First-in-human phase 1 study of DS-1062a in patients with advanced solid tumors

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INTRODUCTION

- DS-1062a is a trophoblast cell-surface antigen 2 (TROP2)–targeting antibody-drug conjugate with a novel topoisomerase I inhibitor (Exatecan derivative; DXd)
- DS-1062a binds to TROP2 on the cell surface, internalizes and releases DXd into the cytoplasm after enzymatic processing which inhibits topoisomerase I and leads to apoptosis of the target cells
- TROP2 is highly expressed in epithelial cancers, including lung cancer,[1] and is associated with poor survival[2-5]
- In preclinical studies, DS-1062a showed promising antitumor activity in xenograft mouse models[6,7]

PURPOSE

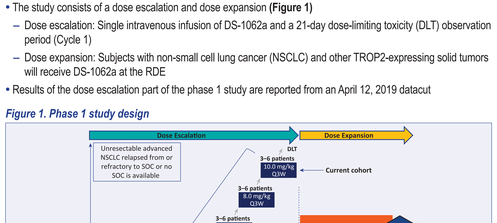
- To evaluate the safety and tolerability of DS-1062a from a phase 1 study and determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE) (clinicaltrials.gov identifier NCT03401385)

STUDY DESIGN AND METHODS

Overall Design

- Ongoing multicenter, open-label, multiple-dose, first-in-human phase 1 study of DS-1062a, enrolling in the United States and Japan
- The study consists of a dose escalation and dose expansion **(Figure 1)**
  - Dose escalation: Single intravenous infusion of DS-1062a and a 21-day dose-limiting toxicity (DLT) observation period (Cycle 1)
  - Dose expansion: Subjects with non-small cell lung cancer (NSCLC) and other TROP2-expressing solid tumors will receive DS-1062a at the RDE
- Results of the dose escalation part of the phase 1 study are reported from an April 12, 2019 datacut

Figure 1. Phase 1 study design



[a]RDE will be used for additional subjects for dose confirmation.
DLT, dose-limiting toxicity; NSCLC, non-small cell lung cancer; POC, proof-of-concept; Q3W, every 3 weeks; RDE, recommended dose for expansion; SOC, standard of care; TROP2, trophoblast cell-surface antigen 2.

Primary Objectives

- Dose escalation: To identify the MTD for RDE and assess safety and tolerability
- Dose expansion: To confirm the safety and tolerability of DS-1062a at the RDE

Secondary and Exploratory Objectives

- Secondary objectives: Measure pharmacokinetic (PK) properties of DS-1062a, total TROP2 antibody, drug component MAAA-1181a, and antitumor activity of DS-1062a
- Exploratory objectives: Evaluate biomarkers that correlate with response to DS-1062a

Key Inclusion and Exclusion Criteria

- Inclusion: Patients aged ≥20 years (Japan) or ≥18 years (United States) with pathologically documented NSCLC without standard treatment option; Eastern Cooperative Oncology Group performance status 0 or 1; measurable disease based on RECIST version 1.1; a life expectancy of ≥3 months; and available tumor tissue for the measurement of recent TROP2 levels by immunohistochemistry
- Exclusion: Patients with multiple primary malignancies (except adequately resected nonmelanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated with no evidence of disease for ≥3 years); or clinically significant/suspected lung disease

Assessments

- Assessments include echocardiogram or multigated acquisition scan, 12-lead electrocardiogram, adverse events, PK, human anti-human antibodies, biomarkers, and tumor assessments at prespecified visits

Statistical Design and Analysis

- Dose escalation of DS-1062a to determine the MTD is guided by the modified continuous reassessment method using a Bayesian logistic regression model following escalation with the overdose control principle
- Safety endpoints, PK parameters of DS-1062a, anti-TROP2 antibody, DXd, and plasma antidrug antibodies were summarized using descriptive statistics

RESULTS

Patient Demographics and Baseline Characteristics

- Thirty-nine patients were enrolled at cut-off among 7 DS-1062a dosing groups **(Table 1)**

Table 1. Patient demographics and baseline characteristics[a]

