A first-in-human Phase 1 dose-escalation study of DS-1471 in patients with advanced/metastatic solid tumors

#1033P

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OBJECTIVE

- To report the primary results, including safety, tolerability, efficacy, PK, and immunogenicity, from the FIH DS1471-079 study of DS-1471 in patients with advanced/metastatic solid tumors

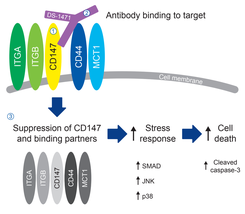
CONCLUSIONS

- DS-1471 was tolerable at doses through 40 mg/kg, with an overall manageable safety profile
  - No DLTs or treatment-related SAEs were reported
  - The most common any-grade TRAEs were pyrexia and headache
  - No TEAEs were associated with treatment discontinuation or death
  - There was 1 AESI, which was a Grade 2 IRR in a patient who received DS-1471 40 mg/kg; the IRR was well managed by dose interruption and standard medication
- PK and receptor occupancy data suggest target-mediated drug disposition of DS-1471
- Despite high baseline tumor CD147 expression across the patient population, neither objective responses by RECIST 1.1 nor reduction of tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) were observed; thus, the clinical development of DS-1471 was terminated after the completion of the dose-escalation part of the study

INTRODUCTION

- CD147, a transmembrane glycoprotein belonging to the Ig superfamily, interacts with integrins, MCTs, and other partners to promote cell proliferation, survival, and metastasis[1,2]
  - CD147 is highly expressed in multiple cancer types, and high expression is associated with poor prognosis in multiple solid tumor types[1]; thus, CD147 is a promising therapeutic target
- DS-1471 is a novel humanized IgG4 monoclonal antibody that targets CD147, reducing its cell-surface expression, inhibiting the formation of CD147-containing protein complexes, and activating stress response pathways[3–6] (**Figure 1**)
  - Preclinical studies have shown antitumor effects of DS-1471 in multiple PDX models[3,5,6]
- DS1471-079 (NCT06074705; EU CTIS 2024-517984-21-00; jRCT2031230234) was a Phase 1 open-label, FIH, multicenter study that assessed DS-1471 in patients with locally advanced or metastatic solid tumors[7]

Figure 1. DS-1471 proposed mechanism of action[3,4]



1. CD147 contains 2 Ig-like domains, which can interact with MCT1, CD44, integrins, and other proteins[3,4]
   - CD44 and integrins bind to extracellular matrix proteins to promote tumor cell survival, proliferation, and metastasis
   - CD147 binding attenuates lysosomal degradation and promotes cell-surface recycling of CD44 and other binding partners
2. DS-1471 inhibits complex formation between CD147 and diverse binding partners, resulting in their delocalization and degradation[3,4]
3. By downregulating CD147, DS-1471 stimulates a stress response that induces cancer cell apoptosis[3,4]

Adapted from: Koganemaru S, et al. Poster presentation at the ESMO Congress. September 13–17, 2024; Barcelona, Spain. Poster 682TiP.[4]

METHODS

- DS1471-079 enrolled patients with locally advanced, metastatic, or unresectable solid tumors who were unable to tolerate standard treatment, had tumors refractory to standard treatment, or had no standard treatment available (**Figure 2**)[4,7]
  - Patients received DS-1471 IV Q4W until disease progression, unacceptable toxicity, or discontinuation for other reasons
- Baseline CD147 expression was assessed by immunohistochemistry using archival or newly obtained biopsy tissue
- For analysis of PK and receptor occupancy of soluble CD147, blood samples were collected on Days 1, 2, 4 (±1), 8 (±1), 15 (±1), and 22 (±1) of Cycles 1 and 3, and on Day 1 of Cycles 2, 4, 6, and 8 (and every 2 cycles thereafter for receptor occupancy)
  - Plasma concentration of DS-1471 was measured using validated assays at bioanalytical laboratories
  - PK parameters were calculated using non-compartmental analysis of concentration–time data
- Immunogenicity was assessed using a validated ADA assay; plasma samples were collected on Days 1 and 8 (±1) of Cycle 1, on Day 1 of Cycles 2–4 and every 2 cycles thereafter, and at end of treatment (+7) and 30-day follow up (+7)
- Tumor markers, including carcinoembryonic antigen (for patients with colorectal cancer) and carbohydrate antigen 19-9 (for patients with pancreatic cancer), were measured in blood samples collected at screening (baseline), before infusion on Day 1 of each cycle, and at the end of treatment

Figure 2. DS1471-079 study design (dose escalation[a])

Key eligibility criteria:

- Age ≥18 years
- Histologically or cytologically documented locally advanced, metastatic, or unresectable solid tumors not amenable to standard treatment
- ≥1 measurable lesion per RECIST 1.1
- ECOG PS 0 or 1
- Willing and able to provide newly obtained or archival tumor tissue
- No history of, current, or suspected ILD/pneumonitis

