Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

DS-7300 Seminar

Agenda

- Overview of DXd-ADC Technology*   * Note: Data of ENHERTU® will be shown.
- About B7-H3
  - What is B7-H3?
  - Relationship between B7-H3 expression and prognosis in cancers
- The characteristics of DS-7300
  - Compound background
  - In vitro efficacy data
  - In vivo efficacy data
  - Competitor's info
- Ph1 study
  - Trial design of J-101 study (First-In-Human trial for DS-7300)

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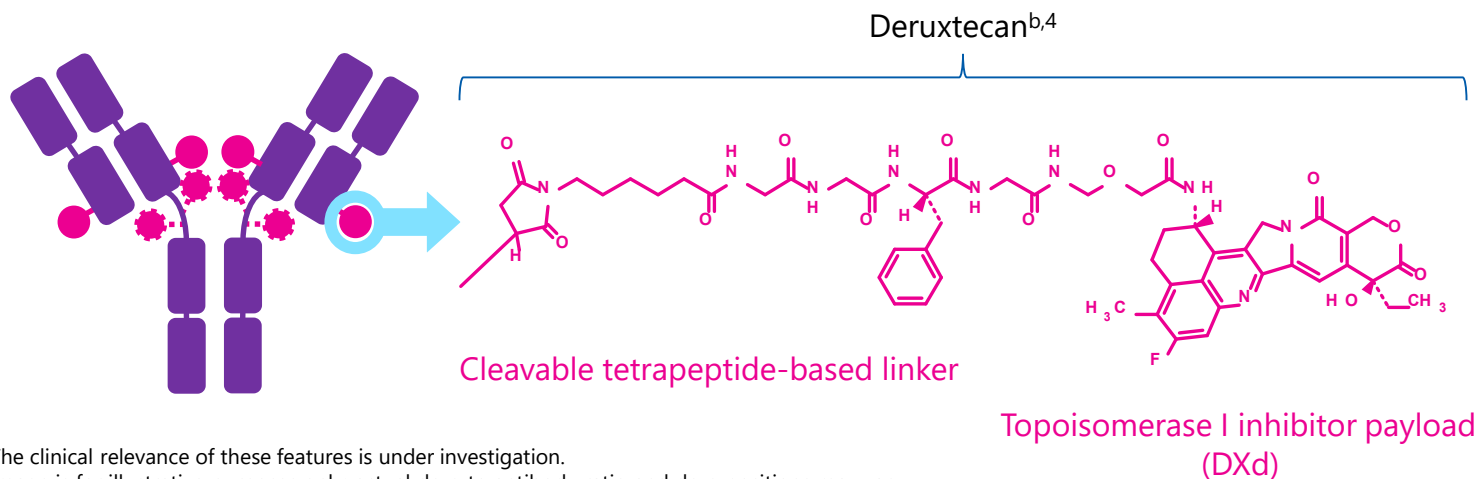   - Trial design of J-101 study (First-In-Human trial for DS-7300)

DXd ADCs are composed of 3 components[1,2]:

- A monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

DXd ADC Technology[b]

Deruxtecan[b,4]

Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

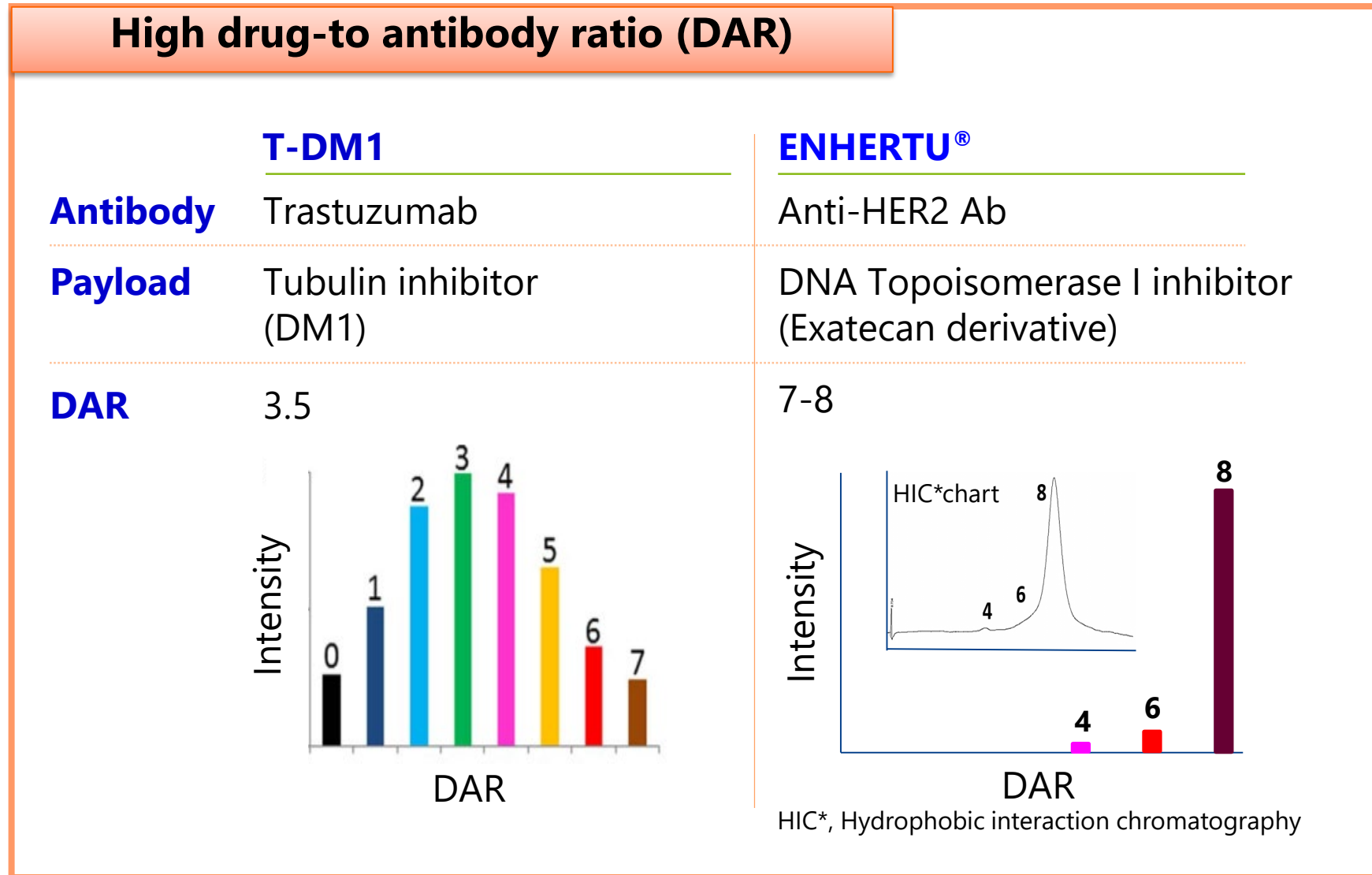| Payload mechanism of action: topoisomerase I inhibitor [a,1-5] |
| --- |
| High potency of payload [a,2-5] |
| Optimized drug to antibody ratio [a,c,1-4] |
| Payload with short systemic half-life [a,c,2,3,] |
| Stable linker-payload [a,2,3,5] |
| Tumor-selective cleavable linker [a,2-6] |
| Bystander antitumor effect [a,2,7] |

[a] The clinical relevance of these features is under investigation.
[b] Image is for illustrative purposes only; actual drug to antibody ratio and drug positions may vary.
[c] Based on animal data.

