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

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## OBJECTIVES

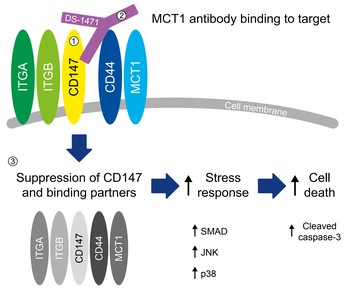
- DS1471-079 (NCT06074705) is a Phase 1, first-in-human study of DS-1471, a novel CD147–targeting monoclonal antibody, in patients with locally advanced/metastatic solid tumors[1,2]
- The primary objective of dose escalation (Part 1) is to evaluate the safety and tolerability of DS-1471 and determine the MTD and/or RDE(s)
- The primary objective of dose expansion (Part 2) is to evaluate the safety of DS-1471 at the RDE(s)



## INTRODUCTION

- CD147, a transmembrane protein of the Ig superfamily, is highly expressed across a range of cancers[3,4]
  - In tumor cells, CD147 regulates processes underlying key hallmarks of cancer, including cell survival, proliferation, immune evasion, invasion, and metastasis[3,4]
  - High CD147 expression in tumor tissue is associated with a poor prognosis in multiple solid tumor types[3,4]
  - CD147 is, therefore, an attractive target for anticancer therapeutics
- DS-1471 is a novel humanized IgG4 monoclonal antibody that targets CD147 to inhibit complex formation between CD147 and diverse binding partners (**Figure 1**)[5,6]

### Figure 1. Proposed DS-1471 mechanism of action

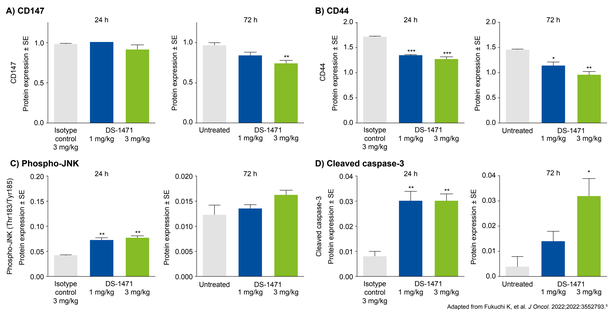



Adapted from Yokoyama M, et al. Presented at the AACR-NCI-EORTC 2023 Meeting. October 11–15, 2023; Boston, Massachusetts. Abstract A138[6]

1. CD147 contains two Ig-like domains, which can interact with proteins such as MCT1, CD44, and integrins[5]
   - CD44 and integrins bind to extracellular matrix proteins to promote tumor cell survival, proliferation, and metastasis[5]
   - CD147 binding attenuates lysosomal degradation and promotes cell surface recycling of CD44 and other binding partners[5]
2. DS-1471 inhibits complex formation between CD147 and diverse binding partners, resulting in their delocalization and degradation[5,6]
3. By downregulating CD147, DS-1471 stimulates a stress response that induces cancer cell apoptosis[5,6]

- Following administration of DS-1471, tumor xenograft models showed[5]:
  - Decreased protein expression of CD147; CD147 binding partners CD44, integrin α3, integrin α6 and MCT1; and cytoskeletal signaling molecules FAK and phospho-FAK[5]
  - Increased stress-response signals phospho-JNK, phospho-c-Jun, phospho-HSP27, and PAI-1, and increased apoptotic protein cleaved caspase-3[5] (select results in **Figure 2**)

### Figure 2. Treatment with DS-1471 induces downregulation of CD147 and its binding partners followed by induction of apoptosis via activation of stress responses

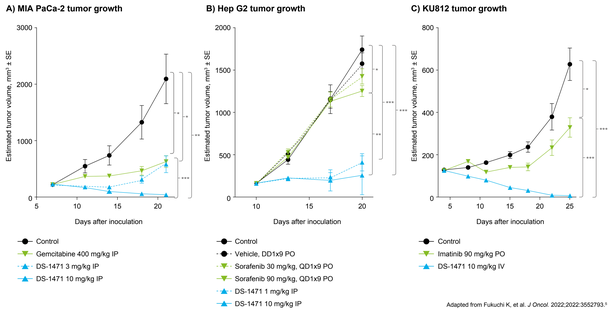



Adapted from Fukuchi K, et al. *J Oncol.* 2022;2022:3552793.[5]

