Period for Collecting Adverse Events, Including Adverse Events of Special Interest and Serious Adverse Events

All SAEs occurring after the subject signs the ICF and up to 35 days (ie, 28 days + 7 days) after the last dose of study medication (ie, the Follow-up Period), whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event eCRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. After the 28-day Safety Follow-up visit, only SAEs considered to be related to study drug by the investigators should be reported.

All ILD/pneumonitis events regardless of severity should be reported beyond the 28-day Safety Follow-up Period. All events of ILD regardless of severity or seriousness will be followed until resolution including after study drug discontinuation.

All AESIs, regardless of severity or seriousness, must be followed until event resolution, end of study including any post-treatment follow-up (if applicable), study termination, withdrawal of consent, or subject's death.

All non-serious AEs occurring after the subject has taken the first dose of DS-1062a until 35 days (ie, 28 days + 7 days) after the last dose of DS-1062a will be recorded on the Adverse Event eCRF.

Exacerbation of a pre-existing medical condition and symptom after the first dose of DS-1062a including increase in severity of the symptom will be recorded as an AE on the Adverse Event eCRF, unless it is a condition of NSCLC.

Reporting Procedure for Investigators

All AEs (including AESIs and SAEs) will be reported in AE eCRF. All AEs (serious and non-serious) must be reported with the investigator's assessment of seriousness, severity, and causality to DS-1062a.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Disease-specific Adverse Events and Serious Adverse Events

Disease progression/worsening of NSCLC will not be recorded as an AE on the AE eCRF. However, events associated with disease progression, such as events that are assessed by investigator as unequivocally associated with worsening of underlying NSCLC (such as events related to brain metastases, spinal cord compression, bone pain, liver metastases, hepatomegaly, and tumor growth), may be recorded as AEs.

Death due to disease progression should be recorded on the Death eCRF.

8.4.1.1. Adverse Events Reporting

The following types of events should be reported by the investigator in the electronic data capture (EDC) within 24 hours of awareness:

- SAEs (Section 10.5.2).
- Hepatic events (both serious and non-serious) that meet the potential Hy's Law criteria (as defined in Section 8.4.1.3). A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- All potential ILD/pneumonitis cases should be reported within 24 hours, including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is defined by the Event Adjudication Site Manual List of Preferred Terms).
- Grade ≥3 IRR events.
- Grade ≥3 ocular surface toxicity events.
- Grade ≥2 keratitis events (includes keratitis, punctate keratitis, and ulcerative keratitis)

Details summarizing the course of the SAE, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of AE onset, treatment, and resolution should be included. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the SAE report. For fatal events, the SAE report should state whether an autopsy was or will be performed and should include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

If using EDC for SAE reporting: Complete the eCRF or Serious Adverse Event Report Form within 24 hours of awareness. If the eCRF is unavailable, report SAEs by faxing or emailing the Serious Adverse Event Report Form to the Sponsor/CRO using the provided fax transmittal form and the appropriate fax number provided for your country or email address. Once EDC becomes available, please enter SAEs reported on the Serious Adverse Event Report Form into the eCRF as soon as possible. Please refer to the eCRF Completion Guide for additional instructions.

Call the local SAE Hotline (see Study Site Manual) or your study monitor for any questions on SAE reporting.

See Section 8.4.1 for details on the time period for collecting SAEs.

Reporting Requirement to Sites and Regulatory Authorities

The Sponsor or CRO will inform investigators and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in study sites or other studies of DS-1062a, as appropriate per institutional and/or local reporting requirements.

The Sponsor and CRO will comply with any additional local safety reporting requirements. The investigator will assess if an AE is to be considered "unexpected" based on the Reference Safety Information section in the current IB.[13]

Follow-up for Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Urgent safety queries and follow-up information, such as an event upgraded to a fatal/life-threatening case, must be followed and addressed promptly. The investigator will submit any important and updated SAE data, as noted above, to the Sponsor/CRO within 24 hours of receipt of the information. Other follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.4.1.1.1. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported to (CRO or Sponsor) within 24 hours of awareness. Overdose will be reported via the Serious Adverse Event Report /Overdose Form or eCRF.

An "excessive and medically important" overdose includes any overdose in which either an SAE or a non-serious AE (Section 10.5.1), or no AE occurs and is considered by the investigator as clinically relevant, ie, poses an actual or potential risk to the subject.

8.4.1.2. Adverse Events of Special Interest

For the Dato-DXd clinical program, based on the available preclinical data, current clinical developmental program, review of the cumulative literature, reported toxicities for drugs with similar monoclonal antibody and payload of Dato-DXd, and biological plausibility, ILD/pneumonitis, IRR, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis, and ocular surface toxicity are considered to be AESIs.

All AESIs, regardless of severity or seriousness, must be followed until event resolution, end of study including any post-treatment follow-up (if applicable), study termination, withdrawal of consent, or subject's death.

Additional relevant information regarding the AESIs for the Dato-DXd clinical program regardless of seriousness is to be collected through the targeted questionnaires (TQs) within the clinical study database.

Interstitial Lung Disease/Pneumonitis

ILD/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee (AC), available data from recent epidemiology/literature, biological plausibility, and safety information from drugs with similar monoclonal antibody and payload as DS-1062a. Refer to the current IB for a summary of preliminary clinical study data.

ILD/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in "Other Non-Laboratory Adverse Events" in Table 6.3.

If the AE is suspected to be ILD/pneumonitis, treatment with Dato-DXd should be delayed pending further evaluations. Evaluations should include high-resolution CT, pulmonologist consultation (infectious disease consultation as clinically indicated), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible, pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2), and clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, C-reactive protein, and a COVID-19 test), and one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed.

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in "Pulmonary Toxicity" in Table 6.3.

All events of ILD/pneumonitis, regardless of severity or seriousness, will be followed until resolution including after Dato-DXd discontinuation. An autopsy in cases of Grade 5 ILD/pneumonitis is encouraged.

For broad surveillance of ILD/pneumonitis, a predefined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual are included for enhanced data collections; additional data for these AEs will be collected via TQs of pulmonary toxicity.

Interstitial Lung Disease Adjudication Committee

An independent ILD/pneumonitis AC for the DS-1062a program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data collection will be triggered based on a predefined list of preferred terms eligible for adjudication as described in the Event Adjudication Site Manual.

Infusion-related Reaction

IRR is an identified risk. A targeted questionnaire will be available as an eCRF to collect relevant additional information. All ≥Grade 3 events of IRR, regardless of seriousness, must be reported in EDC within 24 hours. Refer to the current IB for a summary of preliminary clinical study data.[13]

Premedication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen with or without glucocorticoids.

Monitoring/management of vital signs and clinical symptoms, response to symptomatic treatment, and clinical course are outlined in management guidelines in Section 6.5. Further details of the management of DS-1062a IRRs are outlined in Section 6.5.

For broad surveillance of IRR, selected PTs from Hypersensitivity SMQ and narrow and selected broad PTs from Anaphylactic Reaction SMQ are included for enhanced data collection. Additional data for these ≥Grade 3 AEs will be collected via TQs of IRR.

Oral Mucositis/Stomatitis

Oral mucositis/stomatitis AEs are considered as identified risks associated with Dato-DXd treatment. Mucosal inflammation other than oral mucositis/stomatitis is also an identified risk but is considered as a separate AESI. Refer to Section 8.4.4 for the OCP.

Recommendations for preventing and treating oral mucositis/stomatitis are available in the SoE, Other Safety (Section 8.4.4), and Toxicity Management Guidelines (Table 6.3).