1. Okajima D, et al. Poster presented at: AACR-NCI-EORTC International Conference; October 26-30, 2019; Boston, MA [abstract C026].
2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185.
3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108.
4. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161.
5. Koganemaru S, et al. *Mol Cancer Ther*. 2019;18:2043-2050.
6. Haratani K, et al. *J Clin Invest*. 2020;130(1):374-388.
7. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

High drug-to antibody ratio (DAR)

	T-DM1	ENHERTU®
Antibody	Trastuzumab	Anti-HER2 Ab
Payload	Tubulin inhibitor (DM1)	DNA Topoisomerase I inhibitor (Exatecan derivative)
DAR	3.5	7-8

HIC*, Hydrophobic interaction chromatography

Source: Ogitani-Y et al., Clin. Cancer Res. 2016; 22:5097-5108, Marcoux-J et al., Protein Science 2015; 24:1210-1223

DXd-ADC: Stable Drug-linker in Plasma (e.g., ENHERTU®)

Plasma conc. of ENHERTU® and payload in monkey

Total Ab (ADC + Ab)

DS-8201a (DAR8)
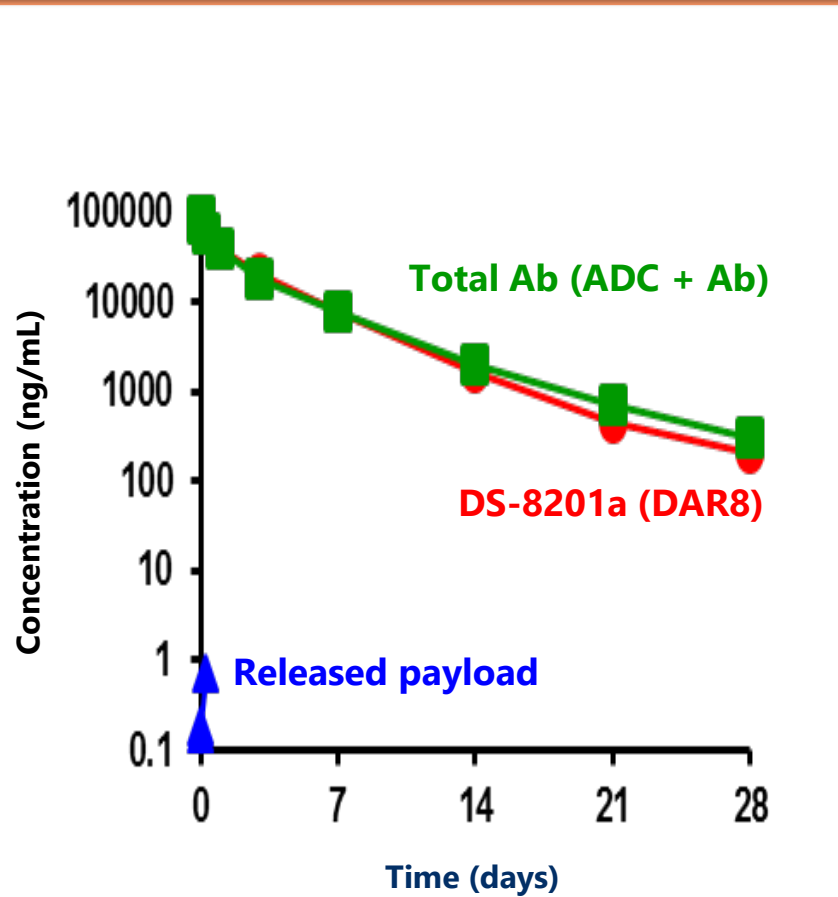
Released payload

Source: Ogitani-Y *et al.*, Clin. Cancer Res. 2016; 22:5097-5108

Release rates of DXd from ENHERTU® in plasma

- Mouse plasma
- Rat plasma
- Monkey plasma
- Human plasma
- PBS + 1%BSA
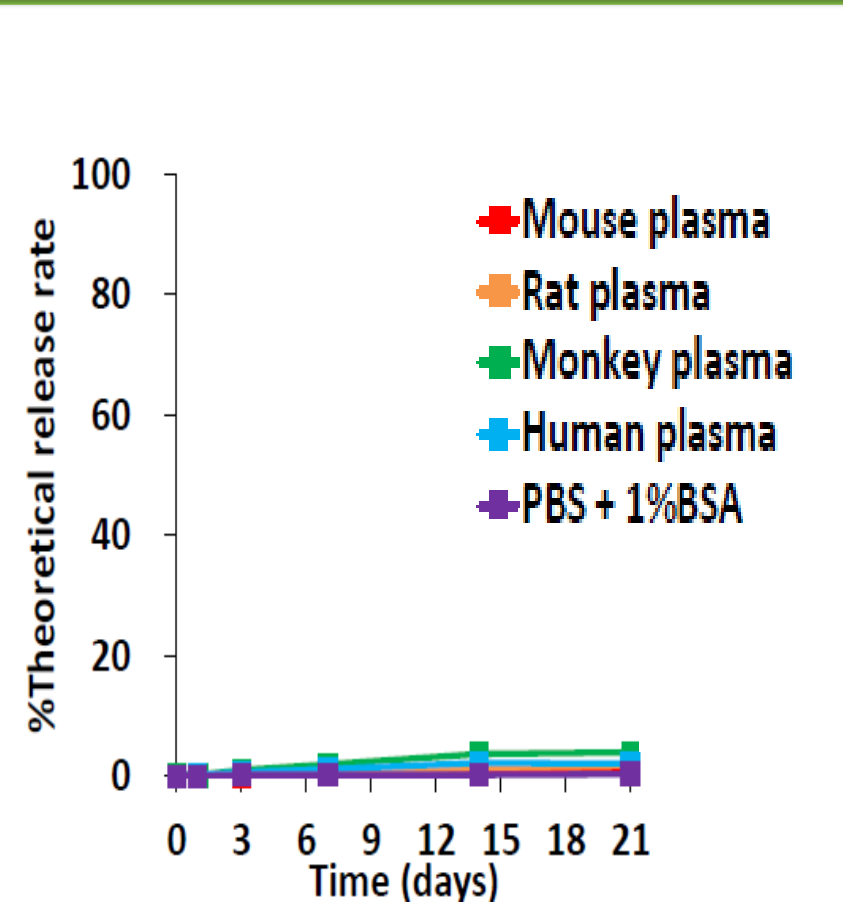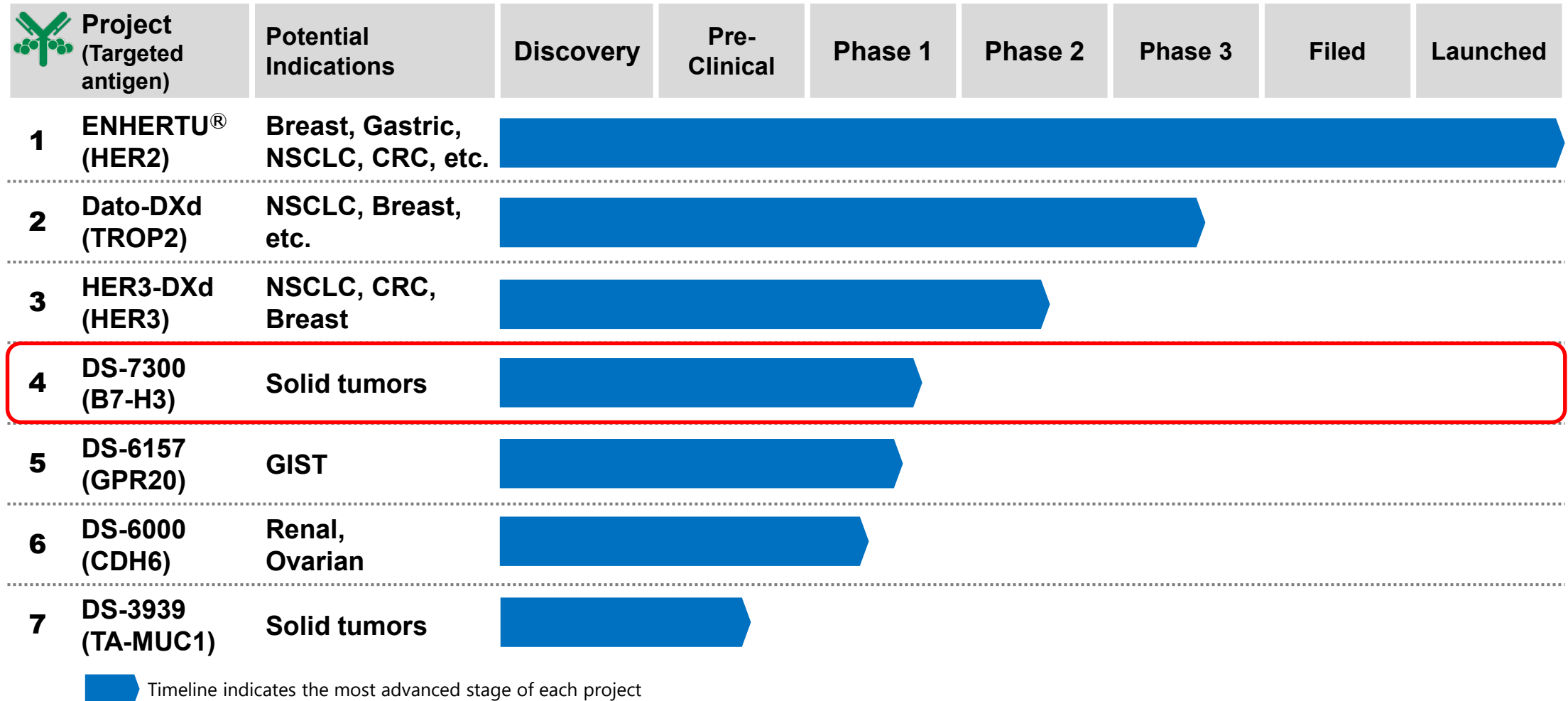
Source: Oitate-M *et al.*, World ADC 2017 San Diego

DXd-ADC: Mode of Action (MOA) (e.g., ENHERTU®)

- ADC selectively targets antigen-expressing tumors
- Payload is released by lysosomal enzymes into tumors
- Membrane-permeable payload attacks neighboring cancer cells which is effective against heterogeneous tumors ➔ **Bystander anti-tumor effect**

MOA of DXd-ADC (ex: ENHERTU®)
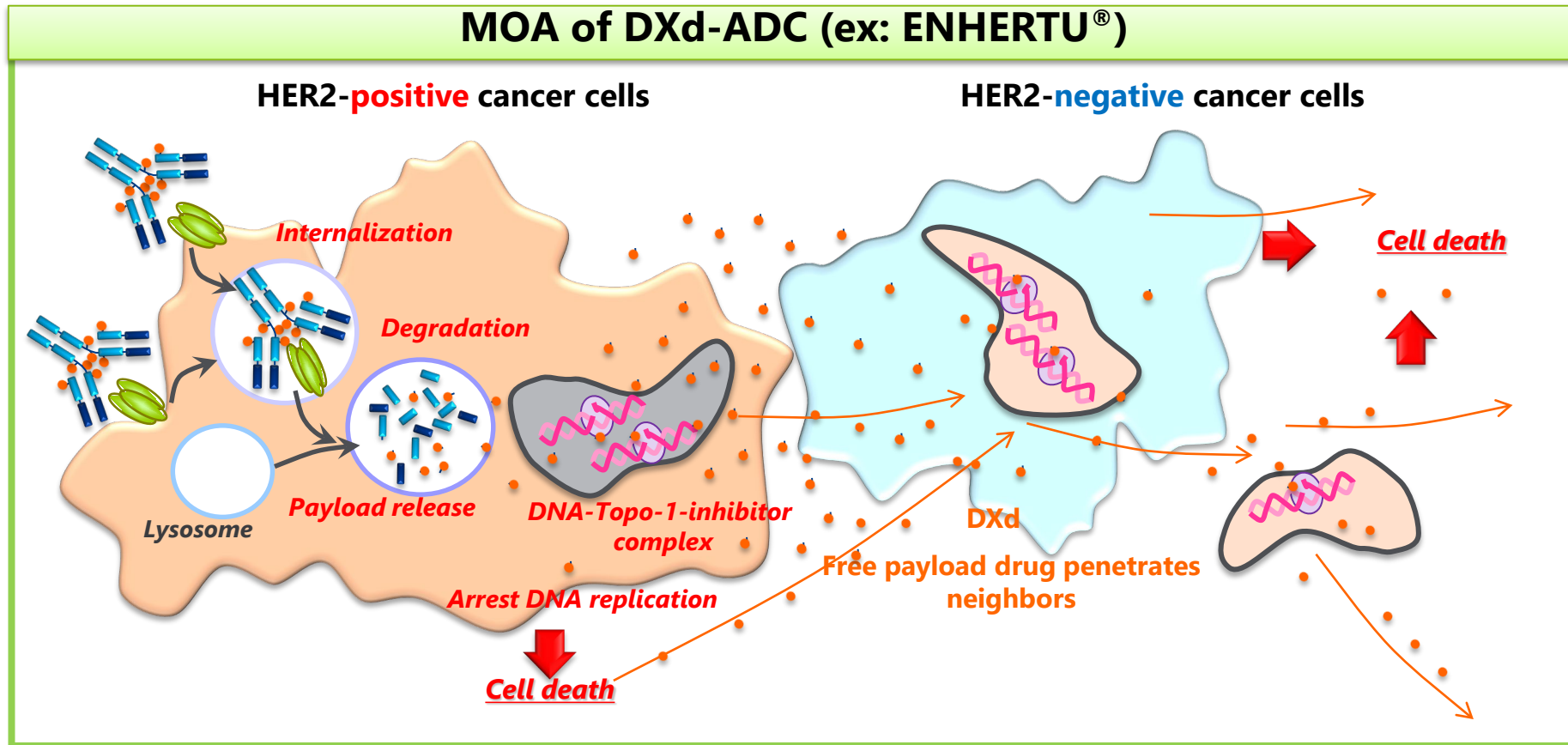
Daiichi Sankyo ADC Franchise

