A phase 1/2, first-in-human study of DS-3939a in patients with advanced solid tumors: a new DXd ADC targeting TA-MUC1

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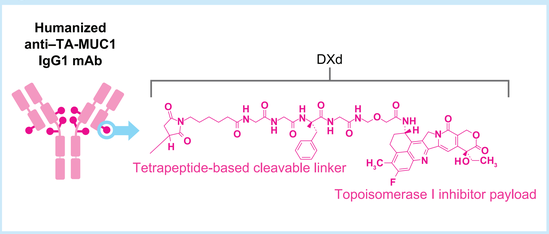
INTRODUCTION

- Mucin 1 (MUC1) is a single-transmembrane glycoprotein that is expressed on the apical membrane of the epithelial surface[1]
- MUC1 is found highly glycosylated in normal tissue, but is hypoglycosylated in cancer cells, which results in the exposure of new epitopes on MUC1 in tumors called tumor-associated MUC1 (TA-MUC1).[1] TA-MUC1 is overexpressed in cancer cells and loses cell polarity, leading to its redistribution over the surface of the cell and within the cytoplasm[1]
- TA-MUC1 has become an attractive therapeutic target due to the association between its overexpression in tumors and poor prognosis and the development of metastases[2-4]
- DS-3939a, a novel antibody-drug conjugate that targets TA-MUC1, is in development for the treatment of malignant tumors
  - The composition of DS-3939a includes a humanized anti–TA-MUC1 antibody and deruxtecan (DXd; MAAA-1181a), which is composed of a tetrapeptide-based cleavable linker and a topoisomerase I inhibitor (DXd; MAAA-1181a; **Figure 1**)
  - DS-3939a exhibited TA-MUC1–dependent in vitro cell-growth inhibition and induced in vivo tumor regression against several cell line–derived and patient-derived xenograft models (for more information, see AACR 2024 oral presentation 6579)

Figure 1. Structure of DS-3939a



DXd, deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody; TA-MUC1, tumor-associated mucin 1.

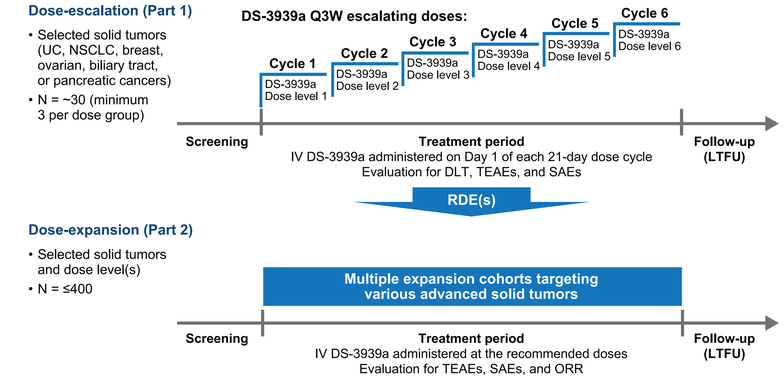
PURPOSE

- To assess the safety, tolerability, and efficacy of DS-3939a in patients with advanced solid tumors

METHODS

- This is a global, phase 1/2, first-in-human, open-label, multicenter, 2-part, dose-escalation and dose-expansion study (ClinicalTrials.gov Identifier: NCT05875168)
- Dose-escalation (Part 1) is currently accruing patients who have locally advanced, metastatic, or unresectable tumors related to urothelial, non-small cell lung, breast, ovarian, biliary tract, or pancreatic cancers (**Figure 2**)
- Dose-expansion (Part 2) will enroll patients with various advanced solid tumors and documented disease progression coinciding with or following their most recent cancer therapy
- The study endpoints, key patient eligibility criteria, and enrollment status are shown in **Table 1**, **Table 2**, and **Figure 3**, respectively

Figure 2. Study Design



DLT, dose-limiting toxicity; IV, intravenous; LTFU, long-term follow-up; NSCLC, non-small cell lung cancer; ORR, objective response rate; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UC, urothelial carcinoma.

