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DS-3939a, a novel TA-MUC1-targeting antibody-drug conjugate (ADC) with a DNA topoisomerase I inhibitor DXd, exhibits potent antitumor activity in preclinical models

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Daiichi Sankyo Co., Ltd.

Daiichi-Sankyo

Disclosure Information

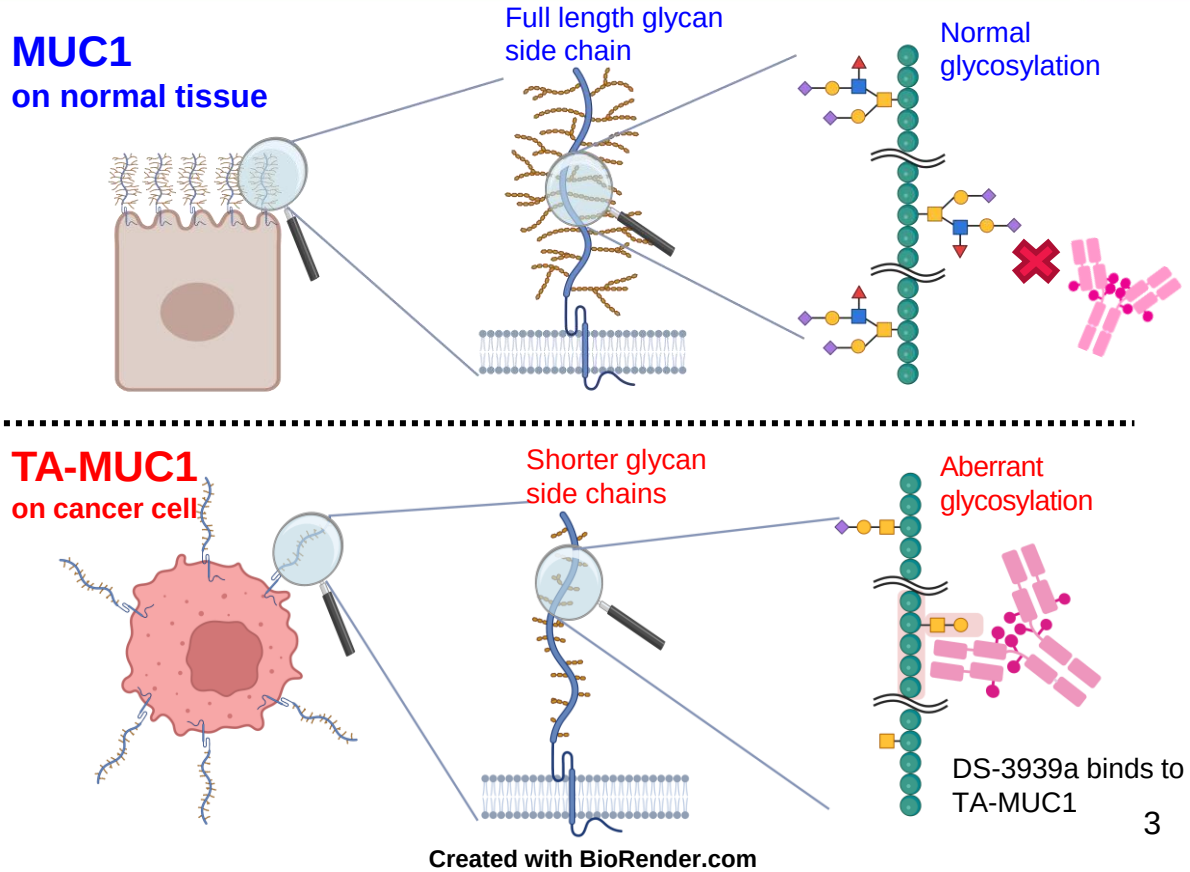
Kohei Takano

I have the following relevant financial relationships to disclose:

Employee of: Daiichi Sankyo Co., Ltd.

