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

TPS3165

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PURPOSE

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

INTRODUCTION

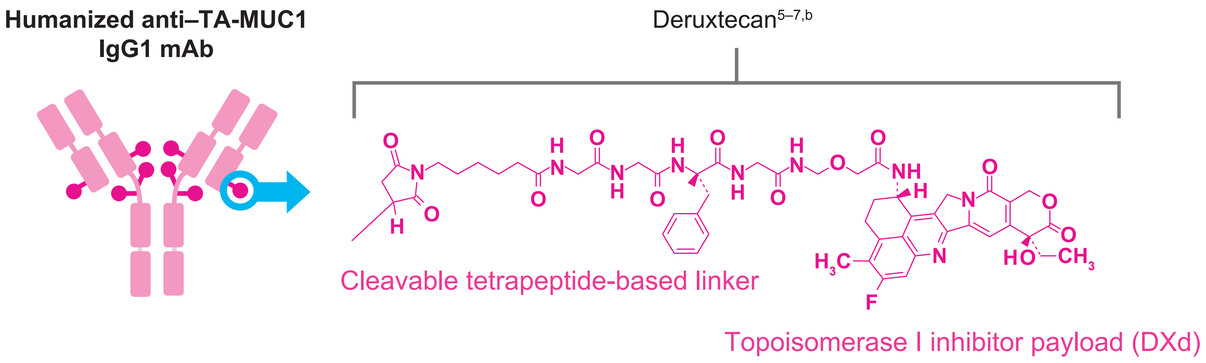
- MUC1 is a single-transmembrane glycoprotein that is expressed on the apical membrane of the epithelial surface[1]
- MUC1 is highly glycosylated in normal tissue but is hypoglycosylated in cancer cells, resulting in the exposure of new MUC1 epitopes in tumors (TA-MUC1)[1]
- TA-MUC1 is overexpressed in cancer cells and loses cell polarity, leading to its redistribution over the surface of the cell and within the cytoplasm.[1] Tumor overexpression of TA-MUC1 is associated with poor prognosis and development of metastases[2–4]
- DS-3939a, a novel DXd ADC that targets TA-MUC1, is undergoing clinical development for the treatment of malignant tumors[5–9]
  - The composition of DS-3939a includes a humanized anti–TA-MUC1 IgG1 mAb, a tetrapeptide-based cleavable linker that covalently binds the antibody and payload, and a topoisomerase I inhibitor payload (an exatecan derivative, DXd; **Figure 1**)[4–8]
  - DS-3939a exhibited TA-MUC1–dependent in vitro cell-growth inhibition and induced in vivo tumor regression against several cell line- and patient-derived xenograft models[9]

Figure 1. DS-3939a Was Designed With 7 Key Attributes

The **mAb** directs the DXd ADC to the tumor cell
1. High drug-to-antibody ratio ≈8[5–7,a]

The **linker** binds the mAb to the payload
2. Plasma-stable linker–payload[5,6,a]
3. Tumor-selective cleavable linker[5,6,a]

The **payload** induces cell death when delivered to the tumor
4. Topoisomerase I inhibitor[5,6,a]
5. High potency[5,6,a]
6. Short systemic half-life[5,6,a,c]
7. Bystander antitumor effect[5,7,a]



[a]The clinical relevance of these features is under investigation. [b]Refers to the linker and payload. [c]Based on animal data.

METHODS

- This is a global, Phase 1/2, first-in-human, open-label, multicenter, 2-part, dose-escalation and dose-expansion study (NCT05875168)
- Dose escalation (Part 1) is currently enrolling patients who have locally advanced, metastatic, or unresectable tumors related to urothelial, non-small cell lung, breast, ovarian, biliary tract, or pancreatic cancers **(Figure 2–3, Table 1–2)**
- 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

Figure 2. Study Design

Dose escalation (Part 1)

- n≈30 (minimum of 3 patients per dose group)

DS-3939a Q3W escalating doses:

