DS-3939, a TA-MUC1 antibody–drug conjugate in advanced/metastatic solid tumors: Initial first-in-human results

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March 28, 2026

Presentation number: MO47-1

JSMO2026 YOKOHAMA 2026 the Japanese Society of Medical Oncology Annual Meeting

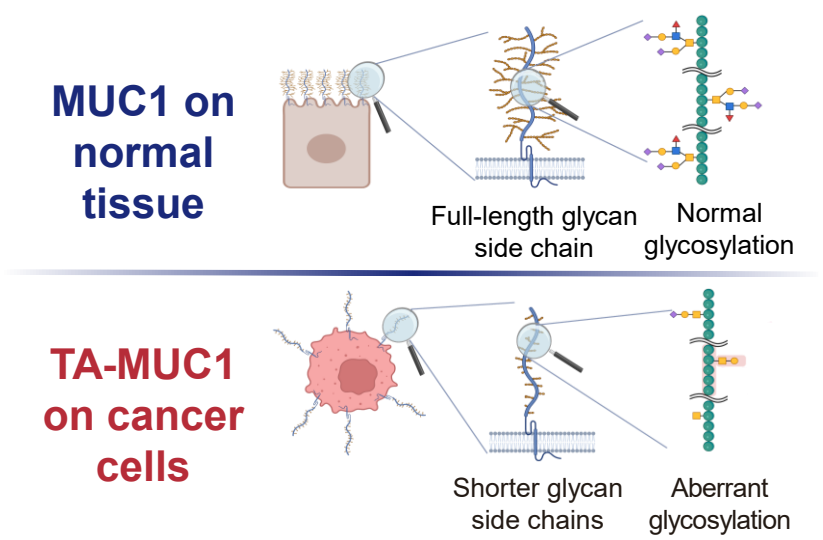
Declaration of Interests

Research fund	✓Scientific research fund □Contract □Donation □Other （） □N/A	Sponsor	Daiichi Sankyo Co., Ltd.
Name of lead presenter	Toshihiko Doi	Institution or company/position	National Cancer Center Hospital East, Kashiwa, Japan

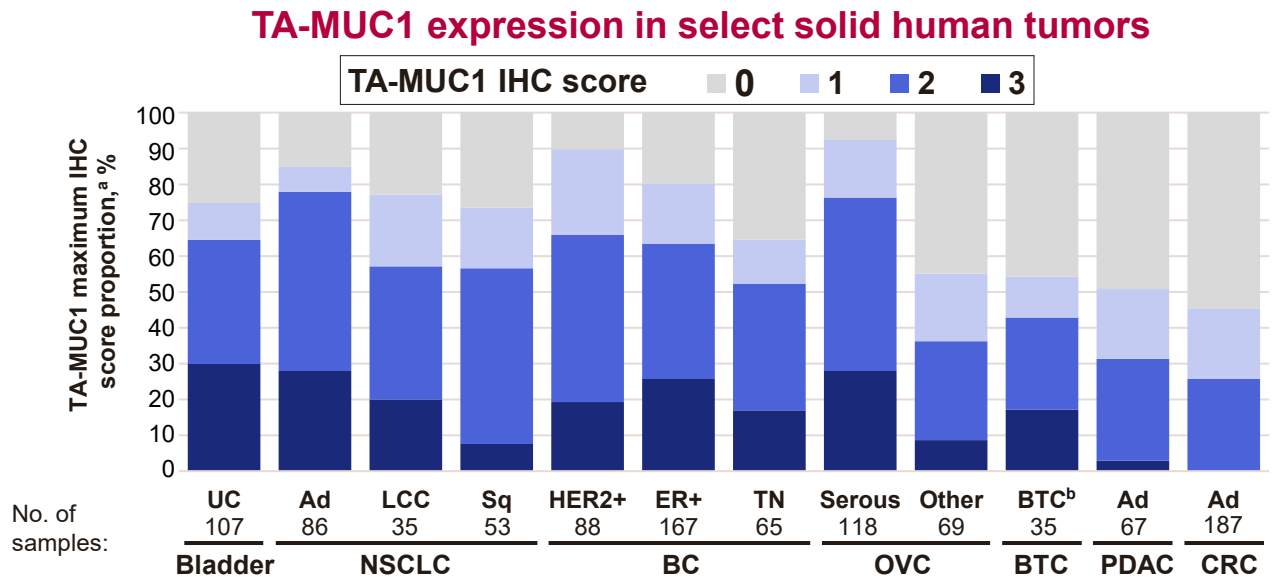
	No	If yes, please specify the name of company, organization, your status.
Employee or adviser of company and/or profit-making organization		Rakuten Medical (Adviser)
Profit of stock	X	
Patent fee	X	
Lecturer fee		Daiichi Sankyo
Manuscript fee	X	
Research expenses from company		**AbbVie, Amgen, Bayer Yakuhin, Boehringer Ingelheim, Chugai Pharmaceutical, Daiichi Sankyo, GlaxoSmithKline, Kyowa Kirin, MSD, Nippon, Pfizer, PRA Health Sciences, Shionogi, Taiho Pharmaceutical, Rin Institute**
Contributions or endowed chair	X	
Fees of testimony, judgment, comment, etc.	X	
Presents or other payment	X	
Representative of organization for clinical study receiving research expenses from company	X	

TA-MUC1 is a tumor-specific target

- MUC1 is a transmembrane protein with highly glycosylated tandem repeat sequences that localizes to the apical membrane of epithelial cells[1–3]
- In many cancers, MUC1 is upregulated, redistributed over the cell surface, and aberrantly glycosylated, leading to the emergence of tumor-associated MUC1 (TA-MUC1)[1–7]
- TA-MUC1 is expressed across a broad range of solid tumors, but has limited expression in normal human tissues[1,3–7]