For broad surveillance of oral mucositis/stomatitis, selected PTs under the MedDRA SMQs of Oropharyngeal conditions (Select Narrow PTs) and Drug reaction with eosinophilia and systemic symptoms syndrome (Select Broad PTs) are included for enhanced data collections; additional data for these AEs **regardless of CTCAE grading** will be collected via TQs of oral mucositis/stomatitis.

Mucosal Inflammation Other than Oral Mucositis/Stomatitis

Mucosal inflammation AEs are considered as identified risks associated with Dato-DXd treatment. The category of "mucosal inflammation other than oral mucositis/stomatitis" is also an identified risk and an AESI.

For broad surveillance of mucosal inflammation other than oral mucositis/stomatitis, the mucosal inflammation PT is included for enhanced data collections; additional data for this AE **regardless of CTCAE grading** will be collected via TQs of mucosal inflammation other than oral mucositis/stomatitis.

Ocular Surface Toxicity

Ocular surface toxicity (eg, dry eye, keratitis) is considered as an AESI associated with Dato-DXd treatment. Dry eye is considered as an identified risk and keratitis as a potential risk within this AESI.

Subjects are advised to use artificial tears 4 times daily as a preventative measure and up to 8 times daily as clinically needed and to avoid the use of contact lenses. The use of other eye medications (eg, topical corticosteroids) for prophylaxis should be at the discretion of an ophthalmologist or, if unavailable, another licensed eye care provider.

Recommendations for preventing and treating ocular surface toxicity are available in the SoE, Other Safety (Section 8.4.4), and Toxicity Management Guidelines (Table 6.3).

For broad surveillance of ocular surface toxicity, selected PTs under the MedDRA Selected PTs from Corneal disorder SMQ and select relevant PTs from Eye disorder system organ class (SOC); additional data for these AEs **regardless of CTCAE grading** will be collected via TQs of ocular surface toxicity.

8.4.1.3. Hepatic Events

Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT and/or AST) ≥3 × ULN and an elevated TBL ≥2 × ULN, regardless if it is due to disease progression per investigator assessment, that may occur at different time points during this study, should always be reported to the Sponsor.[18] These events must be reported either by a Serious Adverse Event Report Form or eCRF, with the investigator's assessment of seriousness, severity, causality, and a detailed narrative. These events should be reported within 24 hours of investigator's awareness of the event regardless of seriousness. A targeted questionnaire is in-built as an eCRF to collect relevant additional information for these potential cases.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical laboratory evaluations as described in Section 10.2 in order to determine the nature and severity of the potential liver injury.

8.4.2. Pregnancy

The Sponsor must be immediately notified of any female subject who becomes pregnant while receiving or within 7 months of the last dose of DS-1062a. Additionally, the Sponsor must be immediately notified of any partner of a male subject who becomes pregnant while receiving or within 4 months of the last dose of DS-1062a.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. If a pregnancy is reported, the investigator must inform the Sponsor within 24 hours of learning of the pregnancy.

This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a female subject or partner of a male subject using the Exposure In Utero (EIU) Reporting Form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The investigator should make every effort to follow the female subject or partner of a male subject (upon obtaining written consent from the partner) until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

Pregnancy Test

For women of childbearing potential (as defined in Section 5.1): document the results of a negative serum pregnancy test. For eligibility, if not performed as a part of routine care, a serum pregnancy test (within 28 days prior to Cycle 1 Day 1) must be performed. Within 3 days before Cycle 1 Day 1, a pregnancy test (urine/serum per institutional guideline) must be done for all female subjects of childbearing potential (see Table 1.1). Repeat pregnancy tests (urine or serum per institutional guidelines) must be performed within 3 days before infusion at each cycle, at

EOT visit, and at the 28-day Safety Follow-up visit. A positive urine pregnancy test must immediately be confirmed using a serum test.

8.4.3. Clinical Laboratory Evaluations

Clinical laboratory tests including hematology, blood chemistry, and pregnancy tests will be performed as per the SoE by the local laboratory (Table 1.1 and Table 1.2). Urinalysis and coagulation will be performed at screening only. Refer to Section 10.2 for the complete list of laboratory parameters.

All laboratory values must be appraised by the investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, an SAE should be reported in the eCRF and other relevant procedures must be followed (see Section 8.4.1.1).

Abnormal laboratory values (NCI CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically relevant. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.4.4. Other Safety

Physical Examinations, Weight, and Height

Physical examinations should be performed as per the SoE (Table 1.1 and Table 1.2). A complete physical examination should include a weight measurement and an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be collected in the subject's study record. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF. Height will be obtained once, prior to Cycle 1 Day 1 dosing.

Vital Signs

Vital signs will be measured and recorded as per the SoE (Table 1.1 and Table 1.2). Vital signs will include the measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures, and temperature. Blood pressure and pulse rate will be measured after the subject has rested in a preferably recumbent position or if recumbent position is not possible, then sitting for 5 minutes or more and prior to laboratory draws.

Pulse Oximetry

Peripheral oxygen saturation (SpO_2) will be measured by pulse oximeter and at the same time vital signs are measured.

Electrocardiograms

12-lead ECGs will be performed and recorded for every subject as per the Schedules of Events (Table 1.1 and Table 1.2). The ECG will be measured after the subject has rested in a recumbent position for 5 minutes or more. At Screening only, ECGs will be taken in triplicate in close succession, no more than approximately 5 minutes apart, and after at least 5 minutes of quiet rest in the supine position.

Single ECGs will be performed as clinically indicated for all subsequent treatment cycles. If an ECG abnormality is detected, ECGs will be performed in triplicate.

At any visit during which a subject exhibits a heart rate ≤50 bpm or other clinical indications for ECG, the ECG will be repeated. Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs. Electrocardiograms will be transmitted electronically to a central reader for determination of heart rate, PR interval, RR interval, QRS amplitude, QT interval, QTcF interval, and any other results.

Multigated Acquisition Scan or Echocardiogram

MUGA/ECHO must be performed as per the Schedules of Events (Table 1.1 and Table 1.2). Subjects must have an LVEF ≥50% to be eligible for the study. The same test must be used throughout the study.

ECOG Performance Status

Assess and record the subject's ECOG PS as per the Schedules of Events (Table 1.1 and Table 1.2).

Ophthalmologic Assessments

Ophthalmologic assessments (OAs), including, but not limited to, visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining, will be performed at screening, as clinically indicated, and at the EOT visit by an ophthalmologist or, if unavailable, another licensed eye care provider. A suitable alternative to fluorescein staining of the cornea may be used in exceptional circumstances where fluorescein is not available. An ophthalmologic assessment should be considered for any ocular symptoms including, but not limited to, dry eye, decreased or blurred vision, foreign-body sensation, photophobia, tearing, pain, and eye redness. All OAs (baseline, as clinically indicated, EOT) should be documented on worksheets in the eCRF, and copies of all consultation reports should be enclosed in the eCRF as applicable.

Subjects should be advised to use artificial tears 4 times daily as a preventative measure and up to 8 times daily as clinically needed and to avoid the use of contact lenses. The use of other eye medications (eg, topical corticosteroids) for prophylaxis should be at the discretion of an ophthalmologist or, if unavailable, another licensed eye care provider.

ILD/Pneumonitis Investigation

For suspected ILD/pneumonitis, treatment with Dato-DXd should be delayed pending the following evaluations:

- High-resolution CT
- Pulmonologist consultation (infectious diseases consultation as clinically indicated)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests (including force vital capacity and CO diffusing capacity) and pulse oximetry (SpO_2)
- Clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, C-reactive protein, and a COVID-19 test)
- One blood sample collection for PK analysis as soon as ILD/ pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

IRR

Premedication is required prior to any dose of Dato-DXd and must include antihistamines and acetaminophen with or without glucocorticoids. Subjects/participants should remain at the site for at least 1 hour post infusion of every dose of Dato-DXd for close observation for possible allergic reaction.