Tumor-associated mucin-1 (TA-MUC1) is an attractive target for cancer therapy

- TA-MUC1 is a tumor-specific transmembrane glycoprotein with aberrant glycosylation.
- TA-MUC1 is highly expressed in various human epithelial cancers.



DS-3939a is a TA-MUC1 targeting ADC using Daiichi Sankyo(DS)'s DXd ADC technology

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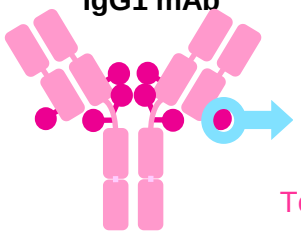
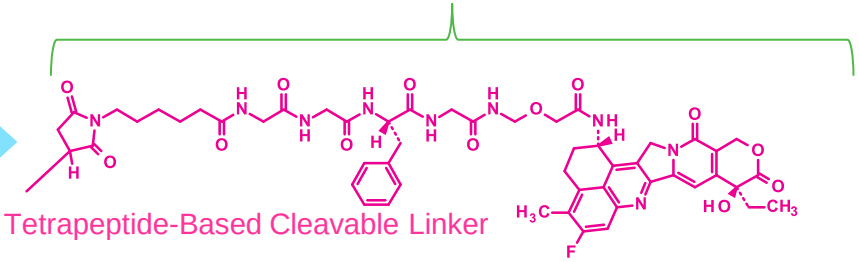
Humanized anti-TA-MUC1 IgG1 mAb



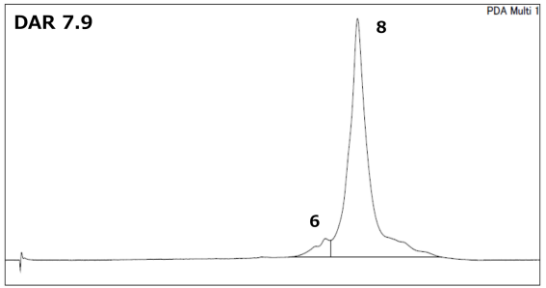
Deruxtecan



Tetrapeptide-Based Cleavable Linker

Topoisomerase I Inhibitor payload (DXd)

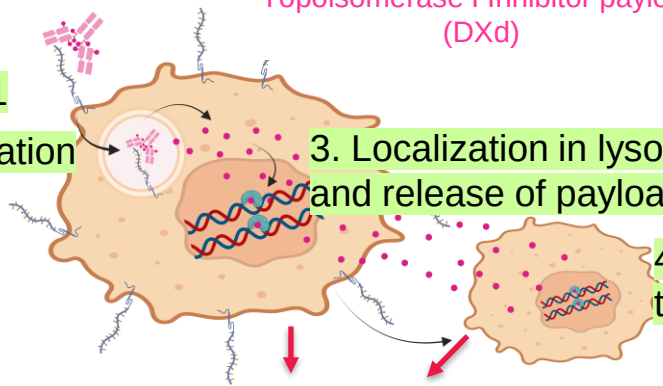
Conjugated drug distribution (*HIC chart)



High *DAR (approx.8)

Mode of Action

1. Binding to TA-MUC1
2. Internalization
3. Localization in lysosome and release of payload
4. Penetration of released payload to neighboring cells



Apoptosis

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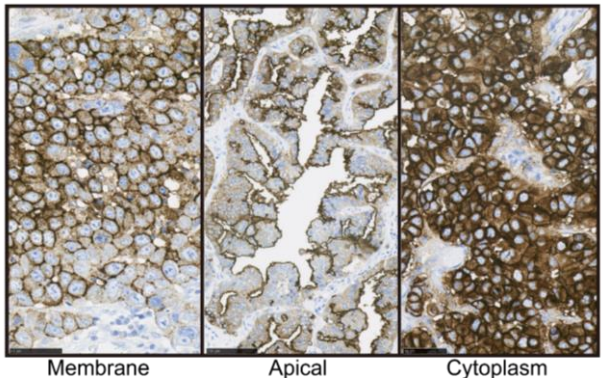
*HIC: Hydrophobic Interaction Chromatography.
*DAR : Drug-to-Antibody Ratio