DS-1471 IV Q4W monotherapy (N=16[b])

40 mg/kg → 24 mg/kg → 12 mg/kg → 6 mg/kg → 3 mg/kg → 1 mg/kg

Primary endpoint:

- Safety and tolerability, including DLTs, TEAEs, SAEs, and AESIs[c,d]

Secondary endpoints:

- BOR, TTR, DOR, and PFS by investigator per RECIST 1.1[e]
- OS
- PK
- Immunogenicity (ADAs)

Key exploratory analyses:

- Receptor occupancy of soluble CD147
- Changes in levels of select tumor markers from baseline over time

[a]Dose escalation was performed using an accelerated titration design starting 1 dose level below the pharmacologically active dose of ≥3 mg/kg. The escalation to the dose level of the next cohort was guided by a Bayesian logistic regression model following the escalation with overdose control principle.[8,9] The originally planned doses for dose escalation were 1, 3, 6, 10, 15, and 20 mg/kg. [b]One additional patient was enrolled but did not receive study treatment and thus was not included in analyses. [c]AESIs were hepatotoxicity, based on combined elevation of aminotransferases and bilirubin, and IRRs. [d]Adverse events were graded per NCI-CTCAE v5.0. [e]Radiographic tumor assessments were performed at baseline, 4 weeks (+7 days) after Cycle 1 Day 1, then Q8W (±7 days) for the first 36 weeks, and then Q12W (±7 days) thereafter until PD, start of new anticancer treatment, death, or loss to follow-up.

RESULTS

- At the December 10, 2025 database lock, a total of 16 patients had been enrolled and received treatment with DS-1471. They comprised 8 patients with pancreatic cancer, 7 with colorectal cancer, and 1 with adenocarcinoma NSCLC. All patients were enrolled in Japan (**Table 1**)
- Patients had received a median of 4 prior lines of systemic therapy (range, 2–10)
- Among the 12 patients for whom data were available, the median H-score of baseline CD147 was 293.0 (range, 35–300)

Table 1. Baseline characteristics

	DS-1471 dose						
	1 mg/kg (n=1)	3 mg/kg (n=3)	6 mg/kg (n=3)	12 mg/kg (n=3)	24 mg/kg (n=3)	40 mg/kg (n=3)	Total (N=16)
Age, median (range), years	48 (48–48)	62 (60–66)	64 (58–75)	58 (49–65)	62 (60–66)	70 (57–73)	62 (48–75)
Sex, n (%)							
Male	1 (100)	3 (100)	2 (66.7)	3 (100)	3 (100)	2 (66.7)	14 (87.5)
Female	0	0	1 (33.3)	0	0	1 (33.3)	2 (12.5)
Japan as country of enrollment, n (%)	1 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	16 (100)
ECOG PS, n (%)							
0	1 (100)	1 (33.3)	1 (33.3)	3 (100)	2 (66.7)	0	8 (50.0)
1	0	2 (66.7)	2 (66.7)	0	1 (33.3)	3 (100)	8 (50.0)
Primary diagnosis, n (%)							
Pancreatic cancer	0	2 (66.7)	3 (100)	0	2 (66.7)	1 (33.3)	8 (50.0)
Colorectal cancer	0	1 (33.3)	0	3 (100)	1 (33.3)	2 (66.7)	7 (43.8)
Adeno-NSCLC	1 (100)	0	0	0	0	0	1 (6.3)
Number of prior LOTs, median (range)	4 (4–4)	2 (2–4)	3 (3–3)	6 (5–6)	3 (2–6)	5 (4–10)	4 (2–10)
Prior cancer surgery, n (%)	0	2 (66.7)	3 (100)	3 (100)	1 (33.3)	3 (100)	12 (75.0)
Prior cancer radiation therapy, n (%)	1 (100)	0	0	2 (66.7)	0	2 (66.7)	5 (31.3)
Tumor CD147 H-score, median (range)[a]	NE	300.0 (35–300)	286.0 (286–286)	290.0 (280–300)	290.0 (287–300)	296.0 (250–297)	293.0 (35–300)

[a]Baseline CD147 H-score was not available for 4 patients (1 mg/kg, n=1; 6 mg/kg, n=2; 12 mg/kg, n=1).