Created with BioRender.com. Adapted from Yukiura M, et al. AACR 2024.[4]



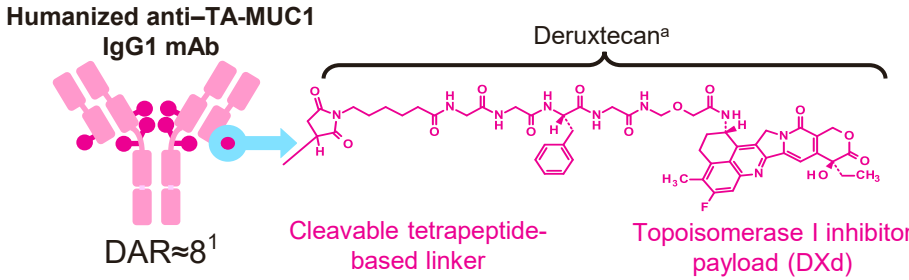
Adapted from Takano K, et al. *Mol Cancer Ther.*[5]

[a]IHC score of TA-MUC1 (staining using anti–human TA-MUC1 antibody) in the membrane, apical membrane, or cytoplasmic regions was visually scored as 0, 1+, 2+, or 3+ based on the highest intensity occupying ≥10% of the evaluated area, then using the maximum score of the 3 regions, then the percentage of each IHC score in the respective cancer type was calculated. Each bar shows the proportion of TA-MUC1 IHC scores in the tumor microarrays of each cancer type. [b]Cholangiocarcinoma.
Ad, adenocarcinoma; BC, breast cancer; BTC, biliary tract cancer; CRC, colorectal cancer; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; IHC, immunohistochemistry; LCC, large cell carcinoma; MUC1, mucin 1; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; Sq, squamous; TA-MUC1, tumor-associated mucin 1; TN, triple-negative; UC, urothelial carcinoma.

1. Nath S and Mukherjee P. *Trends Mol Med*. 2014;20:332–342. 2. Gao T, et al. *Biomed Pharmacother.* 2020;132:110888. 3. Chen W, et al. *Int J Mol Sci.* 2021;22:6567. 4. Yukiura M, et al. Oral presentation at the AACR Annual Meeting. April 5–10, 2024; San Diego, CA. Abstract 6579. 5. Takano K, et al. *Mol Cancer Ther*. 2026;25:7–20. 6. Lee DH, et al. *Pharmaceuticals (Basel)*. 2021;14:1053. 7. Lan Y, et al. *Mol Clin Oncol*. 2022;17:161.

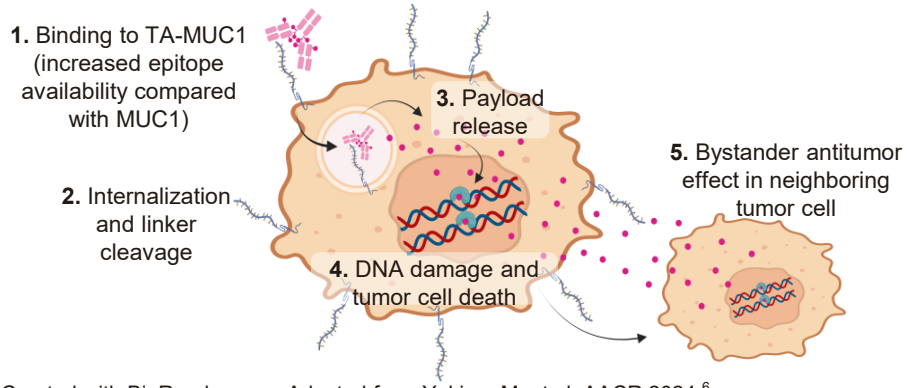
DS-3939: Novel TA-MUC1–directed ADC with significant preclinical activity

- **DS-3939** was designed with 3 components[1–6]



- **DS-3939 specifically binds to TA-MUC1** by recognizing both its glycan and backbone peptide moieties, promoting **high payload delivery into tumor cells**[1–3,6]

DS-3939 MOA[1,6]

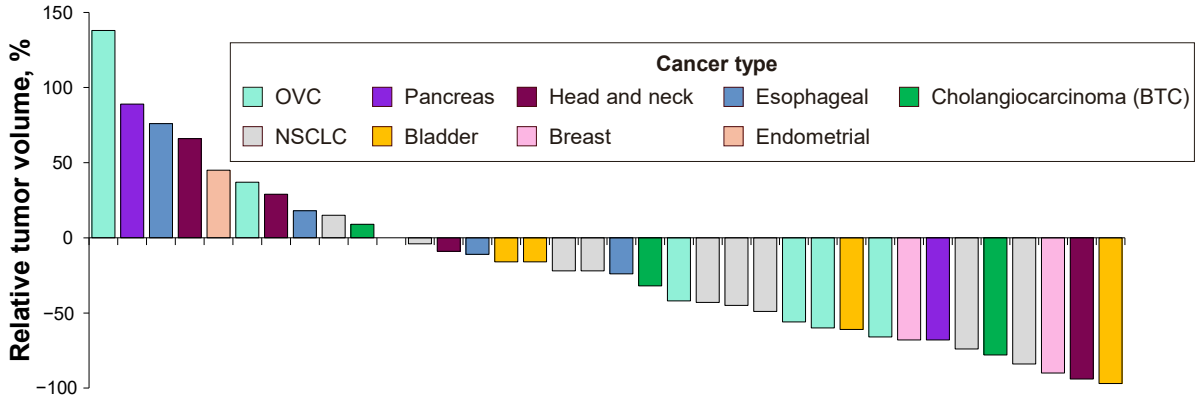


Created with BioRender.com. Adapted from Yukiura M, et al. AACR 2024.[6]

Preclinical activity of DS-3939

- **DS-3939** has exhibited **robust antitumor effects** in multiple TA-MUC1–positive preclinical CDX and PDX models, including in OVC, PDAC, NSCLC, BC, UC, and BTC[1]
- **DS-3939** exhibited **antitumor effects in bladder PDX and TNBC PDX models** following treatment with other cytotoxic ADCs[1]

Tumor regression was exhibited in 25/36 PDX models treated with DS-3939[1]



Adapted from Takano K, et al. *Mol Cancer Ther.*[1]

[a]Refers to the linker and payload.