ADC Franchise

Project (Targeted antigen)	Potential Indications	Discovery	Pre-Clinical	Phase 1	Phase 2	Phase 3	Filed	Launched
1 ENHERTU® (HER2)	Breast, Gastric, NSCLC, CRC, etc.	██ →						
2 Dato-DXd (TROP2)	NSCLC, Breast, etc.	██████████████████████████████████████ →						
3 HER3-DXd (HER3)	NSCLC, CRC, Breast	████████████████████████████ →						
4 DS-7300 (B7-H3)	Solid tumors	██████████████████████ →						
5 DS-6157 (GPR20)	GIST	██████████████████████ →						
6 DS-6000 (CDH6)	Renal, Ovarian	████████████████████ →						
7 DS-3939 (TA-MUC1)	Solid tumors	██████████████ →						

◢ Timeline indicates the most advanced stage of each project

CRC: colorectal cancer, GIST: gastrointestinal stromal tumor, NSCLC: non-small cell lung cancer,

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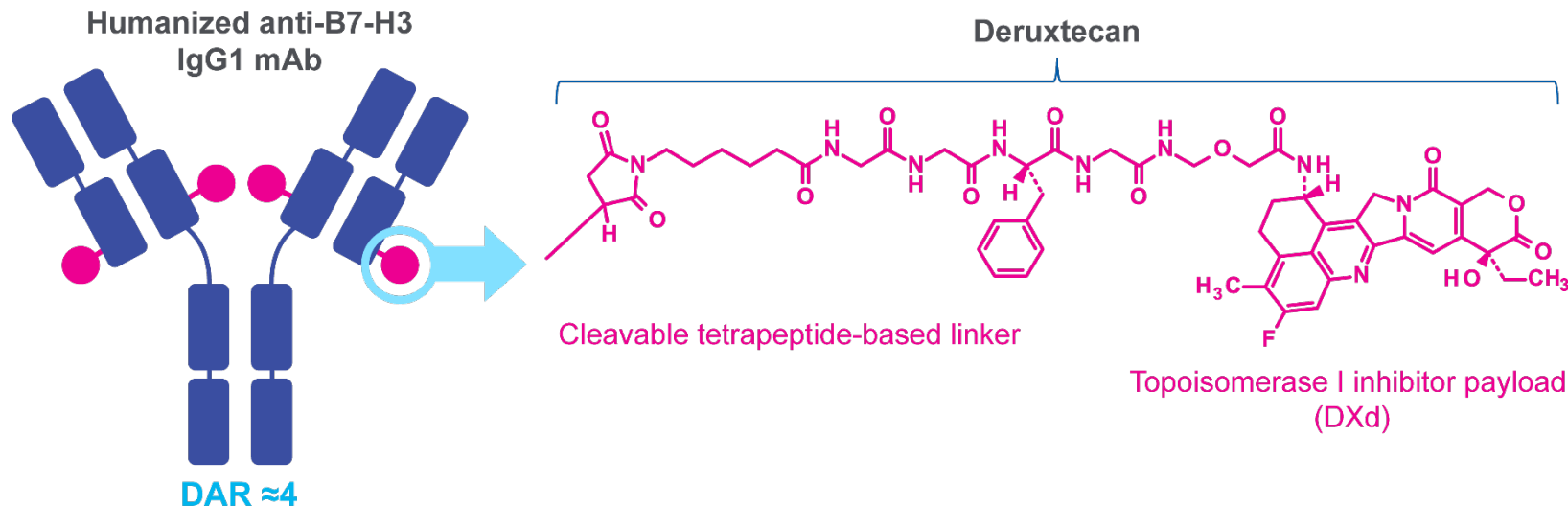   - Trial design of J-101 study (First-In-Human trial for DS-7300)

B7-H3 (CD276) Biology: Overview

- Molecular structure & family:
  - ✓ B7-H3 is a type I transmembrane protein
  - ✓ B7-H3 belongs to the B7 family which includes immune checkpoint molecules such as CTLA-4 ligands, and PD-L1

- Expression:
  - ✓ B7-H3 is highly expressed in various solid cancers, whereas it is expressed at relatively low levels in normal tissues

- Epidemiology:
  - ✓ B7-H3 overexpression is associated with poor prognosis in some cancers including NSCLC and esophageal cancer
  - ✓ B7-H3 expression is suggested to negatively correlated with responsiveness to anti-PD-1 therapy in NSCLC

- Function:
  - ✓ The function of B7-H3 remains to be fully elucidated
  - ✓ B7-H3 has been reported to have immune inhibitor and stimulatory effects
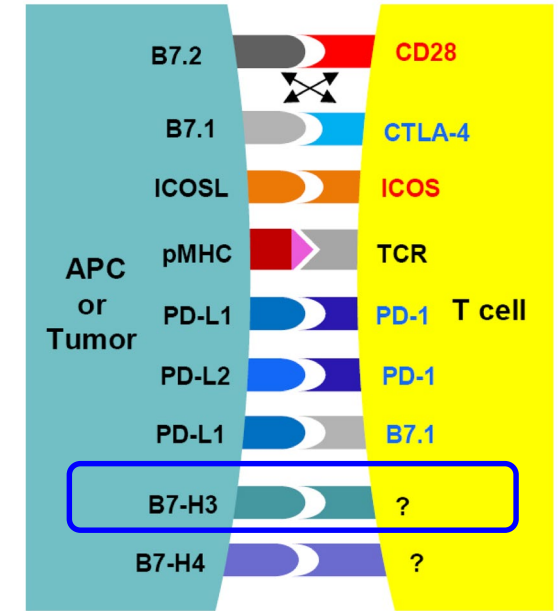
Source: Leung J, et al. *Immune Netw*. 2014

