CLINICAL STUDY PROTOCOL

PHASE 3 RANDOMIZED STUDY OF DS-1062A VERSUS DOCETAXEL IN PREVIOUSLY TREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WITH OR WITHOUT ACTIONABLE GENOMIC ALTERATIONS (TROPION-LUNG01)

(DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer)

PROTOCOL NUMBER: DS1062-A-U301F

(TROPION-LUNG01)

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VERSION 5.0, Date 09 OCT 2023

DAIICHI SANKYO, INC.

211 MOUNT AIRY ROAD
BASKING RIDGE, NEW JERSEY 07920

INVESTIGATOR AGREEMENT

PHASE 3 RANDOMIZED STUDY OF DS-1062A VERSUS DOCETAXEL IN PREVIOUSLY TREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WITH OR WITHOUT ACTIONABLE GENOMIC ALTERATIONS (TROPION-LUNG01)

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 of 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	09 Oct 2023
4.0	20 Jan 2022
3.0	01 Oct 2021
2.0	03 Mar 2021
1.0	05 Oct 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 4.0 (dated 20 Jan 2022) versus protocol Version 5.0 (09 Oct 2023) for the actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS1062-A-U301 clinical study protocol (Version 5.0) by section.

Amendment Rationale:

The main purpose of this amendment is to update the safety information for the DS-1062a investigational product.

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 update to language that does not alter original meaning, update to version numbering, updates to references, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or change in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
1.3 Schedule of Events Tables 1.1, 1.2, and 6.4 2.3.1 Benefit-Risk in Regard to COVID-19 6.5 Guidelines for Dose Modification 8.4.1.2 Adverse Events of Special Interest	(Dose) "interrupted" was replaced with "delayed", with the new term "infusion interruption" meaning stopping a dose during an infusion.	To clarify whether a subject had an interruption of an infused dose versus having an upcoming dose delayed, eg, due to an adverse event.
1.3 Schedule of Events 6.5.1 DS-1062a 8.4.1.2 Adverse Events of Special Interest	For suspected ILD/pneumonitis events, the following changes in evaluations were made: • 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 BAL if clinically indicated and feasible • Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2) • Clinical laboratory tests (a~~A~~rterial 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.
1.3 Schedule of Events 6.1 Study Drug Description 6.2.1 DS-1062a 6.5.1 DS-1062a	Added "If a subject doesn't 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
6.5 Guidelines for Dose Modification 6.5.1 DS-1062a 10.7 Appendix 8: Instructions Related to Coronavirus Disease 2019 (COVID-19)	Increased allowed dose delay time from 49 to 84 days from last dose. The following text was edited to reflect this: Depending on the severity of the TEAE, the dose of ~~DS1062a~~DS-1062a may be ~~interrupted~~delayed for up to ~~49~~12 weeks (~~28~~63 days) from the planned date of the next cycle administration. (ie, up to 12 weeks or 84 days from last infusion). If a subject is assessed as requiring a dose ~~interruption~~delay longer than ~~4~~12 weeks (~~28~~ or 84 days), from last infusion, the subject must discontinue treatment with DS-1062a. 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 Daiichi Sankyo study physician.¶	To allow those subjects receiving clinical benefit but requiring more recovery time to continue to receive treatment without being discontinued.

Section # and Title	Description of Change	Brief Rationale
1.3 Schedule of Events Tables 1.1, 1.2 Section 6.5.1 Table 6.4	The following statement was added: The importance of multiple daily mouth rinses during treatment (eg, prior to dosing) and up to the first follow-up visit should be emphasized.	To aid in preventing oral mucositis/stomatitis AEs, respectively.
1.3 Schedule of Events Tables 1.1, 1.2	The following statement was 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 preventative measure and up to 8 times per day as clinically needed.	To prevent ocular surface toxicity AEs.
2.2 Study Rationale 2.3 Benefit and Risk Assessment 4.3 Justification for Dose 6.5 DS-1062a Table 6.4 8.4.1.1 Serious Adverse Event Reporting 8.4.1.2. Adverse Events of Special Interest	In many cases, the term "IRR including anaphylaxis" was changed to "IRR."	Anaphylaxis is no longer considered an appreciable IRR.
8.4.1.2. Adverse Events of Special Interest	The terms stomatitis and mucosal inflammation were clarified to mean: Oral mucositis/stomatitis TEAEs and mucosal inflammation TEAEs occurring in the GI tract.	These terms are similar but need clarification for classification as AESIs.
4.1.1 Design Overview 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 course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, an IDMC review. 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 a previously recorded death event in the collection tool)."	To ensure survival data are accurately documented.
6.2 Preparation, Handling, Storage, and Accountability for Study Drug 6.2.2 Docetaxel	The storage of docetaxel was clarified, with the following edits: **Storage**¶ Docetaxel supplies must be stored in a secure, limited-access storage area under the recommended storage conditions as noted on the label~~: docetaxel should be stored between 2°C and~~. Do not store above 25~~°C, protected~~ °C. Store in the original package in order to protect from light. Do not freeze.¶	For enhanced clarity

Section # and Title	Description of Change	Brief Rationale
6.5.1 DS-1062a Table 6.4	Dose modifications for DS-1062a were updated by grade for IRR, hematologic, pulmonary, ocular surface, GI, and oral toxicities.	To reflect the most recent safety information.
6.6 Prior and Concomitant Medications	Added, "All concomitant medications administered during the study should be recorded in the eCRF until the end of the Safety Follow-Up Period. Concomitant medications administered as treatment for drug-related AESIs should be recorded until either event resolution, end of study, study termination, withdrawal of consent, or subject death."	To reinforce the importance of following all AESIs.
6.6 Prior and Concomitant Medications	Updated permitted therapies to remove restriction on using bisphosphonates and RANKL targeting agents. Added language to highly recommend the use of anti-emetic agents prior to DS-1062a treatment.	To reflect updated safety information.
6.6 Prior and Concomitant Medications	The following changes were made for when the Sponsor needs to be notified for concomitant use of corticosteroids: 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;~~ inhaled steroids ~~or,~~ 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.	> 10 mg/day of prednisone or an equivalent is an important cutoff the Sponsor is monitoring
7.2 Subject Withdrawal/Discontinuation from the Study	Added, "If the subject refuses 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."	To clarify the option of sparse contacts for survival follow-up only.
8.4.1.1 Serious Adverse Event Reporting	Section title changed to "8.4.1.1. Adverse Event Reporting". Added Grade ≥ 2 keratitis events (including keratitis, punctate keratitis, and ulcerative keratitis) to be reported in 24 hours upon occurrence.	To reflect updated safety information.
8.4.1.2. Adverse Events of Special Interest	Added, "All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study including any post-treatment follow-up (if applicable), study termination, withdrawal of consent, or subject death."	To ensure all AESIs are followed to resolution.
8.4.1.2. Adverse Events of Special Interest	Added "An autopsy in cases of Grade 5 ILD/pneumonitis is encouraged."	An autopsy may provide valuable safety information.
2.2 Study Rationale 2.3 Benefit and Risk Assessment 4.3 Justification for Dose 8.4.1.2. Adverse Events of Special Interest	IRR was downgraded from an important identified risk to an identified risk	Current safety data suggests the incidence and severity of IRR events meet the standards for an identified risk. No additional pharmacovigilance (PV) or risk minimization (RM) activities are planned and IRR is

Section # and Title	Description of Change	Brief Rationale
		integrated and managed through standard clinical practice.
Table 6.4	Toxicity Management Guidelines: The management guidelines for IRR TEAE grades were updated focusing on reducing infusion rates by 50%, yielding a doubling in total infusion times.	This strategy allows full doses while minimizing the severities and durations of IRR TEAEs.
	For Grade 4 decreased ANC and WBC, delay dose until ≤ Grade 2, then maintain dose if this occurs ≤ 14 days or decrease by one dose level if this occurs > 14 days	These cutoffs have been determined from current safety data.
8.4.2 Pregnancy	Added, "Women must not get pregnant, breastfeed, or donate/retrieve ova during the study and for at least 7 months after stopping DS-1062a or for at least 6 months after stopping docetaxel."	To match text present in the informed consent form.

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
Phase 3 Randomized Study of DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer With or Without Actionable Genomic Alterations (TROPION-Lung01)
Protocol Short Title
DS-1062a Versus Docetaxel in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer
Protocol Number
DS1062-A-U301
Sponsor/Collaborators
Sponsor: Daiichi Sankyo, Inc.
Registry Identification(s)
EudraCT Number: 2020-004643-80 NCT Number: NCT04656652
IND Number
IND Number: 136626
Study Phase
Phase 3
Planned Geographical Coverage, Study Sites, and Locations
Global study conducted at approximately 190 study sites located predominantly in North America, South America, Europe, Australia, and Asia.
Study Population
This study will enroll subjects with advanced or metastatic non-small cell lung cancer (NSCLC) with or without actionable genomic alterations (AGAs). **Subjects without AGA:** Subjects without actionable genomic alterations must have been previously treated with platinum-based chemotherapy and α (anti)-programmed cell death 1 (PD-1)/α-programmed cell death ligand 1 (PD-L1) monoclonal antibody, either in combination or sequentially. Subjects with known Kirsten rat sarcoma viral oncogene (KRAS) mutations, in the absence of any driver genomic alteration, are eligible and must meet the prior-therapy requirements as described for subjects without AGA. **Subjects with AGA**: Subjects with advanced or metastatic NSCLC with actionable genomic alterations are those subjects whose tumors have 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), or mesenchymal-epithelial transition (MET) exon 14 skipping, or rearranged during transfection (RET). Subjects with AGA must have progressed on or after 1 platinum-containing therapy and 1 to 2 prior lines of approved targeted therapy for the applicable genomic alteration.
Study Objectives/Outcome Measures and Endpoints
The following table lists primary and secondary study objectives and endpoints that have outcome measures.

Objectives	Outcome Measure	Endpoints	Category
Primary			
To compare the efficacy of DS-1062a with that of docetaxel, as measured by PFS and OS, for subjects with NSCLC with or without actionable genomic alterations	**Title:** PFS **Description:** PFS as assessed by BICR per RECIST v1.1. **Time frame:** At the time of the primary analysis of PFS.	PFS is defined as the time from randomization to the earlier of the dates of the first radiographic disease progression or death due to any cause.	Efficacy
	Title: OS **Description:** OS **Time frame:** At the time of the primary analyses of PFS and OS.	OS is defined as the time from randomization to death due to any cause.	Efficacy
Secondary			
To further evaluate the efficacy of DS-1062a compared with docetaxel	**Title:** PFS **Description:** PFS as assessed by Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	PFS is defined as the time from randomization to the earlier of the dates of the first radiographic disease progression or death due to any cause.	Efficacy
	Title: ORR **Description:** ORR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	ORR is defined as the proportion of subjects who achieved a BOR of CR or PR.	Efficacy
	Title: DoR **Description:** DoR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	DoR is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first radiographic disease progression or death due to any cause, whichever occurs first.	Efficacy

	Title: DCR **Description:** DCR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	DCR is defined as the proportion of subjects who achieved a BOR of CR, PR, or SD.	Efficacy
	Title: TTR **Description:** TTR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	TTR is defined as the time from randomization to the date of the first documentation of objective response (CR or PR) in responding subjects.	Efficacy
	Title: TTD **Description:** TTD in any of the 3 symptoms, chest pain, cough, or dyspnea. **Time frame:** At the time of the primary analyses of PFS and OS.	EORTC-QLQ-LC13 (except questions 36 and 37) The TTD is defined as the time from randomization to first onset of a ≥10-point increase in cough, chest pain, or dyspnea, confirmed by a second ≥10-point increase from randomization in the same symptom at the next scheduled assessment, or confirmed by death within 21 days of the first ≥10-point increase from randomization.	Efficacy
To further evaluate the safety of DS-1062a compared with docetaxel	**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 analyses of PFS and OS.	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 by the most	Safety

		recent version of MedDRA and both AEs and laboratory test results will be graded by NCI-CTCAE v5.0.	
To assess the PK of DS-1062a	**Title:** PK **Description:** Plasma concentrations and PK parameters of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a in the full PK sampling cohort. **Time frame**: At the time of the primary analyses of PFS and OS.	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:** ADA prevalence and incidence. **Time frame:** At the time of the primary analyses of PFS and OS.	ADA prevalence: the proportion of subjects who are ADA positive at any point in time (at baseline and post-baseline). ADA incidence: the proportion of subjects having treatment-emergent ADA. Titer and neutralizing antibodies will be determined when ADA is positive.	Immunogenicity
Exploratory			
To evaluate PFS2 for DS-1062a compared with that of docetaxel	**Title:** PFS2 **Description:** PFS2 as assessed by local standard clinical practice **Time frame:** At the time of the primary analyses of PFS and OS.	PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy or death due to any cause, whichever occurs first.	Efficacy
To evaluate biomarkers that may associate with the clinical benefit from DS-1062a	Not applicable	Tumor TROP2 expression (central laboratory analysis) Other biomarkers including genomic alterations, gene	Biomarkers and pharmacogenomics

used to treat NSCLC.		expression, protein expression, and pharmacogenomics may be measured in tumor and blood samples.	
To explore how changes in biomarkers may relate to exposure and clinical outcomes.	Not applicable	Biomarkers will be assessed in cell-free DNA pre- and post-treatment.	Biomarkers
To evaluate exposure-response relationships for efficacy and safety endpoints.	Not applicable	Characterize population PK and its relationship with efficacy and safety endpoints, and evaluate the effects of covariates (eg, body weight) on PK, efficacy, and safety.	PK
To evaluate PRO endpoints for DS-1062a compared with that of docetaxel.	**Title:** Patient-reported Outcomes • Change from baseline in QLQ-C30 functioning scales. • Change from baseline in global health (QLQ-C30 question No. 29). • Change from baseline in quality of life (QLQ-C30 question No. 30). • Change from baseline in overall health status (EQ-5D Visual Analog Scale). • Summary statistics (ie, frequency distributions) for each PRO-CTCAE. **Time frame:** At the time of the primary analyses of PFS and OS.	EORTC-QLQ-C30 EORTC-QLQ-LC13 (except questions 36 and 37) EQ-5D-5L PRO-CTCAE 1-3; 24;28-29;51;74	Patient-reported outcomes

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; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13; EQ-5D-5L = EuroQol Questionnaire- 5

dimensions-5 levels; Kel = elimination rate constant associated with the terminal phase; MAAA-1181a = released drug; MedDRA = Medical Dictionary for Regulatory Activities; MUGA = multigated acquisition; NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PFS2 = second progression-free survival; PK = pharmacokinetics; PR = partial response; PRO = Patient-reported Outcomes; PRO-CTCAE = Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; t1/2 = terminal half-life; TEAE = treatment-emergent adverse event; Tmax = time to reach maximum plasma concentration; TROP2 = trophoblast cell surface protein 2; TTD = time to deterioration; 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, randomized, active-controlled, open-label Phase 3 study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of DS-1062a versus docetaxel in subjects with advanced or metastatic NSCLC with or without actionable genomic alterations (AGA) (ie, alterations in genes with approved therapies, such as EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET). Subjects without AGA must have been previously treated with platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody, either in combination or sequentially. Patients who received α-PD-1/α-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody in the second-line setting. Subjects with known AGA must have progressed on or after 1 platinum-containing therapy and 1-2 prior lines of approved targeted therapy for the applicable genomic alteration. Subjects with known KRAS mutations, in the absence of any driver genomic alterations, are eligible and must meet the prior therapy requirements for subjects without AGA.

Eligible subjects will be randomized in a 1:1 ratio to DS-1062a 6.0 mg/kg or the control treatment, docetaxel 75 mg/m^2. Randomization will be stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no), and geographical region (United States [US]/Japan/Western Europe versus rest of world [ROW]). No crossover between study treatment arms will be allowed.

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 have a maximum duration of 28 days. Rescreening is permitted 1 time.
- Eligible subjects will be randomized and enter the Treatment Period. The Treatment Period starts on Cycle 1 Day 1 and continues until a subject permanently discontinues DS-1062a or docetaxel. Note: Dosing must occur within 3 days of randomization if all eligibility criteria are met. During the Treatment Period, eligible subjects will receive DS-1062a or docetaxel until they meet 1 of the treatment discontinuation criteria. Subjects will continue to receive DS-1062a or docetaxel in the absence of radiographic disease progression as assessed by Investigator, 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.
  - Subjects will undergo radiographic assessment of tumor response based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), every 6 weeks (±7 days) from randomization until radiographic disease progression as assessed by Investigator, 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 Investigator, death, lost to follow-up, or withdrawal of consent.
- The Follow-up Period will start upon permanent discontinuation of DS-1062a or docetaxel. During the Follow-up Period, subjects will be followed for 28 days (+7 days) for safety. After

discontinuing study treatment, subjects will then enter the LTSFU, during which they will be followed every 3 months for collection of information on subsequent anticancer treatment and survival, including cause and date of death. During LTSFU, subjects who discontinued treatment without radiographic disease progression or started 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 Investigator, death, lost to follow-up, or withdrawal of consent. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator assessed radiographic disease progression will also be required (if blinded independent central review [BICR] has not determined radiographic disease progression). Radiographic imaging scans will be sent to a central imaging vendor for BICR assessment. If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor. The Sponsor will notify the site to stop sending further scans to the central vendor when BICR determines radiographic disease progression OR until 7 months after the date of Investigator-assessed radiographic disease progression for the subject, whichever occurs first. If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. For further details, see Section 8.3. 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. The results of BICR-assessed tumor response will be used for the primary analysis of PFS in this study (see Section 3).
Study Duration
The study start date is the date when the first subject has signed an ICF. A subject is eligible to be randomized 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 randomized. The study will continue until the overall end of study is reached for the final analysis in the study. 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 within 28 days before randomization. Below is a list limited to the key inclusion criteria:

- Subject has pathologically documented Stage IIIB, IIIC or Stage IV NSCLC with or without AGA (note: NSCLC subjects with AGA are eligible under Protocol version 4.0) at the time of randomization (based on the American Joint Committee on Cancer, Eighth Edition) and meets the following criteria for NSCLC:

  Subjects without AGA:

  1. Subjects must have documented negative test results for EGFR and ALK genomic alterations. If test results for EGFR and ALK are not available, subjects are required to undergo testing performed locally for these genomic alterations.
  2. Subjects have no known genomic alterations in ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.
     - **In Argentina only, please see Section 10.9.2 for modified text applicable to Argentina.**
  3. Subjects with known KRAS mutations (testing during screening is not mandatory), in the absence of any driver genomic alterations, are eligible and must meet the prior therapy requirements for subjects without actionable genomic alterations described below. These subjects must be stratified as NSCLC without AGA at the time of randomization.

  Subjects with AGA:

  1. Subjects must have one or more documented actionable genomic alteration: EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.

- Subjects with documentation of radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.
- Subjects must meet the following prior therapy requirements:

  *Subjects **without AGA** must meet ONE of the following prior therapy requirements for advanced or metastatic NSCLC:*

  a. Received platinum-based chemotherapy *in combination* with α-PD-1/α-PD-L1 monoclonal antibody as the only prior line of therapy.
     - Includes subjects who received prior platinum-based chemotherapy with or without radiotherapy with maintenance α-PD-1/α-PD-L1 monoclonal antibody for Stage III disease and relapsed/progressed within 6 months from the last dose of platinum-based chemotherapy.
     - Includes subjects who received prior platinum-based chemotherapy with or without radiotherapy (with or without maintenance α-PD-1/α-PD-L1 monoclonal antibody) for Stage III disease and subsequently received α-PD-1/α-PD-L1 monoclonal antibody therapy (with or without platinum-based chemotherapy) for recurrent disease.

  OR

  b. Received platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody (in either order) *sequentially* as the only 2 prior lines of therapy.

  NOTE:

  i. Subjects who received α-PD-1/α-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody in the second line.

  ii. Subjects with known KRAS mutations, in the absence of other AGA, who received KRAS-approved target therapy (eg, sotorasib) as a separate line of therapy in addition to the prior therapy requirements described above are not eligible.

  *Subjects **with AGA** must meet the following for advanced or metastatic NSCLC:*

a. Subjects who have been treated with 1 or 2 prior lines of applicable targeted therapy that is locally approved for the subject's genomic alteration at the time of screening; OR one or more of the agents specified in the table below:
   - Subjects who have tumors with EGFR L858R or exon 19 deletion mutations must have received prior Osimertinib.
   - 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 alteration (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 approved targeted therapy, if locally available and clinically appropriate, for the applicable genomic alteration, or the subject will not be allowed in the study.

Genomic Alterations	**Applicable Targeted Agents**
EGFR	erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib
EGFR exon 20 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

b. Subjects who have received platinum-based chemotherapy as the only prior line of cytotoxic therapy:
   - One platinum-containing regimen for advanced disease
   - 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.

c. May have received up to one α-PD-1/α-PD-L1 monoclonal antibody alone or in combination with a cytotoxic agent.