ADC, antibody–drug conjugate; BC, breast cancer; BTC, biliary tract cancer; CDX, cell-derived xenograft; DAR, drug-to-antibody ratio; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MOA, mechanism of action; MUC1, mucin 1; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; TA-MUC1, tumor-associated mucin 1; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.

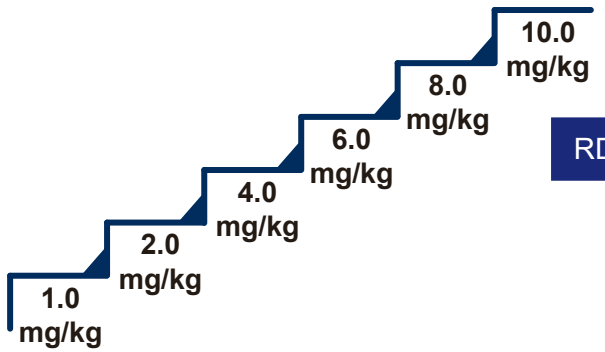
1. Takano K, et al. *Mol Cancer Ther*. 2026;25:7–20. 2. Danielczyk A, et al. *Cancer Immunol Immunother*. 2006;55:1337–1347. 3. Fan XN, et al. *Pathol Res Pract*. 2010;206:585–589. 4. Nakada T, et al. *Bioorg Med Chem Lett*. 2016;26:1542–1545. 5. Ogitani Y, et al. *Bioorg Med Chem Lett*. 2016;26:5069–5072. 6. Yukiura M, et al. Oral presentation at the AACR Annual Meeting. April 5–10, 2024; San Diego, CA. Abstract 6579.

DS3939-077: First-in-human study (NCT05875168)[1,2]

Key eligibility criteria (Part 1):

- Adults with histologically or cytologically documented locally advanced, metastatic, or unresectable solid tumors not amenable to SOC therapy
- ECOG PS 0 or 1
- Adequate organ function
- No history of, or current, or suspected ILD/pneumonitis
- No prior treatment targeting MUC1 or TA-MUC1
- Patients who received prior treatment with a DXd ADC can be eligible (Part 1 only)

Part 1: Dose escalation (n=64)



DS-3939 monotherapy IV Q3W

RDE(s)

Part 2: Dose expansion (n=93)

Multiple expansion cohorts targeting various advanced solid tumors

Dose expansion, including dose optimization, is ongoing

Primary endpoints:

- Safety (DLTs [Part 1 only], TEAEs, SAEs)
- ORR[a] (Part 2 only)

Secondary endpoints:

- ORR[a] (Part 1 only)
- DCR[a]
- DOR[a]
- TTR[a]
- PFS[a]
- OS
- TA-MUC1 expression detected by IHC at baseline and association with DS-3939 efficacy
- Pharmacokinetics
- Immunogenicity

Exploratory endpoints:

- Antitumor activity by G-score
- Exposure–response relationships

- In the dose-escalation portion of this Phase 1/2 study, patients with BC, BTC, CRC, NSCLC, OVC, PDAC, and UC were enrolled due to broad TA-MUC1 expression in these cancer types

Results from the dose-escalation part of the study are presented here

Data cutoff: August 1, 2025.

[a]By investigator per RECIST 1.1.

ADC, antibody–drug conjugate; BC, breast cancer; BTC, biliary tract cancer; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenous; MUC1, mucin 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; OVC, ovarian cancer; PDAC, pancreatic ductal carcinoma; PFS, progression-free survival; Q3W, once every 3 weeks; RDE, recommended dose for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SAE, serious adverse event; SOC, standard-of-care; TA-MUC1, tumor-associated mucin 1; TEAE, treatment-emergent adverse event; TTR, time to response; UC, urothelial carcinoma.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05875168. Accessed February 6, 2026. 2. Yamamoto N, et al. *Cancer Res*. 2024; 84(Suppl 7). Abstract CT291.

DS3939-077: Baseline characteristics and disposition

- At the August 1, 2025, data cutoff, 64 patients had been enrolled and received treatment with DS-3939 across all doses, with a median follow-up of 8.8 months (range, 0.6–22.9)
- Overall, 53.1% of patients had ≥3 prior LOTs in the locally advanced/metastatic setting, and over one-third of patients had treatment with prior topoisomerase I inhibitors (37.5%)[a]