Table 1. Study Endpoints

Primary endpoints	
Safety and tolerability outcome measures	**Efficacy outcome measure**
• Number of patients with dose-limiting toxicities from DS-3939a within 3 weeks of the first dose (Dose-escalation [Part 1] only) • Number of patients with treatment-emergent adverse events and serious adverse events after treatment with DS-3939a	• Number of patients with objective tumor response rate per RECIST version 1.1 (Dose-expansion [Part 2] only)
Secondary endpoints	
• Number of patients with objective tumor response rate following treatment with DS-3939a (Dose-escalation [Part 1] only) • Disease control rate following treatment with DS-3939a • Duration of response following treatment with DS-3939a • Time to response following treatment with DS-3939a • Progression-free survival following treatment with DS-3939a	• Overall survival following treatment with DS-3939a • TA-MUC1 expression detected by immunohistochemistry at baseline and its correlation with DS-3939a efficacy • Pharmacokinetic profile of DS-3939a • Number of patients with treatment-emergent antidrug antibodies following treatment with DS-3939a

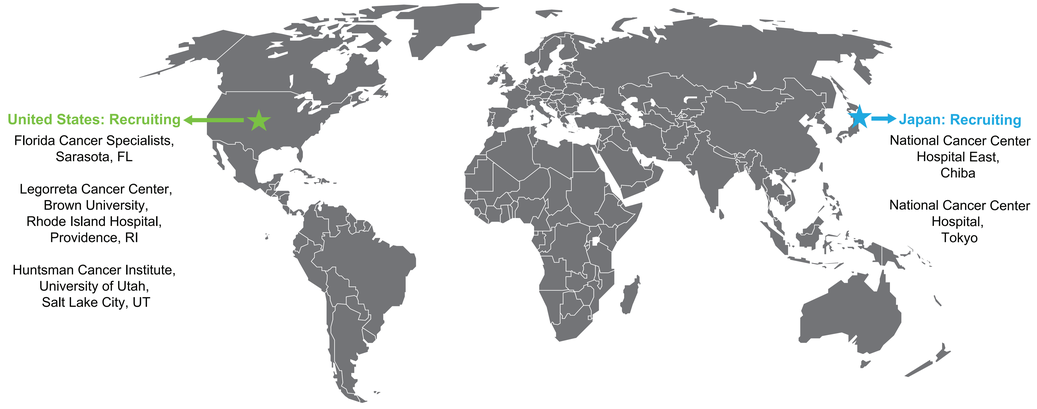
RECIST, Response Evaluation Criteria in Solid Tumors; TA-MUC1, tumor-associated mucin 1.

Table 2. Key Eligibility Criteria

Inclusion criteria	Exclusion criteria
• Adults ≥18 years of age • Completed informed consent form • Adequate organ function • The presence of left ventricular ejection fraction ≥50%, as assessed by echocardiogram or multigated acquisition, within 28 days of enrollment • Measurable disease based on RECIST version 1.1 • Eastern Cooperative Oncology Group performance status of 0 or 1 • Additional criteria for Part 1 (Dose-escalation): histologically or cytologically documented locally advanced, metastatic, or unresectable tumors related to urothelial, non-small cell lung, breast, ovarian, biliary tract, or pancreatic cancers • Additional criteria for Part 2 (Dose-expansion): histologically or cytologically documented locally advanced, metastatic, or unresectable solid tumors and documented radiographic disease progression coinciding with or following their most recent cancer therapy	• Prior treatment that targeted MUC1 or TA-MUC1 • Spinal cord compression or past or present active central nervous system metastases • Multiple primary malignancies, with the exception of adequately resected nonmelanoma skin cancer, in situ disease that was treated and cured, or other curatively treated solid tumors that have shown no evidence of disease for ≥3 years • Any of the following diseases, infections, or events (currently or historically): noninfectious interstitial lung disease/pneumonitis (including suspected cases); active HIV infections; active hepatitis B or C virus infection; autoimmune disease (including suspected); and a cerebrovascular accident, a transient ischemic attack, or other arterial thromboembolic event within the last 6 months • Currently receiving any other therapeutic investigational procedure, with the exception of participation in a treatment-free, long-term follow-up

MUC1, mucin 1; RECIST, Response Evaluation Criteria in Solid Tumors; TA-MUC1, tumor-associated mucin 1.

Figure 3. Enrollment Locations and Status



- Actual study start date: **August 2023**
- Estimated primary completion date: **March 2026**
- Estimated study completion: **July 2027**

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DISCLOSURES

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