Parameter	DS-1062a dose, mg/kg							Total (N=39)
	0.27 (n=4)	0.5 (n=5)	1.0 (n=7)	2.0 (n=6)	4.0 (n=6)	6.0 (n=8)	8.0 (n=3)	
Male sex, n (%)	1 (25.0)	3 (60.0)	4 (57.1)	4 (66.7)	2 (33.3)	6 (75.0)	3 (100)	23 (59.0)
Age, y, median (range)	64.0 (28–75)	66.0 (45–73)	67.0 (57–74)	60.5 (42–70)	60.5 (38–72)	53.5 (47–60)	69.0 (49–71)	60.0 (28–75)
Country, n (%)								
United States	2 (50.0)	4 (80.0)	5 (71.4)	4 (66.7)	5 (83.3)	5 (62.5)	1 (33.3)	26 (66.7)
Japan	2 (50.0)	1 (20.0)	2 (28.6)	2 (33.3)	1 (16.7)	3 (37.5)	2 (66.7)	13 (33.3)
Stage at study entry, n (%)								
IIIA	0	0	0	1 (16.7)	0	0	1 (33.3)	2 (5.1)
IVA	1 (25.0)	1 (20.0)	0	0	3 (50.0)	4 (50.0)	0	9 (23.1)
IVB	0	3 (60.0)	5 (71.4)	2 (33.3)	2 (33.3)	0	1 (33.3)	13 (33.3)
Other[a]	3 (75.0)	1 (20.0)	2 (28.6)	3 (50.0)	1 (16.7)	4 (50.0)	1 (33.3)	15 (38.5)
Histology, n (%)								
Adenocarcinoma	4 (100)	3 (60.0)	6 (85.7)	4 (66.7)	3 (50.0)	6 (75.0)	3 (100)	29 (74.4)
Large cell	0	0	0	0	1 (16.7)	0	0	1 (2.6)
Other (poorly differentiated NSCLC, NOS)	0	1 (20.0)	0	0	0	0	0	1 (2.6)
Squamous	0	1 (20.0)	1 (14.3)	2 (33.3)	2 (33.3)	2 (25.0)	0	8 (20.5)
ECOG PS, n (%)								
0	0	1 (20.0)	2 (28.6)	0	2 (33.3)	2 (25.0)	1 (33.3)	8 (20.5)
1	4 (100)	4 (80.0)	5 (71.4)	6 (100)	4 (66.7)	6 (75.0)	2 (66.7)	31 (79.5)

[a]Stage IV.
ECOG PS, Eastern Cooperative Oncology Group performance score; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

Treatment Exposure

- At the time of data cutoff, patients (N=39) were exposed to a median (range) of 3.0 (1–10) treatment cycles with DS-1062a, over a median (range) duration of 8.86 (3.0–31.1) weeks

Patient Disposition (N=39)

- Two patients required DS-1062a dose interruption (1 in the 4.0-mg/kg group [due to infusion related reaction, chills, and ejection fraction decreased] and 1 in the 8.0-mg/kg group [due to an infusion-related reaction]) and 1 patient in the 6.0-mg/kg group required dose reduction (due to grade 3 maculopapular rash)
- Overall, 23 (54.8%) patients discontinued from treatment with DS-1062a
  - The primary reason for discontinuation was PD per RECIST in 13 patients (n=4 each [0.5 and 2.0 mg/kg]; n=3 [1.0 mg/kg]; n=1 each [0.27 and 4.0 mg/kg])
  - Additionally, 2 patients discontinued due to clinical progression (1 each in the 0.27- and 6.0-mg/kg groups), 2 due to patient withdrawal (1 each in the 0.5- and 4.0-mg/kg groups), 1 due to physician decision (1.0-mg/kg group), and 5 due to 'other' reasons (n=3 in the 1.0-mg/kg and n=2 in the 0.27-mg/kg groups)

Safety (N=39)

- Overall, 87.2% (34/39) of patients reported ≥1 TEAE, regardless of severity or causality **(Table 2)**
  - All grade 3 TEAEs were reported in only 1 patient each, except grade 3 fatigue, which was reported in 2 patients (1 each in the 0.5- and 2.0-mg/kg dosing groups)

Table 2. Number of patients with TEAEs (in ≥10% of patients), regardless of causality