- Must undergo a pre-treatment tumor biopsy procedure.
  OR
  If available, tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent 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 pre-treatment biopsy procedure during Screening. If a documented law or regulation prohibits (or does not approve) sample collection, then such samples will not be collected/submitted.
  Note: Results from the TROP2 testing or any other results of the pre-treatment tumor biopsy will not be used to determine eligibility for the study.
- Has measurable disease based on local imaging assessment using RECIST v1.1.
- Has an Eastern Cooperative Oncology Group performance status of 0 or 1 at Screening.
- Within 7 days before randomization, has adequate bone marrow function defined as:

1. Platelet count ≥100,000/mm^3 (platelet transfusion is not allowed within 1 week prior to Screening assessment)
2. Hemoglobin ≥9.0 g/dL (red blood cell/plasma transfusion is not allowed within 1 week prior to Screening assessment)
3. 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 6.5.2 and Section 6.6 for use of G-CSF and erythropoietin)

- Within 7 days before randomization, has adequate hepatic function defined as:
  1. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) or AST and ALT ≤5.0 × ULN if transferase elevation is due to liver metastases) AND
  2. Total bilirubin ≤1.5 × ULN (or <3.0 × ULN in the presence of documented Gilbert's syndrome [unconjugated hyperbilirubinemia] or liver metastases at baseline). Note: The Investigator should follow local practice guidelines and/or the docetaxel label approved in the country of drug administration for assessing eligibility of subjects for the study.
- Within 7 days before randomization, has adequate renal function, including mild or moderate renal function, defined as:
  1. Creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation.
- Has left ventricular ejection fraction (LVEF) ≥50% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 28 days before randomization.
- Has adequate blood clotting function defined as international normalized ratio/prothrombin time and either partial thromboplastin or activated partial thromboplastin time ≤1.5 × ULN.
- Has an adequate treatment washout period before randomization defined as:

Treatment	Washout Period
Major surgery	≥3 weeks
Radiation therapy including palliative radiation to 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 terminal elimination half-life (t1/2) of the chemotherapeutic agent, whichever is longer; ≥6 weeks for nitrosoureas or mitomycin C; ≥1 week for tyrosine kinase inhibitors approved for the treatment of NSCLC-baseline computed tomography (CT) scan should be completed after discontinuation of tyrosine kinase inhibitors.
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/Hydroxychloroquine	>14 days

In Czech Republic only, please see Section 10.9.1 for modified text applicable to sites in Czech Republic.

Key Exclusion Criteria:

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

- Has spinal cord compression or clinically active central nervous system (CNS) 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 who 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 CT or magnetic resonance imaging (MRI) scan of the brain at baseline is required for all subjects. For those subjects in whom 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 or metastasis.
- Had prior treatment with:
    1. Any agent, including antibody-drug conjugate (ADC), containing a chemotherapeutic agent targeting topoisomerase I.
    2. TROP2-targeted therapy.
    3. Docetaxel.
- Has uncontrolled or significant cardiac disease, including:
    1. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation >470 msec (based on the average of Screening triplicate 12-lead electrocardiogram [ECG] determinations).
    2. Myocardial infarction or uncontrolled/unstable angina within 6 months before randomization.
    3. 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 before randomization) in order to be eligible.
    4. Uncontrolled or significant cardiac arrhythmia.
    5. LVEF <50% by ECHO or MUGA scan within 28 days before randomization.
    6. Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) within 28 days before randomization.
- 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 before randomization, 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, Sjogren's syndrome, sarcoidosis, etc.), or prior pneumonectomy.
- Clinically significant corneal disease.
- Has a history of malignancy, other than NSCLC except a) adequately resected non-melanoma skin cancer, b) curatively treated in situ disease, or c) other solid tumors curatively treated, with no evidence of disease for ≥3 years.
- Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients (including but not limited to polysorbate 80) of DS-1062a or docetaxel.

Investigational Medicinal Product, Dose, and Mode of Administration

DS-1062a

DS-1062a drug product will be provided [redacted]

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 and must include antihistamines and acetaminophen with or without glucocorticoids.

Docetaxel

Docetaxel will be administered as an IV infusion of 75 mg/m^2 over approximately 60 minutes on Day 1 of each 3-week cycle. Investigators should consult the manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel. Subjects should be premedicated with oral corticosteroids, such as dexamethasone 16.0 mg per day (for example, 8.0 mg twice a day) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Additional antiemetic premedication may be used at the discretion of the Investigator.

Active Ingredients/INN

DS-1062a/ datopotamab deruxtecan

DS-1062a is an ADC that comprises a recombinant humanized anti TROP2 immunoglobulin 1 monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug linker, MAAA-1162a, via thioether bonds.

Docetaxel: (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Planned Sample Size

A total of approximately 590 subjects will be randomized to the DS-1062a arm or the docetaxel arm in a 1:1 ratio (295/arm), stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (US/Japan/Western Europe versus ROW). A minimum of 15% of the total study population will comprise subjects with actionable genomic alterations.

For the primary analysis of PFS, approximately 425 PFS events by BICR assessment will be required to have approximately 97% power to detect a hazard ratio of 0.64 at 2-sided significance level of 0.008, which corresponds to an improvement of 2.1 months in median PFS from 3.8 months in the docetaxel arm to 5.9 months in the DS-1062a arm.

For the primary analysis of overall survival (OS), approximately 413 OS events will be required to have at least 90% power to detect a hazard ratio of 0.72 at 2-sided significance level of 0.042, which corresponds to an improvement of 3.1 months in median OS from 8 months in the docetaxel arm to 11.1 months in the DS-1062a arm.

Assuming an exponential distribution of OS time, a ramp-up period of 13 months and 48 subjects per month afterwards, the study needs a total of approximately 590 subjects (295 per arm), over an enrollment period of approximately 19 months.

Statistical Methodology

Interim and Primary Analysis

No interim analysis (IA) is planned for PFS. The primary analysis for PFS as assessed by BICR will be performed when approximately 425 PFS events have been reached and at least 4 months after the last subject has been randomized. The primary analysis for progression-free survival (PFS) is projected to be approximately 23 months after the first subject is randomized.

OS will also be analyzed at the primary analysis of PFS (OS IA). The efficacy boundary will be determined using a group sequential design with Lan-DeMets procedure with O'Brien Fleming stopping boundary. It is projected that approximately 293 deaths will be observed at the IA, ie, 71% of information fraction (IF, ie, 293 out of the target 413 OS events). The study may be stopped at OS IA if the pre-specified superiority boundary is crossed.

The study will continue until the required number of deaths (413 OS events) is reached for the primary analysis of OS at approximately 33 months after the first subject is randomized.

Efficacy Analyses

The primary efficacy analysis of PFS and OS will compare the DS-1062a and docetaxel arms using a stratified log-rank test stratified by the randomization stratification factors.

PFS and OS will be summarized and graphically presented using the Kaplan-Meier method by treatment arm with median and corresponding confidence interval (CI) for the median using the Brookmeyer and Crowley method. In addition, the event-free probability at different time points (eg, 3, 6, 9, 12 months) will be estimated with corresponding CIs using the Greenwood formula for variance derivation.

The stratified Cox regression model, stratified by the randomization stratification factors, will be fitted to estimate the hazard ratio of PFS and OS between the treatment versus the control arm (docetaxel) and the corresponding CI.

The secondary efficacy endpoints include PFS as assessed by Investigator, overall response rate (ORR), duration of response (DoR), disease control rate (DCR), and time to response (TTR), each as assessed by BICR and by Investigator per RECIST v1.1.

PFS as assessed by Investigator will be analyzed in a similar manner as PFS as assessed by BICR.

The estimate of ORR and its 2-sided 95% exact (Clopper-Pearson) CI will be provided by treatment arm.

DoR will be analyzed in a similar manner as the primary endpoints, except that a hazard ratio will not be generated for DoR.

The estimate of DCR and its 2-sided 95% exact (Clopper-Pearson) CI will be provided by treatment arm.

TTR will be summarized descriptively.

The exploratory efficacy endpoint second progression-free survival (PFS2) will be analyzed in a similar manner as PFS.

Subgroup analyses will be conducted for PFS, OS, ORR, and DoR based on randomization period (before and after protocol version 4.0 to include subjects with actionable genomic alterations) as well as by presence of actionable genomic alterations (present versus absent).

Safety Analyses

Safety analyses, in general, will be descriptive and will be presented in tabular format with summary statistics presented by treatment arm for the Safety Analysis Set.

Pharmacokinetic Analyses

Plasma concentrations for DS-1062a (antibody-drug conjugate), total anti-TROP2 antibody, and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics. The following PK parameters will be calculated for each subject in the full PK sampling cohort using non-compartmental analysis of concentration time data of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a: maximum plasma concentration, time to reach maximum plasma concentration, area under the plasma concentration-time curve up to the last quantifiable time, area under the plasma concentration-time curve during dosing interval, and if data permit, area under the plasma concentration-time curve up to infinity, t1/2, total body clearance, volume of distribution at steady state, volume of distribution based on the terminal phase, and elimination rate constant associated with the terminal phase.

Population PK and exposure-response (ER) analyses will be performed to characterize the relationships of dose, exposure, efficacy, and safety endpoints. The effects of intrinsic (eg, body weight) and extrinsic covariates on PK and ER relationship will be evaluated. The results of the population PK and ER analyses will be reported separately from the clinical study report.

Immunogenicity

Immunogenicity will be assessed through characterization of incidence and titer of antidrug antibodies (ADA). The number and proportion of subjects having pre-existing ADA at baseline and treatment-emergent ADA will be summarized.

Patient-reported Outcomes

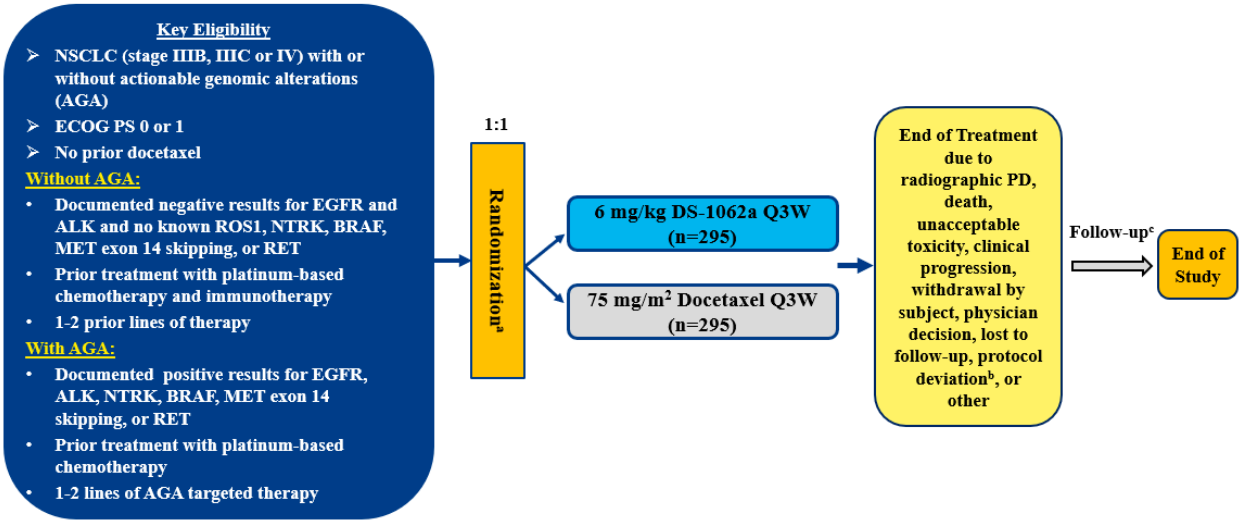
The Kaplan-Meier method will be used to estimate the distribution of TTD in any of the 3 symptoms, cough, chest pain, or dyspnea. The median TTD along with the 95% CI will be presented by treatment arm.

Descriptive analysis will be conducted on Patient-reported Outcomes (PRO) score, including subjects in the Full Analysis Set without a missing baseline PRO score and at least 1 post-baseline score.

All PRO instruments will be scored according to their corresponding scoring manual.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



AGA = actionable genomic alteration; DoR = duration of response; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell lung cancer; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; PK = pharmacokinetic; PRO = Patient-reported Outcomes; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; ROW = rest of world.; TTR = time to response

[a] Randomization will be stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no), and geographical region (US/Japan/Western Europe versus ROW).

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

[c] Subjects who discontinue study treatment without radiographic disease progression will continue to undergo tumor assessments every 6 weeks (±7 days) during follow-up until radiographic disease progression as assessed by Investigator, death, lost to follow-up, or withdrawal of consent.

Note: Two independent primary endpoints: PFS as assessed by BICR per RECIST v1.1 and OS.
Secondary endpoints: PFS as assessed by Investigator; ORR, DoR, DCR, and TTR each as assessed by BICR and by Investigator per RECIST v1.1; safety; PK; immunogenicity; PRO.

The **primary completion date of progression-free survival (PFS)** endpoint is the date when the pre-specified number of PFS events as assessed by BICR is reached and at least 4 months after the last subject has been randomized. This date is used as the data cutoff (DCO) for the primary analysis of PFS.
The **primary completion date of overall survival (OS)** endpoint is the date when the pre-specified number of deaths (413 OS events) is reached. This date is used as the DCO for the primary analysis of OS.
All subjects still on study treatment and continuing to derive benefit at the primary completion date of PFS or OS will continue to follow the study Schedule of Events until the **overall end of study (EOS)** is reached.
The **overall EOS** will occur after all subjects have discontinued the study or have died, 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 at the overall EOS.

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 Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
Informed Consent	ICF	X															A signed and dated ICF must be obtained before any study-specific procedures or assessments are initiated.
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 and Section 8.1.
Safety	Vital Signs	X	X[b,c]	X					X[c]	X			X[c]	X			See full protocol for details. [b] Screening data may be used as C1D1 data if obtained within 72 h of administration of DS-1062a or docetaxel. [c] Within 72 h before administration of DS-1062a or docetaxel.

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	SpO_2	X	X[b,c]	X					X[c]	X			X[c]	X			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 72 h of administration of DS-1062a or docetaxel. [c] Within 72 h before administration of DS-1062a or docetaxel.
	Physical Examination and ECOG PS	X	X[b]						X[c]				X[c]				[b] Screening data may be used as C1D1 data if obtained within 72 h of administration of DS-1062a or docetaxel. [c] Within 72 h before administration of DS-1062a or docetaxel.
	Height	X															Measured in cm.
	Weight	X	X[b]						X[c]				X[c]				Recorded in kg. [b] Screening data may be used as C1D1 data if obtained within 72 h of administration of DS-1062a or docetaxel. [c] Within 72 h before administration of DS-1062a or docetaxel.
	Ophthalmologic Assessment	X	As clinically indicated														Includes a visual acuity test, intraocular pressure test, slit lamp examination, fundoscopy, and fluorescein staining.
	12-Lead ECG	X[d]															[d] Within 7 days before randomization. Screening only, taken in triplicate in close succession, no more than 5 min apart, and after at least 5 min of quiet rest in the supine position. As clinically indicated for all treatment cycles (if ECG abnormality is detected, perform in triplicate).

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	ECHO or MUGA (LVEF)	X[e]															Use the same test throughout the study. [e] Within 28 days before randomization. As clinically indicated during treatment.
Laboratory Assessments	Hematology	X	X[b,c]						X[c]				X[c]				[b] Screening data may be used as C1D1 data if obtained within 72 h of administration of DS-1062a or docetaxel. [c] Within 72 h before administration of DS-1062a or docetaxel. As clinically indicated during treatment.
	Clinical Chemistry	X	X[b,c]						X[c]				X[c]				[b] Screening data may be used as C1D1 data if obtained within 72 h of administration of DS-1062a or docetaxel. [c] Within 72 h before administration of DS-1062a or docetaxel. As clinically indicated during treatment.
	Coagulation	X															
	Urinalysis	X	As clinically indicated														

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	Pregnancy Test	X[f]	X[g]						X[h]				X[h]				[f] A negative serum pregnancy test during Screening is required (within 28 days prior to randomization) for all female subjects of childbearing potential. [g] A negative serum/urine (per institutional procedures) pregnancy test within 72 h before C1D1 for all female subjects of childbearing potential is required; a positive urine test must be confirmed with a serum pregnancy test. Screening data may be used as C1D1 data if obtained within 72 h of administration of DS-1062a or docetaxel. [h] For subsequent treatment cycles, repeat pregnancy test (urine or serum per institutional guidelines) within 72 h BI at each cycle, at EOT, and at the 28-Day Safety Follow-up visit. A positive urine pregnancy test must immediately be confirmed using a serum test.
	HIV Ab Test	X															If required by local regulations or IRB/EC, subjects should be tested for HIV prior to randomization. See Exclusion Criterion 13. HIV antibody test results can be used if performed within 120 days before enrollment.
	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) tests (if HCV Ab is positive, test HCV RNA). Refer to Section 5.2 for exclusion criterion regarding HBV and HCV infection. HBsAg and HCV Ab test results can be used if performed within 120 days before enrollment.

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	COVID-19 Sample		X														Unless prohibited by local restrictions, if subject provides consent, serum samples should be collected prior to DS-1062a or docetaxel infusion. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in the full protocol.
Immunogenicity (only in subjects receiving DS-1062a)	ADA Sample		X[i]				X		X[i]				X[i]				Collected only from subjects receiving DS-1062a. [i] Within 8 h BI of DS-1062a.
Prior/ Concomitant Therapies	Prior Medications, Nondrug Therapies, and Radiotherapy	X	X														
	Concomitant Medications, Nondrug Therapies, and Radiotherapy		X														

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
Biomarker Samples	Tumor Biopsy Sample (Archival or Newly Obtained during Screening)	X															The subject must undergo a pre-treatment tumor biopsy procedure during Screening OR if available, tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent may be substituted for the pre-treatment biopsy procedure during Screening. See Section 5.1 and Section 8.1 If a documented law or regulation prohibits (or does not approve) sample collection, then such samples will not be collected/submitted.
	Pharmacogenomics Blood Sample		X														Scheduled for C1D1 pre-dose but may be collected at any time after the first dose of DS-1062a or docetaxel.
	Blood sample for cfDNA		X						X				X				
	Blood sample for predictive liquid biopsy		X														
	Blood sample for WES/WGS control		X														Scheduled for C1D1 pre-dose but may be collected at any time after the first dose of study treatment.
	Plasma sample for ILD biomarkers		X						X								Additional sample should be collected at time of suspected ILD onset.
	Serum sample for ILD biomarkers		X						X								Additional sample should be collected at time of suspected ILD onset.

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
Tumor Response and Lung Disease Assessment	CT/MRI of the chest, abdomen, and any other sites of disease	X[j]	Every 6 weeks (±7 days) from randomization until radiographic disease progression as assessed by Investigator, death, lost to follow-up, or withdrawal of consent (regardless of discontinuing study treatment or starting new anticancer therapy).[k] The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression). Radiographic scans will be sent to a central imaging vendor for BICR assessment. If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor until the site is notified by the Sponsor to stop sending additional scans (at time of BICR-assessed radiographic disease progression) OR until 7 months after the date of Investigator-assessed PD, whichever occurs first. If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. It is recommended that sites continue to follow a scanning interval frequency of every 6 weeks (±7 days) during the standard of practice follow-up of the subject as long as it is not interfering with the subject's standard of care. BICR results **will not** be shared with the site or Investigator. See Section 8.3. For further instructions, refer to the Imaging Site Manual which will be provided to the site.														[j] All baseline evaluations should NEVER be performed more than 28 days before randomization and never after randomization. Additionally, all radiographic images including CT and MRI, will be submitted to a central imaging vendor. [k] Subjects who discontinue treatment without radiographic disease progression will continue to undergo tumor assessments every 6 weeks (±7 days) until radiographic disease progression as assessed by Investigator, 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.
	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 randomization. Additional brain imaging may be performed as needed clinically. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments.														

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	Bone Scan or 18F FDG PET/CT or CT/MRI	X	Subjects with bone metastases at baseline should have bone scan (bone scintigraphy) **or** 18F FDG PET/CT **or** CT/MRI every 6 weeks (±7 days) from randomization. Otherwise, follow-up bone imaging is required only if new bone metastases are suspected. When disease progression in the bone or new lesion in the bone is suspected, 18F FDG PET/CT should be used to determine disease progression.														Bone scan or 18F FDG PET/CT is required at baseline and when disease progression in the bone is suspected.
Study Drug	Administration of DS-1062a		X						X				X				Premedication is required prior to any dose of DS-1062a and must include antihistamines and acetaminophen with or without glucocorticoids. Subject should remain at the site for at least 1-hour post-infusion for close observation for possible allergic reactions. If a subject doesn't 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. The initial dose of DS-1062a will be infused over approximately 90 min and if there is no IRR after the initial dose, the next dose of DS-1062a will be infused over approximately 30 min and if there is an IRR at any time during treatment, all subsequent doses will be infused over 90 min.