High TA-MUC1 expression in various cancers were confirmed in human tissue micro array

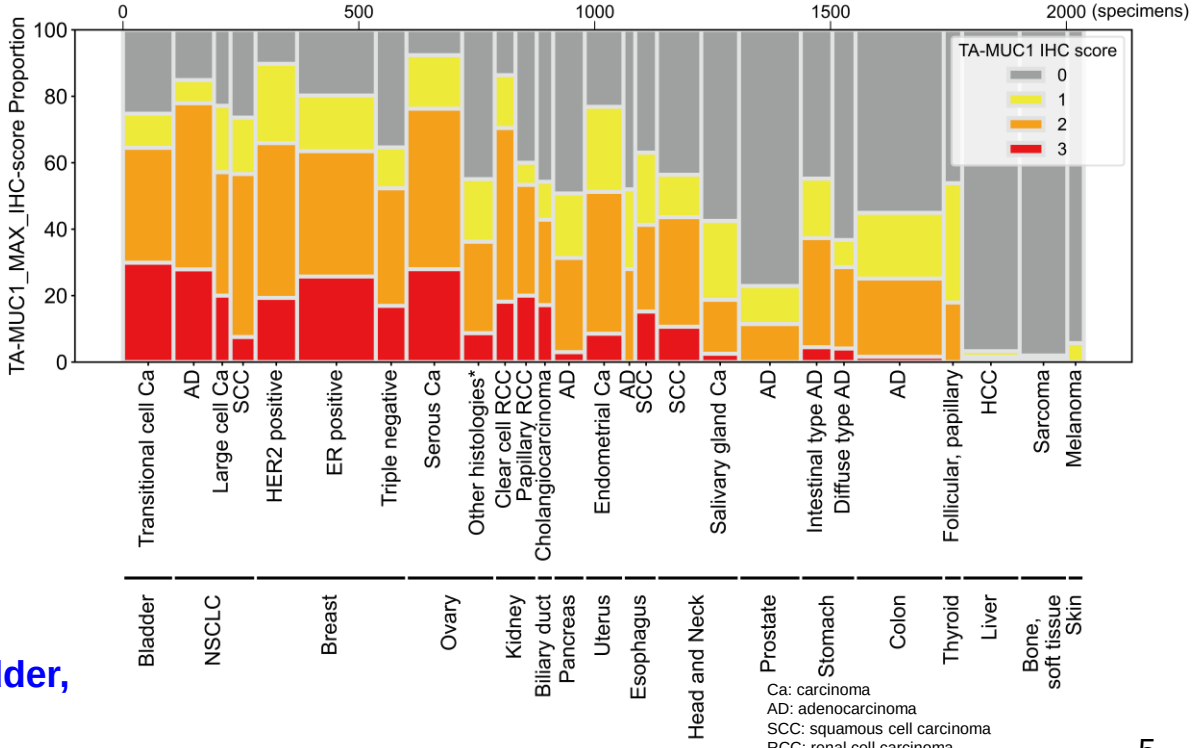
The staining pattern of TA-MUC1



Scoring method
IHC score of TA-MUC1 on membranous, cytoplasmic or apical membranous region were visually scored as 0, 1+, 2+, or 3+ based on the highest intensity occupying ≥ 10% of the evaluated area. The representative IHC score for each specimen was determined by adopting the maximum score of each region.

TA-MUC1 is highly expressed in bladder, lung, breast and ovarian cancer.