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
Age, median (range), years	68.0 (66–69)	56.0 (52–64)	66.0 (32–82)	66.0 (46–78)	64.0 (39–79)	52.0 (52–52)	64.5 (32–82)
Male sex, n (%)	2 (66.7)	0	10 (52.6)	6 (35.3)	15 (71.4)	1 (100)	34 (53.1)
ECOG PS, n (%)							
0	1 (33.3)	3 (100)	4 (21.1)	5 (29.4)	10 (47.6)	1 (100)	24 (37.5)
1	2 (66.7)	0	15 (78.9)	12 (70.6)	11 (52.4)	0	40 (62.5)
Primary diagnosis, n (%)							
BC	0	0	3 (15.8)	2 (11.8)	0	0	5 (7.8)
BTC	1 (33.3)	0	1 (5.3)	0	5 (23.8)	0	7 (10.9)
CRC	0	0	5 (26.3)	0	2 (9.5)	0	7 (10.9)
NSCLC	0	0	6 (31.6)	9 (52.9)	1 (4.8)	0	16 (25.0)
OVC	0	3 (100)	1 (5.3)	2 (11.8)	2 (9.5)	0	8 (12.5)
PDAC	2 (66.7)	0	1 (5.3)	2 (11.8)	7 (33.3)	0	12 (18.8)
UC	0	0	2 (10.5)	2 (11.8)	4 (19.0)	1 (100)	9 (14.1)
Prior LOTs for locally adv/met disease, median (range)	2.0 (1–3)	4.0 (3–8)	2.0 (1–8)	4.0 (1–17)	3.0 (1–8)	3.0 (3–3)	3.0 (1–17)
1, n (%)	1 (33.3)	0	6 (31.6)	3 (17.6)	3 (14.3)	0	13 (20.3)
2, n (%)	1 (33.3)	0	7 (36.8)	4 (23.5)	5 (23.8)	0	17 (26.6)
3, n (%)	1 (33.3)	1 (33.3)	2 (10.5)	1 (5.9)	3 (14.3)	1 (100)	9 (14.1)
≥4, n (%)	0	2 (66.7)	4 (21.1)	9 (52.9)	10 (47.6)	0	25 (39.1)
Prior topoisomerase I inhibitor,[a] n (%)	3 (100)	0	8 (42.1)	4 (23.5)	9 (42.9)	0	24 (37.5)
Treatment duration, median (range), months	1.4 (1.4–2.1)	9.4 (5.6–17.3)	3.2 (1.4–14.5)	3.5 (0.7–14.8)	3.4 (0.7–10.8)	4.7 (4.7–4.7)	3.4 (0.7–17.3)
DS-3939 treatment ongoing, n (%)[b]	0	1 (33.3)	4 (21.1)	4 (23.5)	6 (28.6)	0	15 (23.4)

Data cutoff: August 1, 2025.

[a]Included 20 patients who received irinotecan, 2 patients who received trastuzumab deruxtecan, and 2 patients who received both trastuzumab deruxtecan and sacituzumab govitecan. [b]49 of 64 patients (76.6%) discontinued treatment, including 34 of 64 (53.1%) due to clinical or disease progression and 13 of 64 (20.3%) due to TEAEs (investigator-reported pneumonitis [n=9], cough [n=2], cerebrovascular accident [n=1], and intracranial hemorrhage [n=1]).

Adv/met, advanced/metastatic; BC, breast cancer; BTC, biliary tract cancer; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LOT, line of therapy; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; TEAE, treatment-emergent adverse event; UC, urothelial carcinoma.

DS3939-077: Safety summary

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
TEAEs, n with event (%)							
Any grade	3 (100)	3 (100)	18 (94.7)	17 (100)	21 (100)	1 (100)	**63 (98.4)**
Treatment-related	2 (66.7)	3 (100)	13 (68.4)	17 (100)	20 (95.2)	1 (100)	**56 (87.5)**
Grade ≥3	0	0	7 (36.8)	7 (41.2)	15 (71.4)	1 (100)	30 (46.9)
Treatment-related	0	0	3 (15.8)	5 (29.4)	13 (61.9)	1 (100)	22 (34.4)
Serious	0	0	4 (21.1)	4 (23.5)	9 (42.9)	0	17 (26.6)
Treatment-related	0	0	3 (15.8)	1 (5.9)	4 (19.0)	0	8 (12.5)
Associated with:							
Treatment discontinuation	0	1 (33.3)	4 (21.1)	2 (11.8)	6 (28.6)	0	13 (20.3)[a]
Treatment-related	0	1 (33.3)	3 (15.8)	2 (11.8)	5 (23.8)	0	11 (17.2)
Dose reduction	0	0	1 (5.3)	2 (11.8)	7 (33.3)	1 (100)	11 (17.2)
Treatment-related	0	0	1 (5.3)	2 (11.8)	7 (33.3)	1 (100)	11 (17.2)
Treatment interruption[b]	0	0	2 (10.5)	5 (29.4)	1 (4.8)	0	8 (12.5)
Treatment-related[b]	0	0	1 (5.3)	5 (29.4)	1 (4.8)	0	7 (10.9)
Treatment delay[c]	0	0	5 (26.3)	9 (52.9)	8 (38.1)	1 (100)	23 (35.9)
Treatment-related[c]	0	0	4 (21.1)	6 (35.3)	7 (33.3)	1 (100)	18 (28.1)
Death	0	0	1 (5.3)	0	2 (9.5)	0	3 (4.7)
Treatment-related	0	0	0	0	1 (4.8)	0	1 (1.6)
DLTs	0	0	1 (5.3)	1 (5.9)	2 (9.5)[a]	0	**4 (6.3)[d]**