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	Administration of Docetaxel		X						X				X				Subjects should be premedicated with oral corticosteroids, such as dexamethasone 16 mg per day for 3 days starting 1 day prior to docetaxel administration. The subject's body surface area must be calculated for the initial dose and then recalculated, and the docetaxel dose adapted accordingly before each subsequent cycle. See Section 6.2.2. Consult the manufacturer's instructions for complete prescribing information and follow institutional procedures for the administration of docetaxel. For instructions for storage and docetaxel infusion preparation, consult the study Pharmacy Manual.
PK Blood Samples of DS-1062a (collected only from subjects receiving DS-1062a)	Sparse PK Sampling		X[i]	X[l]			X		X[i]	X[m]			X[i]				[i] Within 8 h BI of DS-1062a. [l] Within 1 h after EOI and 5 h (±1 h) after start of infusion of DS-1062a. [m] Within 30 min after EOI of DS-1062a.
	Full PK Sampling[n] (only for subjects receiving to-be-marketed material of DS-1062a)		X[i]	X[o]	X[p]	X	X	X	X[i]	X[q]			X[i]	X[q]			[i] Within 8 h BI of DS-1062a. [n] For 20 subjects of to-be-marketed material. [o] Within 30 min after EOI and 3, 5, and 7 h (±15 min) after start of DS-1062a infusion. [p] 24 h (±2 h) after the start of Day 1 infusion of DS-1062a. [q] Within 1 h after EOI of DS-1062a.

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
PRO Assessments	EORTC-QLQ-C30	X[r]						X[s]				X[s]				X[s]	[r] Collected at clinical site at baseline. [s] Collected from home or at the study site on **Day 15 (±1 day)** of Cycles 1 to 5 and odd cycles thereafter until PD or EOT, whichever comes first.
	EORTC-QLQ-LC13	X[r]						X[t]				X[t]				X[t]	Not including questions 36 and 37. [r] Collected at clinical site at baseline. [t] Collected from home or at the study site on **Day 15 (±1 day)** of each cycle until PD or EOT.
	EQ-5D-5L	X[r]						X[s]				X[s]				X[s]	[r] Collected at clinical site at baseline. [s] Collected from home or at the study site on **Day 15 (±1 day)** of Cycles 1 to 5 and odd cycles thereafter until PD or EOT, whichever comes first.
	PRO-CTCAE 1-3; 24, 28-29, 51, 74	X[r]		X[u]			X[u]	X[u]		X[u]	X[u]	X[u]		X[u]	X[u]	X[u]	[r] Collected at clinical site at baseline. [u] Collected within a 24-hour window on Day 1 and Day 8, and Day 15 (±1 day).
AEs	Non-serious AEs		X														All non-serious AEs occurring after the subject has taken the first dose of study drug until 35 days after the last dose of study drug will be recorded in the Adverse Event section of the eCRF. See Section 8.4.1 and Section 10.5

Assessment		SCR[a]	Cycle 1						Cycle 2				Cycle 3				Comments
	Visit Day	-28 to Rand	1		2	4	8	15	1		8	15	1		8	15	[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)					±1	±1	±1	±2		±2	±2	±2		±2	±2	
	SAEs	X[v]	X														All SAEs occurring after the subject signs the ICF and up to 35 days after the last dose of study drug (ie, the Follow-up Period), whether observed by the Investigator or reported by the subject, will be recorded in the Adverse Event section of the eCRF. See Section 8.4.1 and Section 10.5 [v] Unless documentation of other AEs is required by local regulations, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

18F-FDG = 18F-fluorodeoxyglucose; Ab = antibody; ADA = antidrug antibody; AE = adverse event; BI = before infusion; BICR = blinded independent central review; C = cycle; cfDNA = cell-free deoxyribonucleic acid; COVID-19 = Coronavirus disease 2019; CRO = contract research organization; CT = computed tomography; D = day; EC = ethics committee; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; EOI = end of infusion; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire; EORTC-QLQ-LC13 = European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Lung Cancer-13; EOT = end of treatment; EQ-5D-5L = EuroQoL–5 dimensions–5 levels; EOT = end of treatment; EQ-5D-5L = EuroQol Questionnaire-5 dimensions-5 levels; FVC = forced vital capacity; h = hour; HBV = hepatitis B virus; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; ILD = interstitial lung disease; IRB = Institutional Review Board; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; min = minute; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small cell lung cancer; OCP = oral care protocol; PET = positron emission tomography; PRO = Patient-reported Outcomes; PRO-CTCAE = Patient-reported Outcome version of the Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; Rand = randomization; SAE = serious adverse event; SCR = Screening; SpO_2 = peripheral oxygen saturation; WES = whole exome sequencing; WGS = whole genome sequencing

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

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)
- 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.

Note: For prevention of oral mucositis/stomatitis, initiate a daily oral care protocol (OCP) (see Section 6.2.1). The importance of multiple daily mouth rinses during treatment (eg, prior to dosing) and up to the first follow-up visit should be emphasized.
Note: 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 preventative measure and up to 8 times per day as clinically needed.
Note: Ophthalmologic assessments including 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
	Visit Day	1			28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
Safety	Vital Signs	X[a]	X	X	X			See full protocol for details. [a] Within 72 h before administration of DS-1062a or docetaxel.
	SpO_2[b]	X[a]	X	X	X			[a] Within 72 h before administration of DS-1062a or docetaxel. [b] Measured by pulse oximeter and at the same time vital signs are measured.
	Physical Examination and ECOG PS	X[a]		X	X			[a] Within 72 h before administration of DS-1062a docetaxel.
	Weight	X[a]		X	X			Recorded in kg. [a] Within 72 h before administration of DS-1062a or docetaxel.
	Ophthalmologic Assessment[c]	As clinically indicated		X				[c] Includes a visual acuity test, intraocular pressure test, slit-lamp examination, fundoscopy, and fluorescein staining.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
	12-Lead ECG	X[d,e,f]		X[f]	X[f]			[d] Within 72 h BI of DS-1062a or docetaxel. [e] Every 4 cycles BI of DS-1062a or docetaxel. As clinically indicated for all other treatment cycles (if ECG abnormality is detected, perform in triplicate). [f] Single ECG only.
	ECHO/MUGA (LVEF)			X				Use the same test throughout the study. As clinically indicated during treatment.
Laboratory Assessments	Hematology	X[a]		X	X			[a] Within 72 h before administration of DS-1062a or docetaxel. As clinically indicated during treatment.
	Clinical Chemistry	X[a]		X	X			[a] Within 72 h before administration of DS-1062a or docetaxel. As clinically indicated during treatment.
	Urinalysis	As clinically indicated						

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [5]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
	Pregnancy Test	X		X	X			For all female subjects of childbearing potential, a positive urine pregnancy test must immediately be confirmed using a serum test. Repeat pregnancy test (urine or serum per institutional guidelines) within 72 h BI at each cycle, at EOT, and at the 28-Day Safety Follow-up visit.
	COVID-19 Sample	X		X				Unless prohibited by local restrictions, if subject provides consent, serum samples should be collected prior to DS-1062a or docetaxel infusion. Starting at Cycle 5 Day 1 and every 4 cycles thereafter. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in the full protocol.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
	Visit Day	1			28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
Immunogenicity (only in subjects receiving DS-1062a)	ADA Sample	X[d,g]		X	X[h]	X		Collected only from subjects receiving DS-1062a. [d] Within 8 h BI of DS-1062a. [g] 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.) [h] Footnote no longer being used.
Concomitant Therapies	Concomitant Medications, Nondrug Therapies, and Radiotherapy	X						
Biomarker Sample	Blood Sample for cfDNA	Before infusion at C6D1 and C9D1 only		X				
	Plasma for ILD Biomarkers	Additional sample should be collected at time of suspected ILD onset.						
	Serum for ILD Biomarkers	Additional sample should be collected at time of suspected ILD onset.						

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
Tumor Response and Lung Disease Assessment[i]	CT/MRI of the chest, abdomen, and any other sites of disease	Every 6 weeks (±7 days) from randomization until radiographic disease progression as assessed by Investigator, death, lost to follow-up, or withdrawal of consent (regardless of discontinuing study treatment or starting new anticancer therapy). The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression). Radiographic scans will be sent to a central imaging vendor for BICR assessment. If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor until site is notified by the Sponsor to stop sending additional scans (at time of BICR-assessed radiographic disease progression) OR until 7 months after the date of Investigator-assessed radiographic disease progression, whichever occurs first. If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. It is recommended that sites continue to follow a scanning interval frequency of every 6 weeks (±7 days) during the standard of practice follow-up of the subject as long as it is not interfering with the subject's standard of care. BICR results **will not** be shared with the site or Investigator. See Section 8.3. For further instructions, refer to the Imaging Site Manual which will be provided to the site.		X[j]		[i] All images including CT and MRI will be submitted to a central imaging vendor. [j] Subjects who discontinued treatment without radiographic disease progression will continue to undergo tumor assessments every 6 weeks (±7 days) until radiographic disease progression as assessed by Investigator, 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.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
	Visit Day	1			28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
	CT/MRI of Brain	Subjects with brain metastases at baseline should have brain MRI or CT scan performed every 6 weeks (±7 days) from randomization. Additional brain imaging may be performed as needed clinically. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments.				X[k]		[k] Subjects with brain metastases at baseline who discontinued treatment without radiographic disease progression will continue to undergo brain MRI or CT scans every 6 weeks (±7 days) until radiographic disease progression as assessed by Investigator, 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 tumor assessments and survival.
	Bone Scan or 18F-FDG PET/CT or CT/MRI	Subjects with bone metastases at baseline should have bone scan (bone scintigraphy) **or** 18F FDG PET/CT **or** CT/MRI every 6 weeks (±7 days) from randomization. Otherwise, follow-up bone imaging is required only if new bone metastases are suspected. When disease progression in the bone or new lesion in the bone is suspected, 18F FDG PET/CT should be used to determine disease progression.				X[l]		[l] Subjects with bone metastases at baseline who discontinued treatment without radiographic disease progression will continue to undergo bone scan **or**18F FDG PET **or** CT/MRI every 6 weeks (±7 days) until radiographic disease progression as assessed by Investigator, death, lost to follow-up, or withdrawal of consent. In addition, all subjects with bone metastases at baseline who have not had disease progression at the time of the primary completion date will continue to be followed for tumor assessments and survival.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [5]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
Study Drug	Administration of DS-1062a	X						Premedication is required prior to any dose of DS-1062a and must include antihistamines and, acetaminophen with or without glucocorticoids. Subject should remain at the site for at least 1-hour post infusion for close observation for possible allergic reactions. If a subject doesn't 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.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
	Administration of Docetaxel	X						Subjects should be premedicated with oral corticosteroids, such as dexamethasone 16 mg per day for 3 days starting 1 day prior to docetaxel administration. The subject's body surface area must be calculated for the initial dose and then recalculated, and the docetaxel dose adapted accordingly before each subsequent cycle. See Section 6.2.2. Consult the manufacturer's instructions for complete prescribing information and follow institutional procedures for the administration of docetaxel For instructions for storage and docetaxel infusion preparation, consult the study Pharmacy Manual.
PK Blood Samples of DS-1062a (Collected Only from Subjects	Sparse PK Sampling	$X^{d,m}$	$X^{m,n}$					[d] Within 8 h BI of DS-1062a. [m] C4, C6, and C8 only. No PK sampling after C8. [n] Within 1 h after EOI of DS-1062a.

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	Comments
	Visit Day	1			28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
Receiving DS-1062a)	Full PK Sampling (only for subjects receiving to-be-marketed material of DS-1062a)	X[d,m]	X[m,n]					[d] Within 8 h BI of DS-1062a. [m] C4, C6, and C8 only. No PK sampling after C8. [n] Within 1 h after EOI of DS-1062a.
AEs	Non-serious AEs	X						All non-serious AEs occurring after the subject has taken the first dose of study drug until 35 days after the last dose of study drug will be recorded in the Adverse Event section of the eCRF. See Section 8.4.1 and Section 10.5
	SAEs	X				X[o]		All SAEs occurring after the subject signs the ICF and up to 35 days after the last dose of study drug (ie, the Follow-up Period), whether observed by the Investigator or reported by the subject, will be recorded in the Adverse Event section of the eCRF. [o] Only SAEs considered related by the Investigator should be reported during Long-Term Survival Follow-up. See Section 8.4.1 and Section 10.5

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
OS	Survival FU					X		In cases where subject withdraws consent and refuses to undergo any further study procedures, subjects will be asked to be followed for long-term survival only (eg, study personnel contacting the subject by telephone). Subjects who agree to survival follow-up only will be documented by the site in the source document and in the eCRF. See Section 7.2.
PRO Assessment	EORTC-QLQ-C30	X at Day 15 of C4, then collected on odd number cycles thereafter (5, 7, 9, etc.)[p]		X[p]		X[p]		[p] Collected from home or at the study site at C4 and then every odd number cycle on **Day 15 (±1 day)** until PD or EOT and then once more at EOT +90 days over a window of 14 days (ie, ±7 days from EOT +90 days).
	EORTC-QLQ-LC13	X at Day 15 of every cycle		X[q]		X[q]		[q] Collected from home or at the study site at every cycle on **Day 15 (±1 day)** until PD or EOT and then once more at EOT +90 days over a window of 14 days (ie. ±7 days from EOT +90 days).
	EQ-5D-5L	X at Day 15 of C4, then collected on odd number cycles thereafter (5, 7, 9, etc.)[p]		X[p]		X[p]		[p] Collected from home or at the study site at C4 and then every odd number cycle on **Day 15 (±1 day)** until PD or EOT and then once more at EOT +90 days over a window of 14 days (ie, ±7 days from EOT +90 days).

Assessment		Cycle 4 and Subsequent Cycles		EOT	Follow-up		EOS	
					28-Day Safety Follow-up [s]	Long-Term Survival Follow-up (Every 3 Months)		Comments
	Visit Day	1						
	Infusion	BI	EOI					
	Visit Window (Days)	±2		+7	+7	±14		
	PRO-CTCAE 1-3; 24; 28-29; 51, 74	X at Days 1, 8, and 15 of Cycles 4-10[r]		X	X			[r] Collected from home at every cycle within a 24-hour window on Day 1 and Day 8, and Day 15 (±1 day) until PD or EOT, or up to C10, whichever comes first.
Reason for Treatment Discontinuation				X				
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; cfDNA = cell-free deoxyribonucleic acid; CO = carbon monoxide; 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; eCRF = electronic Case Report Form; EOI = end of infusion; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-LC13 = European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Lung Cancer- EOS = end of study; EOT = end of treatment; EQ-5D-5L = EuroQoL–5 dimensions–5 levels FU = follow-up; FVC = forced vital capacity; h = hour; IRR = infusion-related reaction; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; OCP = oral care protocol; OS = overall survival; PET = positron emission tomography; PD = progressive disease; PRO = Patient-reported Outcomes; PRO-CTCAE = Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; SAE = serious adverse event; SpO_2 = peripheral oxygen saturation.

s. 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, this 28-day follow-up assessment is not needed.

Note: For suspected ILD/pneumonitis, study drug should be delayed pending evaluation.
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)
- 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.

Note: For prevention of oral mucositis/stomatitis, initiate a daily OCP (see Section 6.2.1). The importance of multiple daily mouth rinses during treatment (eg, prior to dosing) and up to the first follow-up visit should be emphasized.
Note: 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 preventative measure and up to 8 times per day as clinically needed.
Note: Ophthalmologic assessments including 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.[1] Advances in early detection of lung cancer have been slow, and more than half of lung cancers are still diagnosed at an advanced stage.[2] Only 18.6% of all patients with lung cancer are alive 5 years or more after diagnosis.[3] Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers.[4]

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.[5,6] A number of genomic alterations that have an impact on therapy selection have been identified in NSCLC and molecular testing is part of the standard of care in the evaluation of NSCLC.[6] These include epidermal growth factor receptor (EGFR) gene mutations, anaplastic lymphoma kinase (ALK) gene rearrangements, ROS proto-oncogene 1 (ROS1) rearrangements, neurotrophic tyrosine receptor kinase (NTRK) gene fusions, and proto-oncogene B-raf (BRAF) point mutations.[6]

The expression of programmed cell death ligand 1 (PD-L1) is often assessed to select patients for immune checkpoint inhibitors.[6] For patients with metastatic NSCLC, negative test results for EGFR and ALK, and PD-L1 levels of 50% or more (approximately 27% of patients), the National Comprehensive Cancer Network (NCCN) guidelines[6] recommend the immune checkpoint inhibitor pembrolizumab monotherapy in first-line therapy. The recommended first-line option for patients with metastatic NSCLC, negative or unknown test results for EGFR and ALK, and PD-L1 expression levels of 1% to 49% (approximately 32% of patients) depends on the background histology: for patients with nonsquamous NSCLC, the standard of care is a combination regimen of pembrolizumab plus carboplatin/cisplatin plus pemetrexed based on the results from the KEYNOTE-189 study.[7] For patients with squamous NSCLC, the standard of care is a combination regimen of pembrolizumab plus carboplatin plus paclitaxel (or nab paclitaxel) based on results from the KEYNOTE-407 study.[8] For patients with less than 1% expression of PD-L1, first-line therapy usually includes platinum-based chemotherapy with or without immunotherapy.[6]

Among patients relapsing or progressing after frontline platinum-containing doublet therapy, the Checkmate-017 and -057 studies demonstrated superior OS of nivolumab over docetaxel monotherapy in patients with squamous and nonsquamous NSCLC, respectively.[9,10] Notably, the median progression-free survival (PFS) of the docetaxel control arms were 2.8 months and 4.2 months, respectively, and the median OS were 6.0 months and 9.4 months, respectively.[9,10]

As a result of these and similar studies, patients with NSCLC generally receive platinum doublets and immune checkpoint inhibitors, either in combination or in sequence, as the first 1 or 2 lines of therapy. None of these therapies, however, are considered curative, and once patients have progressed after them, therapeutic options are generally limited to cytotoxic agents deployed as monotherapy, and median survival times are less than 1 year. In the multicenter, double-blind, randomized Phase 3 study (REVEL)[11] of docetaxel plus ramucirumab or placebo

as second-line treatment for patients with Stage IV NSCLC after platinum-based therapy, the median OS for patients treated with ramucirumab plus docetaxel versus those treated with placebo plus docetaxel was 10.5 months versus 9.1 months, respectively, and the median PFS was 4.5 months versus 3.0 months, respectively.[10] However, the addition of ramucirumab to docetaxel adds significant toxicities and the relevance of the results to a population that has failed prior immune checkpoint inhibitors remains unclear. As such, global usage of ramucirumab with docetaxel remains limited, despite broad regulatory approval.

For patients who have actionable genomic alterations (eg, EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, or RET kinase inhibitors), targeted therapies are recommended during the course of treatment as systemic treatments for the subset of patients with NSCLC whose tumors have driver genomic alterations. However, once patients have developed acquired resistance to the various targeted therapies and platinum-based chemotherapy, there are limited treatment options.

Docetaxel monotherapy remains perhaps the most widely used treatment for patients whose NSCLC has progressed after platinum-based chemotherapy and immune checkpoint inhibitors (in the case of NSCLC without AGA), or targeted therapies (in the case of NSCLC with AGA), consistent with NCCN guidelines.[6] The Checkmate 017, Checkmate 057, and REVEL studies suggest that these patients have median PFS of 3 months to 4 months and median survival of 6 months to 9 months. Therefore, there remains significant unmet need in patients with advanced or metastatic NSCLC.

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.[12] TROP-2 expression has been correlated with aggressive tumor behavior and has been used as a prognostic factor in several types of cancer.[12,13,14]

DS-1062a (datopotamab deruxtecan; Dato-DXd) is an antibody-drug conjugate (ADC) that comprises a recombinant humanized anti TROP2 immunoglobulin 1 monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug linker, MAAA-1162a, via thioether bonds. The released drug, MAAA-1181a, inhibits DNA topoisomerase I and leads to apoptosis of the target cells. To date, there have not been any registrational studies for TROP2-directed ADCs in the advanced or metastatic setting for NSCLC.

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[15,16] and other solid tumors[17] and have been shown to indicate a poor prognosis for these patients.[12]

DS-1062a showed antitumor activity in both in vitro and in vivo nonclinical studies and a mean terminal half-life (t1/2) of 4.62 days (6.0 mg/kg) in humans, which allows a once-every-3-weeks (Q3W) dosing schedule.[18]

Clinical data are available from the ongoing Phase 1 first-in-human study, DS1062-A-J101, evaluating escalating doses of DS-1062a (0.27 mg/kg to 10.0 mg/kg) in unselected subjects with advanced NSCLC relapsed or refractory to standard of care therapy. As described in the IB,[18] dose-limiting toxicities 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 maculo-papular rash). The maximum tolerated dose (MTD) was determined at 8.0 mg/kg.

As of the data cutoff (DCO) date of 04 Sep 2020, data are available for 208 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.[18] 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 4.0 mg/kg, 6.0 mg/kg, and 8.0 mg/kg dose levels.

As of the DCO date of 04 Sep 2020, 189 subjects were evaluable for response 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.[18] The overall response rate (ORR) by blinded independent central review (BICR) was 17.5% (7 PR in 40 subjects) in the 4.0 mg/kg dose group, 15.4% (6 partial responses [PRs] in 39 subjects) in the 6.0 mg/kg dose group, and 23.8% (19 PRs in 80 subjects) in the 8.0 mg/kg dose group. The disease control rate (DCR) was 72.5% (7 PRs and 21 stable diseases [SDs] in 40 subjects) in the 4.0 mg/kg dose group, 66.7% (6 PRs and 18 SDs in 39 subjects) in the 6.0 mg/kg dose group, and 80.0% (19 PRs and 43 SDs in 80 subjects) in the 8.0 mg/kg dose group. Results for DS-1062a among NSCLC subjects with AGA have become available with a DCO of 06 Apr 2021. The ORR by BICR was 35.3% (12/34 [95% CI, 19.7-53.5]) among the 34 subjects treated with DS-1062a at doses of 4, 6, or 8 mg/kg. The overall DCR was 82.4%, and the median DoR was 9.5 months (95% CI, 3.3-NE) in this subgroup. These results support the inclusion of NSCLC subjects with AGA into this Phase 3 study.[33]

As of 04 Sep 2020, treatment-emergent adverse events (TEAEs) were reported in 199 (96%) of 208 subjects, including 48 (96%) of 50 subjects in the 4.0 mg/kg dose group, 42 (91%) of 46 subjects in the 6.0 mg/kg dose group, and 81 (99%) of 82 subjects in the 8.0 mg/kg dose group.[18] The most frequent (≥20% of subjects) TEAEs across all doses, all grades, regardless of dose and causality were: nausea (47%), stomatitis (39%), fatigue (34%), alopecia (34%), decreased appetite (25%), vomiting (23%), and constipation (21%).