B7-H3 Expression in Various Solid Tumors
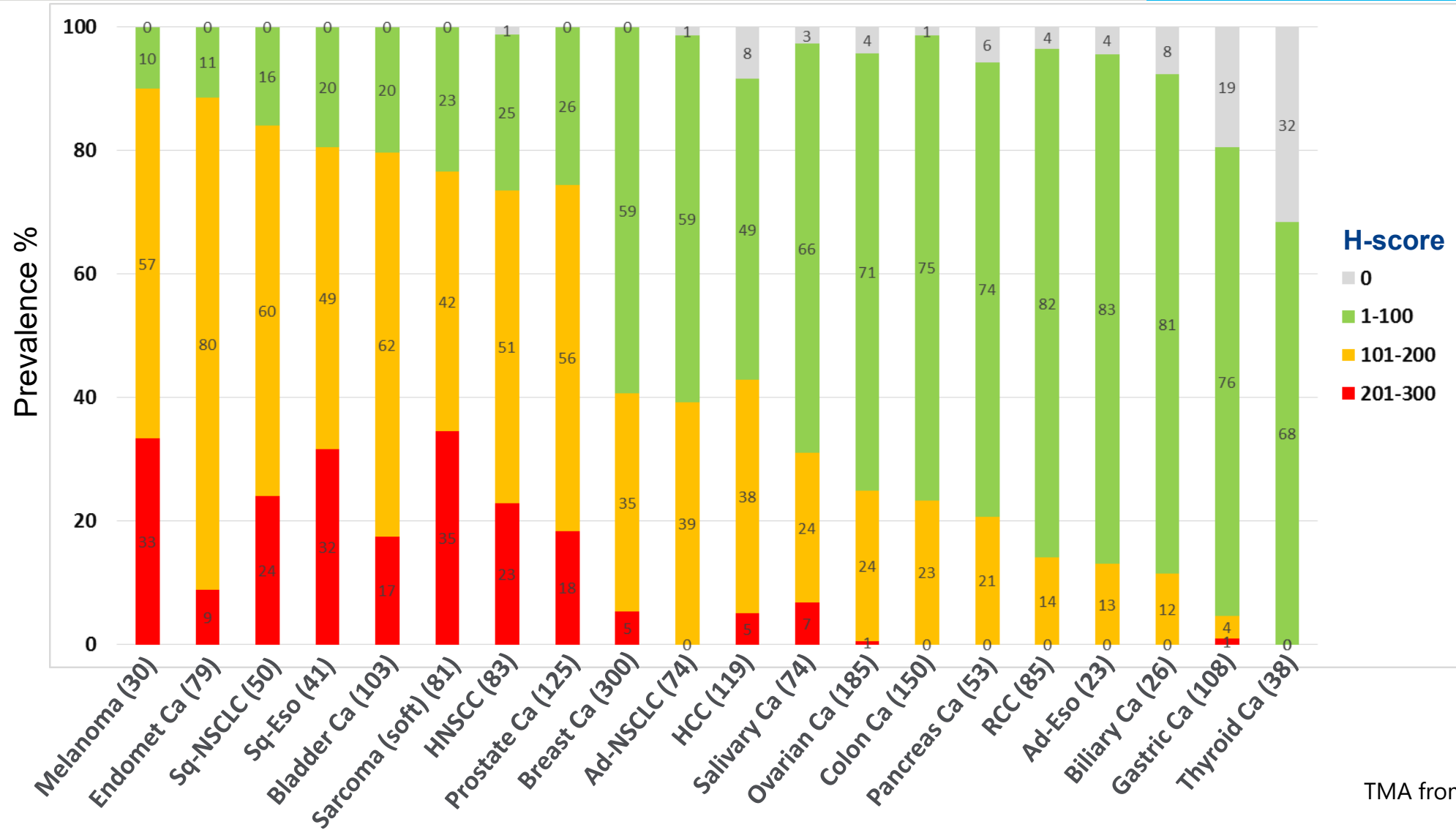
TMA from University Basel

B7-H3 Overexpression Is Associated with Poor Prognosis/Outcome in Cancer

- High B7-H3 protein level was associated with poor overall survival in <u>NSCLC</u>

  Altan M, et al. *Clin Cancer Res.* 2017;23(17): 5202–5209

- Higher B7-H3 expression was associated with poorer survival outcomes in <u>ESCC</u>

  Song J et al. *Onco Targets Ther.* 2016;9:6257-6263

- High B7-H3 expression was significantly associated with decreased OS and PFS in <u>bladder cancer</u>

  Xu Z, et al. *Oncol Lett.* 2018;15(5):6519-6526

- Overexpression of B7-H3 in tumor cells was associated with shortened overall survival in <u>endometrial cancer</u>

  Brunner A, et al. *Gynecol Oncol.* 2012;124(1):105-111

- Patients with strong intensity for B7-H3 were at significantly increased risk of clinical cancer recurrence and cancer-specific death in <u>prostate cancer</u>

  Zhan X, et al. *Proc Natl Acad Sci U S A.* 2007;104(49):19458-19463

- B7-H3 expression was correlated critically with <u>nonresponsiveness to anti-PD-1 immunotherapy</u> in <u>NSCLC</u>

  <u>Yonesaka K, et al. *Clin Cancer Res.* 2018;24(11):2653-2664</u>

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DS-7300 is an antibody-drug conjugate (ADC) composed of a humanized anti–B7-H3 immunoglobulin G1 (IgG1) monoclonal antibody conjugated to a drug linker that releases its payload (DXd) upon internalization by cancer cells

DS-7300 ADC

Humanized anti-B7-H3 IgG1 mAb

DAR ≈4

Deruxtecan

Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

7 Key Attributes[a] of DXd-ADC

- Payload MOA: DNA Topoisomerase I inhibitor
- High potency of payload
- Optimized DAR
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