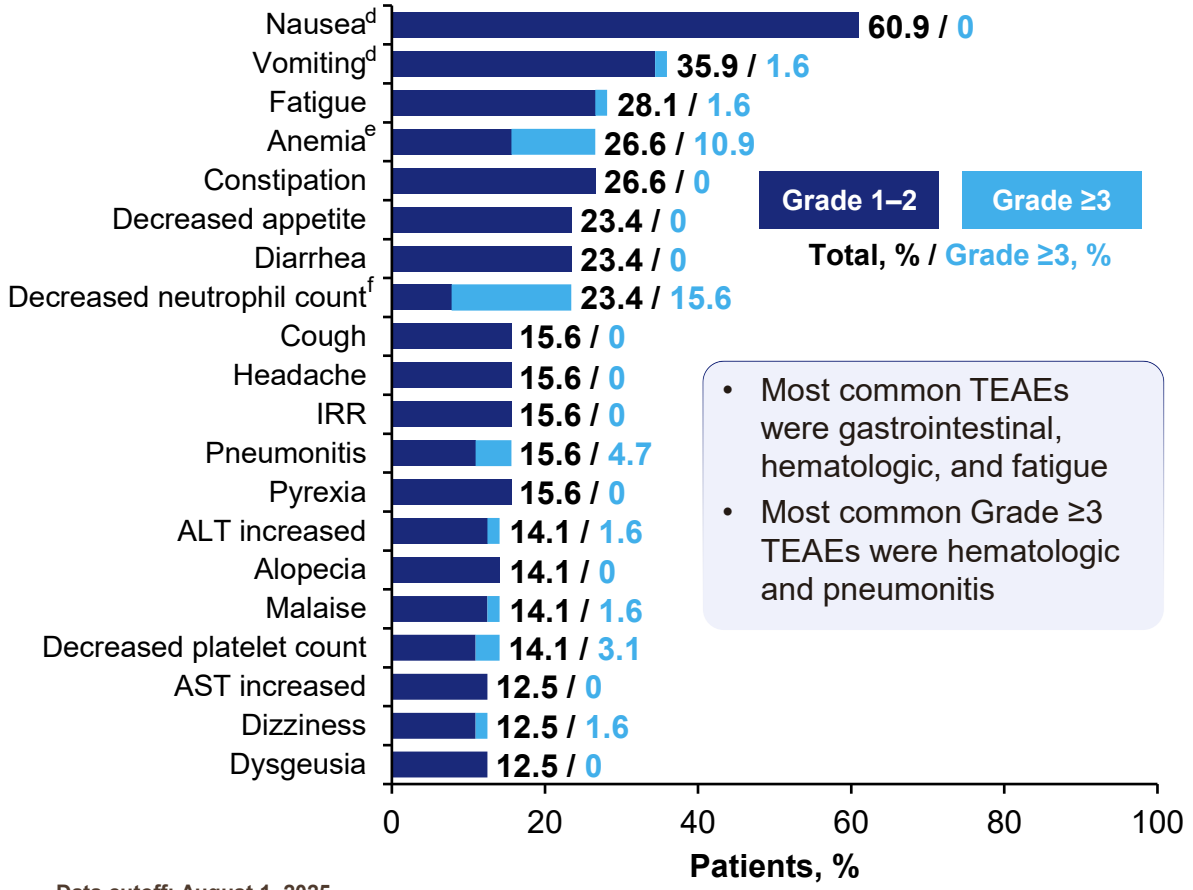
- Any-cause and treatment-related TEAEs were reported in 63 of 64 (98.4%) and 56 of 64 (87.5%) patients, respectively, across all doses
- Doses of ≥8.0 mg/kg were associated with higher rates of dose reduction and treatment discontinuation
- DLTs were reported in 4 of 64 patients (6.3%) across all doses[d]
  - Grade 3 anemia needing transfusion (4.0 mg/kg)
  - Grade 3 abdominal pain (6.0 mg/kg)
  - Grade 4 decreased platelet count (8.0 mg/kg)
- Treatment discontinuations[a] and interruptions[b] were primarily due to ILD/pneumonitis and IRRs, respectively

Data cutoff: August 1, 2025.

[a]Included investigator-reported pneumonitis (n=9), cough (n=2), cerebrovascular accident (n=1), and intracranial hemorrhage (n=1). [b]Treatment interruption: study drug infusion was temporarily stopped and then restarted during the same study visit/dosing cycle. [c]Treatment delay: study drug was not administered at the scheduled cycle/dosing visit but was administered at a later date. [d]An event of Grade 1 malaise was reported as a DLT but was later confirmed as a data entry error.
DLT, dose-limiting toxicity; ILD, interstitial lung disease; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