A total of 89 (43%) of 208 subjects experienced at least 1 ≥Grade 3 TEAE regardless of causality including 11 (22%) of 50 subjects in the 4.0 mg/kg dose group, 17 (37%) of 46 subjects in the 6.0 mg/kg dose group, and 46 (56%) of 82 subjects in the 8.0 mg/kg dose group. The frequency of ≥Grade 3 TEAEs appears to be dose-related (22%, 4.0 mg/kg; 37%, 6.0 mg/kg; and 56%, 8.0 mg/kg dose group).

Forty-two (20%) of 208 subjects experienced ≥Grade 3 TEAEs assessed by the Investigator as study drug related, including 5 (10%) of 50 subjects in the -4.0 mg/kg dose group, 7 (15%) of 46 subjects in the 6.0 mg/kg dose group, and 27 (33%) of 82 subjects in the 8.0 mg/kg dose

group.[18] A dose-related effect was noted with an observed increase in the proportion of subjects reporting ≥Grade 3 TEAEs assessed by the Investigator as study drug related with a higher dose of DS-1062a compared with the lower dose groups. 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 [3%]).

A numeric increase by dose was observed in TEAEs associated with study drug withdrawal, reduction, and interruption (4.0 mg/kg compared to 6.0 mg/kg or 8.0 mg/kg). A total of 20 (10%) of 208 subjects experienced TEAEs associated with study drug withdrawal, including 4 (8%) of 50 subjects in the 4.0 mg/kg dose group, 4.0 (9%) of 46 subjects in the 6.0 mg/kg dose group, and 12 (15%) of 82 subjects in the 8.0 mg/kg dose group. The most frequent TEAE across all doses leading to study drug withdrawal was pneumonitis (8 subjects [4%]). A total of 35 (17%) of 208 subjects experienced TEAEs associated with dose reduction, including 1 (2%) of 50 subjects in the 4.0 mg/kg dose group, 4 (9%) of 46 subjects in the 6.0 mg/kg dose group, and 25 (31%) of 82 subjects in the 8.0 mg/kg dose group. The most frequent (≥5 subjects) TEAEs associated with dose reduction across all doses were stomatitis (12 subjects [6%]) and mucosal inflammation (7 subjects [3%]). A total of 28 (14%) of 208 subjects experienced TEAEs associated with dose interruption including 2 (4%) of 50 subjects in the 4.0 mg/kg dose group, 9 (20%) of 46 subjects in the 6.0 mg/kg dose group, and 16 (20%) of 82 subjects in the 8.0 mg/kg dose group. The most frequent (≥4 subjects) TEAEs across all doses associated with dose interruption were lung infection and pneumonitis (4 subjects [2%] each).

As of 04 Sep 2020 across all doses, there were 14 subjects (7%) with interstitial lung disease (ILD)/pneumonitis events that were independently adjudicated as drug-related: 12 subjects (15%) on 8.0 mg/kg, 1 subject (2%) on 6.0 mg/kg, and 1 subject (2%) on 4.0 mg/kg. Of the 14 subjects with events adjudicated as drug-related ILD, 3 (1%) who had Grade 5 events; these 3 subjects were in the 8.0 mg/kg dose group.

Across all doses, 40 (19%) of 208 subjects treated have experienced TEAEs of infusion-related reaction.[18] All events of infusion-related reaction, were Grade 1 or Grade 2 except for 2 Grade 3 events (1 at 4.0 mg/kg and 1 at 6.0 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, anaemia, stomatitis/mucosal inflammation, diarrhoea, nausea, decreased appetite, alopecia, vomiting, dry eye, and rash/rash maculopapular. Potential risks include keratitis, skin pigmentation, AST increased, ALT increased, and constipation. Adverse events of special interest (AESIs) include ILD/pneumonitis, stomatitis/mucosal inflammation, infusion-related reaction, and ocular surface toxicity. Established treatment guidelines are in place to manage these and other toxicities associated with DS-1062a.

Refer to the most recent IB for additional DS-1062a information.[18]

There is a significant unmet medical need for patients with advanced or metastatic NSCLC after receiving platinum-based chemotherapy and an α (anti)-programmed cell death 1 (PD-1)/α-PD-L1 monoclonal antibody (patients without actionable genomic alterations) or with additional lines of target therapy specific to actionable genomic alterations (patients with actionable genomic alterations). DS-1062a has the potential to offer a treatment option for patients with advanced or metastatic NSCLC with and without actionable genomic alterations.

This Phase 3 study will be conducted to evaluate the efficacy and safety of DS-1062a versus control treatment with docetaxel in this population. Docetaxel is a microtubule inhibitor that is approved globally as a single agent for the treatment of locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy.[6,9,10,19,20,21]

2.3. Benefit and Risk Assessment

A total of 208 subjects have been treated with DS-1062a in the ongoing DS1062-A-J101 Phase 1 study.[18] Data from this study show efficacy across dose groups with tumor responses observed at starting doses of 4.0-, 6.0-, and 8.0-mg/kg and 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 of safety data, important identified risks for DS-1062a are ILD/pneumonitis. Other identified risks include IRR, fatigue, anaemia, stomatitis/mucosal inflammation, diarrhoea, nausea, decreased appetite, alopecia, vomiting, dry eye, and rash/rash maculopapular. The potential risks include keratitis, skin pigmentation, AST increased, ALT increased, and constipation.

The identified/potential risks have been generally manageable through dose modification and routine clinical practice. As with any therapeutic antibodies, there is a possibility of IRRs and immune responses causing allergic or anaphylactic reactions of DS-1062a.

In the DS-1062a clinical program, inclusion/exclusion criteria and monitoring/management guidelines are currently included in the study protocols to mitigate the identified and potential risks of DS-1062a, including the important identified risk of ILD/pneumonitis.

Potential ILD cases are monitored closely for signs/symptoms of ILD and reviewed by an independent ILD Adjudication Committee (AC) established for the DS-1062a program. The study protocols include detailed dose modification and supportive care guidelines for the proactive management of ILD. In the ongoing DS1062-A-J101 Phase 1 study, the majority of drug-induced ILD occurred at 8.0 mg/kg.

Infusion-related reactions are also monitored closely in the DS-1062a clinical program. Protocol eligibility criteria excluding potential subjects with a history of hypersensitivities reaction to any of the DS-1062a excipients, guidance on required premedication, and detailed dose modification guidelines are provided to mitigate the risk of IRR. In the ongoing DS1062-A-J101 Phase 1 study, all observed IRR, except for one Grade 3 event, have been mild or moderate, and manageable by close observation and dose modification.

Overall, the DS-1062a safety profile remains acceptable and manageable and supports continued clinical development of DS-1062a in NSCLC. Ongoing review of emerging Phase 1 study data has allowed a closer evaluation of benefit:risk by dose. Based on the most recent review of safety and efficacy data, DS-1062a is less tolerated at the 8.0 mg/kg dose compared to the 4.0 mg/kg and 6.0 mg/kg doses, and thus, 8.0 mg/kg is not an optimal dose for further evaluation. In addition, DS-1062a at the 6.0 mg/kg dose has a more favorable benefit:risk profile compared with that of the 8.0 mg/kg and 4.0 mg/kg doses, respectively. Subject to continual review of emerging data, current evaluation of benefit:risk supports the selection of 6.0 mg/kg as the optimal dose for further development of DS-1062a in patients with advanced or metastatic NSCLC.

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

2.3.1. Benefit-Risk in Regard to COVID-19

With the emergence of the Coronavirus disease 2019 (COVID-19) comes an increased safety risk for all subjects. As a result of the potential 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 and docetaxel study subjects. For any subjects with suspected or confirmed COVID-19, study treatment will be delayed until they fully recover for treatment resumption (as outlined in the dose modification guidance; Section 6.5). All clinical study protocols have been updated to include language on dose modification for COVID-19.

As the subjects included in this study are at high risk of recurrence, and improved therapies are still needed for this population, the Sponsor considers the potential benefit of DS-1062a for subjects in this study outweighs any potential risks associated with COVID-19.

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 analyses).

Table 3.1 lists the primary and secondary study objectives and endpoints that have outcome measures.

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

Objectives	Outcome Measure	Endpoints	Category
Primary			
To compare the efficacy of DS-1062a with that of docetaxel, as measured by PFS and OS, for subjects with NSCLC with or without actionable genomic alterations	**Title:** PFS **Description:** PFS as assessed by BICR per RECIST v1.1. **Time frame:** At the time of the primary analysis of PFS.	PFS is defined as the time from randomization to the earlier of the dates of the first radiographic disease progression or death due to any cause.	Efficacy
	Title: OS **Description:** OS **Time frame:** At the time of the primary analyses of PFS and OS.	OS is defined as the time from randomization to death due to any cause.	Efficacy
Secondary			
To further evaluate the efficacy of DS-1062a compared with docetaxel	**Title:** PFS **Description:** PFS as assessed by Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	PFS is defined as the time from randomization to the earlier of the dates of the first radiographic disease progression or death due to any cause.	Efficacy
	Title: ORR **Description:** ORR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	ORR is defined as the proportion of subjects who achieved a BOR of CR or PR.	Efficacy
	Title: DoR **Description:** DoR as assessed by BICR and Investigator per RECIST v1.1.	DoR is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first radiographic disease	Efficacy

Objectives	Outcome Measure	Endpoints	Category
	Time frame: At the time of the primary analyses of PFS and OS.	progression or death due to any cause, whichever occurs first.	
	Title: DCR **Description:** DCR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	DCR is defined as the proportion of subjects who achieved a BOR of CR, PR, or SD.	Efficacy
	Title: TTR **Description:** TTR as assessed by BICR and Investigator per RECIST v1.1. **Time frame:** At the time of the primary analyses of PFS and OS.	TTR is defined as the time from randomization to the date of the first documentation of objective response (CR or PR) in responding subjects.	Efficacy
	Title: Time to deterioration (TTD) **Description:** TTD in any of the 3 symptoms, chest pain, cough, or dyspnea **Time frame:** At the time of the primary analyses of PFS and OS.	**Description:** • EORTC-QLQ-LC13 (except questions 36 and 37) The TTD is defined as the time from randomization to first onset of a ≥10-point increase in cough, chest pain, or dyspnea, confirmed by a second ≥10-point increase from randomization in the same symptom at the next scheduled assessment, or confirmed by death within 21 days of the first ≥10-point increase from randomization.	Efficacy
To further evaluate the safety of DS-1062a compared with docetaxel.	**Title:** TEAEs and other safety parameters during the study **Description:** Descriptive statistics of safety endpoints. **Time frame:** Continuous monitoring and	TEAEs, SAEs, AESIs, ECOG PS, vital sign measurements, standard clinical laboratory parameters (hematology, serum chemistry, and urinalysis), ECG	Safety

Objectives	Outcome Measure	Endpoints	Category
	reported at the time of the primary analyses of PFS and OS.	parameters, ECHO/MUGA scan findings, and ophthalmologic findings. AEs will be coded by the most recent version of MedDRA and both AEs and laboratory test results will be graded by NCI-CTCAE v5.0.	
To assess the PK of DS-1062a	**Title:** PK **Description:** Plasma concentrations and PK parameters of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a in the full PK sampling cohort. **Time frame**: At the time of the primary analyses of PFS and OS.	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:** ADA prevalence and incidence. **Time frame:** At the time of the primary analyses of PFS and OS.	ADA prevalence: the proportion of subjects who are ADA positive at any point in time (at baseline and post-baseline). ADA incidence: the proportion of subjects having treatment-emergent ADA. Titer and neutralizing antibodies will be determined when ADA is positive.	Immunogenicity
Exploratory			
To evaluate PFS2 for DS-1062a compared with that of docetaxel	**Title:** PFS2 **Description:** PFS2 as assessed by local standard clinical practice **Time frame:** At the time of the primary analyses of PFS and OS.	PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy or death due to any cause, whichever occurs first.	Efficacy

Objectives	Outcome Measure	Endpoints	Category
To evaluate biomarkers that may associate with the clinical benefit from DS-1062a used to treat NSCLC.	Not applicable.	Tumor TROP2 expression (central laboratory analysis) Other biomarkers including genomic alterations, gene expression, protein expression, and pharmacogenomics may 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 will be assessed in cell-free DNA pre- and post-treatment.	Biomarkers
To evaluate exposure-response relationships for efficacy and safety endpoints.	Not applicable.	Characterize population PK and its relationship with efficacy and safety endpoints, and evaluate the effects of covariates (eg, body weight) on PK, efficacy, and safety.	PK
To evaluate PRO endpoints for DS-1062a compared with that of docetaxel.	**Title:** Patient-reported Outcomes • Change from baseline in QLQ-C30 functioning scales. • Change from baseline in global health (QLQ-C30 question No. 29). • Change from baseline in quality of life (QLQ-C30 question No. 30). • Change from baseline in overall health status (EQ-5D Visual Analog Scale). • Summary statistics (ie, frequency distributions) for each PRO-CTCAE. **Time frame:** At the time of the primary analyses of PFS and OS.	**Description:** EORTC-QLQ-C30 EORTC-QLQ-LC13 (except questions 36 and 37) EQ-5D-5L PRO-CTCAE 1-3; 24; 28-29; 51; 74	Patient-reported outcomes

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; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13; EQ-5D-5L = EuroQol Questionnaire- 5 dimensions-5 levels; Kel = elimination rate constant associated with the terminal phase; MAAA-1181a = released drug; MedDRA = Medical Dictionary for Regulatory Activities; MUGA = multigated acquisition; NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PFS2 = second progression-free survival; PK = pharmacokinetics; PR = partial response; PRO = Patient-reported Outcomes; PRO-CTCAE = Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; t1/2 = terminal half-life; TEAE = treatment-emergent adverse event; Tmax = time to reach maximum plasma concentration; TROP2 = trophoblast cell surface protein 2; TTD = time to deterioration; 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

This study has 2 independent primary endpoints of OS and PFS. The study will be considered positive if the hypothesis test for either one of these primary endpoints is successful.

PFS is a relevant measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile.[22] PFS is also not confounded by subsequent therapies and is a direct measure of therapeutic agent's direct benefit.

Historically, OS is a clinically meaningful and direct measure of overall efficacy in incurable, metastatic NSCLC disease and is considered the gold standard. The majority of drug approvals for NSCLC have been based on a significant improvement in OS.[22] However, it can take longer to read and potentially can be confounded by the use of subsequent therapies in this setting.

Hence for study DS1062-A-U301, both PFS and OS will serve as 2 independent endpoints.

The secondary endpoints described in Table 3.1 are intended to further assess antitumor activity of the study treatments, both radiographically and in terms of patient symptomatology.

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, randomized, active-controlled open-label Phase 3 study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of DS-1062a versus docetaxel in subjects with advanced or metastatic NSCLC with or without actionable genomic alterations (ie, alterations in genes with approved therapies, such as EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping or RET).

Subjects without actionable genomic alterations must have been previously treated with platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody, either in combination or sequentially. Patients who received α-PD-1/α-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody in the second-line setting. Subjects with known KRAS mutations, in the absence of any driver genomic alterations, are eligible and must meet the prior therapy requirements for subjects without actionable genomic alterations.

Subjects with known actionable genomic alterations must have progressed on or after a platinum-containing therapy and 1-2 prior lines of approved targeted therapy for the applicable genomic alteration. The study population is described in Section 5.

The primary objective of the study is to compare the efficacy of DS-1062a with that of docetaxel and demonstrate superiority in terms of either PFS or OS for subjects with NSCLC with or without actionable genomic alterations previously treated with platinum-based chemotherapy and at least one prior line of therapy as detailed in Section 5.

PFS as assessed by BICR per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and OS are the 2 independent primary endpoints of the study. The study will be considered positive if the hypothesis test for either one of the 2 primary endpoints is successful.

The study will be conducted at approximately 190 study sites predominantly located in North America, South America, Europe, Australia, and Asia.

The study start date is the date when the first subject has signed an informed consent form (ICF). A subject is eligible to be randomized 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.

A study level flow diagram is presented in Figure 1.1.

4.1.1. Design Overview

A total of approximately 590 eligible subjects will be randomized to the DS-1062a arm or docetaxel arm in a 1:1 ratio (295/arm), stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (United States [US]/Japan/Western Europe versus rest of world [ROW]). A minimum of 15% of the total study population will comprise subjects with actionable genomic alterations. No crossover between study treatment arms will be allowed.

The study will include subjects who have advanced or metastatic NSCLC with and without actionable genomic alterations (ie, alterations in genes with approved therapies, such as EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping or RET). Subjects without actionable genomic alterations must have been previously treated with platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody, either in combination or sequentially. Patients who received α-PD-1/α-PD-L1 monoclonal antibody as frontline therapy may have received the combination of platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody in the second-line setting. Subjects with known actionable genomic alterations must have progressed on or after 1 platinum-containing therapy and 1-2 prior lines of approved targeted therapy for the applicable genomic alteration. Subjects with known KRAS mutations, in the absence of any driver genomic alterations, are eligible and must meet the prior therapy requirements for subjects without actionable genomic alterations. See washout period for prior treatments in Section 5.1.

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 ICF and have a maximum duration of 28 days. Rescreening is permitted 1 time. 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 tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent may be substituted for the pre-treatment biopsy procedure during Screening.
- The genomic alteration status of tumors will be addressed as follows:
  - Subjects without actionable genomic alterations must have documented negative results for EGFR and ALK genomic alterations for inclusion in the study. If test results for EGFR and ALK are not available from subject's medical history, subjects are required to undergo testing performed locally for these genomic alterations during Screening. For the rare ROS1, NTRK, and BRAF, MET exon 14 skipping, and RET genomic alterations, if the tumor genomic status is unknown, it will be assumed the tumor is wild type for these genes (see Section 8.1).
  - Subjects **with** actionable genomic alterations must have one or more documented actionable genomic alteration(s) in EGFR, ALK, ROS1, NTRK, BRAF, MET exon skipping, or RET for inclusion in the study as a subject with AGA.
- Eligible subjects will be randomized and enter the Treatment Period. The Treatment Period starts on Cycle 1 Day 1 and continues until a subject permanently discontinues DS-1062a or docetaxel. Note: Dosing must occur within 3 days of randomization if all eligibility criteria are met. During the Treatment Period, eligible subjects will receive DS-1062a or docetaxel until they meet 1 of the discontinuation criteria (see Section 7.1). Subjects will continue to receive DS-1062a or docetaxel in the absence of 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. Subjects will undergo radiographic assessment of tumor response based on RECIST v1.1 every 6 weeks (±7 days) from randomization until radiographic disease progression as assessed by Investigator, 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 Investigator, death, lost to follow-up, or withdrawal of consent.

- The Follow-up Period will start upon permanent discontinuation of DS-1062a or docetaxel. 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, 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 LTSFU, subjects who discontinued treatment without radiographic disease progression or started 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 Investigator, death, lost to follow-up, or withdrawal of consent. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression).
- To ensure accurate survival data are available at the time of any database lock, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, an IDMC review. 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 a previously recorded death event in the collection tool).

Radiographic imaging scans will be sent to a central imaging vendor for BICR assessment. If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor. The Sponsor will notify the site to stop sending further scans to the central vendor when BICR determines radiographic disease progression OR until 7 months after the date of Investigator-assessed radiographic disease progression for the subject, whichever occurs first. If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. It is recommended that sites continue to follow a scanning interval frequency of every 6 weeks (±7 days) during the standard of practice follow-up of the subject as long as it is not interfering with the subject's standard of care. For further instructions, refer to the Imaging Site Manual which will be provided to the site.

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. The results of BICR-assessed tumor response will be used for the primary analysis of PFS in the study (see Section 3).

The PK of DS-1062a will be evaluated in all subjects who receive DS-1062a; see Section 8.5. Approximately 20 subjects receiving to-be-marketed material of DS-1062a will partake in full PK sampling. All other subjects receiving DS-1062a will partake in sparse PK sampling.

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

The Schedules of Events are presented in Table 1.1 (Screening and Cycles 1 through 3 of Treatment Period) and Table 1.2 (Cycle 4 onwards, End of Treatment [EOT], and the Follow-up Period). The primary analysis for PFS will be performed when approximately 425 PFS events by BICR assessment have been reached and at least months after the last subject has been randomized. The primary analysis of PFS is projected to be approximately 23 months after the first subject is randomized.