[a]The clinical relevance of these features is under investigation.
Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185., Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108., Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142., Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.
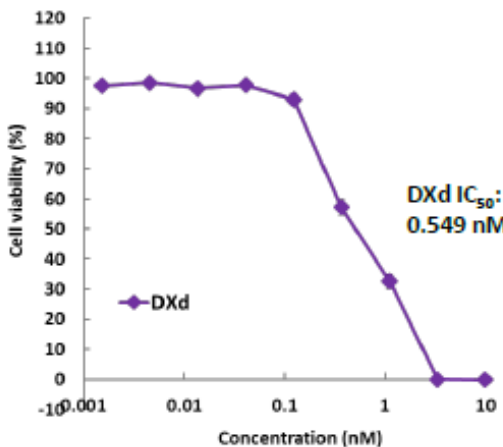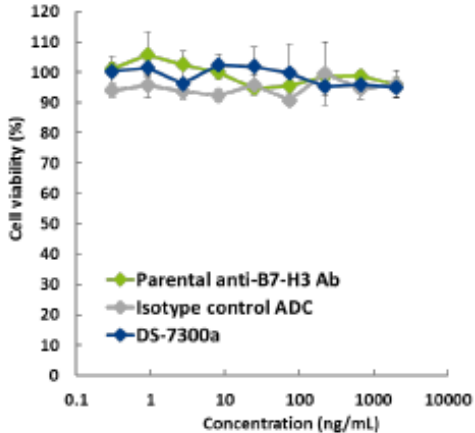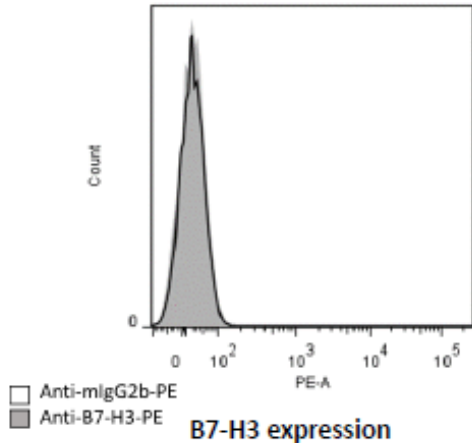
B7-H3 expression of human cancer cells and *in vitro* cell growth inhibition by DS-7300a
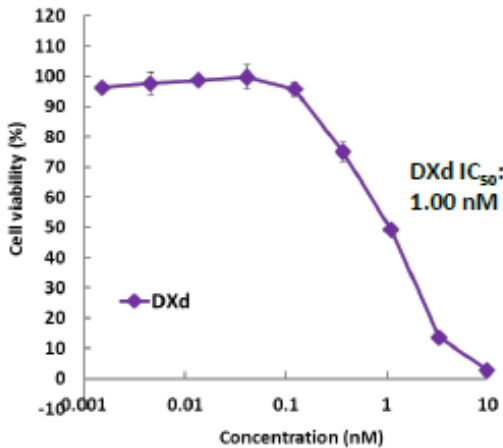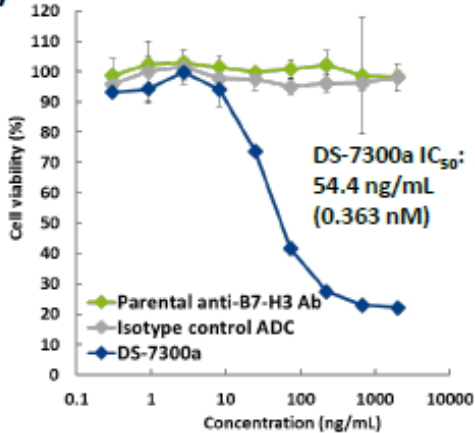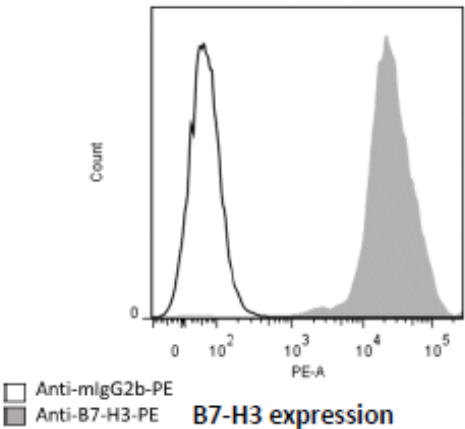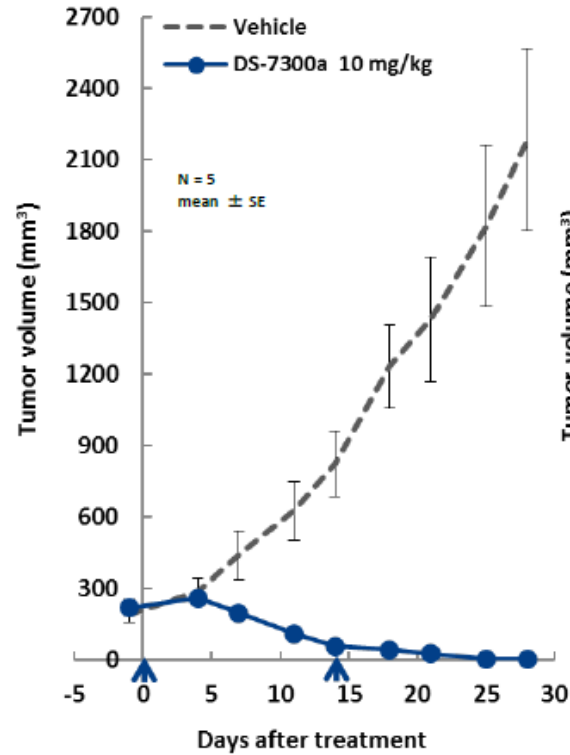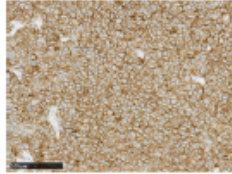

Yamato M, et al. EORTC-NCI-AACR 2020. Abstract 28.

DS-7300a showed potent anti-tumor effects in various tumor types of high B7-H3-expressing patient-derived xenograft (PDX) models
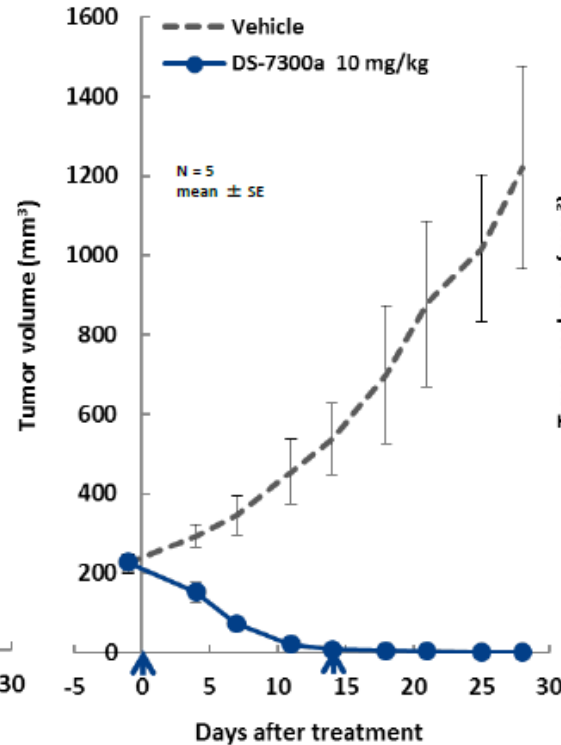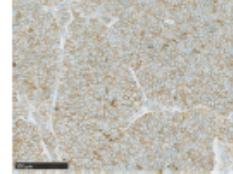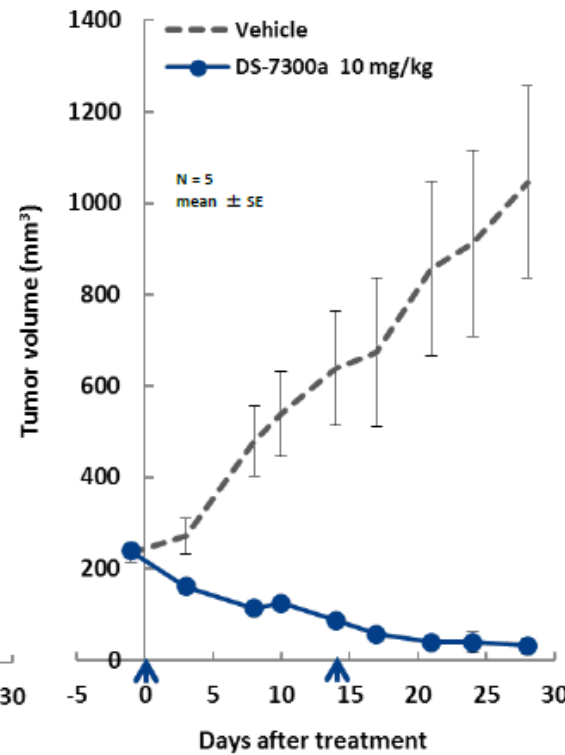