If a subject does not experience any IRR during or after the first 2 cycles, the post-infusion observation period can be shortened to at least 30 minutes for subsequent cycles. Subjects with identified IRR related to the study drug should be observed post-infusion for at least 1 hour for the 2 cycles after the IRR event and for at least 30 minutes at each subsequent cycle.

Oral Care Plan (Stomatitis/Oral Mucositis)

Subjects/participants should adhere to the following guidance:

- Gently brush their teeth after meals and at bedtime using a soft or ultra-soft toothbrush (or swab) and a bland-flavored fluoride-containing toothpaste,
- Floss their teeth every day, if able to do so without pain or causing gingival bleeding.
- Daily use of prophylaxis with a steroid-containing mouthwash (eg, dexamethasone oral solution 0.1 mg/mL 10 mL 4 times daily swish for 1 to 2 minutes then spit out; or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines) is highly recommended.
    - Note: Subjects/participants are allowed to take oral nystatin suspension or other topical antifungal agents after the steroid-containing mouthwash according to clinician preference based on institutional/local guidelines.
- In the absence of a prophylactic steroid-containing mouthwash, daily use of inert, bland mouth rinses (eg, with a non-alcoholic and/or bicarbonate-containing mouthwash, 4 to 6 times a day) is recommended.
- Prophylactic cryotherapy (ice chips or ice water held in the mouth throughout the infusion) should also be considered.

The following algorithm, to be followed from steps 1 to 4, may be used as a guidance to select an appropriate prophylaxis mouthwash:

20. Dexamethasone mouthwash formulated at 0.5 mg/5mL. If not available, then use→
21. Dexamethasone mouthwash compounded at site/locally. If not available, then use→
22. Other steroid-based mouthwash available at site/locally. If not available, then use→
23. Non-steroid mouthwash or other local mouthwash

Nausea and Vomiting

Based on the currently available clinical safety data, it is highly recommended that subjects receive prophylactic antiemetic agents prior to infusion of Dato-DXd and on subsequent days as needed (see Section 6.7).

8.5. Pharmacokinetic Assessments

Blood samples for PK analyses will be obtained based on the SoE (Table 1.1 and Table 1.2) at time points outlined in Table 8.1. Details on the analysis of PK assessments are provided in the Statistical Analysis Plan (SAP).

Plasma concentration-time profiles of the 3 analytes (DS-1062a, total anti-TROP2 antibody, and MAAA-1181a) will be established from blood PK samples collected from Cycle 1 Day 1 to Cycle 8 Day 1 for the following cohorts:

- *Full PK cohort*: Approximately the first 30 subjects with adequate hepatic function in the study and additional subjects (up to 9) with moderate hepatic dysfunction will undergo full PK sampling.
- *Sparse PK cohort*: All other subjects will undergo sparse PK sampling.

In addition, a blood sample for PK analysis will be collected as soon as ILD/pneumonitis is suspected in a subject.

Table 8.1: Schedule of Pharmacokinetic Sample Collection

Cycles	Days	Full Sampling Pharmacokinetic Cohort	Sparse Sampling Pharmacokinetic Cohort
1	1	Predose: Within 8 hours before infusion Postdose: • Within 30 minutes after end of infusion • 3 hours (± 15 minutes) after infusion start • 5 hours (± 15 minutes) after infusion start • 7 hours (± 15 minutes) after infusion start	Predose: Within 8 hours before infusion Postdose: • Within 30 minutes after end of infusion • 5 hours (± 1 hour) after infusion start
	2	24 hours (± 2 hours) after Day 1 infusion start	
	4	3 days (± 1 day) after Day 1 infusion start	

Cycles	Days	Full Sampling Pharmacokinetic Cohort	Sparse Sampling Pharmacokinetic Cohort
	8	7 days (± 1 day) after Day 1 infusion start	
	15	14 days (± 1 day) after Day 1 infusion start	None
2	1 (±2)	Predose: Within 8 hours before infusion Postdose: Within 1 hour after end of infusion	
3	1 (±2)	Predose: Within 8 hours before infusion Postdose: Within 1 hour after end of infusion	None
4	1 (± 2)	Predose: Within 8 hours before infusion Postdose: Within 1 hour after end of infusion	
6	1 (± 2)	Predose: Within 8 hours before infusion Postdose: Within 1 hour after end of infusion	
8	1 (± 2)	Predose: Within 8 hours before infusion Postdose: Within 1 hour after end of infusion	

Plasma concentrations of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a will be measured using validated assays at the bioanalytical laboratory.

Instructions for the collection and handling of biological samples will be included in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample collection should be recorded.

The following PK parameters will be calculated for the subjects in the full PK cohort using non-compartmental analysis of concentration–time data of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a in plasma: maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curve up to the last quantifiable time (AUClast), area under the plasma concentration-time curve during dosing interval (AUCtau), and if data permit, area under the plasma concentration-time curve up to infinity (AUCinf), t1/2, total body clearance (CL), volume of distribution at steady-state (Vss), volume of distribution based on the terminal phase (Vz), and elimination rate constant associated with the terminal phase (Kel).

Population PK and exposure-response (ER) analyses may be performed to characterize the relationships between dose and exposure and between exposure and efficacy/safety endpoints. If performed, the results of the PopPK and ER analyses will be reported separately from the clinical study report (CSR).

8.6. Biomarker and Pharmacodynamic Assessments

Note: Unless restricted by local/site policies or country-specific regulations, blood and tissue collections for exploratory biomarker and pharmacogenomic analyses as described below must be followed, and any deviations from the protocol should be reported as protocol deviations. The Sponsor must be notified of the specific local or country-specific restriction or regulation that applies, and the restriction or regulation must be documented appropriately in the applicable study files.

Biomarker Analysis for Potential In Vitro Assay

Collected samples may be assessed for the purpose of analytical validation and/or bridging studies of diagnostic tests (including for the detection of TROP2), which may be proposed as an in vitro diagnostic (IVD). The results of these studies will determine the ability of the companion diagnostic test(s) to classify subjects as positive for the biomarker with a proposed threshold in relation to clinical efficacy. Data obtained from biomarker analysis may be used to perform clinical efficacy analysis as described in the SAP.

8.6.1. Exploratory Biomarker Assessments in Blood Samples

Cell-free DNA (cfDNA) from blood samples collected during the study to assess changes in tumor mutations or other genomic alterations in response to treatment will be analyzed with the intent of monitoring the biological or antitumor impact of treatment with DS-1062a. Additional candidate blood-based biomarkers may be considered as suggested by updated literature.

Biomarkers will be assessed using validated assays in blood collected at the time points specified in the Schedules of Events in Table 1.1 and Table 1.2.

One or more of the biomarkers may also be assessed for correlation with efficacy.

A blood sample will be collected at the time point specified in Table 1.1 to serve as a liquid biopsy to identify subjects who are likely to derive clinical benefit.

A whole blood sample will be collected at the time point specified in Table 1.1 to serve as a control for whole exome sequence/whole genome sequence tissue analysis.

Plasma and serum samples will be collected at timepoints specified in the SoE (Table 1.1 and Table 1.2) and at the time of suspected ILD onset. Samples may be analyzed to look for biomarkers predictive of ILD.

Biomarker samples will be shipped to a central laboratory. Sample collection, preparation, handling, storage, and shipping instructions are provided in the Laboratory Manual.