OS will also be analyzed at the primary analysis of PFS (OS interim analysis [IA]). The efficacy boundary will be determined using a group sequential design with Lan-DeMets procedure with O'Brien Fleming stopping boundary. It is projected that approximately 293 deaths will be observed at the IA. The study may be stopped at the OS IA if the pre-specified superiority boundary is crossed.

The study will continue until the required number of deaths, approximately 413 OS events, is reached for the primary analysis of OS at approximately 33 months after the first subject is randomized.

4.1.2. Study Completion

The **primary completion date** of the PFS endpoint is the date when the pre-specified number of PFS events as assessed by BICR is reached and at least 4 months after the last subject has been randomized. This date is used as the DCO for the primary analysis of PFS.

The **primary completion date** of OS endpoint is the date when the pre-specified number of deaths (413 OS events) is reached. This date is used as the DCO for the primary analysis of OS.

All subjects still on study treatment and continuing to derive benefit at the primary completion date of PFS or OS will continue to follow the study Schedule of Events until the **overall EOS** is reached.

The **overall EOS** will occur after all subjects have discontinued 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 at the overall EOS.

4.1.3. Dose Regimen

4.1.3.1. DS-1062a

DS-1062a will be administered as an intravenous (IV) infusion once 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 and must

include antihistamines and acetaminophen with or without glucocorticoids. CCI [redacted]

Subjects will continue to receive DS-1062a in the absence of radiographic disease progression as assessed by Investigator, 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). 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 as shown in Table 6.3. Once the dose of DS-1062a is reduced, no dose re-escalation is permitted.

4.1.3.2. Docetaxel

Docetaxel will be administered as an IV infusion of 75 mg/m^2 over approximately 60 minutes on Day 1 of each 3-week cycle. Subjects should be premedicated with oral corticosteroids, such as dexamethasone 16.0 mg per day (for example, 8.0 mg twice a day) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Additional antiemetic premedication may be used at the discretion of the Investigator.

Subjects will continue to receive docetaxel in the absence of radiographic disease progression as assessed by Investigator, 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). See Table 6.2 for complete details on dose regimen.

For dose delay and dose modification guidelines for docetaxel, see Section 6.5.2.

Investigators should consult the locally approved manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel.[19] For instructions for storage and docetaxel infusion preparation, consult the study Pharmacy Manual.

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.

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. Only eligible subjects who have completed all Screening procedures and meet all study entry criteria (defined in Section 5.1 and Section 5.2) will be randomized to receive either DS-1062a at 6.0 mg/kg or docetaxel at 75 mg/m^2.

Duration of Treatment and Subject Participation

Subjects will continue to receive DS-1062a or docetaxel in the absence of radiographic disease progression as assessed by Investigator, 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 standard of care 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 LTSFU) projected to continue for approximately 24 months after the last subject is randomized. The study will continue until the overall EOS is reached for the final analysis in the study. 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.

China Extension Study

If the country-level enrollment target for China that is required by the Chinese regulatory authority has not been achieved (approximately 90 subjects) when enrollment in the global study is complete, enrollment in China will continue until the required number of subjects are randomized. A minimum of 15% of the total number of subjects enrolled in China will be comprised of subjects with actionable genomic alterations as defined in the eligibility criteria of the study (Section 5). Subjects in the China extension study who are enrolled prior to completion of global enrollment will be randomized using the following 4 stratification factors: documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included α-PD-1/α-PD-L1 immunotherapy (yes versus no), and geographical region (US/Japan/Western Europe versus ROW). Subjects in the China extension study who are enrolled after completion of global enrollment will be randomized using 3 stratification factors: documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous) and most immediate prior therapy included α-PD-1/α-PD-L1 immunotherapy (yes versus no). Subjects randomized after global enrollment ends will not be included in the planned analysis of the global study.

4.2. Rationale for Study Design

This is a global, multicenter, randomized, active-controlled, open-label Phase 3 study designed to evaluate the efficacy and safety of DS-1062a versus docetaxel in subjects with advanced or metastatic NSCLC with or without actionable genomic alterations. Subjects without actionable genomic alterations must have been previously treated with platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody, either in combination or sequentially. Subjects with known actionable genomic alterations must have progressed on or after 1 platinum-containing

therapy and 1-2 prior lines of approved targeted therapy for the applicable genomic alteration. The study is designed to address the unmet need of patients with advanced or metastatic NSCLC whose disease has relapsed or progressed following standards of care in initial lines of therapy.

Docetaxel monotherapy is the active comparator treatment in this study and remains perhaps the most widely used treatment for NSCLC patients whose disease has progressed after platinum-based chemotherapy and immune checkpoint inhibitors (in the case of NSCLC without AGA) or targeted therapies (in the case of NSCLC with AGA), consistent with NCCN guidelines.[6] The Checkmate 017, Checkmate 057, and REVEL studies suggest that these patients face a median PFS of 3 months to 4 months and median overall survival of 6 months to 9 months with standard treatment docetaxel. Therefore, there remains an area of significant unmet need in patients with advanced or metastatic NSCLC. Available aggregate clinical data for DS-1062a support the hypothesis that this drug will improve outcomes relative to docetaxel and present a new standard of care for these patients.

The primary objective of the study is to compare the efficacy of DS-1062a with that of docetaxel and demonstrate superiority in terms of either PFS or OS for subjects with NSCLC with or without actionable genomic alterations previously treated with platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody (subjects without actionable genomic alterations) or with platinum-based chemotherapy and additional lines of target therapy specific to the actionable genomic alteration (subjects with actionable genomic alterations).

Eligible subjects will be randomized in a 1:1 ratio to DS-1062a 6.0 mg/kg or docetaxel 75 mg/m^2. Randomization will be stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (US/Japan/Western Europe versus ROW). DS-1062a will be administered as an IV infusion Q3W on Day 1 of 21-day cycles at a dose of 6.0 mg/kg. Docetaxel will be administered as an IV infusion of 75 mg/m^2 over approximately 60 minutes on Day 1 of each 3-week cycle. No crossover between study treatment arms will be allowed.

The 1:1 randomization is a clear standard that provides best odds of balance in baseline demographic and disease features and that compares DS-1062a and the control arm in a scientifically rigorous fashion. Stratification factors were chosen to address potential treatment effects by actionable genomic alteration status, histology, significant regional differences in first and second-line therapies and likely differences in post-study salvage therapies, and control for variability that may emerge based on prior therapies.

PFS as assessed by BICR per RECIST v1.1 and OS are the 2 independent primary endpoints of the study. The study will be considered positive if the hypothesis test for either one of these primary endpoints is successful.

PFS is a relevant measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile.[22] PFS is also not confounded by subsequent therapies and is a direct measure of therapeutic agent's direct benefit. OS is a clinically meaningful and direct measure of overall efficacy in incurable, metastatic NSCLC disease and is considered the gold standard. The majority of drug approvals for NSCLC have been based on a

significant improvement in OS.[22] However, it can take longer to read and potentially can be confounded by the use of subsequent therapies in this setting.

The secondary endpoints described in Section 3 are intended to further assess antitumor activity of the study treatments, both radiographically and in terms of patient symptomatology.

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

4.3. Justification for Dose

DS-1062a

The 6.0 mg/kg dose of DS-1062a was selected based on preliminary results of the ongoing first-in-human Phase 1 study DS1062-A-J101 which has enrolled approximately 210 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 where 2 subjects had Grade 3 dose-limiting toxicities of mucosal inflammation and stomatitis. One subject at 6.0 mg/kg had a dose-limiting toxicity of Grade 3 maculo-papular 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 of the DCO date of 04 Sep 2020, data are available for 208 subjects treated with DS-1062a in the 0.27 mg/kg to 10.0 mg/kg Q3W cohorts.[18] Out of 189 response-evaluable subjects (defined as having at least 1 dose of DS-1062a and at least 1 post-baseline tumor assessment or discontinued treatment), the ORR by BICR was 17.5% (7 PRs in 40 subjects) in the 4.0 mg/kg dose group, 15.4% (6 PRs in 39 subjects) in the 6.0 mg/kg dose group, and 23.8% (19 PRs in 80 subjects) in the 8.0 mg/kg dose group. The DCR was 72.5% (7 PRs and 21 SDs in 40 subjects) in the 4.0 mg/kg dose group, 66.7% (6 PRs and 18 SDs in 39 subjects) in the 6.0 mg/kg dose group, and 80.0% (19 PRs and 43 SDs in 80 subjects) in the 8.0 mg/kg dose group.

As of 04 Sep 2020, TEAEs were reported in 96% of subjects; 43% of subjects had TEAEs ≥Grade 3 and serious TEAEs occurred in 34% of subjects.[18] The most frequent (≥20% of subjects) TEAEs, all grades, regardless of dose and causality were: nausea (47%), stomatitis (39%), fatigue (34%), alopecia (34%), decreased appetite (25%), vomiting (23%), and constipation (21%). Twenty-eight subjects (14%) and 35 subjects (17%) had TEAEs that are associated with dose interruption or dose reduction, respectively, and 20 subjects (10%) had a TEAE that are associated with discontinuation of study treatment.

DS-1062a has an important identified risk of ILD/pneumonitis that can have a life-threatening or fatal outcome.[18] As of the 04 Sep 2020 IB cutoff date, 3 cases with a fatal outcome have been reported, all of which occurred in the 8.0 mg/kg dose group. The drug-related adjudicated ILD events occurred more frequently in the 8.0 mg/kg dose group where these TEAEs also resulted in the highest rate of study drug withdrawals due to ILD. Dose modification treatment guidelines are in place to address toxicity. For details, see Section 6.5.1.

Infusion-related reactions are classified as an identified risk. A majority of infusion-related reaction events were mild or moderate in severity, occurred during Cycle 1 or 2 of study treatment and were manageable (Study DS1062-A-J101). One subject did develop a Grade 3 anaphylaxis TEAE during infusion, which resolved without sequelae with intervention.

Based on available safety and efficacy data and a relative evaluation of benefit:risk by dose level, DS-1062a is less tolerated at the 8.0 mg/kg dose compared with the 4.0 and 6.0 mg/kg doses, and thus, 8.0 mg/kg is not an optimal dose for further evaluation. While the safety data show that DS-1062a is relatively well tolerated at both the 4.0 and 6.0 mg/kg doses and there is evidence that DS-1062a is active in NSCLC at both doses, better efficacy is observed at 6.0 mg/kg compared with 4.0 mg/kg in the context of an acceptable toxicity profile.

The most recent review of safety and efficacy data support selection of 6.0 mg/kg as the dose for further evaluation in the randomized Phase 3 study. 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 the optimal dose for DS-1062a monotherapy studies in NSCLC.

With respect to the dosing schedule, the mean terminal half-life of DS-1062a was 4.84 days at the 6.0 mg/kg dose in clinical studies, thus supporting a Q3W dosing schedule.

Docetaxel

The docetaxel starting dose of 75 mg/m^2 Q3W as a standard therapy in the second-line setting for NSCLC was established in the 2 Phase 3 studies TAX 317 and TAX 320.[23,24] Additional information can be found in the locally approved docetaxel package insert.[19]

5. STUDY POPULATION

The study population includes adult subjects with advanced or metastatic NSCLC with or without actionable genomic alterations, as per the inclusion and exclusion criteria described below.

Note: The Investigator should follow local practice guidelines and/or the docetaxel label approved in the country of drug administration for assessing eligibility of subjects for the study.

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study within 28 days before randomization into the study:

1. Has the ability to provide written informed consent by signing and dating the ICF prior to the start of any study-specific qualification procedures.
2. Adults ≥18 years (if the legal age of consent is >18 years old, then follow local regulatory requirements[23]).
3. Has a life expectancy ≥3 months based on Investigator's opinion.
4. Has pathologically documented Stage IIIB, IIIC, or Stage IV NSCLC with or without actionable genomic alteration(s) (AGA) at the time of randomization (based on the American Joint Committee on Cancer, Eighth Edition) and meets the following criteria for NSCLC: (Note: Subjects with NSCLC with AGA are eligible from Protocol version 4.0):

   Subjects Without AGA:

   - Subjects must have documented negative test results for EGFR and ALK genomic alterations. If test results for EGFR and ALK are not available, subjects are required to undergo testing performed locally for these genomic alterations.
   - Subjects have no known genomic alterations in ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.

     In Argentina only, please see Section 10.9.2 for modified text applicable to Argentina.
   - Subjects with known KRAS mutations (testing during screening is not mandatory), in the absence of any driver genomic alterations, are eligible and must meet the prior therapy requirements for subjects without actionable genomic alterations described below. These subjects must be stratified as NSCLC without AGA at the time of randomization.

   Subjects With AGA:

   - Subjects must have 1 or more documented actionable genomic alteration: EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET.

     In Argentina only, please see Section 10.9.2 for modified text applicable to Argentina.

5. Subjects must have documentation of radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.
6. Subject must meet the following prior therapy requirements:

   *Subjects **without AGA** must meet ONE of the following prior therapy requirements for advanced or metastatic NSCLC:*

   a. Received platinum-based chemotherapy *in combination* with α-PD-1/α-PD-L1 monoclonal antibody as the only prior line of therapy.

   – Includes subjects who received prior platinum-based chemotherapy with or without radiotherapy with maintenance α-PD-1/α-PD-L1 monoclonal antibody for Stage III disease and relapsed/progressed within 6 months from the last dose of platinum-based chemotherapy.

   – Includes subjects who received prior platinum-based chemotherapy with or without radiotherapy (with or without maintenance α-PD-1/α-PD-L1 monoclonal antibody) for Stage III disease and subsequently received α-PD-1/α-PD-L1 monoclonal antibody therapy (with or without platinum-based chemotherapy) for recurrent disease.

   OR

   b. Received platinum-based chemotherapy and α-PD-1/α-PD-L1 monoclonal antibody (in either order) *sequentially* as the only 2 prior lines of therapy.

   NOTE:

   i. Subjects who received α-PD-1/α-PD-L1 monoclonal antibody as first-line therapy may have received the combination of platinum-based chemotherapy and α-PD1/α-PD-L1 monoclonal antibody in the second line.
   ii. Subjects with known KRAS mutation, in the absence of other AGA, who received KRAS-approved target therapy (eg, sotorasib) as a separate line of therapy in addition to the prior therapy requirements described above are not eligible.

   Subjects with AGA must meet the following prior therapy requirements for advanced or metastatic NSCLC:

   a. Has been treated with 1 or 2 prior lines of applicable targeted therapy that is locally approved for the subject's genomic alteration at the time of screening; OR one or more of the agents specified in the table below:

      – Subjects who have tumors with EGFR L858R or exon 19 deletion mutations must have received prior Osimertinib.

      – 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 alteration (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 approved targeted therapy, if locally available and clinically appropriate, for the applicable genomic alteration, or the subject will not be allowed in the study.

Genomic Alterations	Applicable Targeted Agents
EGFR	erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib
EGFR exon 20 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

b. Has received platinum-based chemotherapy as the only prior line of cytotoxic therapy:
   - One platinum-containing regimen for advanced disease
   - 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.

c. May have received up to one α-PD-1/α-PD-L1 monoclonal antibody alone or in combination with a cytotoxic agent.

7. Must undergo a pre-treatment tumor biopsy procedure.

   OR

   If available, tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent 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 pre-treatment biopsy procedure during Screening. If a documented law or regulation prohibits (or does not approve) sample collection, then such samples will not be collected/submitted.

   Note: Results from the TROP2 testing of the pre-treatment tumor biopsy will not be used to determine eligibility for the study.

8. Inclusion Criterion removed.

9. Has measurable disease based on local imaging assessment using RECIST v1.1.

10. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at Screening.

11. Within 7 days before randomization, 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 6.5.2 and Section 6.6 for use of G-CSF and erythropoietin)

12. Within 7 days before randomization, has adequate hepatic function defined as:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) or AST and ALT ≤5.0 × ULN if transferase elevation is due to liver metastases AND
    - Total bilirubin ≤1.5 × ULN (or <3.0 × ULN in the presence of documented Gilbert's syndrome [unconjugated hyperbilirubinemia] or liver metastases at baseline).
      Note: The Investigator should follow local practice guidelines and/or the docetaxel label approved in the country of drug administration for assessing eligibility of subjects for the study.
13. Within 7 days before randomization, has adequate renal function, including mild or moderate renal function, defined as:
    - Creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation
14. Has left ventricular ejection fraction (LVEF) ≥50% by either ECHO or MUGA scan within 28 days before randomization.
15. Has adequate blood clotting function defined as international normalized ratio/prothrombin time and either partial thromboplastin or activated partial thromboplastin time ≤1.5 × ULN.
16. Has an adequate treatment washout period before randomization, defined as:

Treatment	**Washout Period**
Major surgery	≥3 weeks
Radiation therapy including palliative radiation to 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 tyrosine kinase inhibitors approved for the treatment of NSCLC-baseline computed tomography (CT) scan should be completed after discontinuation of tyrosine kinase inhibitors.

Treatment	Washout Period
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/Hydroxychloroquine	>14 days

In Czech Republic only, please see Section 10.9.1 for modified text applicable to sites in Czech Republic.

17. 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 at least 7 months, after the last dose of DS-1062a or for at least 6 months after the last dose of docetaxel. Non-childbearing potential is defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >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 one 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 post-menopausal 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 post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
18. If male, the subject must be surgically sterile or must use a condom in addition to highly effective birth control if his partners are of reproductive potential upon enrollment, during the Treatment Period, and for at least 4 months after the last dose of DS-1062a or for at least 6 months after the last dose of docetaxel.
19. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and for at least 4 months after the last dose of DS-1062a or for at least 6 months after the last dose of docetaxel. Preservation of sperm should be considered before enrollment in the study.
20. 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 last dose of DS-1062a or for at least 6 months after the last dose of docetaxel. Preservation of ova should be considered prior to enrollment in the study.
21. Be willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

5.2. Exclusion Criteria

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

1. Has mixed small-cell lung cancer (SCLC) and NSCLC histology.

2. Has spinal cord compression or clinically active central nervous system (CNS) 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 who 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 CT or magnetic resonance imaging (MRI) scan of the brain at baseline is required for all subjects. For those subjects in whom 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).
3. Has leptomeningeal carcinomatosis or metastasis.
4. Had prior treatment with:
    a. Any agent, including an ADC, containing a chemotherapeutic agent targeting topoisomerase I.
    b. TROP2-targeted therapy.
    c. Docetaxel.
5. Had prior treatment with platinum-based chemotherapy and prior immunotherapy for Stage II NSCLC disease (eg, in the neo-adjuvant or adjuvant setting) without subsequently meeting the prior therapy requirements for Stage III or metastatic NSCLC disease as described in Inclusion Criterion 6.
6. Has NSCLC disease that is eligible for definitive local therapy alone.
7. Uncontrolled or significant cardiac disease, including:
    a. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation >470 msec (based on the average of Screening triplicate 12-lead ECG determinations).
    b. Myocardial infarction or uncontrolled/unstable angina within 6 months before randomization.
    c. 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 before randomization) in order to be eligible (see criteria in Section 10.3.2).
    d. Uncontrolled or significant cardiac arrhythmia.
    e. LVEF <50% by ECHO or MUGA scan within 28 days before randomization.
    f. Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) within 28 days before randomization.
8. 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.

9. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months before randomization, 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, Sjogren's syndrome, sarcoidosis, etc.), or prior pneumonectomy.
10. Has significant third-space fluid retention (for example ascites or pleural effusion) and is not amenable for required repeated drainage.
11. Clinically significant corneal disease.
12. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections (eg, prodromal symptoms); or inability to rule out infections. Note: Subjects with localized fungal infections of skin or nails are eligible.
13. Has known human immunodeficiency virus (HIV) infection that is not well controlled. All 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, the subject's viral RNA load and CD4+ cell count should be monitored per local standard of care (eg, every 3 months). Subjects should be tested for HIV prior to randomization if required by local regulations or Institutional Review Board (IRB)/Ethics Committee (EC).
14. 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 antibody [anti-HBs], anti-hepatitis B core antibody [anti-HBc], or hepatitis B virus [HBV] DNA), and/or hepatitis C infection (as per hepatitis C virus [HCV] RNA) within 28 days of randomization.

    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 that 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.

15. Has a history of malignancy, other than NSCLC except a) adequately resected non-melanoma skin cancer, b) curatively treated in situ disease, or c) other solid tumors curatively treated, with no evidence of disease for ≥3 years.

16. Concomitant medical condition that would increase the risk of toxicity in the opinion of the Investigator.
17. 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 randomization and managed with standard of care treatment) which 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
d. Skin hypopigmentation (vitiligo)

18. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients (including but not limited to polysorbate 80) of DS-1062a or docetaxel.
19. History of severe hypersensitivity reactions to other monoclonal antibodies.
20. Is pregnant or breastfeeding or planning to become pregnant.
21. 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.
22. 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.
23. 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 of the study will not be replaced.