The distribution of IHC scores in each cancer type



Ca: carcinoma
AD: adenocarcinoma
SCC: squamous cell carcinoma
RCC: renal cell carcinoma
HCC: hepatocellular carcinoma
* : Mucinous Ca, Endometrioid Ca, Clear cell Ca

DS-3939a specifically bound to TA-MUC1 by recognizing both of its glycan and backbone peptide

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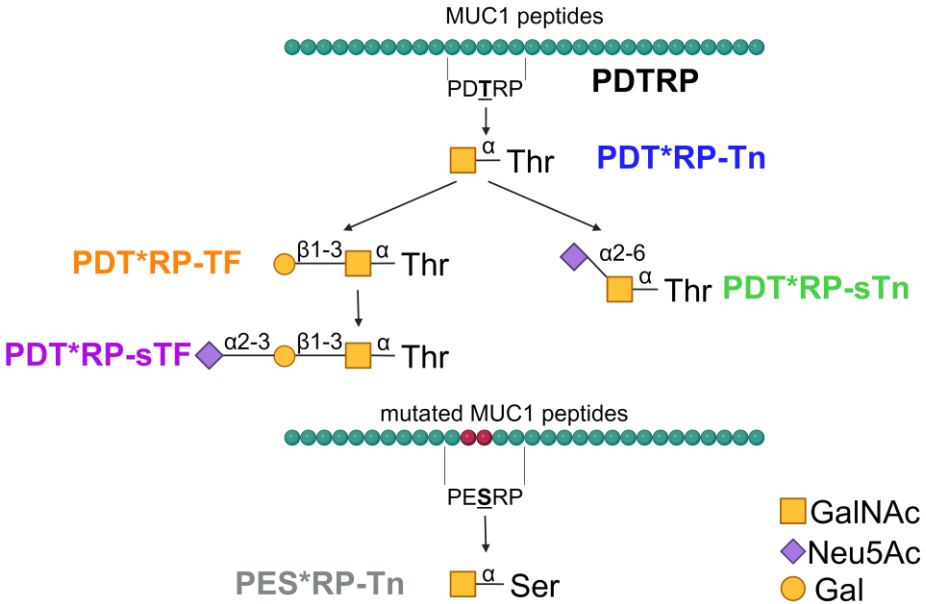
Schematic diagram of variously glycosylated MUC1 tandem repeat sequence peptides



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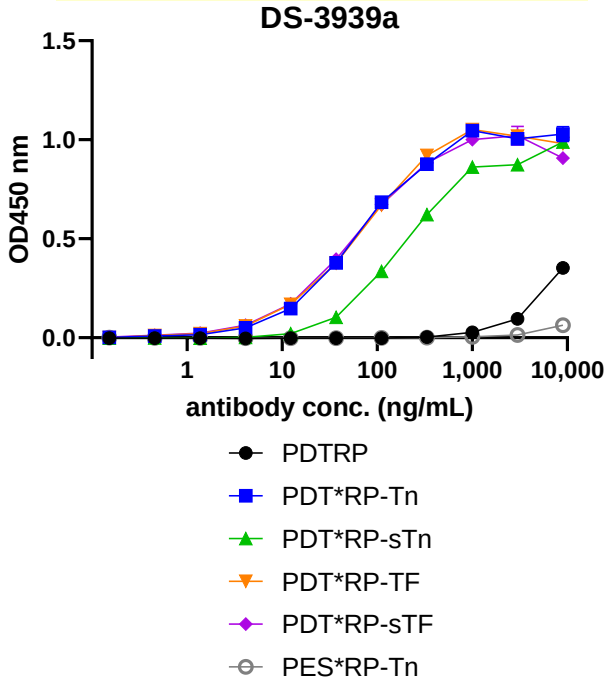
Binding activity (ELISA)



DS-3939a is strongly bound to glycosylated MUC1 peptides (PDT*RP-Tn, sTn, TF, sTF), but had minimal binding to non-glycosylated MUC1 peptides (PDTRP) and an amino acid-substituted MUC1 peptide with Tn glycan (PES*RP-Tn).