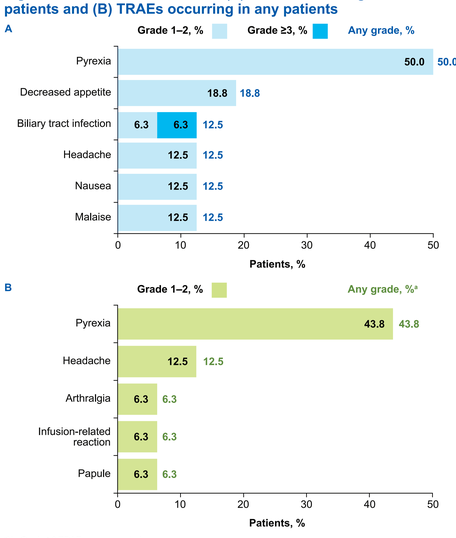
- No DLTs were observed
- There were no TEAEs associated with dose reduction, treatment discontinuation, or death
- Nine (56.3%) patients experienced TRAEs, of which none were Grade ≥3 (**Table 2**)
- The most common any-grade TRAEs were pyrexia (43.8%) and headache (12.5%; **Figure 3**)
- There was 1 AESI, which was a Grade 2 IRR that was not considered an SAE in a patient who received DS-1471 40 mg/kg; the IRR was well managed with dose interruption (temporary stopping of infusion) and standard medication
- There were no TRAEs associated with dose delay, dose reduction, treatment discontinuation, or death; there were no treatment-related SAEs

Table 2. Safety summary

	DS-1471 dose						
	1 mg/kg (n=1)	3 mg/kg (n=3)	6 mg/kg (n=3)	12 mg/kg (n=3)	24 mg/kg (n=3)	40 mg/kg (n=3)	Total (N=16)
Number of patients with event, n (%)							
Any TEAE	0	3 (100)	3 (100)	2 (66.7)	3 (100)	2 (66.7)	13 (81.3)
Grade ≥3	0	0	1 (33.3)	0	1 (33.3)	0	2 (12.5)
Any TRAE	0	1 (33.3)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	9 (56.3)
Grade ≥3	0	0	0	0	0	0	0
Any SAE	0	0	1 (33.3)	0	1 (33.3)	0	2 (12.5)
Grade ≥3	0	0	1 (33.3)	0	1 (33.3)	0	2 (12.5)
Treatment-related	0	0	0	0	0	0	0
Any AESI	0	0	0	0	0	1 (33.3)[a]	1 (6.3)[a]
Treatment-related	0	0	0	0	0	1 (33.3)[a]	1 (6.3)[a]
Any TEAE associated with death	0	0	0	0	0	0	0
Treatment duration, median (range), months[b]	1.0 (1.0–1.0)	1.0 (1.0–2.8)	1.0 (0–2.8)	1.9 (1.0–3.0)	1.0 (1.0–2.1)	1.0 (1.0–1.0)	1.0 (0–3.0)

[a]Grade 2 IRR (n=1). [b]Treatment duration was calculated as (last dose date − first dose date + 1)/30.4375. All patients had discontinued treatment by the time of database lock.

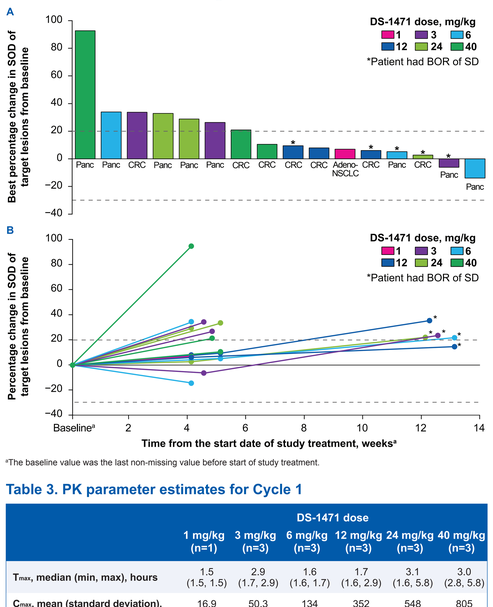
Figure 3. Across all dose levels, (A) TEAEs occurring in ≥10% of patients and (B) TRAEs occurring in any patients



[a]No Grade ≥3 TRAEs were reported.

- Best responses by investigator were stable disease in 5 patients (2 with pancreatic cancer and 3 with colorectal cancer) and PD in 11 patients (6 with pancreatic cancer, 4 with colorectal cancer, and 1 with adenocarcinoma NSCLC; **Figure 4**)
- DS-1471 systemic exposure increased in a dose-dependent manner (**Table 3**); an S-shaped PK profile, suggesting target-mediated drug disposition, was observed at 24 and 40 mg/kg (**Figure 5**)
- ADAs were observed in 1 patient who received DS-1471 40 mg/kg, and had no apparent effect on PK
- Receptor occupancy of soluble CD147 in blood at trough increased with dose, reaching ~80–90% at 40 mg/kg (**Figure 6**)
- Among patients with abnormal baseline values, no reductions in carcinoembryonic antigen in those with colorectal cancer or carbohydrate 19-9 in those with pancreatic cancer were observed (**Figure 7**)

Figure 4. (A) Best percentage change and (B) percentage change over time in sum of diameters of target lesions from baseline



[a]The baseline value was the last non-missing value before start of study treatment.