Rescreening is permitted 1 time for any subject. The Rescreening Period for subjects who are rescreened is also 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

6.1.1. DS-1062a

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

Table 6.1: DS-1062a Dosing Information

Study Drug Name	DS-1062a (Datopotamab Deruxtecan; Dato-DXd)
Dosage Formulation	DS-1062a DP will be provided CCI [redacted]
Dosage Levels	6.0 mg/kg
Route of Administration	IV infusion
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 and must include antihistamines and acetaminophen, with or without glucocorticoids. Subjects should remain at the site for at least 1-hour post infusion of DS-1062a for close observation for possible allergic reaction. If a subject doesn't 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 minutes on Cycle 1 Day 1. In the absence of an IRR, the subsequent doses will be infused over approximately 30 minutes. In case of IRR at any time during treatment, all subsequent doses will be infused over 90 minutes. Additional details are provided in Table 6.4.
Packaging	DS-1062a will be supplied by the Sponsor. The packaging will be clearly labeled "For Clinical Study Trial 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; h = hour; IRR = infusion-related reaction; IV = intravenous; CCI [redacted] min = minute

6.1.2. Docetaxel

Table 6.2 describes the formulation, dose, regimen, duration, packaging, and labeling of docetaxel.

Table 6.2: Docetaxel Dosing Information

Study Drug Name	Docetaxel
Dosage Formulation	Docetaxel will be provided as an injection vial consisting of 80 mg/4 ml in a single-use vial, to be used in an infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution
Dosage Levels	75 mg/m^2
Route of Administration	IV infusion
Dosing Instructions/Regimen	One IV infusion on Day 1 of each 3-week cycle. Subjects should be premedicated with oral corticosteroids, such as dexamethasone 16.0 mg per day (for example, 8.0 mg twice a day) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Additional antiemetic premedication may be used at the discretion of the Investigator.
Duration	Docetaxel will be infused over approximately 60 minutes on Day 1 of each 3-week cycle. Investigators should consult the locally approved manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel.[19] For instructions for storage and docetaxel infusion preparation, consult the study Pharmacy Manual.
Packaging	Docetaxel will be supplied by the Sponsor but can be supplied by the study site if required such as in case of Sponsor supply disruption or local regulatory requirements. The packaging will be clearly labeled "For Clinical Trial 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	Docetaxel glass vials will be labeled as required per local regulatory requirement.

DP = drug product; h = hour; IRR = infusion-related reaction; IV = intravenous; CCI [redacted] min = minute

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

6.2.1. DS-1062a

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 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 and must include antihistamines and acetaminophen, with or without glucocorticoids. All premedication administered must be adequately documented in the electronic Case Report Form (eCRF).

For prevention of oral mucositis/stomatitis, subjects are advised to initiate a daily oral care protocol (OCP) 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 minute 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 Investigator 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 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, all subsequent doses will be infused over 90 minutes. Additional details are provided in Table 6.4. Subjects should remain at the site for at least 1-hour post infusion of DS-1062a for close observation for possible allergic reaction. If a subject doesn't 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.

The subject's weight at screening will be used as the baseline weight to calculate the initial dose of DS-1062a, see Table 1.1. If during the course of 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 and body surface area (BSA) will be used as the new baseline weight. The site may follow local institutional policy for re-calculating dose based on weight changes less than 10%.

CCI [redacted]

Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions as noted on the label: CCI [redacted]

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 and 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 Interactive Response Technology (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 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. Please see the Pharmacy Manual for details.

6.2.2. Docetaxel

Docetaxel is a commercially available product and will be supplied by the study Sponsor.

Administration

Docetaxel will be administered as an IV infusion of 75 mg/m^2 over approximately 60 minutes on Day 1 of each 3-week cycle. Subjects should be premedicated with oral corticosteroids, such as dexamethasone 16.0 mg per day (for example, 8.0 mg twice a day) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Additional antiemetic premedication may be used at the discretion of the Investigator. All premedication administered must be adequately documented in the eCRF.

The subject's BSA must be recalculated, and the docetaxel dose adapted accordingly before each subsequent cycle. Applied dosages should be no more than 10% above or below calculated ones.

Investigators should consult the locally approved manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel.[19] For instructions for storage and docetaxel infusion preparation, consult the study Pharmacy Manual.

Storage

Docetaxel supplies must be stored in a secure, limited-access storage area under the recommended storage conditions as noted on the label. Do not store above 25 °C. Store in the original package in order to protect from light. Do not freeze.

If storage conditions are not maintained per specified requirements, then the Sponsor or CRO should be contacted. See the Pharmacy Manual for additional information on storage conditions of docetaxel and storage conditions of the prepared 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 docetaxel will be returned or destroyed as per local laws or site policy and only after the CRO 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. Please see the Pharmacy Manual for details.

6.3. Measure to Minimize Bias: Randomization and Blinding

Method of Treatment Allocation

Eligible subjects will be randomized in a 1:1 ratio to DS-1062a 6.0 mg/kg or the control treatment, docetaxel. Randomization will be stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (US/Japan/Western Europe versus ROW).

Randomization will be managed through an IRT for subjects meeting all eligibility criteria. The system will assign a unique randomization number and dose group for that subject. The instructions on how to use the system will be provided in the IRT Manual.

This is an open-label study. No crossover between study treatment arms will be allowed.

6.4. Treatment Compliance

DS-1062a or docetaxel 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 eCRF.

6.5. Guidelines for Dose Modification

All dose modifications (ie, infusion interruptions, dose delays, re-initiation, 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 dose 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 medical monitor for guidance regarding scheduling of these procedures.

6.5.1. DS-1062a

Dose Modification Guidelines

Depending on the severity of the TEAE, the dose 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 last infusion). If a subject is assessed as requiring a dose delay longer than 12 weeks or 84 days from last infusion, the subject must discontinue treatment with DS-1062a. 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 Daiichi Sankyo study physician.

Up to 3 dose reductions will be permitted for subjects receiving DS-1062a (Table 6.3). Once the dose of DS-1062a is reduced, no dose re-escalation will be permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurs, the subject will be withdrawn from the study treatment.

Table 6.3: 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

Infusion Interruptions, Dose Delays, and Other Dose Modifications – Toxicity Management Guidelines

Dose modification criteria for subjects with suspected or confirmed COVID-19, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are presented in Section 10.7.

Specific criteria for DS-1062a infusion interruptions, dose delays, re-initiation, 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 6.4, which is applicable only to TEAEs that are assessed as related to use of DS-1062a by the Investigators. For non-drug-related TEAEs or if nothing is noted in Table 6.4, standard clinical practice should be followed. Appropriate experts should be consulted as deemed necessary. The Investigator may consider infusion interruptions, dose delays, or DS-1062a discontinuation based on other events not listed in Table 6.4 according to the subject's condition.

There will be no dose modifications for Grade 1 or Grade 2 TEAEs unless specified in Table 6.4. 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 or 84 days from the last infusion, the subject must discontinue treatment with DS-1062a.

Treatment cycles for 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 6.4: Dose Modifications for Non-hematologic and Hematologic Toxicity Related to DS-1062a

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
Infusion-Related Reaction	
Premedication is required prior to any dose of DS-1062a and must include antihistamines and acetaminophen with or without glucocorticoids. Subjects should remain at the site for at least 1-hour post infusion of DS-1062a for close observation for possible allergic reaction. If a subject doesn't 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 any signs or symptoms of infusion-related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, 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 DS-1062a should be interrupted briefly. 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 DS-1062a 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 DS-1062a can be administered at the initial planned infusion rate (90 or 30 minutes) for subsequent treatment cycles.

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
Grade 3	Administration of DS-1062a 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 DS-1062a. • If the IRR resolves within the same day of DS-1062a infusion, no recurrence of symptoms occurs following initial improvement, and no hospitalization is necessary for clinical sequelae, then for the next cycle, administer DS-1062a 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 DS-1062a 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 DS-1062a at the same infusion rate (90 or 30 minutes). • If a new IRR occurs that is Grade 2 or greater with subsequent cycles, permanently discontinue DS-1062a and initiate treatment of the IRR symptoms.
Grade 4	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.
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 <0.5-0.5 ×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	Delay dose until resolved, then reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment.

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
Lymphocyte Count Decreased	
Grade 4	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.
Anaemia	
Grade 3	Delay dose until resolved to ≤Grade 2, then maintain dose.
Grade 4	Delay dose until resolved to ≤Grade 2, then reduce dose by 1 level.
Platelet Count Decreased	
Grade 3	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	• 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. 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: • High-resolution CT • Pulmonologist consultation (infectious disease consultation, as clinically indicated) • Bronchoscopy and BAL if clinically indicated and feasible • Pulmonary function tests (including FVC 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 If the AE is confirmed to be ILD/pneumonitis as per the above evaluations, follow the ILD/pneumonitis management guidance as outlined below.	

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
All events of ILD/pneumonitis regardless of severity or seriousness must be followed until resolution including after DS-1062a discontinuation.	
Grade 1	The administration of DS-1062a 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 to 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 event worsens despite initiation of corticosteroids, then follow Grade 2 guidelines.[a] For Grade 1 events, DS-1062a 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 subject is asymptomatic but is given steroid treatment, then event should be considered as Grade 1. 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.

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**

Grade 2	Permanently discontinue subject from study treatment.
	• 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,
	  o Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone).
	  o Re-consider additional workup for alternative etiologies as described previously.
	  o Escalate care as clinically indicated.

Grade 3 and 4	Permanently discontinue subject from study treatment.
	• Hospitalization is required.
	• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500 to 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,
	  o Re-consider additional workup for alternative etiologies as described above.
	  o Consider other immuno-suppressants and/or treat per local practice.

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
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 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 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
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 Total Bilirubin Increased	
AST/ALT ≥3.0 × ULN with simultaneous total bilirubin >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 total bilirubin twice weekly until resolution or return to baseline.

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
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 reduce 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 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.
Total Bilirubin	
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 Toxicity NCI-CTCAE v5.0 Grade (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 DS-1062a.
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	
Treatment of 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.

Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for DS-1062a**
	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	Consider a dose delay or reduction if clinically indicated. Optimize prophylactic and supportive medications.
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, 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 and then reduce dose by 1 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 and then reduce dose by 1 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; CO = carbon monoxide;

COVID 19 = Coronavirus disease 2019; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ESMO = European Society for Medical Oncology; FVC = forced vital capacity; Hb = hemoglobin; ILD = interstitial lung disease; IRR – infusion-related reaction; IV = intravenous; LVEF = left ventricular ejection fraction; CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; SpO_2 = peripheral oxygen saturation; ULN = upper limit of normal; WBC = white blood cell.
All dose modifications should be based on the worst preceding toxicity.

6.5.2. Docetaxel

Dose Delay Guidelines

Docetaxel dosing may be delayed for up to 4 weeks (28 days) from the planned date of administration. If a subject is assessed as requiring a dose delay longer than 4 weeks (28 days), the subject must discontinue treatment with docetaxel.

Docetaxel administration should be delayed for the following:

Investigators should use discretion in accordance with locally approved docetaxel label and institutional guidance.

- Either febrile neutropenia or neutropenia <500 cells/mm³ for greater than 1 week despite the use of growth factors
- Any Grade ≥2 non-skin, drug-related adverse event (AE), except for fatigue or laboratory abnormalities. (Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay)
- Any Grade 3 drug-related laboratory abnormality (except lymphopenia, neutrophil count, AST, ALT, or total bilirubin):
  - Grade 3 lymphopenia does not require a dose delay
  - Should not be given if neutrophil counts are <1500 cells/mm^3
  - May be withheld at the discretion of the Investigator when total bilirubin > ULN and must be withheld when total bilirubin is ≥ 1.5 × ULN, and should not be given if AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN
- Any Grade 3 skin drug-related AE
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study medication.

Subsequent dose reductions may be required per the dose reduction and modification guidelines below (Table 6.5).

Subjects receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the Investigator.

Dose Reduction and Modification Guidelines

Up to 2 dose reductions will be permitted for subjects receiving docetaxel (Table 6.5). Once the dose of docetaxel is reduced, no dose re-escalation will be permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurs, the subject will be withdrawn from study treatment.

Table 6.5: Dose Reduction Levels for Docetaxel

Starting Dose[a]	First Dose Reduction[b]	Second Dose Reduction[b]
75 mg/m^2	55 mg/m^2 or Per Investigator	Per Investigator

[a] The starting dose for all subjects randomized to docetaxel treatment arm is 75 mg/m^2.
[b] All dose reductions should be made in accordance with the locally approved docetaxel label and/or local clinical practice guidelines for docetaxel.

Dose Delays and Modification – Docetaxel Toxicity Management Guidelines

Subjects dosed initially at 75 mg/m^2 who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week despite growth factor support, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity according to the dose delay aforementioned guidelines. Once the toxicity resolves, docetaxel treatment may resume at 55 mg/m^2 for the remainder of the study. One additional dose reduction or additional dose delays based on toxicity are at the discretion of the Investigator per local guidelines (Table 6.5).

Note: All dose reductions should be made per Investigator in accordance with the locally approved docetaxel label and/or local clinical practice guidelines for docetaxel.

Subjects who develop ≥Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.[13]

Investigators should consult the locally approved manufacturer's instructions for additional information on docetaxel dose adjustments due to toxicities.

In East Asian countries, dose reductions after the starting dose of 75 mg/m^2 may be considered per Investigator discretion depending on the patient's condition and should be made in accordance with the locally approved docetaxel label and/or local clinical practice for docetaxel usage.

Criteria to resume treatment with docetaxel

Subjects may resume treatment with docetaxel when the drug-related AE(s) resolve(s) to Grade ≤1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with decreased neutrophil counts, or with elevations in total bilirubin, AST or ALT must meet criteria for resuming treatment according to the boxed warning contained within the docetaxel manufacturer's instructions.
  - Subjects with concurrent Grade 2 AST/ALT > 3 × ULN AND total bilirubin >2 × ULN should have treatment permanently discontinued.

When resuming docetaxel treatment, please follow the dose reduction recommendations noted previously.

Docetaxel should be discontinued for the following:

- Cystoid macular edema (CME) has been reported in patients treated with docetaxel. If CME is diagnosed, docetaxel treatment should be discontinued, and appropriate treatment initiated.
- Severe hypersensitivity reactions require immediate discontinuation of docetaxel and initiation of appropriate therapy.
- Severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis have been reported with docetaxel treatment. Subjects should be informed about the signs and symptoms of serious skin manifestations and closely monitored. If signs and symptoms suggestive of these reactions appear, discontinuation of docetaxel should be considered.

6.6. 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 randomization 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 the eCRF until the end of the Safety Follow-Up Period. Concomitant medications administered as treatment for drug-related AESIs should be recorded until either event resolution, end of study, study termination, withdrawal of consent, or subject death.

Prohibited Therapies/Products

With the exception of medications that are under investigation in the study (eg, standard of care, 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 hormone replacement therapy] is acceptable).
- 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.

Restricted Therapies/Products

- The use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited.
- The concomitant use of docetaxel with strong cytochrome P450 (CYP) 3A4 inhibitors should be avoided. If the concomitant use of a strong CYP3A4 inhibitor cannot be avoided, a close clinical surveillance is warranted, and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor.
- 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 (BCRP), and multidrug resistance-associated protein (MRP) 1. For a list of inhibitor drugs, refer to the US Food and Drug Administration Table of Substrates, Inhibitors and Inducers[25] or locally available sources.
- Live vaccines are not recommended during the study, except for emergency use per Investigator's discretion. **In Czech Republic only, please see Section 10.9.1 for text applicable to sites in Czech Republic.**

Permitted Therapies/Products

- Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator.
  - Subjects receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion 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 may be used per Investigator's discretion and/or institutional guidelines.
- Based on the currently available clinical safety data, it is highly recommended that subjects receive prophylactic anti-emetic agents prior to infusion of DS-1062a and on subsequent days as needed. Anti-emetics such as 5-hydroxytryptamine 3 antagonists (5-HT3), neurokinin-1 (NK-1) receptor antagonists, 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.
- 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 for the treatment of AEs or SAEs.
- Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (eg, albuterol) will be included in this study.

In Czech Republic only, please see Section 10.9.1 for modified text applicable to sites in Czech Republic.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Treatment

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

- Death
- Adverse event
- Disease progression
- Clinical progression
- Withdrawal by subject (**to discontinue study treatment**)
  - Note: this section only refers to withdrawal from treatment with DS-1062a or docetaxel, 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 Sponsor
- Other

After study treatment 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 treatment 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 radiographic disease progression will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by Investigator, death, lost to follow up, or withdrawal of consent.

Once radiographic disease progression is determined by the Investigator, 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression).

If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor.

The Sponsor will notify the site to stop sending further scans to the central vendor when BICR determines radiographic disease progression OR 7 months after the date of Investigator-assessed radiographic disease progression for the subject, whichever occurs first. If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. BICR results will not be shared with the site or Investigator.

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 Schedule of Events (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 Schedule of Events (Table 1.2).
- If subject has not discontinued due to disease progression, continue tumor assessments until disease progression, death, lost to follow-up, or withdrawal of consent, and survival as described in the Schedule of Events (Table 1.2).
- LTSFU evaluations will be performed to assess survival as described in the Schedule of Events (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 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.
- 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 (**discontinuation from the study**)
  - NOTE: this indicates that the subject withdraws consent and refuses to undergo any further study procedures. In such cases, subjects will be asked to be followed for long-term survival only (eg, study personnel contacting the subject by telephone). Subjects who agree to survival follow-up only will be documented by the site in the source document and in the eCRF.
- 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 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 refuse 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 refuses all of the aforementioned 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 refuses 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 refuse 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 Schedule of Events (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 s/he fails to 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 Schedule of Events in Table 1.1 for study procedures during the Screening Period and the first 3 cycles of 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, nondrug 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, and laboratory assessments) and compare against the eligibility criteria (Section 5.1 and Section 5.2). See Section 5.3 for rescreening.

Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing and with the date specified, 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 to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population. See Section 10.1.2 for additional details.

Qualifying Tumor Tissue Specimen

A pre-treatment biopsy procedure to collect fresh tumor tissue from the primary or metastatic lesions performed after termination of the most recent anticancer treatment is required for all subjects. Alternatively, tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing the informed consent that has a minimum of 10 × 4 micron sections or a tissue block equivalent of 10 × 4 micron sections (minimum of 10 slides at 4 microns; 20 slides preferred) may be substituted for the pre-treatment biopsy procedure during Screening. If a documented law or regulation prohibits (or does not approve) sample collection, then such samples will not be collected/submitted. Availability of previously collected tissue must be documented 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.

Results from the TROP2 testing or any other results 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 subject informed consent are acceptable, collection during the Screening Period using Sponsor-provided neutral-buffered formalin in kits is preferred to standardize tissue fixation for subsequent analysis.

Previously collected tissue samples from surgery, endoscopy, or core needle biopsy already collected and formalin-fixed paraffin-embedded may be used. Tissue samples can be formalin-fixed paraffin-embedded 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. The subject must have pathologically documented NSCLC that is Stage IIIB, IIIC or Stage IV NSCLC disease at the time of randomization (based on the American Joint Committee on Cancer, Eighth Edition).

Actionable Mutation Status

Subjects without actionable genomic alterations must have documented negative test results for EGFR and ALK genomic alterations to be randomized in the study. If test results for EGFR and ALK are not available, subjects are required to undergo testing performed locally for these genomic alterations. As ROS1, NTRK, and BRAF genomic alterations in NSCLC are rare, known status is not required for randomization and it will be assumed the tumor is wild type for these genes if unknown.

Subjects with actionable genomic alterations must have one or more documented known alterations in EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, or RET to be randomized 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 or docetaxel 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 required by local regulations or independent Institutional Review Board (IRB)/Ethics Committee (EC). HIV antibody test results can be used if performed within 120 days before enrollment.

Hepatitis Screening

HbsAg and HCV antibody testing must be performed prior to enrollment (if HCV antibody is positive, test HCV RNA). Subjects with known active hepatitis or uncontrolled hepatitis B and/or hepatitis C infection and who are positive for HBV or HCV 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 14 (Section 5.2). HBsAg and HCV antibody test results can be used if performed within 120 days before enrollment.

Patient-reported Outcomes

Patient-reported outcome (PRO) assessments will include:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)
- The EORTC Quality of Life Questionnaire Lung Cancer-13 (EORTC-QLQ-LC13; except questions 36 and 37)
- The EuroQol Questionnaire- 5 dimensions-5 levels (EQ-5D-5L)
- The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) 1-3; 24; 28-29; 51; 74

8.2. Randomization

After all Screening procedures are performed, results of Screening tests are available (ie, between the Screening visit and randomization), and subjects are confirmed to meet all eligibility criteria, eligible subjects will be randomized in a 1:1 ratio to DS-1062a 6.0 mg/kg or the control treatment, docetaxel 75 mg/m^2.

Randomization will be performed by an IRT. Randomization will be stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (US/Japan/Western Europe versus ROW). No crossover between study treatment arms will be allowed.

If subjects do not meet eligibility criteria on the day of randomization, they will not be randomized.

Subjects must receive the study drug within 3 days of randomization or on the same day as randomization.

For subjects randomized to receive DS-1062a treatment, the subject's weight at screening will be used as the baseline weight to calculate the initial dose of DS-1062a. If during the course of treatment, the subject's weight changes by ±10% of the baseline weight, the dose will be recalculated. After the recalculation, the recalculated subject's weight will be used as the new "baseline" weight. The site may follow local institutional policy for re-calculating dose based on weight changes less than 10%. The subject weight and BSA at each cycle will be documented in the eCRF.