DS-3939a exhibited TA-MUC1-dependent cytotoxic activity *in vitro* by inducing DNA damage and apoptosis

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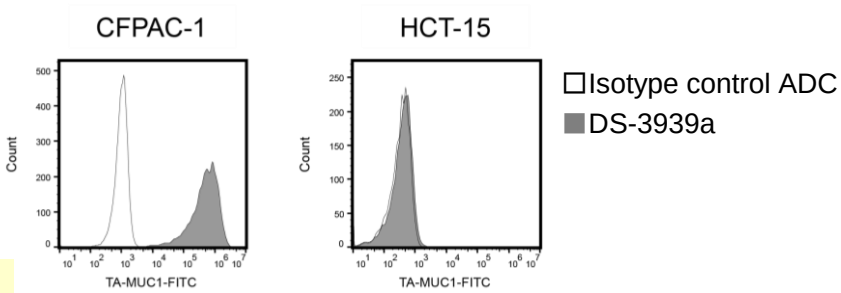
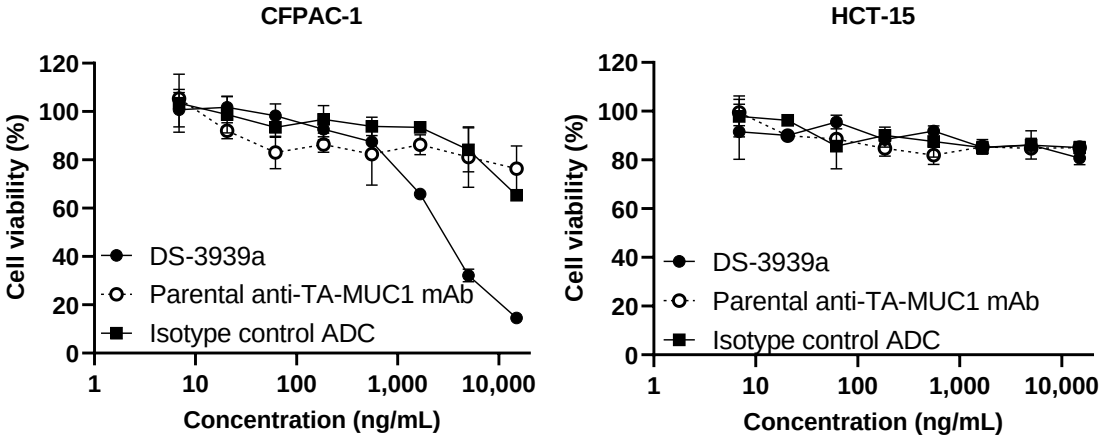
TA-MUC1 expression

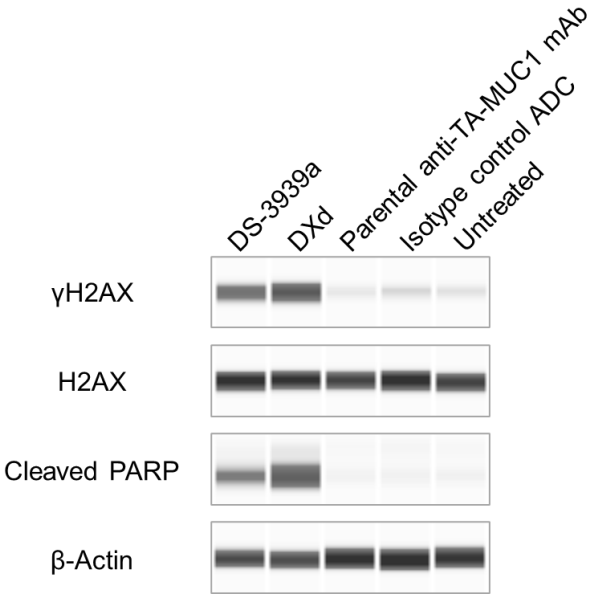


Cell growth inhibition assay



DS-3939a specifically inhibited the growth of the TA-MUC1 positive cell line.

Western Blotting with DNA damage (γH2AX) and apoptosis (cleaved PARP) marker



Both γH2AX and cleaved PARP were induced in CFPAC-1 cells treated with either DS-3939a or DXd payload.