8.6.2. Exploratory Biomarker Assessments in Tumor Tissues

Biomarker analyses will be used to investigate the effect of DS-1062a at the molecular and cellular level as well as to determine how changes in the biomarkers may relate to exposure and clinical outcomes. Biopsies may be collected from a lesion that has been irradiated, provided that it can be documented that the lesion has increased/appeared since radiation occurred and that the biopsy is collected at least 3 months after radiation. The following samples for biomarker research are required and will be collected from all subjects in this study as specified in Table 1.1 and Table 1.2:

- Mandatory biopsy procedure to collect fresh tumor biopsy tissue before study entry (see inclusion criterion 6; Section 5.1). If available, a tumor biopsy that was collected (within 3 months of Screening) after completion of the most recent anticancer treatment regimen and that has a minimum of 10 × 4 micron sections or a tissue block equivalent to 10 × 4 micron sections, may be substituted for the mandatory pre-treatment biopsy procedure before study entry.
- Archival tumor tissue (if available; see inclusion criterion 6; Section 5.1).

In addition to the biomarkers specified above, exploratory biomarker research may be conducted on any samples. The following optional samples for biomarker research should be collected from study subjects where possible:

- Optional on-study Cycle 2 biopsy if clinically feasible and not contraindicated at the time of on-treatment biopsy.
- Optional EOT biopsy.

The sample collection information as required should be recorded on the eCRF pages and central laboratory requisition forms. Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Laboratory Manual.

8.6.3. Additional Exploratory Biomarker Assessments

During the study, in addition to the biomarkers specified above, exploratory research may be conducted on these collected samples. Biomarker assessments may include but are not limited to IHC or other analyses of proteins and whole exome/whole genome or targeted genetic analysis of DNA/RNA in tumor and blood samples. These studies would extend the search for other potential biomarkers relevant to the effects of DS-1062a, cancer, and/or the response/resistance to the study treatment. This may include the development of ways to detect, monitor, or treat NSCLC. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability.

If the subject agrees, remaining samples (tumor, blood, or other specimen obtained during the study) may be stored for a maximum of 15 years (or according to local regulations) following finalization of the CSR at a facility selected by the Sponsor to enable further analysis and address scientific questions of biomarkers relevant to DS-1062a and/or malignancies. The banked samples may be analyzed to design or improve methods for analyzing the development of diagnostic tests, characteristics of cancer, and, possibly, research related to other diseases that may lead to new treatments or the development of a diagnostic test that could be commercialized in the future to benefit other patients, or in response to a Health Authority request. If performed, the results of the biomarker analyses will be reported separately from the CSR.

8.6.4. TROP2 Immunohistochemistry Analysis

TROP2 expression levels may be measured using an IHC assay on all tumor biopsy samples collected during this study, including archival tumor material.

8.6.5. Pharmacogenomic (Inherited Genetic) Analysis

A single blood sample for pharmacogenetic analysis will be collected from each subject. The pharmacogenomic blood sample will be scheduled for Cycle 1 Day 1 predose (see Table 1.1) but may be collected at any time after the first dose of DS-1062a. Detailed instructions for the collection, handling, and shipping of samples are outlined in the Laboratory Manual.

Pharmacogenomic samples may be analyzed for genes involved in absorption, metabolism, elimination, safety, and efficacy of the study drug. Additionally, samples may be analyzed for genes involved in study drug-related signaling pathways, or to examine diseases or physiological processes or safety related to the study drug, such as ILD/pneumonitis.

Genetic analyses will not be performed on blood samples collected for PK or safety assessments. Subject confidentiality will be maintained.

If subjects agree, the remaining DNA will be stored, as outlined in Section 8.6.5.1 for performing future pharmacogenetic analysis. Otherwise, all remaining DNA samples will be destroyed.

8.6.5.1. Banking of Specimens for Inherited Genetic Analysis

Procedures for the long-term preservation (banking) of blood and/or DNA specimens extracted from subjects' blood samples for each subject who consented are described in the Laboratory Manual.

The banked samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of DS-1062a. Additionally, samples may be analyzed for genes involved in DS-1062a related signaling pathways, or to examine diseases or physiologic processes related to DS-1062a. DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Storage and Disposal of Specimens

Banked DNA samples will be stored for a maximum of 15 years after the finalization of the CSR for this protocol. These specimens will be kept for pharmacogenetic analysis in case new genomic or genetic information is obtained in the future regarding the response (PK or pharmacodynamic) to DS-1062a, or in case serious adverse drug reactions (ADRs) are noted in a clinical study and pharmacogenetic analysis is to be conducted for investigation into the cause.

During the storage period, the samples will be coded with labels having no personal information and will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time. However, the data will not be discarded if analysis has been completed before the subject withdraws consent.

Disclosure of the Results of Future Pharmacogenetic Analysis

Because the nature and value of future pharmacogenetic analysis cannot be known at this time, any results obtained from research involving pharmacogenetic samples will not be disclosed to the subject or investigators now or in the future.

8.6.6. Immunogenicity

Blood samples for plasma antidrug antibody (ADA) analyses will be collected in all subjects as at the time points specified in the Schedules of Events (Table 1.1 and Table 1.2).

Details for ADA plasma sampling, processing, and storage will be provided in the Laboratory Manual.

The ADA testing will be performed using a validated ADA assay following tiered assay steps including screening, confirmatory as well as titer determination. If ADA is confirmed, further analysis to profile the immunogenicity of DS-1062a (eg, neutralizing antibody assay) will be conducted. Plasma concentrations of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a may also be measured using the same ADA samples for purpose of ADA assessment.

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

The DCO date for the primary analysis will occur when all subjects have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study, whichever occurs first. All data collected up to the DCO date will be included in the primary analysis. Data from all sites will be pooled for analyses.

The final analysis of the study will occur after all subjects have discontinued from the study. Data collected beyond the primary analysis DCO may be presented as appropriate in a CSR addendum if deemed necessary.

Descriptive statistics on continuous data will include mean, median, standard deviation, and range (as well as geometric mean and geometric coefficient of variation for PK data). Categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. Time-to-event endpoints except for time to response (TTR) will be reported using Kaplan-Meier estimates.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last non-missing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing data will not be imputed for the purpose of data analysis, unless otherwise specified.

9.2. Statistical Hypothesis

The primary objective of this study is to estimate the antitumor activity of DS-1062a among subjects with advanced or metastatic NSCLC with actionable genomic alterations specified in Section 5.1 that has progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy, as measured by the ORR as assessed by BICR per RECIST v1.1. Confirmation of response (CR/PR) is required for ORR.

9.3. Sample Size Determination

A sample size of approximately 150 subjects, including approximately 50% (75 subjects) with EGFR genomic alterations, will provide sufficient statistical precision for the estimate of the ORR. The exact 95% CIs based on the Clopper-Pearson method at various ORRs is provided in Table 9.1. When the observed ORR is greater than or equal to 30%, the lower bound of the 95% CI is greater than 20% for all subjects and for the EGFR gene mutation subgroup, if there are 75 subjects with EGFR genomic alterations.[1,2] If there are 60 subjects with EGFR genomic alterations, then the lower bound of the 95% CI is greater than 20% when the observed ORR is greater than or equal to 32%.