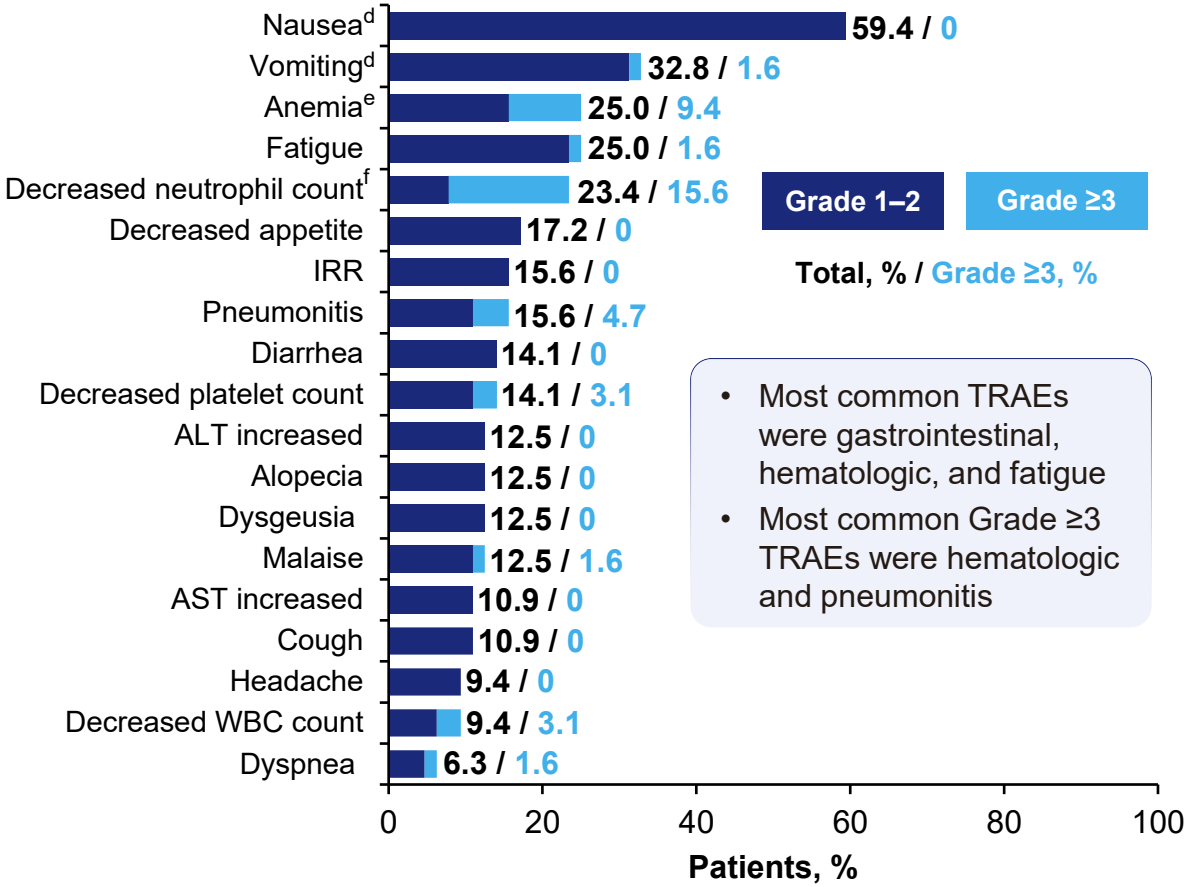
DS3939-077: Most common TEAEs and TRAEs

Any-grade TEAEs (≥12% of patients)[a,b]



- Most common TEAEs were gastrointestinal, hematologic, and fatigue
- Most common Grade ≥3 TEAEs were hematologic and pneumonitis

Any-grade TRAEs (≥5% of patients)[b,c]



- Most common TRAEs were gastrointestinal, hematologic, and fatigue
- Most common Grade ≥3 TRAEs were hematologic and pneumonitis

Data cutoff: August 1, 2025.

[a]TEAEs occurring at any grade in ≥12% of patients and Grade ≥3 TEAEs occurring for those preferred terms in the overall population (N=64). [b]Adverse events were coded using the MedDRA, Version 28.0. [c]TRAEs occurring at any grade in ≥5% of patients and Grade ≥3 TRAEs occurring for those preferred terms in the overall population (N=64). [d]Premedication for the prevention of nausea and vomiting was recommended before each dose of DS-3939. [e]There were no Grade ≥4 anemia events. [f]Included "decreased neutrophil count" and "neutropenia." Three patients experienced Grade 4 decreased neutrophil count. One patient experienced Grade 3 febrile neutropenia (not included in the figure).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

DS3939-077: Adverse events of special interest

Adjudicated treatment-related ILD/pneumonitis[a]

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
Events, n (%)							
Any grade	0	1 (33.3)	2 (10.5)	1 (5.9)	7 (33.3)	0	**11 (17.2)**
Grade 1	0	0	0	0	1 (4.8)	0	**1 (1.6)**
Grade 2	0	1 (33.3)	1 (5.3)	0	4 (19.0)	0	**6 (9.4)**
Grade 3	0	0	1 (5.3)	1 (5.9)	0	0	**2 (3.1)**
Grade 4	0	0	0	0	0	0	**0**
Grade 5	0	0	0	0	2 (9.5)	0	**2 (3.1)**

- Adjudicated treatment-related ILD/pneumonitis was reported in 11 of 64 patients (17.2%) across all doses
  - Per protocol, DS-3939 was permanently discontinued for Grade ≥2 ILD/pneumonitis
  - Most events of adjudicated treatment-related ILD/pneumonitis were Grade 2

IRRs

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
Events, n (%)							
Any grade	0	1 (33.3)	1 (5.3)	6 (35.3)	2 (9.5)	0	**10 (15.6)**
Grade 1	0	1 (33.3)	0	2 (11.8)	1 (4.8)	0	**4 (6.3)**
Grade 2	0	0	1 (5.3)	4 (23.5)	1 (4.8)	0	**6 (9.4)**
Grade 3	0	0	0	0	0	0	**0**
Grade ≥4	0	0	0	0	0	0	**0**

- IRRs were reported in 10 of 64 patients (15.6%) across all doses
  - No Grade ≥3 events
  - No treatment discontinuations due to IRRs
  - Infusion interrupted due to IRRs in 6 of 64 patients (9.4%)
  - 7 patients (10.9%) experienced IRRs during Cycle 1; for most of those patients, IRRs did not reoccur later in treatment

Data cutoff: August 1, 2025.