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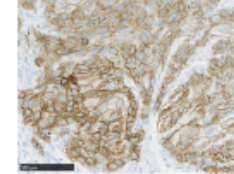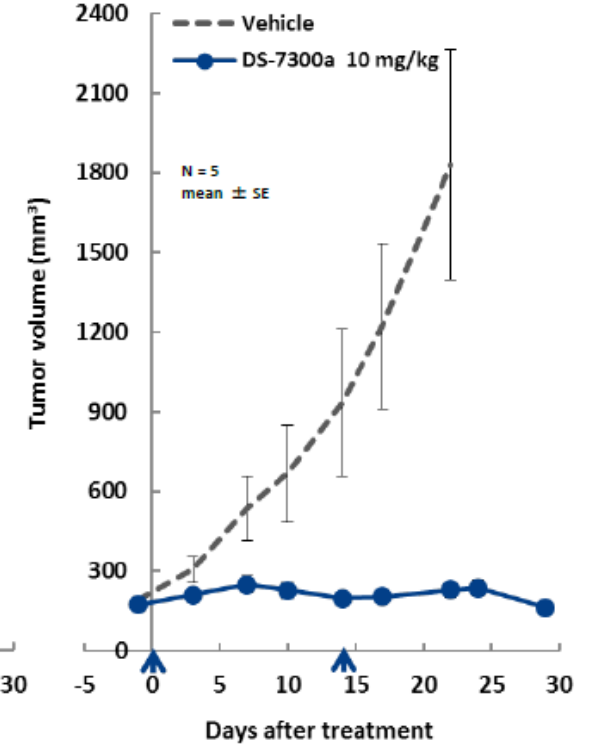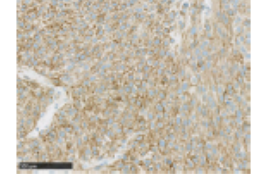
MGC018: B7-H3 Directed ADC with Duocarmycin-based Linker Payload

vc-seco-DUBA

MGC018

Cleavable Peptide

Proteolytic Cleavage and Release of Toxin

Self-elimination Module

H_2N

B7-H3 mAb

MGC018

Duocarmycin Payload

Humanized IgG1

DUBA

Drug-antibody ratio ~2.7
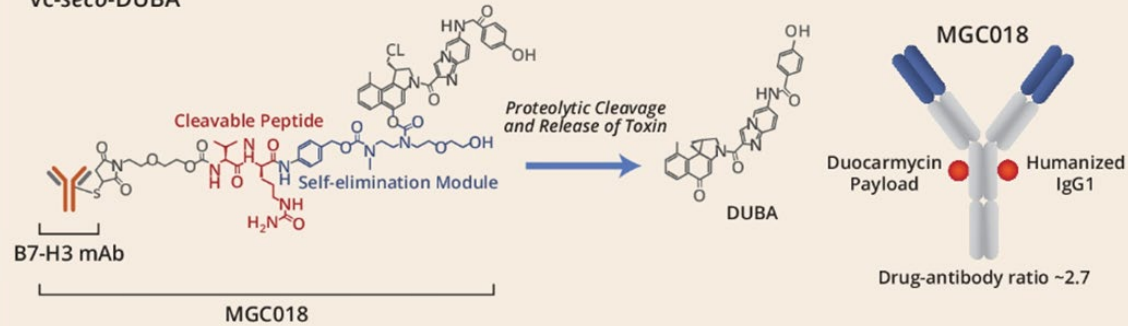
- MGC018 is an anti-B7-H3 antibody-drug conjugate (ADC) with a duocarmycin payload
- vc-seco-DUocarmycin-hydroxyBenzamide Azaindole (DUBA) is a DNA alkylating agent
- DUBA cytotoxic activity is cell-cycle independent
- DUBA retains potency in multidrug-resistant cell lines
- Cleavable peptide linker – facilitates bystander effect
- Induces immunogenic cell death in preclinical models

DUBA Linker Payload provided and conjugated by *Byondis*.

Treatment-Emergent Adverse Events
Manageable Safety Profile

| Patients Experiencing at Least One Adverse Event	0.5 mg/kg (N=3)	1.0 mg/kg (N=6)	2.0 mg/kg (N=7)	3.0 mg/kg* (N=7)	4.0 mg/kg (N=6)	All (N=29)
Adverse Event	3 (100%)	6 (100%)	7 (100%)	7 (100%)	6 (100%)	29 (100%)
Treatment-Related Adverse Event[1]	3 (100)	5 (83.3)	6 (85.7)	7 (100)	6 (100)	27 (93.1)
Adverse Event ≥ Grade 3[2]	3 (100)	4 (66.7)	7 (100)	5 (71.4)	5 (83.3)	24 (82.8)
Treatment-Related Adverse Event ≥ Grade 3[2]	2 (66.7)	2 (33.3)	6 (85.7)	4 (57.1)	5 (83.8)	19 (65.5)
Serious Adverse Event	1 (33.3)	1 (16.7)	3 (42.9)	2 (28.6)	2 (33.3)	9 (31.0)
Dose-limiting Toxicity	0	0	1 (14.3)[3]	0	1 (16.7)[4]	2 (6.9)
Event that Resulted in Study Discontinuation	1 (33.3)	2 (33.3)	3 (42.9)	4 (57.1)	2 (33.3)	10 (34.5)
Event that Resulted in MGC018 Withdrawal	1 (33.3)	1 (16.7)	3 (42.9)	4 (57.1)	2 (33.3)	11 (37.9)
Event that Resulted in MGC018 Dose Reduction	0	0	1 (14.3)	2 (28.6)	2 (33.3)	5 (17.2)
Event that Resulted in MGC018 Interruption	1 (33.3)	0	1 (14.3)	5 (71.4)	5 (83.3)	12 (41.4)
Fatal Adverse Event (pneumonitis/pneumonia)	1 (33.3)	0	0	0	0	1 (3.4)
Adverse Event of Special Interest (AESI) – Infusion Reaction	0	0	2 (28.6)	5 (71.4)	2 (33.3)	9 (31.0)

[1]Includes events with causality assessments of 'Possible', 'Probable' or 'Definite'. [2]Based on CTCAE criteria version 4.0.3. [3]Grade 4 neutropenia resolved to baseline.
[4]G3 fatigue > 72 hours. *Amendment during 3.0 mg/kg dose level applied to allow dose modification.
Data were extracted on 03May2021.