DS-3939a exhibited significant antitumor effects against preclinical *in vivo* models

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Human cancer cell line derived xenograft (CDX) models

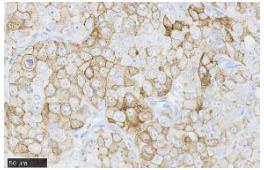
Patient derived xenograft (PDX) model

CFPAC-1

(pancreatic adenocarcinoma cell line)

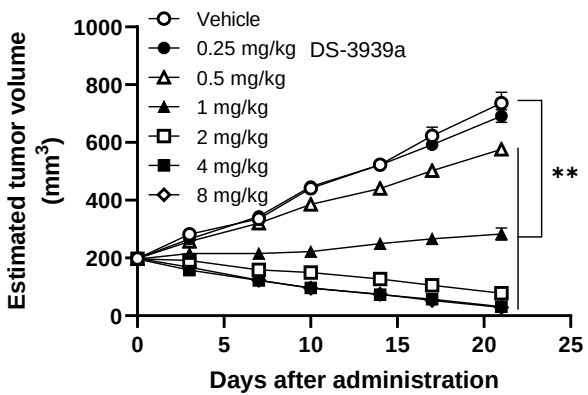
NCI-H2110

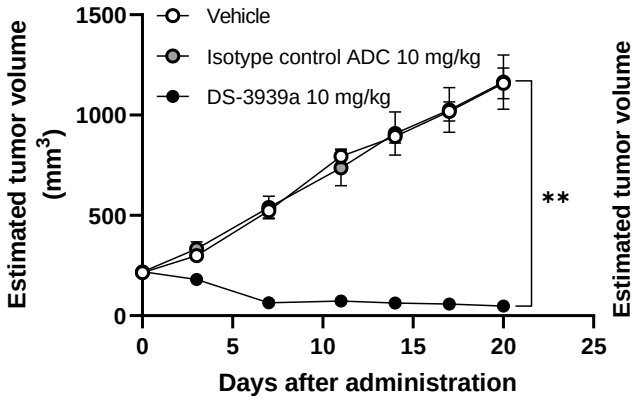
(non-small cell lung cancer cell line)

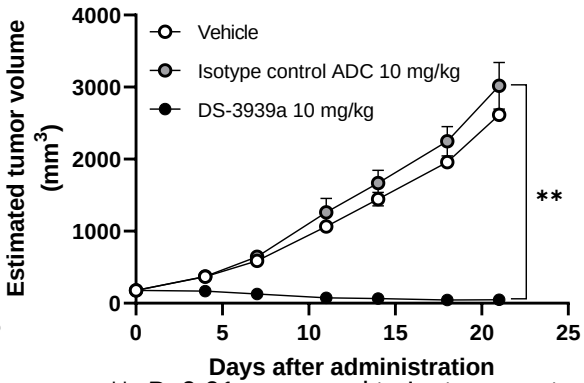


NIBIO-NS1

(non-small cell lung cancer PDX)







**, *P*<0.01 compared to Isotype control ADC

DS-3939a (single administration) exhibited significant antitumor effects against both CDX and PDX models.