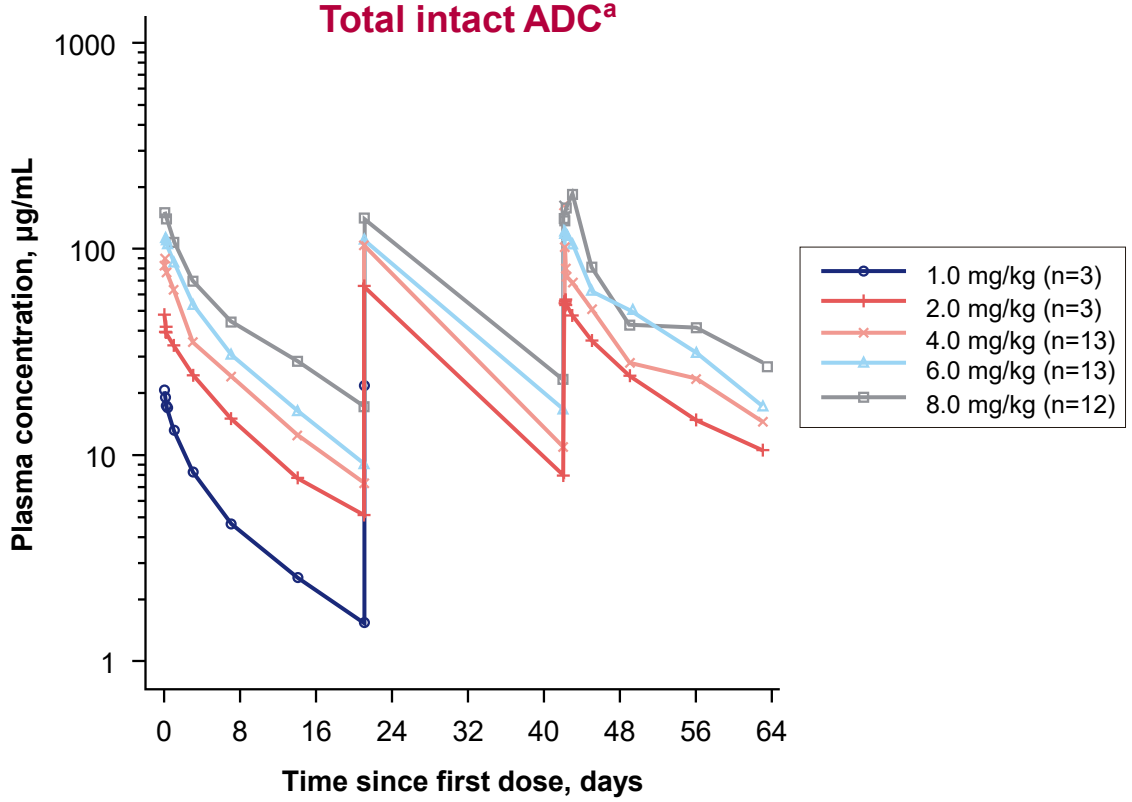
[a]In this dataset with a data cutoff of August 1, 2025, 4 ILD/pneumonitis events were adjudicated as treatment-related after the data cutoff.

ILD, interstitial lung disease; IRR, infusion-related reaction.

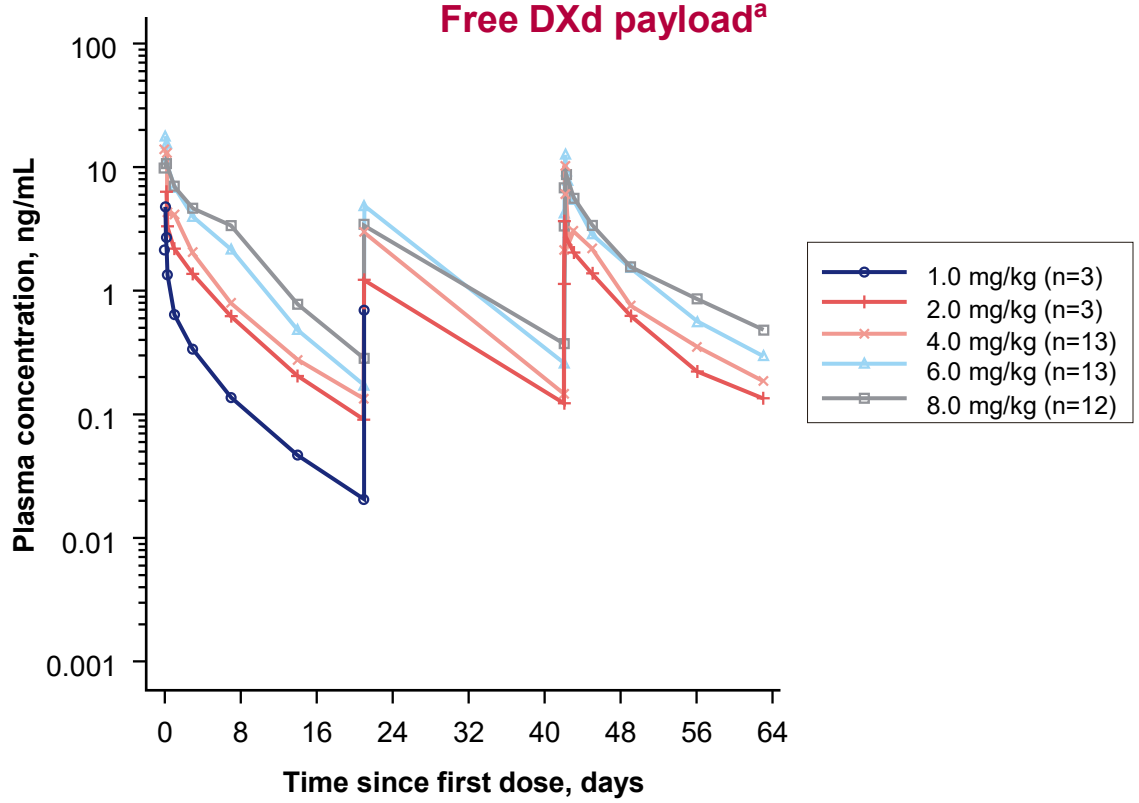
DS3939-077: PK profile supports Q3W dosing

- Total DS-3939 ADC and free DXd payload increased in a dose-proportional manner
- Intact DS-3939 elimination half-life ranged from ~7–11 days, supporting Q3W dosing

Total intact ADC[a]



Free DXd payload[a]