Table 9.1: Exact 95% Confidence Intervals for Sample Size of All Subjects and Subjects with EGFR Genomic Alterations at Various Observed Objective Response Rates

Sample Size	Number of Responders	Observed ORR (%)	Exact 95% CI
N=150 (All Subjects)	38	25	18.6, 33.1
	45	30	22.8, 38.0
	53	35	27.7, 43.6
	60	40	32.1, 48.3
	68	45	37.2, 53.7
	75	50	41.7, 58.3
N=75 (Subjects with EGFR Genomic Alteration)	19	25	16.0, 36.7
	23	31	20.5, 42.4
	26	35	24.0, 46.5
	30	40	28.9, 52.0
	34	45	33.8, 57.3
	38	51	38.9, 62.4

CI = confidence interval; EGFR = epidermal growth factor receptor; ORR = objective response rate

The exact 95% CIs for the observed ORRs are based on binomial distribution and calculated using SAS® version 9.4.

9.4. Population for Analysis Sets

Analysis Sets

- The **Safety Analysis Set** will include subjects who received at least 1 dose of study drug.
- The **Full Analysis Set (FAS)** will include all subjects who received at least 1 dose of study drug. The FAS is the same as the Safety Analysis Set in this study.
- The **PK Analysis Set** will include all subjects in the Safety Analysis Set who had at least 1 PK sample with measurable plasma concentration of DS-1062a, total anti-TROP2 antibody, or MAAA-1181a.

9.5. Statistical Analysis

The SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Additional analytical conventions and details will be described in the SAP.

9.5.1. Efficacy Analyses

Table 3.1 lists the primary and secondary endpoints and their corresponding definitions. Additional details for the analysis and censoring rules are noted in the following sections. Detailed censoring rules for the primary and applicable secondary efficacy endpoints will be specified in the SAP.

The FAS will be used for all efficacy analyses, unless otherwise specified.

9.5.1.1. Primary Efficacy Analyses

The primary efficacy endpoint, ORR, is defined as the proportion of subjects who achieve a BOR of confirmed CR or confirmed PR as assessed by BICR. CR/PR will be confirmed with a follow-up tumor assessment at least 4 weeks (28 days) apart.

The BOR will be determined using tumor assessments at different evaluation time points from the date of first dose of study treatment until radiographic disease progression as assessed by BICR or start of any further non-palliative anticancer treatment, whichever is earlier. Clinical deterioration will not be considered as radiographic disease progression.

The estimate of ORR and its 2-sided 95% exact (Clopper-Pearson)[19] CI will be provided.

9.5.1.2. Secondary Efficacy Analyses

Secondary efficacy endpoints include: DoR, best percentage change in the sum of diameters (SoD) of measurable tumors, DCR, clinical benefit rate (CBR), progression-free survival (PFS), and TTR, as assessed by BICR and by investigator per RECIST v1.1; ORR as assessed by the investigator per RECIST v1.1; and overall survival (OS).

A brief description of each endpoint is provided below:

- DoR is defined as the time from the date of the first documentation of response (confirmed CR or confirmed PR) to the date of the first documentation of PD or death due to any cause. Duration of response will be measured for responding subjects (subjects with confirmed CR or confirmed PR) only. Detailed censoring rules for DoR will be specified in the SAP.
- Best percentage change in the SoD of measurable tumors is defined as the percentage change in the smallest SoD from all post-baseline tumor assessments, taking as reference the baseline SoD.
- DCR is defined as the proportion of subjects with a BOR of confirmed CR, confirmed PR, or SD.
- CBR is defined as the proportion of subjects with confirmed CR, confirmed PR, or SD that lasts for at least 180 days.
- PFS is defined as the time from the start of study treatment to the earlier of the dates of the first documentation of PD or death due to any cause. Detailed censoring rules for PFS will be specified in the SAP.

- TTR is defined as the time from the start of study treatment to the date of the first documentation of response (confirmed CR or confirmed PR). The TTR will be measured for responding subjects (confirmed CR or confirmed PR) only.
- OS is defined as the time from the start of study treatment to the date of death due to any cause. If there is no death reported for a subject before the DCO for the OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

For DoR, PFS, and OS, the survival distribution of these endpoints will be summarized and presented graphically using the Kaplan-Meier method; median event times and their 2-sided 95% CIs will be presented using Brookmeyer and Crowley methods. In addition, the event-free probability at different time points (eg, 3, 6, 9, 12 months) will be estimated with corresponding 2-sided 95% CIs using the Greenwood formula for variance derivation. TTR will be summarized descriptively.

Descriptive statistics for the best percentage change from baseline in the SoD of measurable tumors will be provided. A waterfall plot of the best percent change in the SoD for each subject will be presented.

ORR, DCR, and CBR, as assessed by investigator, will be analyzed in the same manner as the primary efficacy endpoint.

9.5.1.3. Multiplicity Adjustment

Not applicable.

9.5.2. Safety Analyses

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. Safety analyses will be performed using the Safety Analysis Set.

The overall study period will be divided into 3 mutually exclusive segments for statistical analysis and reporting purposes:

- Pre-treatment period: from date of informed consent (inclusive) to the start of study treatment − 1.
- On-treatment period: from the start of study treatment (inclusive) to 35 days (ie, 28 days + 7 days) after the last dose date of study treatment (inclusive).
- Post-treatment period: starting from 36 days after the last dose date of study treatment.

Only data from the on-treatment period will be summarized, unless otherwise specified, except in cases where data from the pre-treatment period will be used for baseline calculation.

Adverse Events

Adverse events will be coded using MedDRA and graded using NCI CTCAE v5.0.

A TEAE is defined as an AE with a start or worsening date on or after the start date of study treatment until 35 days since date of last dose (ie, on-treatment period). The AE summary will only include TEAEs. However, SAEs starting or worsening after the on-treatment period, if reported as related to the study treatment, will also be summarized.

The TEAEs will be summarized using MedDRA SOC and preferred term. Additional summaries will be provided by the worst NCI CTCAE grade and relationship to the study treatment (ie, regardless of relationship to study drug, study drug related).

Treatment-emergent AEs associated with study drug reduction, infusion interruption, dose delay, study treatment discontinuation, or death will also be summarized.

If the subjects reported more than 1 AE with the same PT, the AE with the greatest severity will be presented. If the subjects reported more than 1 AE with the same primary SOC, the subject will be counted only once with the greatest severity at the SOC level, where applicable.

Adverse events of special interest will also be summarized.

All AEs will be listed including, but not limited to, verbatim term, PT, SOC, NCI CTCAE grade, relationship to study drug, start and end dates, and outcome. Non-TEAEs will be flagged in the listing.

Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation including the EOT visit, as well as for the change from baseline.

Abnormal clinical laboratory results will be graded according to NCI CTCAE v5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst on-treatment value according to the CTCAE grade, will be provided for clinical laboratory tests. A listing of abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or above will be generated.

Electrocardiogram

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation including the EOT visit, as well as for the change from baseline. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated for QT and QTcF (eg, QTc ≤450 msec, >450 to ≤480 msec, >480 msec to ≤500 msec, and >500 msec; and change from baseline ≥30 msec and ≥60 msec).

A listing of ECG data will be generated.

Vital Signs

Descriptive statistics will be provided for the vital sign measurements by scheduled time of evaluation including the EOT visit, as well as for the change from baseline. A listing of vital sign data will be generated.

Other

All other safety endpoints (eg, physical examination findings including ECOG PS, ECHO/MUGA, and ophthalmologic findings) will be listed and summary tables will be generated.

9.5.3. Other Analyses

Biomarkers

Biomarkers (eg, tumor and/or blood gene expression, genomic alteration, gene signatures, and TROP2 expression) may be summarized using descriptive statistics. Association between biomarkers, efficacy, and safety from DS-1062a may also be explored as appropriate.

Pharmacokinetics/Pharmacodynamics

Pharmacokinetic analyses will be performed using the PK Analysis Set. Plasma concentrations for DS-1062a, total anti-TROP2 antibody, and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics at each study day and time point for the full and sparse PK cohorts. PK parameters will be calculated for the full PK cohort using non-compartmental analysis and will be listed and summarized using descriptive statistics.