DS-3939a exhibited strong antitumor effects against various PDX models

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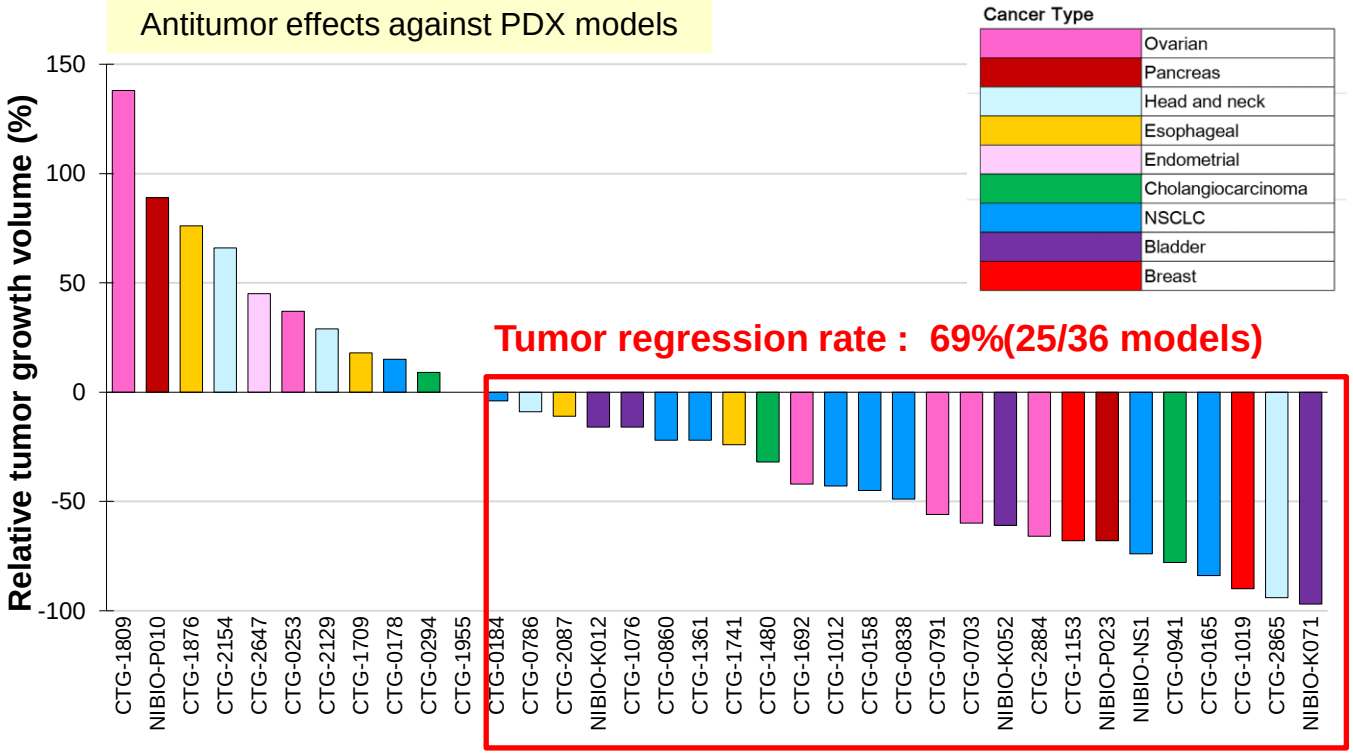
Antitumor effects against PDX models



DS-3939a (10 mg/kg, single administration) demonstrated robust antitumor activity against multiple cancer types in PDX models.

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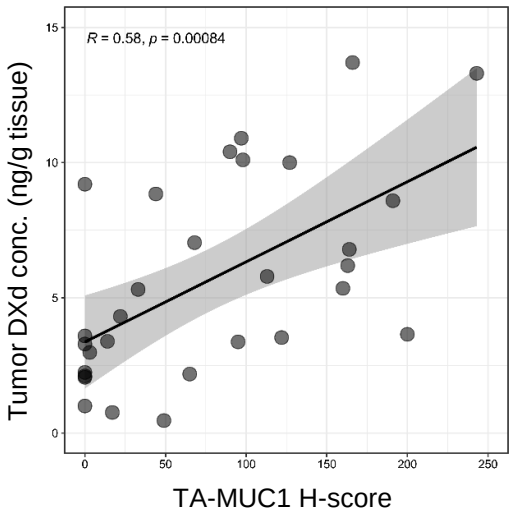
Correlation plot of TA-MUC1 expression with payload conc. in tumor



The concentration of DXd payload showed a modest correlation with TA-MUC1 H-score.