Administration of DS-1471 resulted in downregulation of (**A**) CD147 and (**B**) binding partners, such as CD44, and increases in both (**C**) stress-response proteins, such as phospho-JNK and (**D**) the apoptotic protein cleaved caspase-3 in a MIA PaCa-2 PDAC xenograft tumor model. Bar graphs show mean protein expression ± SE for expression and luminescence signal ratio of the target protein to β-actin in tumor lysate samples from control tumors (isotype-control treated at 24 h or untreated at 72 h) and DS-1471–treated tumors (1 mg/kg or 3 mg/kg; n=3 for all). Asterisks indicate significant differences between control tumors and corresponding DS-1471–treated tumors (*$P$<0.05, **$P$<0.01, ***$P$<0.001). For the full reported results of this assay, please see Fukuchi K, et al.[5]

- DS-1471 has shown potent, dose-dependent antitumor activity in mouse xenograft models, with tumor growth inhibition of 99% (10 mg/kg DS-1471) in a PDAC model, 76% (1 mg/kg DS-1471) and 85% (10 mg/kg DS-1471) in an HCC model, and 99% (10 mg/kg DS-1471) in a CML model[5,6] (**Figure 3**)

### Figure 3. Antitumor activity of DS-1471 in mouse xenograft models




Adapted from Fukuchi K, et al. *J Oncol.* 2022;2022:3552793.[5]

Antitumor activity of DS-1471 versus standard anticancer therapy in NOD SCID xenograft models harboring (**A**) PDAC [MIA PaCa-2], (**B**) HCC [Hep G2], and (**C**) CML [KU812] cells. DS-1471 injection (IP or IV) was performed on the day of group allocation (n=5 or 6 mice per group). Tumor size was measured twice weekly. Data represent the mean ± SE. Asterisks indicate significant differences between each group connected by a bracket (*$P$<0.05, **$P$<0.01, ***$P$<0.001).

- A first-in-human study is being conducted to evaluate DS-1471 in patients with advanced/metastatic solid tumors[1]

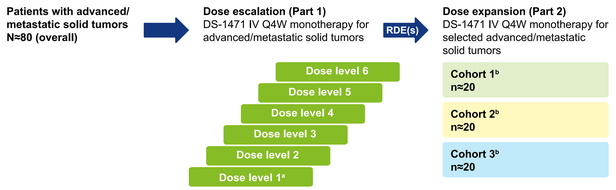
## METHODS

- DS1471-079 (NCT06074705) is a Phase 1, open-label, multicenter, multinational, two-part, dose-escalation and -expansion study[1,2]
- Eligible patients have locally advanced or metastatic solid tumors and are unable to tolerate standard treatment, have tumors refractory to standard treatment, or have no standard treatment available (**Table 1**)
- Dose escalation (Part 1) aims to evaluate the safety, tolerability, preliminary antitumor activity, PK, and immunogenicity of DS-1471 IV Q4W and to determine the MTD and/or RDE(s)
- Dose expansion (Part 2) will evaluate the safety, preliminary antitumor activity, PK, and immunogenicity of DS-1471 IV Q4W at the RDE(s) in three tumor-specific cohorts
- Study endpoints are summarized in **Table 2**
- Patients will receive DS-1471 as monotherapy by IV infusion Q4W until radiologic or clinical progression, unacceptable toxicity, withdrawal of consent, or discontinuation for other reasons (**Figure 4**)