Immunogenicity

ADA prevalence, which is the percentage of subjects who were ADA positive at any time point (baseline or post-baseline), will be summarized. ADA incidence, which is the proportion of subjects having treatment-emergent ADA will also be reported. This includes subjects who were ADA negative at baseline and became ADA positive post-baseline (treatment-induced ADA); subjects who were ADA positive at baseline and post-baseline but had an increase in ADA titer of at least 4-fold from baseline to post-baseline (treatment-boosted ADA); or subjects who had missing ADA data at baseline and were ADA positive post-baseline.

Titer and neutralizing antibodies will be determined when ADA is positive. The number of subjects with neutralizing antibodies will be summarized.

9.5.4. Interim Analysis

Not applicable.

10. APPENDICES – SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the IB, available safety information, recruitment procedures (eg, advertisements), subject information and consent form, any subject written instructions to be given to the subject, information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the independent IRB or EC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP. Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB or EC.

The investigator should notify the IRB or EC of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

The Sponsor will appoint a coordinating investigator. Among other possible duties, the coordinating investigator will be responsible for reviewing the final CSR and testifying to the accuracy of the description of the study conduct. Because the coordinating investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those investigators who have enrolled and treated at least 1 subject. However, where an investigator has special knowledge of the field or of the study, the coordinating investigator can be chosen prior to enrollment of the first subject. In all cases, the coordinating investigator must be chosen prior to locking the database.

Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive and/or;
- US FDA GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 (27 Mar 1997) and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 (25 Nov 2014);
- Other applicable local regulations.

In addition, the investigator will inform the Sponsor in writing within 24 hours of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, Independent Ethics Committees (IECs)/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the EC/IRB. The investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

10.1.2. Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The ICF and any revision(s) should be approved by the EC/IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed ICF should be provided to the subject. The date and time (if applicable) that informed consent was given must be recorded in the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to their participation. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

A separate special consent for inherited genetic analysis will be obtained from subjects in accordance with health authorities in their particular region/country.

Suggested model text for the ICF for the study and any applicable subparts (PK, pharmacodynamic, etc.) is provided in the Sponsor's ICF template for the investigator to prepare

the documents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

For study sites in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

10.1.3. Subject Confidentiality

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

For European study sites, the Sponsor will observe the rules laid down in the General Data Protection Regulation 2016/679/EU on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identification (SID) as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the independent IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

10.1.4. Data Integrity and Quality Assurance

Monitoring and Inspections

The CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visits will vary based on the activity at each study site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the investigator and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings.

In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

Data Collection

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via an "audit trail."

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the investigator via the EDC system's electronic signature. This signature will indicate that the investigator reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

Data Management

Each subject will be identified in the database by a unique SID.

To ensure the quality of clinical data across all study sites and subjects, a review will be performed by the CRO according to specifications approved by the Sponsor. Data will be vetted both electronically by programmed data rules within the application and manually. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

All AEs will be coded using MedDRA. Serious AEs in the clinical database will be reconciled with the safety database.

All concomitant medications and prior cancer therapies will be coded using the World Health Organization Drug Reference (WHODRUG) Dictionary.

10.1.5. Committees

Interstitial Lung Disease Adjudication Committee

An external ILD AC will be used for this study. Details on the membership, responsibilities, and working procedures of the external ILD AC will be described in its own charter, provided as a separate document. The ILD AC will adjudicate all cases of potential ILD/pneumonitis on an ongoing basis.

Adjudication of ILD/pneumonitis cases will be based on evaluation of eCRFs and source documents including, but not limited to, chest high-resolution CT, arterial blood gases, and carbon monoxide diffusing capacity. The ILD AC will review ongoing cases of ILD/pneumonitis to make the final determination of ILD/pneumonitis diagnoses to guide Sponsor decisions regarding trial suspension or trial discontinuation and to provide assessment of ILD/pneumonitis prevalence at the end of the study. Findings of the ILD AC with its recommendations will be provided to the Sponsor.

10.1.6. Study Documentation and Storage

The investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to obtain informed consent and make entries and/or corrections on eCRFs will be included on the Signature List.

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited information of the subjects, date, and outcome of the screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential Subject Identification Code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, EC/IRB correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (site-specific Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by local laws or regulations or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to provide further instruction.

Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (site-specific Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting source documentation.
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the independent IRB/EC and the Sponsor.
- Records related to the study drug including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All essential documentation will be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable laws or regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

10.1.7. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the CRO. This agreement will include the financial information agreed upon by the parties.

Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.8. Publication, Public Disclosure Policy, and Data Sharing

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, EU, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. The Sponsor will follow the principles set forward in "Good Publication Practice for Communicating Company-sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

The data from this study may be shared with or used by third parties, including commercial partners.

10.1.9. Protocol Deviations

The investigator must conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the ECs/IRBs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject.

The Sponsor must be notified of all major deviations to the protocol (eg, inclusion/exclusion criteria, dosing, or missed study visits) in accordance with the clinical study agreement between the parties on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the investigator should notify the EC/IRB of deviations from the protocol in accordance with local procedures.

10.1.10. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the EC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study intervention development.

Study termination may also be requested by (a) competent authority/ies.

In the event of early termination of the study, the Sponsor will consider providing DS-1062a to subjects who benefit from treatment according to legal regulations in the corresponding countries. Alternatively, these subjects may also be treated with SoC per investigator's decision.

10.1.11. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative form the Sponsor.

For product complaints, refer to the Pharmacy Manual for instructions and details.

10.2. Appendix 2: Laboratory Tests

The clinical laboratory tests listed in Table 10.1 are to be performed by local laboratory in this study.

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Blood Chemistry	albumin alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bilirubin (total) blood urea nitrogen (BUN) Urea (if BUN is not available) calcium (Ca) chloride (Cl)	creatinine cholesterol (total) creatine phosphokinase lactate dehydrogenase (LDH) magnesium (Mg) potassium (K) protein (total) sodium (Na) uric acid
Hematology	hemoglobin hematocrit platelet count red blood cell (RBC) count white blood cell (WBC) count	differential WBC count: basophils eosinophils lymphocytes monocytes neutrophils
Coagulation	prothrombin time - international normalized ratio (INR) partial thromboplastin time or/and activated partial thromboplastin time	
Urinalysis (abbreviated)	Urine dipstick testing: bilirubin protein glucose nitrites blood white blood cells pH specific gravity color clarity microscopic analyses: to be performed if clinically indicated or based on significant abnormal findings from the urine dipstick testing RBC WBC bacteria crystals other	
Pregnancy test (serum or urine)		

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight in kilograms (1 kilogram = 2.2 pounds):[20]

Conventional – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) – serum creatinine in µmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113} \times 0.85$$

10.3.2. New York Heart Association

The NYHA classification is summarized in Table 10.2.[21]

Table 10.2: New York Heart Association Classifications

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American Heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition March 14, 1994.

10.3.3. Eastern Cooperative Oncology Group Performance Status

The ECOG PS scale scores are summarized in Table 10.3.[22]

Table 10.3: Eastern Cooperative Oncology Group Performance Status

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649 55.

10.3.4. Highly Effective Contraception

Methods considered to be highly effective contraception include:[23]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence, defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months for females and for at least 4 months for males after the last dose of DS-1062a. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

10.4. Appendix 4: Response Evaluation Criteria in Solid Tumors (Version 1.1)

Assessment of tumor responses will be performed according to revised RECIST guidelines, Version 1.1.[24] Some of these definitions and criteria are highlighted below.