For subjects randomized to receive docetaxel treatment, the subject's BSA must be calculated for the initial dose and then recalculated, and the docetaxel dose adapted accordingly, before each subsequent cycle. The subject weight and calculated BSA at each cycle will be documented in the eCRF. Investigators should consult the local manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional guidelines/procedures for dose calculation and administration of docetaxel.[19] For instructions for storage and docetaxel infusion preparation, consult the study Pharmacy Manual.

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 chest and abdomen CT or MRI scans, and 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 randomization. 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 prior to randomization. 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 randomization.

A complete set of the scans is required in this study (see Section 8.3). 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 by Investigator at baseline (Screening) and every 6 weeks (±7 days) from randomization independent of treatment cycle until radiographic disease progression, 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). Tumor assessments will continue until Investigator-assessed radiographic disease progression is determined, regardless of study treatment discontinuation or start of new anticancer therapy.

Subjects who discontinue study treatment for reasons other than radiographic disease progression will continue to undergo tumor assessments every 6 weeks during the Follow-up Period until radiographic disease progression as assessed by Investigator, death, lost to follow-up, or withdrawal of consent. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression).

Imaging timing should follow calendar days. In addition, radiographic tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). Tumor measurements will be performed as per RECIST v1.1 (see Section 10.4).

The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline will be used in the subsequent tumor assessments.

Bone scan (bone scintigraphy) or 18F-fluorodeoxyglucose positron emission tomography/CT is required at baseline. If bone metastases are present at baseline, subjects should have bone scan (bone scintigraphy) **or** 18 FDG PET/CT **or** CT/MRI every 6 weeks (±7 days) from randomization. Otherwise, follow-up bone imaging is required only if new bone metastases are suspected. When disease progression in the bone or new lesion in the bone is suspected, 18F FDG PET/CT should be used to determine disease progression.

When tumor assessment at a visit is performed over multiple days, the date of response (CR, PR, stable disease, Non-CR/nonprogressive disease [PD; subjects with non-target lesions only], or not evaluable) 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 unless increase in size has been observed after completion of radiation therapy.

BICR Radiographic Tumor Assessment

Radiographic imaging scans will be sent to a central imaging vendor for BICR assessment. Sites will send subject scans to the central imaging vendor after each tumor assessment visit. If BICR has not determined radiographic disease progression by the time of the 1 additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression, then sites will retrieve and send subject radiographic scans that are performed as part of local standard clinical practice to the central vendor during the subject's follow-up, or as part of subsequent therapy, including investigational agents, until BICR determines radiographic disease progression. The Sponsor will notify the site to stop sending further scans to the central vendor when BICR determines radiographic disease progression OR until 7 months after the date of Investigator-assessed radiographic disease progression for the subject, whichever occurs first. If BICR determines radiographic disease progression before the Investigator, sites will not be notified to stop sending scans until the Investigator determines radiographic disease progression. It is recommended that sites continue to follow a scanning interval frequency of every 6 weeks (±7 days) during the standard of practice follow-up of the subject as long as it is not interfering with the subject's standard of care. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline should be used in the subsequent tumor assessments. For further instructions, refer to the Imaging Site Manual which will be provided to the site.

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.

The results of BICR-assessed tumor response will be used for the primary analysis of PFS in this study (see Section 3).

Response Assessment

Assessment of response will be made by BICR and the Investigator based on RECIST v1.1 (Section 10.4). Tumor assessments will continue regardless of study treatment discontinuation or start of new anticancer therapy until radiographic disease progression is assessed by Investigator and by 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 EOS. Best response and the date of disease progression on subsequent therapies, as assessed by local standard clinical practice, will be recorded in the eCRF.

Disease Progression

Subjects who discontinue study treatment for reasons other than radiographic disease progression or subjects who start new anticancer treatment will continue to undergo tumor assessments every 6 weeks (±7 days) during the Follow-up Period until radiographic disease progression as assessed by Investigator, death, lost to follow up, or withdrawal of consent. One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression).

Best response and the date of disease progression on subsequent therapies, as assessed by local standard clinical practice, will be recorded in the eCRF regardless of subsequent anticancer treatments.

See BICR Radiographic Tumor Assessment for information on the collection of scans for BICR.

Survival Follow-up

All subjects should be followed for survival at least every 3 months after discontinuing study drug until EOS (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 course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, an IDMC review. 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 a previously recorded death event in the collection tool).

Assessment of Second Progression-free Survival (PFS2)

Following the first objective progression, subjects will have their progression status recorded every 3 months to assess PFS2 after start of subsequent therapy. A subject's progression status is defined according to the local standard clinical practice and may involve any of: objective radiographic (preferred) progression, symptomatic progression, or other. Scans will be performed according to the local practice and formal RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and Investigator opinion of progression status at each assessment will be recorded in the eCRF.

8.4. Safety Assessments

8.4.1. Adverse Event

Method to Detect Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Section 10.5. AEs may be directly observed, reported spontaneously by the subject, or collected 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, are considered related to the study drug or study procedures, or that caused the subject to discontinue DS-1062a or docetaxel.

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 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 AE eCRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow up.

If a tumor biopsy is needed, report any SAEs directly related to tissue Screening procedure (ie, tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue Screening.

All events of ILD regardless of severity or seriousness will be followed until resolution including after study treatment discontinuation.

All non-serious AEs occurring after the subject has taken the first dose of DS-1062a or docetaxel until 28 days (+7 days) after the last dose of DS-1062a or docetaxel will be recorded on the AE eCRF.

Exacerbation of a pre-existing medical condition and symptom after the first dose of DS-1062a or docetaxel 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 the AE eCRF. All AEs (serious and non-serious) must be reported with the Investigator's assessment of seriousness, severity, and causality to DS-1062a or docetaxel.

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 (eg, 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 Event 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 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 described by the Event Adjudication Site Manual).
- Grade ≥ 3 IRR events.
- Grade ≥ 3 ocular surface toxicity events.
- Grade ≥ 2 keratitis events (including keratitis, punctate keratitis, and ulcerative keratitis)

Additional relevant information regarding the AESIs for DS-1062a is to be collected through the targeted questionnaires (TQs) within the clinical study database (eCRF):

- For broad surveillance of ILD/pneumonitis, a pre-defined 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 are collected via TQs of pulmonary toxicity.
- For broad surveillance of IRR, selected PTs from Hypersensitivity standardized MedDRA queries (SMQ) and narrow and selected broad PTs from Anaphylactic Reaction (SMQ) are included for enhanced data collections; additional data for these ≥ Grade 3 AEs will be collected via TQs of IRR.
- 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.
- 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.
- 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

SOC; additional data for these AEs regardless of CTCAE grading will be collected via TQs of ocular surface toxicity.

Overdose is always serious. By definition, an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including DS-1062a or docetaxel dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the eCRF.

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: Sites must complete the eCRF or Serious Adverse Event Report Form within 24 hours of awareness. In the event that the eCRF is unavailable, SAEs should be reported 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 in the site's country or email address. Once EDC becomes available, sites will enter SAEs reported on the Serious Adverse Event Report Form into the eCRF as soon as possible. Sites should refer to the eCRF Completion Guide for additional instructions.

Sites should call the local SAE Hotline (see the Investigator site file provided to the sites) or the 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.[18]

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 must be followed and addressed promptly. The Investigator will submit any updated SAE data to the Sponsor/CRO within 24 hours of receipt of the information.

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 for DS-1062a or docetaxel must be reported to the Sponsor within 24 hours of awareness. Overdose will be reported via Serious Adverse Event Report /Overdose Form or eCRF.

An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, 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 DS-1062a clinical program, based on the available pre-clinical data, review of the cumulative literature, reported toxicities for drugs with similar monoclonal antibody and payload of DS-1062a, 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.

These events should be reported in the eCRF, and if applicable (see Section 8.4.1.1), within 24 hours of the Investigator's awareness of the event. Additional relevant information regarding these AESIs regardless of seriousness will be collected through eCRF targeted questionnaires within the clinical study database, which includes the completion of TQs for any grades of ILD/pneumonitis; for ≥ Grade 3 of IRR; for any grades of oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis; and any grade of ocular surface toxicity.

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

The AESIs for the DS-1062a clinical program are presented below:

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 AC, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs with a similar monoclonal antibody and/or payload as DS-1062a. Please refer to the most recent IB for preliminary clinical study data.[18]

Management Guidance:

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 the

designated "Other Non-Laboratory Adverse Events" dose modification section of the study protocol.

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be delayed pending further evaluations. Evaluations should include high-resolution CT, pulmonologist consultation (infectious disease consultation as clinically indicated), bronchoscopy and bronchoalveolar lavage (BAL) if clinically indicated and feasible, pulmonary function tests (including FVC 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, and 1 blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible). Unless prohibited by local restrictions, if the subject consents and to the extent it is available, a tissue sample from a bronchoalveolar lavage or lung biopsy may be collected for histopathological, immuno-profiling, biomarker, or other study analysis relating to the safety of DS-1062a.

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of the study protocol.

All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

An autopsy in cases of Grade 5 ILD/pneumonitis is encouraged.

Interstitial Lung Disease Adjudication Committee

An independent ILD 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, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data collection will be triggered based on a pre-defined list of preferred terms eligible for adjudication as described in the Event Adjudication Site Manual.

Infusion-related Reaction

IRR is an identified risk. A Grade 3 IRR was reported and was assessed by an external consultant as anaphylaxis. A targeted questionnaire for ≥ Grade 3 IRR will be available as an eCRF to collect relevant additional information for these potential cases. **All Grade ≥3 events of infusion-related reaction, regardless of seriousness, must be reported in the eCRF within 24 hours.** Refer to the current IB for a summary of preliminary clinical study data.[18]

Management Guidance:

Premedication is required prior to any dose of DS-1062a and must include antihistamines and acetaminophen with or without glucocorticoids. If there are any signs or symptoms of a Grade 1 or Grade 2 IRR, the infusion of DS-1062a must be either slowed down or interrupted based on severity of the infusion-related reaction. If the IRR is Grade 3 or Grade 4, or if there are any signs of anaphylaxis, the infusion of DS-1062a must be discontinued.

Oral Mucositis/Stomatitis

Oral mucositis/stomatitis AEs are considered as identified risks and AESIs associated with DS-1062a treatment.

Subjects 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 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:

1. Dexamethasone mouthwash formulated at 0.5 mg/5 mL. If not available, then use→
2. Dexamethasone mouthwash compounded at site/locally. If not available, then use→
3. Other steroid-based mouthwash available at site/locally. If not available, then use→
4. Non-steroid mouthwash or other local mouthwash

Recommendations for preventing and treating oral mucositis/stomatitis are available in the Schedules of Events (Table 1.1 and Table 1.2), study drug administration guidelines (Section 6.2.1), and Toxicity Management Guidelines (Table 6.4) sections of the protocol.

Mucosal Inflammation Other Than Oral Mucositis/Stomatitis

Mucosal inflammation AEs are considered as identified risks associated with DS-1062a treatment. The category of "mucosal inflammation other than oral mucositis/stomatitis" is also an identified risk and an AESI.

Ocular Surface Toxicity

Ocular surface toxicity (eg, dry eye, keratitis) is considered an AESI associated with DS-1062a. Dry eye is considered as an identified risk and keratitis as a potential risk within this AESI. Subjects should be advised to use artificial tears daily and to avoid the use of contact lenses.

Recommendations for preventing and treating ocular surface toxicity are available in the Schedule of Events (Table 1.1 and Table 1.2), Toxicity Management Guidelines (Table 6.4), and Section 8.4.1.1 of the protocol.

8.4.1.3. Hepatic Events

Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria are defined as an elevated (ALT or AST) ≥ 3 × ULN and an elevated TBL ≥ 2 × ULN that may occur either at different time points within a 3-week interval or simultaneously at any time during this study. A targeted questionnaire (TQ) is built within the eCRF to collect relevant additional information for these potential cases. If the subject discontinues DS-1062a due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 10.2 of the protocol 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 or within 6 months of the last dose of docetaxel. 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 or within 6 months of the last dose of docetaxel.

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 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, post-partum 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.

Women must not get pregnant, breastfeed, or donate/retrieve ova during the study and for at least 7 months after stopping DS-1062a or for at least 6 months after stopping docetaxel.

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 randomization) must be performed. Within 72 hours before Cycle 1 Day 1, a pregnancy test (urine/serum per institutional procedures) 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 72 hours before infusion at each cycle, at the 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 Schedules of Events by the local laboratory (Table 1.1 and Table 1.2). Urinalysis and coagulation will be performed at Screening and as clinically indicated during the study. 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 CRF 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 Schedules of Events (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 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 Schedules of Events (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 in sitting position if recumbent position is not possible, for 5 minutes or more and prior to laboratory draws.

Pulse Oximetry

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, within 7 days before randomization, triplicate ECGs are required in close succession, no more than 5 minutes apart, and after at least 5 minutes of quiet rest in the supine position.

Single ECGs will be performed per the Schedules of Events (Table 1.1 and Table 1.2) and as clinically indicated for all other 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 visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining will be performed at screening, as clinically indicated, and at the end of treatment (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.

The ophthalmologic assessment must be performed as per the Schedules of Events (Table 1.1 and Table 1.2) and must include a visual acuity test, intraocular pressure test, slit-lamp examination, fundoscopy, and fluorescein staining. Consider obtaining an ophthalmological assessment to ensure accurate diagnosis, event grading, appropriate treatment, and event resolution, as appropriate. 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 (Table 6.4).

Patient-reported Outcomes

PROs will be directly reported by the subject. PROs will be collected electronically on site at baseline and at home thereafter. Subjects will be able to use apps on their own smartphones or personal electronic devices to access the electronic PRO questionnaires. Paper PRO questionnaires may be made available under special circumstances to be approved by the Sponsor. However, electronic PROs are the preferred method. A study specific user manual for Monitors, site staff, and the project team will be provided which will include details on how to access the PRO questionnaires from the subject's personal electronic device(s). PRO questionnaires at site visits will be evaluated in the following order: EORTC-QLQ-LC13, EORTC-QLQ-C30, EQ-5D. PRO-CTCAE items will be evaluated in the order they appear in the PRO-CTCAE item bank (1-3; 24; 28-29; 51; 74).

The following PROs will be performed:

- EORTC-QLQ-LC13: 13-item lung cancer-specific questionnaire module except questions 36 and 37
- EORTC-QLQ-C30: assessment of the quality of life of cancer patients
- EQ-5D-5L: standardized instrument for measuring generic health status required for health technology assessments
- PRO-CTCAE: assessment of the impact of AEs on quality of life of cancer patients

PROs must be performed as per the Schedules of Events (Table 1.1 and Table 1.2). To allow for treatment delays between cycles, the timing of the questionnaires is updated in real time according to treatment schedules and changes that may occur.

8.5. Pharmacokinetic Assessments

Blood samples for PK analyses of DS-1062a will be obtained from subjects receiving DS-1062a based on the Schedules of Events (Table 1.1 and Table 1.2) at time points outlined in Table 8.1. In addition, a blood sample for PK will be collected as soon as ILD/pneumonitis is suspected in a subject. 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 ADC, 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 20 subjects receiving to-be-marketed material of DS-1062a.
- Sparse PK cohort: All other subjects receiving DS-1062a will undergo sparse PK sampling.

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

Table 8.1: Pharmacokinetic Sampling Collection

Cycles	Days	Full Sampling Pharmacokinetic Cohort (only for 20 subjects receiving to-be-marketed material)	Sparse Sampling Pharmacokinetic Cohort
1	1	Pre-dose: Within 8 hours before infusion Post-dose: • 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	Pre-dose: Within 8 hours before infusion Post-dose: • Within 1 hour after end of infusion • 5 hours (±1 hour) after infusion start
	2	24 hours (±2 hours) after Day 1 infusion start	None
	4	3 days (±1 day) after Day 1 infusion start	None
	8	7 days (±1 day) after Day 1 infusion start	
	15	14 days (±1 day) after Day 1 infusion start	None
2	**1 (± 2)**	Pre-dose: Within 8 hours before infusion Post-dose: Within 1 hour after end of infusion	Pre-dose: Within 8 hours before infusion Post-dose: Within 30 minutes after end of infusion
3	1 (± 2)	Pre-dose: Within 8 hours before infusion Post-dose: Within 1 hour after end of infusion	Pre-dose: Within 8 hours before infusion
4	1 (± 2)	Pre-dose: Within 8 hours before infusion Post-dose: Within 1 hour after end of infusion	
6	1 (± 2)	Pre-dose: Within 8 hours before infusion Post-dose: Within 1 hour after end of infusion	
8	1 (± 2)	Pre-dose: Within 8 hours before infusion Post-dose: Within 1 hour after end of infusion	

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.

See Section 9.5.3 for a description of the planned analyses of PK data.

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 Companion Diagnostics

Collected samples may be assessed for the purpose of analytical validation and bridging of potential in vitro diagnostics such as TROP2 immunohistochemistry. The output of the study will determine the ability of the companion diagnostic to classify subjects as positive for the biomarker with a proposed threshold in relation to clinical efficacy. Data obtained from the biomarker analysis may be used to perform clinical efficacy analyses as described in the SAP.

8.6.1. Exploratory Biomarker Assessments in Blood Samples

Cell-free DNA 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 or control therapy, docetaxel. 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 (Table 1.1 and Table 1.2).

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

Plasma and serum will be collected at the time points specified in the Schedules of Events (Table 1.1 and Table 1.2) and at the time of suspected ILD onset. Samples may be analyzed to assess biomarkers predictive of ILD.

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

A whole blood sample will be collected at the time point specified at Cycle 1 Day 1 to serve as a control for whole exome sequence/whole genome sequence tissue analysis.

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 sample for biomarker research is required and will be collected from all subjects in this study as specified in Table 1.1:

- Pre-treatment biopsy procedure to collect fresh tumor tissue before study entry (see Inclusion Criterion 7). If available, tumor tissue previously retrieved from a biopsy procedure performed within 2 years prior to the subject signing informed consent 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 pre-treatment biopsy procedure during Screening.

In addition to the biomarkers specified, exploratory biomarker research may be conducted on any samples.

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 previously, exploratory research may be conducted on these collected samples. Biomarker assessments may include but are not limited to immunohistochemistry 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) after the finalization of the clinical study report (CSR) for the study 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 immunohistochemistry assay on all tumor biopsy samples collected during this study. Results from the TROP2 testing of the tumor biopsy samples will not be used to determine eligibility for the study.

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 pre-dose (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.

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 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 from subjects receiving DS-1062a 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 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 primary completion date of the PFS endpoint is the date when the pre-specified number of PFS events as assessed by BICR is reached. This date is used as the DCO for the primary analysis of PFS.

The primary completion date of OS endpoint is the date when the pre-specified number of deaths (413 OS events) is reached and at least 4 months after the last subject has been randomized. This date is used as the DCO for the primary analysis of overall survival.

All subjects still on study treatment and continuing to derive benefit at the primary completion date of PFS or OS will continue to follow the study Schedules of Events until the overall EOS is reached.

The overall EOS will occur after all subjects have discontinued 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 at the overall EOS.

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. For efficacy, the last assessment on or before randomization will be used as the baseline value. For safety, the last assessment on or before the date of the firs dose will be used as the baseline value. In general, missing data will not be imputed for the purpose of data analysis, unless otherwise specified.

Data will be summarized by treatment arm.

China Extension Study

Subjects from China randomized after global enrollment ends will not be included in the planned analyses of the global study. Details of the analyses of the data for these subjects will be provided in the SAP.

9.2. Statistical Hypothesis

The primary objective of the study is to compare the efficacy of DS-1062a with that of docetaxel and demonstrate superiority in terms of either PFS or OS for subjects with NSCLC with or without actionable genomic alterations previously treated with platinum-based chemotherapy and at least one prior line of therapy as detailed in Section 5.

PFS as assessed by BICR per RECIST 1.1 and OS are the 2 independent primary endpoints of the study. The study will be considered positive if the hypothesis test for either of the 2 primary endpoints is successful.

The following statistical hypotheses will be tested:

- null hypothesis (H_{01}): hazard ratio (HR) of PFS = 1 versus alternative hypothesis (H_{11}): hazard ratio of PFS ≠ 1;
- null hypothesis (H_{02}): hazard ratio of OS = 1 versus alternative hypothesis (H_{12}): HR of OS ≠ 1

Multiplicity adjustment is specified in Section 9.5.1.4.

9.3. Sample Size Determination

A total of approximately 590 subjects will be randomized to the DS-1062a arm or the docetaxel arm in a 1:1 ratio (295/arm), stratified by documented actionable genomic alteration (present versus absent), histology (squamous versus nonsquamous), most immediate prior therapy included anti-PD-1/anti-PD-L1 immunotherapy (yes versus no) and geographical region (US/ Japan/Western Europe versus ROW). A minimum of 15% of the total study population will comprise subjects with actionable genomic alterations.

For the primary analysis of PFS, approximately 425 PFS events by BICR assessment will be required to have approximately 97% power to detect a hazard ratio of 0.64 at a 2-sided significance level of 0.008, which corresponds to an improvement of 2.1 months in median PFS from 3.8 months in the docetaxel arm to 5.9 months in the DS-1062a arm.

For the primary analysis of OS, approximately 413 OS events will be required to have at least 90% power to detect a hazard ratio of 0.72 at 2-sided significance level of 0.042, which corresponds to an improvement of 3.1 months in median OS from 8 months in the docetaxel arm to 11.1 months in the DS-1062a arm.