TEAE, n (%)	N=39	
	All grades[a]	Grade ≥3[a,b]
Any TEAE	34 (87.2)	16 (41.0)
TEAE, by preferred term (in ≥10% of patients)		
Fatigue	13 (33.3)	2 (5.1)
Nausea	12 (30.8)	0
Anemia	9 (23.1)	0
Decreased appetite	9 (23.1)	0
Alopecia	8 (20.5)	0
Infusion related reaction	8 (20.5)	0
Constipation	6 (15.4)	0
Vomiting	6 (15.4)	0
Cough	5 (12.8)	0
Dyspnea	5 (12.8)	1 (2.6)
Rash	5 (12.8)	0
Diarrhea	4 (10.3)	0
Pain	4 (10.3)	1 (2.6)
Weight decreased	4 (10.3)	0

[a]TEAEs include 'uncoded' (all grades: n=5, 12.8%; grade ≥3, n=1, 2.6%); [b]The majority of TEAEs were grade 3 (n=8; 20.5%), except for one grade 2 and 1 grade 5 TEAE (grade 5 sepsis; 6.0 mg/kg treatment group).
TEAE, treatment-emergent adverse event.

- Drug-related TEAEs were reported in 23/39 (59.0%) patients, with 21/23 (91.3%) of these of patients having these TEAEs as grade 1 or 2 in severity
  - The most frequent TEAEs (in ≥3 patients) by descending order of frequency were nausea (n=10); infusion-related reactions (n=8); fatigue (n=7); alopecia (n=6); vomiting (n=5); anemia and rash (n=4 each); and decreased appetite and stomatitis (n=3 each)
    - Infusion-related reactions were grade 1 or 2 events and resolved
- Serious TEAEs were reported in 10/39 (25.6%) patients; the majority of which were grade ≥3 (grade 3 in 8 patients and grade 5 [sepsis; 6-mg/kg dosing group] in 1 patient)
  - Only 1 serious TEAE was considered drug-related (pyrexia, grade 2; 4.0-mg/kg dosing group)
- One DLT (maculopapular rash, grade 3; resolved) occurred in a patient in the 6.0-mg/kg dosing group; the MTD has not been reached

Antitumor Activity

- Of 35 tumor-evaluable patients, 7 partial responses (PRs; based on RECIST, but including single-point PRs, not yet confirmed responses) were observed **(Table 3)**
  - Following the April 12, 2019 datacut, 3 additional PRs (all in the 8.0-mg dosing group), for a total of 10 PRs, were observed

Table 3. Tumor response (N=35)

Parameter	DS-1062a dose, mg/kg							Total (N=35)[a]
	0.27 (n=4)	0.5 (n=5)	1.0 (n=7)	2.0 (n=6)	4.0 (n=5)	6.0 (n=7)	8.0 (n=1)	
Best overall response, n (%)								
PR[b]	0	0	0	1 (16.7)	2 (40.0)	3 (42.9)	1 (100)	7 (20.6)
SD	0	1 (25.0)	6 (85.7)	3 (50.0)	2 (40.0)	4 (57.1)	0	16 (47.1)
PD	4 (100)	3 (75.0)	1 (14.3)	2 (33.3)	1 (20.0)	0	0	11 (32.4)

[a]The total number of patients (N=35) includes 1 non-evaluable patient due to no post-treatment response data; [b]Per RECIST, but including single-point PRs, not confirmed responses.
PD, progressive disease; PR, partial response; SD, stable disease.

- Computed (A, C, D) and positron emission (B) tomography scans from 3 patients are shown in **Figure 2**
  - Two patients in the 4.0-mg/kg dosing group demonstrated a maximum 36.6% **(Figure 2A)** and 38.4% **(Figure 2B)** decrease in tumor size 4.5 months following initiation of treatment with DS-1062a **(Figure 2A)**
  - Another patient in the 2-mg/kg dosing group demonstrated a maximum 65.5% decrease in tumor size 3 months following initiation of treatment with DS-1062a **(Figure 2C)** and a notable decrease in the number of multiple lung metastases (non-target lesions) at 3- and 7-months post treatment initiation **(Figure 2D)**