Table 3. PK parameter estimates for Cycle 1

	DS-1471 dose					
	1 mg/kg (n=1)	3 mg/kg (n=3)	6 mg/kg (n=3)	12 mg/kg (n=3)	24 mg/kg (n=3)	40 mg/kg (n=3)
T_{max}, median (min, max), hours	1.5 (1.5, 1.5)	2.9 (1.7, 2.9)	1.6 (1.6, 1.7)	1.7 (1.6, 2.9)	3.1 (1.6, 5.8)	3.0 (2.8, 5.8)
C_{max}, mean (standard deviation), μg/mL	16.9 (NE)	50.3 (18.4)	134 (25.0)	352 (110)	548 (74.8)	805 (92.3)
AUC_{last}, mean (standard deviation), μg*day/mL	37.1 (NE)	133 (41.3)	465 (117)	1620 (234)	3240 (350)	4670 (684)
$t_{1/2}$, mean (standard deviation), days	9.3 (NE)	13.7 (2.5)	6.7 (2.7)	4.1 (0.3)	4.8 (0.7)	5.8 (1.4)

Figure 5. Plasma concentration of DS-1471 in Cycles 1 and 3

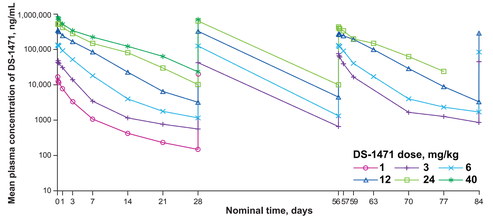
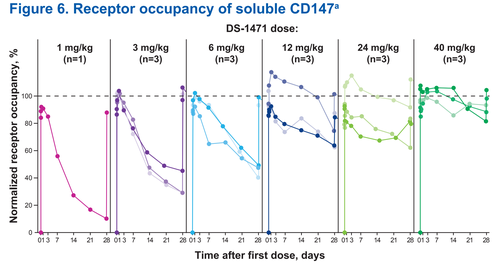
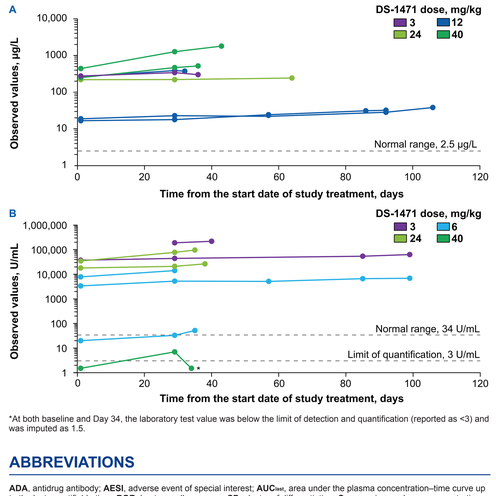


Figure 6. Receptor occupancy of soluble CD147[a]



[a]Each line (with different color shade) represents samples from 1 patient.

Figure 7. Change over time in serum levels of (A) carcinoembryonic antigen in patients with colorectal cancer and (B) carbohydrate antigen 19-9 in patients with pancreatic cancer



[a]At both baseline and Day 34, the laboratory test value was below the limit of detection and quantification (reported as <3) and was imputed as 1.5.

ABBREVIATIONS

ADA, antidrug antibody; **AESI**, adverse event of special interest; **AUC_{last}**, area under the plasma concentration–time curve up to the last quantifiable time; **BOR**, best overall response; **CD**, cluster of differentiation; **C_{max}**, maximum plasma concentration; **CRC**, colorectal cancer; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **FIH**, first-in-human; **Ig**, immunoglobulin; **ILD**, interstitial lung disease; **IRR**, infusion-related reaction; **ITGA**, integrin alpha; **ITGB**, integrin beta; **IV**, intravenous; **JNK**, c-Jun N-terminal kinase; **LOT**, line of therapy; **max**, maximum; **MCT**, monocarboxylate transporter; **min**, minimum; **NCI-CTCAE v5.0**, National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; **NE**, not estimable; **(adeno-)NSCLC**, adenocarcinoma non-small cell lung cancer; **OS**, overall survival; **Panc**, pancreatic cancer; **PD**, progressive disease; **PDX**, patient-derived xenograft; **PFS**, progression-free survival; **PK**, pharmacokinetics; **QXW**, once every X weeks; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SAE**, serious adverse event; **SD**, stable disease; **SOD**, sum of diameters; **$t_{1/2}$**, terminal elimination half-life; **TEAE**, treatment-emergent adverse event; **T_{max}**, time to maximum plasma concentration; **TRAE**, treatment-related adverse event; **TTR**, time to response.

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