DS-3939a Dose level 1 → DS-3939a Dose level 2 → DS-3939a Dose level 3 → DS-3939a Dose level 4 → DS-3939a Dose level 5 → DS-3939a Dose level 6

Screening | **Treatment period**: DS-3939a administered IV on Day 1 of each 21-day dose cycle (Q3W); Evaluation for DLTs, TEAEs, and SAEs | **Long-term follow-up**

RDE(s)

Dose expansion (Part 2)

- Selected solid tumors and dose level(s)
- n≈400

Multiple expansion cohorts targeting various advanced solid tumors

Screening | **Treatment period**: DS-3939a administered IV at the RDE; Evaluation for TEAEs, SAEs, and ORR | **Long-term follow-up**

Table 1. Study Endpoints

Primary endpoints	
Safety and tolerability outcome measures	**Efficacy outcome measure**
• DLTs within 3 weeks of the first dose (dose escalation only) • TEAEs • SAEs	• ORR[a] (dose expansion only)

Secondary endpoints	
• ORR[a] (dose escalation only) • DCR[a] • DOR[a] • TTR[a] • PFS[a]	• OS • TA-MUC1 expression detected by IHC at baseline and correlation with DS-3939a efficacy • PK • ADAs

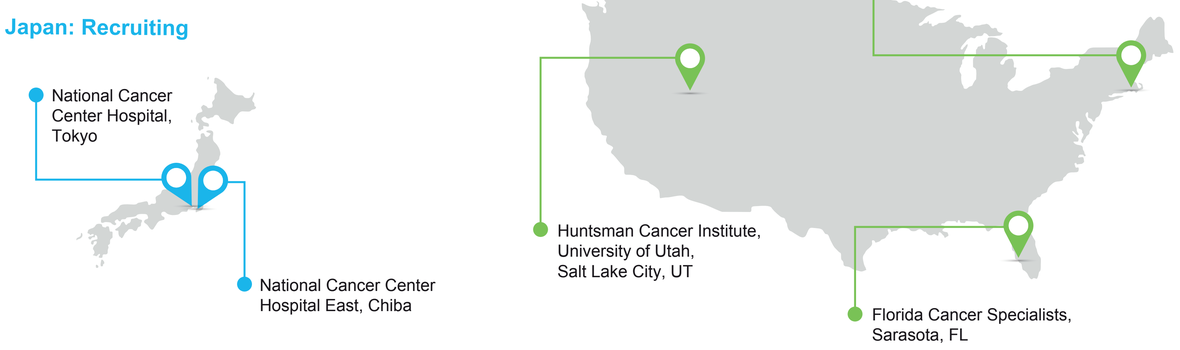
[a]By Investigator per RECIST v1.1.

Table 2. Key Eligibility Criteria

Inclusion criteria	Exclusion criteria
• Adults ≥18 years of age • Measurable disease based on RECIST v1.1 • ECOG PS 0 or 1 • Histologically or cytologically documented locally advanced, metastatic, or unresectable solid tumors with documented radiographic disease progression coinciding with or following their most recent cancer therapy • Completed informed consent form • Adequate organ function	• Prior treatment that targeted MUC1 or TA-MUC1 • Multiple primary malignancies, except 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 infection; active hepatitis B or C virus infection; autoimmune disease (including suspected); or a cerebrovascular accident, a transient ischemic attack, or other arterial thromboembolic event within the last 6 months • Currently receiving any other therapeutic investigational procedure, except participation in treatment-free, long-term follow-up

Figure 3. Enrollment Locations and Status

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



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ABBREVIATIONS

ADA, antidrug antibody; **ADC**, antibody–drug conjugate; **DCR**, disease control rate; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HIV**, human immunodeficiency virus; **IHC**, immunohistochemistry; **IV**, intravenously; **mAb**, monoclonal antibody; **MUC1**, mucin 1; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **Q3W**, every 3 weeks; **RDE**, recommended dose for expansion; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SAE**, serious adverse event; **TA-MUC1**, tumor-associated mucin 1; **TEAE**, treatment-emergent adverse event; **TTR**, time to response.

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