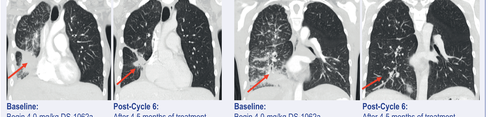
Figure 2. Response in target (A, B, C) and nontarget (D) lesions after DS-1062a treatment

A. Reduction in the size of *target* lesion in a patient treated with 4.0 mg/kg DS-1062a

Baseline: Begin 4.0-mg/kg DS-1062a — **Post-Cycle 6:** After 4.5 months of treatment *Maximum percent decrease in tumor size 36.6%*

Baseline: Begin 4.0-mg/kg DS-1062a — **Post-Cycle 6:** After 4.5 months of treatment *Maximum percent decrease in tumor size 36.6%*

B. Reduction in the size of *target* lesion in another patient treated with 4.0 mg/kg DS-1062a

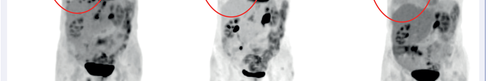


Baseline: Begin 4.0-mg/kg DS-1062a — **Post-Cycle 2:** After 6 weeks of treatment — **Post-Cycle 6:** After 18 weeks of treatment (ongoing PR) *Maximum percent decrease in tumor size: 38.4%*

C. Reduction in the size of *target* lesions in a patient treated with 2.0 mg/kg DS-1062a

Baseline: Begin 2.0-mg/kg DS-1062a — **Post-Cycle 4:** After 3 months of treatment *Maximum percent decrease in tumor size: 65.5%* — **Post-Cycle 10:** After 7 months of treatment *Maximum percent decrease in tumor size: 62.0%*

D. Decrease in the number of *nontarget* lesions in the same patient (as panel 2B) treated with 2.0 mg/kg DS-1062a



Baseline: Begin 2.0-mg/kg DS-1062a — **Post-Cycle 4:** After 3 months of treatment — **Post-Cycle 10:** After 7 months of treatment

Images courtesy of Dr. Jacob S. Sands (A), Dr. Jessica Lin (B), and Dr. Toshio Shimizu (C and D).

- The best percent change in sum of longest dimensions from baseline in target lesion is illustrated in **Figure 3**
  - The best percent change (68% tumor reduction) was observed in a patient in the 2.0-mg/kg dosing group
- The spider plot illustrates the decrease in tumor burden with increasing dosing of DS-1062a **(Figure 4)**

Figure 3. Best percent change in sum of longest dimension from baseline in target lesions (N=33)

PD, progressive disease; PR, partial response; SD, stable disease.

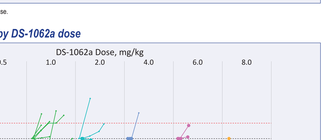
Figure 4. Change in tumor burden, by DS-1062a dose

Circle dots indicate on-going patients and small diamonds indicate discontinued patients with post-treatment response data.

Pharmacokinetics

- Systemic exposure to DS-1062a increased in an approximate dose-proportional manner **(Figure 5)**
- Plasma levels of DS-1062a and total anti-TROP2 antibody were similar, suggesting DS-1062a was stable in the circulation
- Exposure of DXd was lower than that of DS-1062a

Figure 5. Mean plasma concentrations of DS-1062a in Cycle 1 (PK analysis set)



PK, pharmacokinetics.

SUMMARY

- As of the April 12, 2019 datacut, DS-1062a was well tolerated; 1 DLT of grade 3 skin rash, which was transient and reversible, was observed in the 6.0-mg/kg dosing group
- 10 PRs were observed with DS-1062a; 2 of the patients with PRs had prior EGFR- or ALK-inhibitor treatments
- PFS and OS will be reported when the data is more mature
- The dose-escalation part of the study is ongoing and enrollment in the dose-expansion part has not yet started
  - Additional study information is available on ClinicalTrials.gov (NCT03401385)

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ACKNOWLEDGMENTS

Third-party writing assistance for this poster was provided by Ashfield Healthcare Communications, part of UDG Healthcare PLC, and supported by Daiichi Sankyo, Inc.

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Presented at the 2019 Annual Meeting of the American Society of Clinical Oncology (ASCO); May 31 – June 4, 2019; Chicago, IL, USA