### Table 1. Key eligibility criteria

| Key inclusion criteria |
|---|
| Adults ≥18 years |
| Histologically or cytologically documented, locally advanced, metastatic, or unresectable solid tumor |
| Tumor refractory to standard treatment, patient unable to tolerate standard treatment, or standard treatment not available |
| ≥1 measurable lesion per RECIST 1.1 |
| Consent to provide tumor tissue (newly obtained or archival) |
| ECOG performance status 0 or 1 |
| LVEF ≥50% |
| Adequate hepatic, renal, and bone marrow function |
| **Key exclusion criteria** |
| History of or current untreated CNS metastases or prior leptomeningeal carcinomatosis |
| History of or current ILD or suspected ILD that cannot be ruled out by imaging |
| Unresolved toxicities from previous anticancer treatment |
| Exposure to another investigational medical product in the past 4 weeks |

### Figure 4. DS1471-079 study design




[a]The proposed starting dose is 1.0 mg/kg, based on preclinical PK/PD and safety analyses.[4] Dose escalation (Part 1) will be performed using an accelerated titration design at dose level(s) below the pharmacologically active dose of 3 mg/kg. The escalation to the dose level of the next cohort will be guided by a Bayesian logistic regression model following the escalation with overdose control principle.[7,8] [b]Tumor type to be selected based on the nonclinical and clinical data available before the start of Part 2. Up to 40 patients may be enrolled in each cohort.

### Table 2. Study endpoints

| Primary | |
|---|---|
| **Part 1** | **Part 2** |
| Safety, including DLTs and TEAEs | Safety, including TEAEs |
| **Secondary** | |
| **Part 1** | **Part 2** |
| BOR[a] | BOR[a] |
| TTR[a] | ORR[a] |
| DOR[a] | DCR[a] |
| PFS[a] | TTR[a] |
| OS | DOR[a] |
| PK | PFS[a] |
| Immunogenicity | OS |
| | PK |
| | Immunogenicity |

[a]As assessed by the investigator per RECIST 1.1.

### Key statistical considerations

- BOR and DCR will be summarized with 95% CI using the Clopper–Pearson method
- Time-to-event variables, including DOR, PFS, and OS, will be summarized and represented graphically using the Kaplan–Meier method. Median event times and their corresponding 95% CIs using the Brookmeyer and Crowley method will be presented
- Efficacy endpoints will be reported as listings only for dose escalation (Part 1) unless otherwise specified and will be listed and summarized by tumor-specific cohort for dose expansion (Part 2)
- Descriptive statistics for best percentage change from baseline in the sum of diameters of measurable lesions selected per RECIST 1.1 will be presented

### Study sites

- Part 1 is currently ongoing at two sites in Japan (**Figure 5**), with approximately 10 global sites planned for Part 2

### Figure 5. Study site locations (Part 1)


## REFERENCES

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## ABBREVIATIONS

**BOR**, best overall response; **CD**, cluster of differentiation; **CI**, confidence interval; **CML**, chronic myeloid leukemia; **CNS**, central nervous system; **DCR**, disease control rate; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **FAK**, focal adhesion kinase; **HCC**, hepatocellular carcinoma; **HSP27**, heat shock protein 27; **Ig**, immunoglobulin; **IgG4**, immunoglobulin G4; **ILD**, interstitial lung disease; **IP**, intraperitoneal; **ITGA**, integrin alpha; **ITGB**, integrin beta; **IV**, intravenous; **JNK**, c-Jun N-terminal kinase; **LVEF**, left ventricular ejection fraction; **MCT1**, monocarboxylate transporter 1; **MTD**, maximum tolerated dose; **NOD**, non-obese diabetic; **ORR**, objective response rate; **OS**, overall survival; **PAI-1**, plasminogen activator inhibitor-1; **PD**, pharmacodynamics; **PDAC**, pancreatic ductal adenocarcinoma; **PFS**, progression-free survival; **phospho**, phosphorylated; **PK**, pharmacokinetics; **PO**, by mouth; **QD**, daily; **Q4W**, every 4 weeks; **RDE(s)**, recommended dose(s) for expansion; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SCID**, severe combined immunodeficiency disease; **SE**, standard error; **SMAD**, mothers against decapentaplegic family protein; **TEAE**, treatment-emergent adverse event; **TTR**, time to response.

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## DISCLOSURES

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