Assuming an exponential distribution of OS time, a ramp-up period of 13 months and 48 subjects per month afterwards, the study needs a total of approximately 590 subjects (295 per arm), over an enrollment period of approximately 19 months. The primary analysis for PFS as assessed by BICR will be performed when approximately 425 PFS events have been reached, and at least 4 months after the last subject has been randomized. The total of approximately 413 OS events would be achieved by approximately 33 months for the primary analysis of OS.

9.4. Population for Analysis Sets

Analysis Sets

- The **Safety Analysis Set** will include all randomized subjects who received at least 1 dose of study drug. Subjects will be analyzed according to the study treatment received, where treatment received is the randomized study drug if the subject took at least 1 dose of the randomized study drug; otherwise, the first treatment received will be used.

- The **Full Analysis Set** (FAS**)** will include all subjects who have been randomized to the study. Following the Intent-to-Treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization process. FAS will be the primary analysis set for all efficacy analysis.
- 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.
- The **Per-protocol Analysis Set** (PPS) will include all subjects in FAS who did not have major protocol violations. Details about the major protocol deviations will be specified in the SAP.

The analysis sets defined in this section are for analyses of the global study.

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

This study has 2 independent primary endpoints of OS and PFS as assessed by BICR. The study will be considered positive if the hypothesis test for either one of these primary endpoints is successful.

PFS is defined as the time from randomization to the earlier of the dates of the first radiographic disease progression or death due to any cause. OS is defined as the time from randomization to death due to any cause. Detailed censoring rules for PFS and OS will be specified in the SAP. PFS primary analysis will only be conducted after the enrollment has been completed.

The primary efficacy analysis of PFS and OS will compare the DS-1062a and docetaxel arms, using a stratified log-rank test stratified by the randomization stratification factors.

PFS and OS will be summarized and graphically presented using the Kaplan-Meier method by treatment arm with median and corresponding confidence interval (CI) for the median using the Brookmeyer and Crowley method. In addition, the event-free probability at different time points (eg, 3, 6, 9, 12 months) will be estimated with corresponding CIs using the Greenwood formula for variance derivation.

The stratified cox regression model, stratified by the randomization stratification factors, will be fitted to estimate the hazard ratio of PFS and OS between the treatment versus the control arm (docetaxel) and the corresponding CI.

9.5.1.2. Secondary Efficacy Analyses

There is no key secondary endpoint of the study.

Secondary efficacy endpoints include: PFS as assessed by Investigator, and ORR, DoR, disease control rate (DCR), and TTR each as assessed by BICR and by Investigator per RECIST v1.1, and PROs, including TTD in any of the 3 symptoms, chest pain, cough, or dyspnea.

A brief description of each endpoint is as follows:

- PFS is defined as the time from randomization to the earlier of the dates of the first radiographic disease progression or death due to any cause.
- ORR is defined as the proportion of subjects who achieved a best overall response (BOR) of CR or PR.
- DoR is defined as the time from the date of the first documentation of response (CR or PR) to the date of the first documentation of radiographic disease progression or death due to any cause, whichever occurs first. Duration of response will be measured for responding subjects (CR or PR) only. Detailed censoring rules for DoR will be specified in the SAP.
- DCR is defined as the proportion of subjects who achieved a BOR of CR, PR, or SD.
- TTR is defined as the time from the date of randomization to the date of the first documentation of response (CR or PR) in responding subjects.

PFS as assessed by Investigator will be analyzed in a similar manner as PFS by BICR.

The estimate of ORR and its 2-sided 95% exact (Clopper-Pearson[26]) CI will be provided by treatment arm.

DoR will be analyzed in a similar manner as the primary endpoints, except that a hazard ratio will not be generated for DoR.

The estimate of DCR and its 2-sided 95% exact (Clopper-Pearson[26]) CI will be provided by treatment arm.

TTR will be summarized descriptively.

Subgroup analyses will be conducted for PFS, OS, ORR, and DoR based on randomization period (before and after protocol version 4.0 to include subjects with actionable genomic alterations) as well as by presence of actionable genomic alterations (present versus absent).

9.5.1.2.1. Patient-Reported Outcomes

PRO assessments in the study will include EORTC-QLQ-C30, EORTC-QLQ-LC13 (except questions 36 and 37), EQ-5D-5L, and PRO-CTCAE (1-3; 24; 28-29; 51; 74).

Time to deterioration (TTD) in any of the 3 symptoms, cough, chest pain, or dyspnea is defined as the time from randomization to the first clinically meaningful symptom deterioration in any of

the 3 symptoms, cough, chest pain, or dyspnea. Clinically meaningful symptom deterioration is defined as an increase of ≥10 points in severity in the linearly transformed scale, which is subsequently confirmed by a second increase of ≥10 points for the same symptom at the next scheduled assessment or death within 21 days after the ≥10-point increase.

The Kaplan-Meier method will be used to estimate the distribution of TTD in any of the 3 symptoms, cough, chest pain, or dyspnea. The median TTD along with the 95% CI will be presented by treatment arm. A stratified log-rank test stratified by the randomization stratification factors will be used to compare the 2 treatment arms.

Descriptive analysis will be conducted on PRO score, including subjects in the FAS without a missing baseline PRO score and at least 1 post-baseline score.

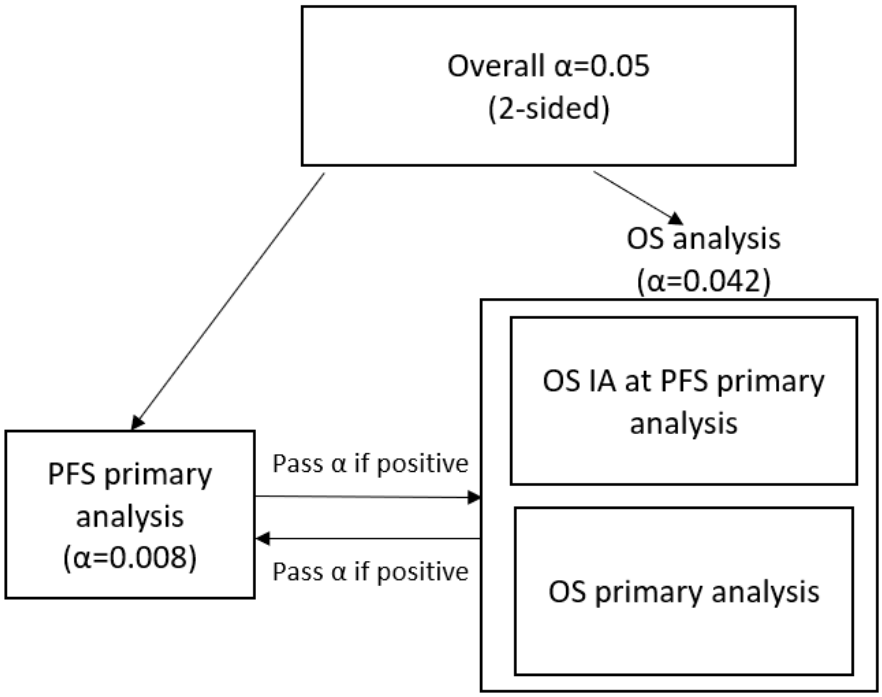
All PRO instruments will be scored according to their corresponding scoring manual.

9.5.1.3. Exploratory Efficacy Analyses

The exploratory efficacy endpoint PFS2 will be analyzed in a similar manner as PFS. Additional exploratory efficacy analyses, such as subgroup analyses, will be defined in the SAP.

9.5.1.4. Multiplicity Adjustment

The overall type I error rate is controlled at 2-sided 0.05 for the entire study. PFS will be tested under 2-sided alpha of 0.008, and OS will be tested under 2-sided alpha of 0.042. Alpha is subject to rollover between PFS and OS. For example, the overall alpha for OS will be 2-sided 0.05 if PFS is positive, and 2-sided 0.042 if PFS is negative. A graphic presentation of the testing process and alpha splitting is shown below.



IA = interim analysis; OS = overall survival; PFS = progression-free survival.

An IA of OS will be performed at the time of primary PFS analysis. The nominal significance levels for the interim and final analyses of OS will be determined using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. The overall significance level for OS will be preserved at 0.042 (2 sided). Please see Section 9.6 for more details on the IA.

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 and subjects will be analyzed according to their actual treatment received.

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 date of study treatment minus 1 day.
- 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

AEs 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 (ie, 28 days +7 days) since date of last dose of study treatment (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 system organ class (SOC) and preferred term. Additional summaries will be provided by the worst NCI-CTCAE grade, relationship to the study treatment (ie, regardless of relationship to study drug, study drug related), and seriousness. Treatment-emergent AEs associated with study drug reduction, infusion interruption, or 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.

AESIs 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 by treatment group the 2-way frequency tabulation for baseline and the worst on-treatment value according to the NCI-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 greater 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

Pharmacokinetics

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.

Full PK samples will be collected in approximately 20 subjects who receive the to-be-marketed drug product. The following PK parameters will be calculated for each subject in the full PK sampling cohort using non-compartmental analysis of concentration time data of DS-1062a, total anti-TROP2 antibody, and MAAA-1181a: maximum plasma concentration, time to reach maximum plasma concentration, area under the plasma concentration-time curve up to the last quantifiable time, area under the plasma concentration-time curve during dosing interval, and if data permit, area under the plasma concentration-time curve up to infinity, t1/2, total body clearance, volume of distribution at steady state, volume of distribution based on the terminal

phase, and elimination rate constant associated with the terminal phase. These parameters will be summarized using descriptive statistics. Additional analyses will be defined in the SAP.

Population PK and exposure-response (ER) analyses will be performed to characterize the relationships of dose, exposure, efficacy, and safety endpoints. The effects of intrinsic (eg, body weight) and extrinsic covariates on PK and ER relationship will be evaluated. The results of the population PK and ER analyses will be reported separately from the CSR.

Immunogenicity

Immunogenicity will be assessed using Safety Analysis Set unless specified otherwise.

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 will also be reported, which is the proportion of subjects having treatment-emergent ADA during the study period. Treatment-emergent ADA 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), and 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.

Biomarkers

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

9.6. Interim Analyses

No IA is planned for PFS. The primary analysis for PFS as assessed by BICR will be performed when approximately 425 PFS events have been reached, and at least 4 months after the last subject has been randomized.

OS will also be analyzed at the primary analysis of PFS (OS IA). The overall 2-sided alpha is to be controlled at 0.042 for the interim OS analysis and final OS analysis using the Lan-DeMets alpha spending function with an O'Brien-Fleming stopping boundary. The boundaries used at the interim and final OS analyses will be calculated based on the actual number of observed deaths. It is projected that approximately 293 deaths will be observed at the IA, ie, 71% of information fraction (IF, ie, 293 out of the target 413 OS events). The study may be stopped at OS IA if the pre-specified superiority boundary is crossed.

If the study is not stopped at OS IA, then the study will continue until the required number of deaths (413 OS events) is reached for the primary analysis of OS at approximately 33 months after the first subject is randomized.

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 before enrollment of the first subject. In all cases, the coordinating Investigator must be chosen before 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 [R2] for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive and/or;
- US Food and Drug Administration 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/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 may be obtained from subjects if required 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.

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 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 (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 visit 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, standard operating procedures, 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 subject identification.

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. SAEs 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 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.

Data Monitoring Committee

An independent data monitoring committee (DMC) will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring the progress and results. The DMC will comprise qualified physicians and scientists who are not Investigators in the study and not otherwise directly associated with the Sponsor.

The DMC will periodically review unblinded safety data in this study. The details about the reviews of the study data and other DMC processes will be described in the DMC charter. The DMC may recommend modification of the study protocol or study based on pre-specified rules described in the DMC charter.

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.

In order to ensure compliance with the public disclosure policies and the International Council of Medical Journal Editors 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) and 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 standard of care 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 ALT ALP AST bilirubin (total) BUN Urea (if BUN is not available) calcium chloride	creatinine cholesterol (total) creatine phosphokinase lactate dehydrogenase magnesium potassium protein (total) sodium uric acid
Hematology	hemoglobin hematocrit platelet count red blood cell count WBC count	differential WBC count: basophils eosinophils lymphocytes monocytes neutrophils

Test	Analytes	
Coagulation	prothrombin time INR partial thromboplastin time and/or activated partial thromboplastin time	
Urinalysis (abbreviated)	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 • red blood cells • white blood cells • bacteria • crystals • other	
Pregnancy test (serum or urine)		

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; WBC = white blood cell

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):[27]

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 New York Heart Association classification is summarized in Table 10.2.[28]

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.[29]

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(6):649-55.

10.3.4. Highly Effective Contraception

Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid 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 or for at least 6 months for males and females after the last dose of docetaxel. Methods considered to be highly effective contraception include:[30]

- 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 or for at least 6 months for males and females after the last dose of docetaxel. 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 v1.1 guidelines.[31] 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, positron emission tomography (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 target lesions.

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 randomization.

- **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 target lesions (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 new lesions is also considered progression).
  - **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest 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 (NTLs)**
  - **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 one 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 new lesions 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 (NLs)**

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 not 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 scan.

When subjects have non-measurable, therefore non-target, disease only, Table 10.5 is to be used.

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

Target Lesions	Non-target Lesions	New Lesions	Overall 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: Overall Response: Subjects with Non-target Disease Only

Non-target Lesions	New Lesions	Overall 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 not evaluable (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: Overall 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, PD
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, PD
NE	NE	NE

CR = complete response; PR = partial response; SD = stable disease; NE = not evaluable; PD = progressive 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 subject 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 Can. 2009:45(2);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 new lesions; 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) until Investigator-assessed radiographic disease progression as specified in the Schedules of Events or sooner if clinically indicated (see Table 1.1 and Table 1.2). One additional tumor assessment performed at 6 weeks (±7 days) after Investigator-assessed radiographic disease progression will also be required (if BICR has not determined radiographic disease progression). It is recommended that sites continue to follow a scanning interval frequency of every 6 weeks (±7 days) during the standard of practice follow-up of the subject as long as it is not interfering with the subject's standard of care. 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 (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 randomization.

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 standard of care 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 6: 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.[32]

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, diarrhoea, 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.[32] 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 v5.0. 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 temporarily stopped.
- Dose Delayed: The study drug was delayed for 1 or more cycles.
- 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 7: Key Data Analysis Requirements

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

BICR = blinded independent central review DCO = data cutoff; eCRF = electronic Case Report Form; ILD = interstitial lung disease; PF = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TROP2 = trophoblast cell surface protein 2

10.7. Appendix 8: Instructions Related to Coronavirus Disease 2019 (COVID-19)

Due to the potential impact of Coronavirus disease 2019 (COVID-19, due to severe acute 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 or docetaxel in this study. All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Dose modifications will be based on the worst NCI-CTCAE grade. **Use NCI-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 or docetaxel and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 6.4.
- 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 transcriptase 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)	**DS-1062a**	**Docetaxel**
Grade 1	Resume study drug at the same dose[a]	Follow local institutional policy/ practice/regulations for the management of subjects with COVID-19 receiving docetaxel.
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; NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events

[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.

Additional considerations

In addition to the recommendations outlined in Table 10.7, Investigators may consider dose modifications of the study treatment 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 6.4).

Dosing of DS-1062a or docetaxel 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 or 84 days from the last infusion, the subject must discontinue treatment with DS-1062a or docetaxel.

Before resuming study treatment with DS-1062a or docetaxel, a tumor assessment should be performed if the subject's last scheduled tumor assessment was missed due to COVID-19.

Prior and Concomitant Medications - Prohibited Therapies/Products

- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment (Section 6.6). If chloroquine or hydroxychloroquine is administered, then a washout period of no less than 14 days is required before restarting study treatment.

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 reverse transcription-polymerase chain reaction is not available at the site, a sample kit may 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, 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, serum and nasopharyngeal swab/saliva 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.

10.8. Appendix 9: Patient-reported Outcomes

10.8.1. EORTC-QLQ-C30

The EORTC-QLQ-C30 is a 30-item questionnaire used in international clinical trials to evaluate the quality of life of cancer patients.

10.8.2. EORTC-QLQ-LC13

The EORTC-QLQ-LC13 is an extension to the EORTC-QLQ-C30 specific to lung cancer. Questions 36 and 37 will not be administered to avoid duplication with PRO-CTCAEs 1, 2, and 3.

10.8.3. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for measuring generic health status used in economic evaluation.

10.8.4. PRO-CTCAE 1-3; 24; 28-29; 51; 74

Eight items from the PRO-CTCAE will be administered to understand the impact of specific AEs on quality of life.

10.9. Appendix 10: Country-specific Protocol Text

This appendix lists protocol text that applies specifically to Czech Republic (Section 10.9.1) or Argentina (Section 10.9.2).

10.9.1. Czech Republic

The **bold text is applicable to the Czech Republic,** and ~~strikethrough text~~ is not applicable to the Czech Republic.

Section 5.1, Inclusion Criterion 16:

Treatment	**Washout Period**
Major surgery	≥3 weeks
Radiation therapy including palliative radiation to 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 tyrosine kinase inhibitors approved for the treatment of NSCLC-baseline computed tomography (CT) scan should be

Treatment	Washout Period
	completed after discontinuation of tyrosine kinase inhibitors.
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/Hydroxychloroquine	>14 days
Live vaccines	**>30 days**

Section 6.6 Prohibited Therapies/Products

Live vaccines. The subject must not be vaccinated with a live vaccine within 30 days before, during the Treatment Period, and for 90 days after the last dose of DS-1062a or docetaxel.

Restricted Therapies/Products

~~Live vaccines are not recommended during the study, except for emergency use per Investigator's discretion~~.

10.9.2. Argentina

The **bold text is** applicable to Argentina, and ~~strikethrough text~~ is not applicable to Argentina.

Section 5.1, Inclusion Criterion #4:

Has pathologically documented NSCLC:

- Has Stage IIB, IIIC, or Stage IV NSCLC disease at the time of randomization (based on the American Joint Committee on Cancer, Eighth Edition).
- **For inclusion into the study in Argentina, the patient must have** ~~has~~ documented negative test results for EGFR, ALK, **ROS 1, and BRAF** genomic alterations. If test results for EGFR, ALK, **ROS 1, and BRAF** are not available, subjects are required to undergo testing performed locally for these genomic alterations.
- ~~Has no unknown genomic alterations in ROS1, NTRK, BRAF, or other~~ **While the study is enrolling, if any new** actionable driver oncogenes with approved therapies (actionable genomic alteration) **become available in Argentina, then subject must have documented negative test results of such actionable genomic alterations as described above.**

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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
18F-FDG	18F-fluorodeoxyglucose
5-HT3	5-hydroxytryptamine 3 antagonists
α-PD-L1	anti-programmed cell death ligand 1
α-PD1	anti-programmed cell death 1
AC	Adjudication Committee
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AGA	actionable genomic alteration(s)
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-HBc	anti-hepatitis core antibody
Anti-HBs	anti-hepatitis B surface antibody
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
BCRP	breast cancer resistance protein
BI	before infusion
BICR	blinded independent central review
BOR	best objective response
BRAF	proto-oncogene B-raf
BSA	body surface area
BUN	blood urea nitrogen
cfDNA	cell-free deoxyribonucleic acid
CHF	congestive heart failure
CI	confidence interval
CL	total body clearance
Cmax	maximum plasma concentration
CME	cystoid macular edema

Abbreviation	Definition
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
CSR	clinical study report
CYP	cytochrome P450
Dato-Dxd	datopotamab deruxtecan
DCO	data cutoff
DCR	disease control rate
DMC	data monitoring committee
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
EOI	end of infusion
EORTC-QLQ-C30	The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC-QLQ-LC13	The EORTC Quality of Life Questionnaire Lung Cancer-13
EOS	End of study
EOT	end of treatment
EQ-5D-5L	EuroQol Questionnaire-5 dimensions-5 levels
ER	exposure-response
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FU	follow-up

Abbreviation	Definition
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
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
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
CCI	CCI
MAAA-1162a	drug linker
MAAA-1181a	released drug
MAAP-9001a	anti-TROP2 monoclonal antibody
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
MRP	multidrug resistance-associated protein
msec	millisecond
MTD	maximum tolerated dose

Abbreviation	Definition
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI - CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NE	not evaluable/not estimable
NK-1	neurokinin-1
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
NTRK	neurotrophic tyrosine receptor kinase
OATP	organic anion transporting polypeptide
OCP	oral care protocol
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFS2	second progression-free survival, ie, time from date of randomization to the first documented progression on next-line therapy or death due to any cause, whichever occurs first
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PRO-CTCAE	Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events
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
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1
ROW	rest of world

Abbreviation	Definition
RT-PCR	reverse transcriptase - polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small-cell lung cancer
SCR	Screening
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	system organ class
SoD	sum of diameters
SpO_2	peripheral oxygen saturation
t1/2	terminal elimination half-life
TEAE	treatment-emergent adverse event
TL	target lesion
Tmax	time to maximum plasma concentration
TQ	targeted questionnaire
TROP2	trophoblast cell surface protein 2
TTD	time to deterioration
TTR	time to response
ULN	upper limit of normal
US	United States
Vss	volume of distribution at steady state
Vz	volume of distribution based on the terminal phase
WBC	white blood cell
WES	whole-exome sequencing
WGS	whole-genome sequencing