Measurability of Tumor at Baseline Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

- **Measurable**

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

- **Non-measurable**

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

- **Special Considerations Regarding Lesion Measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as

CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as TLs.
- **Lesions with prior local treatment:**
  - Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion since the therapy.

Specifications by Methods of Measurements

- **Measurement of Lesions**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should NEVER be performed more than 4 weeks (28 days) before the beginning of the treatment.

- **Method of Assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Tumor Response Evaluation

- **Assessment of Overall Tumor Burden and Measurable Disease**

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

In this study, only subjects with measurable disease at baseline should be included in the study.

- **Baseline Documentation of Target and Non-Target Lesions**

When more than 1 measurable lesion is present at baseline all lesions, up to a total of 2 lesions per organ and a maximum of 5 lesions total representative of all involved organs should be identified as TLs and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions, respectively, will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as TLs must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered NTLs. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all TLs will be calculated and reported as the baseline SoD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline SoD will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as NTLs and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple NTLs involving the same organ as a single item on the eCRF (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

- **Evaluation of Target Lesions**
  - **Complete Response (CR):** Disappearance of all TLs. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
  - **Partial Response (PR):** At least a 30% decrease in the SoD of TLs, taking as reference the baseline SoD.

- **PD:** At least a 20% increase in the SoD of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of 1 or more NLs is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SoD while on study.

- **Special Notes on the Assessment of Target Lesions (TLs)**
  - **Lymph nodes:** Lymph nodes identified as TLs should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as TLs, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of TLs.
  - **Target lesions that become 'too small to measure':** While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as TLs at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is unlikely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retro-peritoneum). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error.

    If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.
  - **Lesions that split or coalesce on treatment:** When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the TL sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion.'

- **Evaluation of Non-Target Lesions**
  - **CR:** Disappearance of all NTLs and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
  - **Non-CR/Non-PD:** Persistence of 1 or more NTL(s) and/or maintenance of tumor marker level above the normal limits.
  - **PD:** Unequivocal progression (see comments below) of existing NTLs. (Note: The appearance of 1 or more NLs is also considered progression).
- **Special Notes on Assessment of Progression of Non-target Disease**

The concept of progression of non-target disease requires additional explanation as follows, when the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will, therefore, be extremely rare.

- **New Lesions**

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of NLs are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a NL should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a NL and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI of the brain which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a NL is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a NL, then progression should be declared using the date of the initial scan that indicated its presence.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study treatment until the EOT. Confirmatory measurement for CR or PR is required in this study. The subject's BOR

assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of NLs.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 10.4 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

All post-baseline scans must be compared with the baseline (Cycle 1 Day 1) scan.

When subjects have non-measurable, therefore non-target, disease only, is to be used.

Table 10.4: Time Point Response: Subjects with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Objective Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 10.5: Objective Response: Subjects with Non-target Disease Only

Non-target Lesions	New Lesions	Objective Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease

Missing Assessments and In-evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is NE at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed,

but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The BOR is determined once all the data for the subject are known. The BOR when confirmation of CR or PR is required is displayed in Table 10.6.

Table 10.6: Best Overall Response When Confirmation of CR and PR Required

Overall response		Overall response
First time point	**Subsequent time point**	**Best**
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Table 3. Euro J of Can. 2009:45;228-47

Special Notes on Response Assessment

When nodal disease is included in the sum of TLs and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR might not have a total sum of '0' on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of DS-1062a without objective evidence of disease progression at that time should be reported as 'clinical progression.' Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study drug. The objective response status of such subjects is to be determined by evaluation of target and non-target disease. If a radiographic tumor assessment has not been performed within 4 weeks (28 days) of the time of clinical progression, then another radiographic assessment should be performed without waiting for the next regularly scheduled scan.

For equivocal findings of progression (eg, very small and uncertain NLs; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at Screening, and every 6 weeks (± 7 days) from Cycle 1 Day 1, independent of treatment cycle, until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent regardless of discontinuation of study treatment or initiation of new anticancer therapy as specified in the Schedule of Events (see Table 1.1 and Table 1.2). Subjects who discontinue study treatment for reasons other than disease progression per BICR will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by BICR, death, lost to follow-up, or withdrawal of consent. Tumor measurement will be performed during the EOT visit if it was not done within the previous 6 weeks or the previous assessment demonstrated disease progression. When tumor assessments at a visit are performed over multiple days, the date of response (CR, PR, SD, Non-CR/Non-PD [subjects with NTLs only] or NE) should be recorded as the date of the last radiographic evaluation included in the series for that assessment, and the date of progression (PD) should be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

Baseline tumor assessments must be performed within the Screening Period of 28 days prior to the start of study treatment.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the chest and abdomen. Any additional suspected sites of disease should also be imaged. All evaluations should meet the SoC for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and non-target sites are evaluated at each time point of tumor assessment.

10.5. Appendix 5: General Information – Adverse Events

10.5.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[25]

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiographic scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events NOT Meeting the AE Definition

Any clinically relevant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.5.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline or for administration of anticancer therapy after discontinuation of study drug is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is an important medical event
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Events Exempted from SAE Reporting

Serious events that are also efficacy endpoints, including death for OS, will be exempted from SAE processing and expedited reporting.[25] These events are clinically anticipated events in the target treatment population and will be periodically reviewed in an unblinded manner to ensure prompt identification of any clinically concerning safety issues.

10.5.3. Grade Assessment

The severity of AEs will be graded using NCI CTCAE version 5.0. For each episode, the highest severity grade attained should be reported.

The NCI CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI CTCAE guidelines should be followed closely.

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Difference Between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.5.4. Causality Assessment

The investigator should assess causal relationship between an AE and the study drug based on his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study (or its chemical group) or is predicted by known pharmacology.

- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

10.5.5. Action Taken Regarding Study Drug

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Infusion Interrupted: The study drug administration was started and then temporarily stopped.
- Dose Delayed: The study drug was not administered at the next scheduled cycle/dosing visit but was administered at a later date.
- Not Applicable: Subject died, study drug completed/permanently discontinued prior to reaction/event, or reaction/event occurred prior to start of treatment.
- Unknown: Subject is lost to follow-up

10.5.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or over-the-counter medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

10.5.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no sequelae observed.
- Recovered/Resolved with Sequelae
  - The subject fully recovered from the AE but with sequelae.
- Recovering/Resolving
  - The AE is improving but not recovered
- Not Recovered/Not Resolved
  - The AE continues without improving.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE
- Unknown

10.6. Appendix 6: Key Data Analysis Requirements

Endpoint/Analysis	Key Data Requirements
Primary Analysis	All eCRF collected data and key external source data (eg, tumor data as assessed by BICR, ILD, PK data, TROP2 expression data) collected up to the DCO date are required for the primary analysis.
Primary Endpoint - ORR	All tumor assessment data (eg, target, non-target, new lesion, overall response) as assessed by BICR and investigator per RECIST v1.1 is required.

BICR = blinded independent central review; DCO = data cutoff; eCRF = electronic case report form; ILD = interstitial lung disease; ORR = objective response rate; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TROP2 = trophoblast cell surface protein 2

10.7. Appendix 7: Instructions Related to COVID-19

Due to the potential impact of COVID-19 (due to severe respiratory syndrome coronavirus 2 [SARS-CoV-2]), on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with DS-1062a. Dose modifications will be based on the worst CTCAE grade. Use CTCAE version 5.0 general grading criteria to evaluate COVID-19. All dose modifications (discontinuation, delay, infusion interruptions, or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification Criteria for Suspected or Confirmed COVID-19

If COVID-19 infection is suspected, delay DS-1062a and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 6.3.
- If COVID-19 is confirmed or is still suspected after evaluation, follow dose modification as outlined in Table 10.7 below and manage COVID-19 per local guidance until recovery of COVID-19. COVID-19 recovery is defined as no signs/symptoms of COVID-19, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 10.7: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for DS-1062a
Grade 1	Resume study drug at the same dose[a]
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved[a] Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

COVID-19 = coronavirus disease 2019; CT = computed tomography

[a] Closely monitor signs/symptoms after resuming DS-1062a, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

In addition to the recommendations outlined in Table 10.7, investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 6.3).