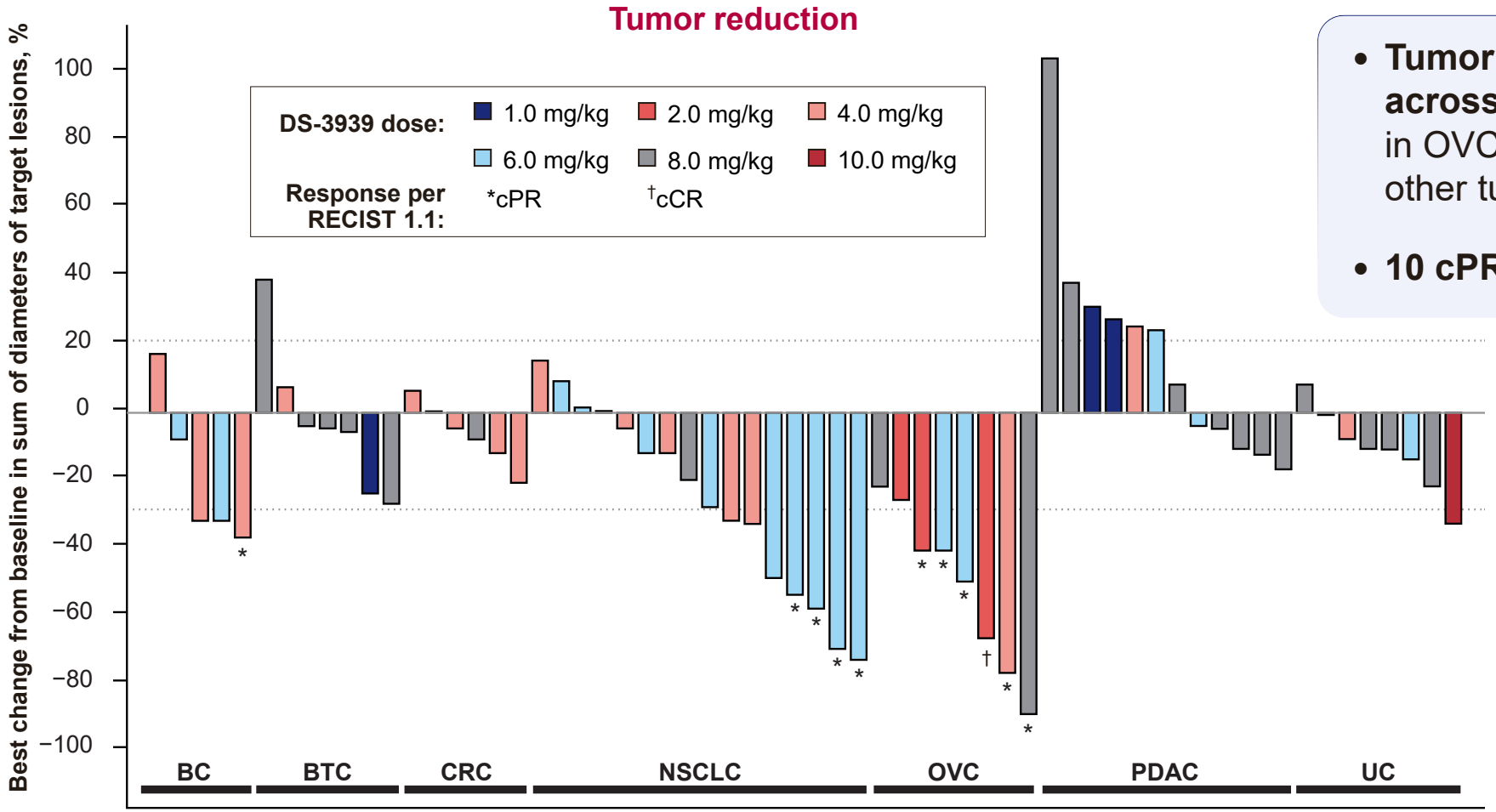


Data cutoff: February 7, 2025

[a]Mean plasma concentration versus time curve over Cycles 1–3. Data points were included where samples were available from ≥2 patients.

ADC, antibody–drug conjugate; PK, pharmacokinetic; Q3W, once every 3 weeks.

DS3939-077: Tumor reductions across doses: 10 cPRs and 1 cCR



- **Tumor reduction was observed across dose levels,** from 2.0 mg/kg in OVC and from 4.0 mg/kg in most other tumor types
- **10 cPRs and 1 cCR[a]**

Data cutoff: August 1, 2025. Median follow-up: 8.8 months (range, 0.6–22.9).

[a]The patient with cCR had lymph nodes only as target lesion.

BC, breast cancer; BTC, biliary tract cancer; cCR, confirmed complete response; cPR, confirmed partial response; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PDAC, primary ductal adenocarcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; UC, urothelial carcinoma.

DS3939-077: Conclusions

Preliminary data from the novel TA-MUC1 ADC DS-3939 FIH study, DS3939-077, show:

- **A manageable safety profile in patients with previously treated advanced/metastatic solid tumors**
  - The most common TRAEs were gastrointestinal, hematologic, and fatigue; most were Grade 1 or 2
  - Adjudicated treatment-related ILD/pneumonitis was reported in 11 of 64 patients (17.2%); most were Grade 2
    - Grade 5 treatment-related ILD/pneumonitis occurred in 2 patients at the 8 mg/kg dose
  - IRRs were reported in 10 of 64 patients (15.6%) across all doses; all were Grade 1 or 2
- **DS-3939 demonstrated promising preliminary antitumor activity across dose levels and tumor types in previously treated patients**

Dose expansion and optimization are ongoing; patients with various tumor types are being enrolled

Data cutoff: August 1, 2025.
ADC, antibody–drug conjugate; FIH, first-in-human; ILD, interstitial lung disease; IRR, infusion-related reaction; TA-MUC1, tumor-associated mucin 1; TRAE, treatment-related adverse event.

Acknowledgments

We thank the patients, their families, and their caregivers for participating, and the study staff for their contributions

This study is sponsored by Daiichi Sankyo, Inc. Medical writing support was provided by Alexandra Mascaro, PhD, of BOLDSCIENCE, Inc., and was funded by Daiichi Sankyo, Inc.
Editorial support was provided in accordance with Good Publication Practice Guidelines 2022 (www.ismpp.org/gpp-2022).