DS-3939a induced strong tumor regression even after treatment of other FDA approved ADCs

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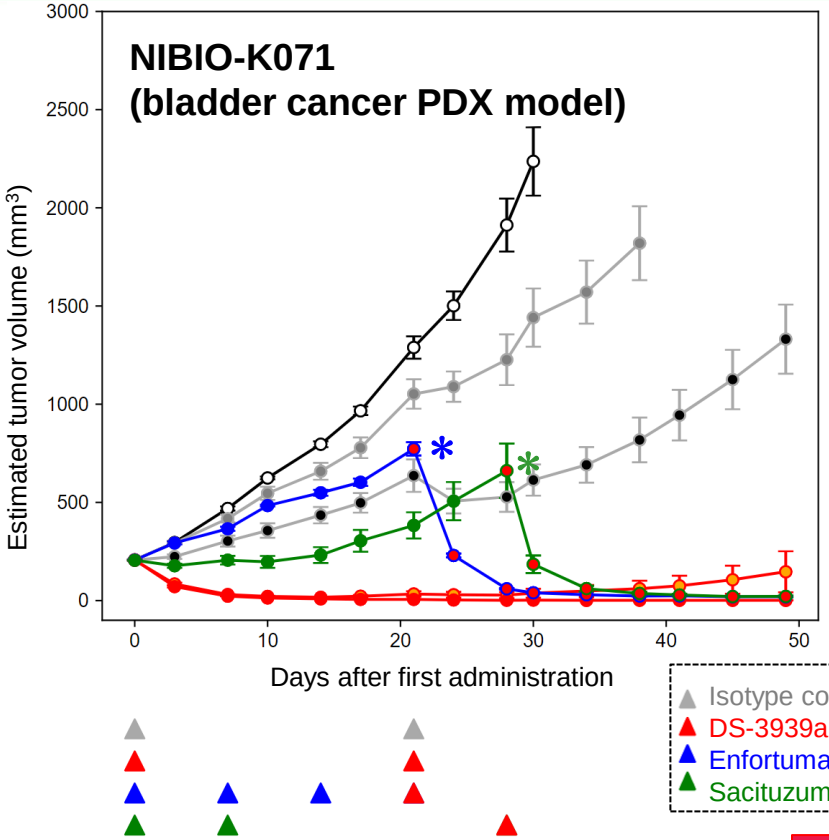

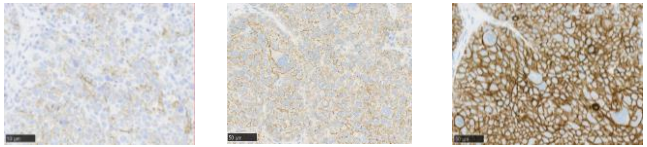

- Vehicle
- Isotype control ADC 3mg/kg
- Isotype control ADC 10mg/kg
- DS-3939a 3mg/kg
- DS-3939a 10mg/kg
- Enfortumab vedotin 3mg/kg → DS-3939a 10mg/kg *
- Sacituzumab govitecan 10mg/kg → DS-3939a 10mg/kg *

- Isotype control ADC
- DS-3939a
- Enfortumab vedotin (Nectin-4 MMAE)
- Sacituzumab govitecan (TROP2 SN38)

Subsequent treatment with DS-3939a after Enfortumab vedotin or Sacituzumab govitecan rapidly induced robust tumor regression.

Conclusion

- DS-3939a exhibited TA-MUC1-dependent *in vitro* cell growth inhibition and *in vivo* tumor regression against several CDX models and various PDX models.

- DS-3939a also induced strong tumor regression even after treatment of other FDA approved ADCs in xenograft model.

- A first-in-human phase 1/2 study in patients with advanced solid tumors is currently ongoing (NCT05875168).

【Trial in Progress: Abstract Presentation Number #CT291】

Acknowledgement

- Glycotope GmbH
- University Hospital Basel (for providing TMA)
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- All the contributors to DXd-ADC projects in Daiichi Sankyo

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