Dosing of DS-1062a may be delayed for up to 9 weeks (63 days) from the planned date of the next cycle administration (ie, up to 12 weeks or 84 days from the last infusion). If a subject is assessed as requiring a dose delay longer than 12 weeks (84 days) from the last infusion, the subject must discontinue study treatment.

Before resuming study treatment with DS-1062a, a tumor assessment should be performed if the subject's last scheduled tumor assessment was missed.

Prior and Concomitant Medications - Prohibited Therapies/Products

- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment (Section 6.7). If chloroquine or hydroxychloroquine is administered per local clinical practice and regulations, then a washout period of no less than 14 days is required before resumption of DS-1062a.

COVID-19 Assessment(s)

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, but the real-time RT-PCR test is not available at the site, a sample kit will be provided for sample collection to be tested at a central laboratory. The results will be provided to the site from the central laboratory.

Serum samples will be used for COVID-19 testing from each subject who provides consent, unless prohibited by local restrictions. Samples will be collected prior to the study drug infusion, at the time points specified in the Schedule of Events (Table 1.1 and Table 1.2), shipped to a central laboratory, and stored there until the tests become available.

If subject consents, the remaining serum samples will also be stored for future analysis.

Unless prohibited by local restrictions, sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

Statistical Analysis - Assessment of the Impact of COVID-19

If deemed appropriate, analyses will be performed to explore the impact of COVID-19 on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of COVID-19 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the SAP.

11. REFERENCES

1. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019; 30:1321-8.
2. Douillard J-Y, Shepherd FA, Hirsh V, et al. Molecular Predictors of Outcome With Gefitinib and Docetaxel in Previously Treated Non–Small-Cell Lung Cancer: Data From the Randomized Phase III INTEREST Trial. J Clin Oncol. 2010; 28:744-52.
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6):394-424.
4. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2019. CA Cancer J Clin. 2019; 69:7-34.
5. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Bethesda, MD: National Cancer Institute; 2018.
6. American Cancer Society. Key statistics for lung cancer. Available at: https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html [Accessed Dec 2019].
7. Ricciardi GRR, Russo A, Franchina T, et al. NSCLC and HER2. Between lights and shadows. J Thorac Oncol. 2014; 9(12):1750-62.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 1.2020 – November 6, 2019.
9. Kobayashi H, Minami Y, Anami Y, et al. Expression of the GA733 gene family and its relationship to prognosis in pulmonary adenocarcinoma. Virchows Arch. 2010; 457:69-76.
10. Jiang A, Gao X, Zhang D, et al. Expression and clinical significance of the Trop-2 gene in advanced non-small cell lung carcinoma. Oncol Lett. 2013; 6(2):375-80.
11. Inamura K, Yokouchi Y, Kobayashi M, et al. Association of tumor TROP2 expression with prognosis varies among lung cancer subtypes. Oncotarget. 2017; 8(17):28725-35.
12. Stepan LP, Trueblood ES, Hale K, et al. Expression of Trop2 cell surface glycoprotein in normal and tumor tissues: Potential implications as a cancer therapeutic target. J Histochem Cytochem. 2011; 59(7):701-10.
13. DS-1062a Investigator's Brochure. Version 5.0. 08 Feb 2021.
14. Food and Drug Administration. Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. December 2018.
15. Mansfield AS, Rudek MA, Vulih D, et al on behalf of the NCI Organ Dysfunction Working Group. The effect of hepatic impairment on outcomes in Phase I clinical trials in cancer subjects. Clin Cancer Res. 2016; 22(22):5472-9.

16. Washington University in St. Louis. Human Research Protection Office. Determining the legal age to consent to research. It's not always 18! [Cited 2019 Mar 26].
17. US Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. [cited 08 Mar 2021]. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#classSub.
18. Food and Drug Administration. Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. July, 2009.
19. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404–16.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
21. American Heart Association. Classification of functional capacity and objective assessment. Ninth edition, March 14, 1994. http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp.
22. Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-55.
23. Heads of Medicines Agencies. Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 2014.
24. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Euro J Can. 2009: 45;228–47.
25. ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994.

12. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT3	5-hydroxytryptamine 3 antagonists
AC	Adjudication Committee
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
anti-HBc	anti-hepatitis B core antibody
anti-HBs	anti-hepatitis B surface antigen
AST	aspartate aminotransferase
AUCinf	area under the plasma concentration-time curve up to infinity
AUClast	area under the plasma concentration-time curve up to the last quantifiable time
AUCtau	area under the plasma concentration-time curve during dosing interval
BICR	blinded independent central review
BOR	best overall response
BRAF	proto-oncogene B-raf
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CDx	companion diagnostic
cfDNA	cell-free deoxyribonucleic acid
CHF	congestive heart failure
CI	confidence interval
CL	total body clearance
Cmax	maximum plasma concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPI	Checkpoint inhibitor
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
Dato-Dxd	Datopotamab deruxtecan
DCO	data cutoff
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
DP	drug product
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EIU	Exposure In Utero
EOS	end of study
EOT	end of treatment
ER	exposure-response
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IgG1	immunoglobulin 1
IHC	immunohistochemistry
ILD	interstitial lung disease
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
IV	intravenous
Kel	elimination rate constant associated with the terminal phase
LTSFU	Long-term Survival Follow-up
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized powder drug product
MAAA-1162a	drug linker
MAAA-1181a	released drug
MAAP-9001a	anti-TROP2 monoclonal antibody
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NK1	neurokinin-1
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
NTRK	neurotrophic tyrosine receptor kinase
NYHA	New York Heart Association
OCP	oral care plan
ORR	objective response rate
OS	overall survival
PD	progressive disease (disease progression)

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response
PT	preferred term
Q3W	every 3 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANKL	receptor activator of nuclear factor kappa B ligand
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SID	subject identification
SMQ	standardized MedDRA query
SoC	standard of care
SOC	system organ class
SoD	sum of diameters
SoE	Schedule of Events
SOP	Standard Operating Procedure
SpO_2	peripheral oxygen saturation
t1/2	terminal half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TL	target lesion
TMG	toxicity management guideline
Tmax	time to reach the maximum plasma concentration
TROP2	trophoblast cell surface protein 2
TTR	time to response
ULN	upper limit of normal
US	United States

Abbreviation	Definition
Vss	volume of distribution at steady-state
Vz	volume of distribution based on the terminal phase
WBC	white blood cell
WHODRUG	World Health Organization Drug Reference Dictionary

Signature Page for VV-CLIN-107948
DS1062-A-U202 final amendment V5

Approval with eSign	PPD Clinical Development/Science 26-Sep-2023 16:23:35 GMT+0000

Approval with eSign	PPD CSPV 26-Sep-2023 17:01:21 GMT+0000

Approval with eSign	PPD BDM 26-Sep-2023 17:10:26 GMT+0000

Approval with eSign	PPD Regulatory 26-Sep-2023 17:16:41 GMT+0000

Approval with eSign	PPD Clinical Development/Science 28-Sep-2023 13:08:33 GMT+0000

Signature Page for VV-CLIN-107948