Response by RECIST

[1]Patients who received at least one dose and had at least one post-baseline tumor evaluation. CRC = Colorectal cancer. NA = Not available.
Data were extracted on 03MAY2021.

>50% PSA Reduction in 11/22 (50%) mCRPC Expansion Patients; (16/31 [52%] in Escalation + Expansion)

Response by PSA
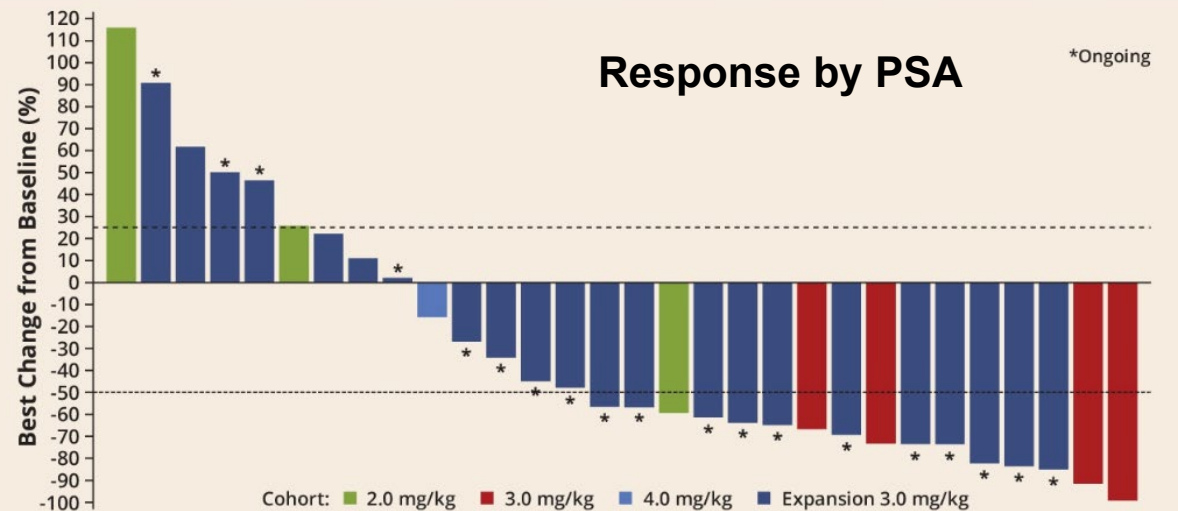
Patients who received at least one dose.
Data were extracted on 03MAY2021.

Mirzotamab clezutoclax is a First-in-Class Antibody-Drug Conjugate Targeting the Intrinsic Apoptosis Pathway

- Mirzotamab clezutoclax (ABBV-155) is a B7H3-targeted ADC with a BCL-X_L inhibitor warhead that is being investigated to treat advanced solid tumors

- B7H3 is an immunomodulatory transmembrane N-linked glycoprotein that is overexpressed in a number of solid tumors including SCLC, NSCLC, breast cancer, and others
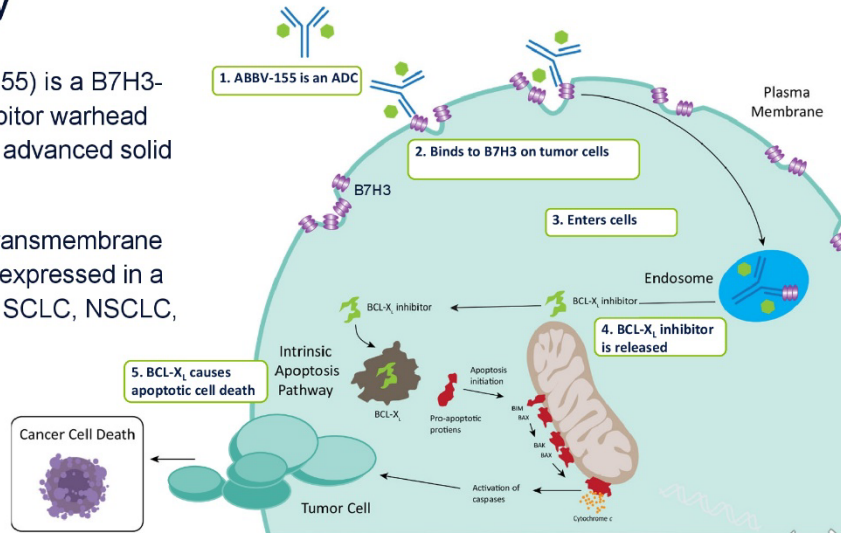
No Dose-Limiting Toxicities Encountered in Monotherapy Escalation

- Two DLTs related to cytopenias for combination therapy

n (%)	Monotherapy N=31	Combination Therapy N=28
Any AE	30 (97)	27 (97)
AE related to mirzotamab clezutoclax	19 (61)	25 (89)
Any grade 3/4 AE	14 (45)	19 (68)
Any grade 3/4 AE related to mirzotamab clezutoclax	4 (13)	10 (36)
Serious AE	11 (36)	11 (39)
Serious AE related to mirzotamab clezutoclax	3 (10)	3 (11)
Dose-limiting toxicities:	0	2 (7)
Grade 4 neutrophil count decreased[a]	0	1 (4)
Grade 3 lymphocyte count decreased[b]	0	1 (4)
Fatal AE:	1 (3)	0
Cardiac arrest	1 (3)	0

Objective Responses seen in Combination Therapy

n (%)	Monotherapy N=31	Combination Therapy N=28
Best Response:		
Partial Response	0	6 (21)
Stable Disease	16 (52)	13 (46)
Progressive Disease	12 (39)	3 (11)
Missing post-baseline assessment • Discontinued • Ongoing at data cut	3 (10) 3 0	6 (21) 2 4
Clinical Benefit Rate (CR+PR+SD) [95% CI]	16 (52) [33, 70]	19 (68) [48, 84]

Tumor Lesion Size Change from Baseline with Combination Therapy
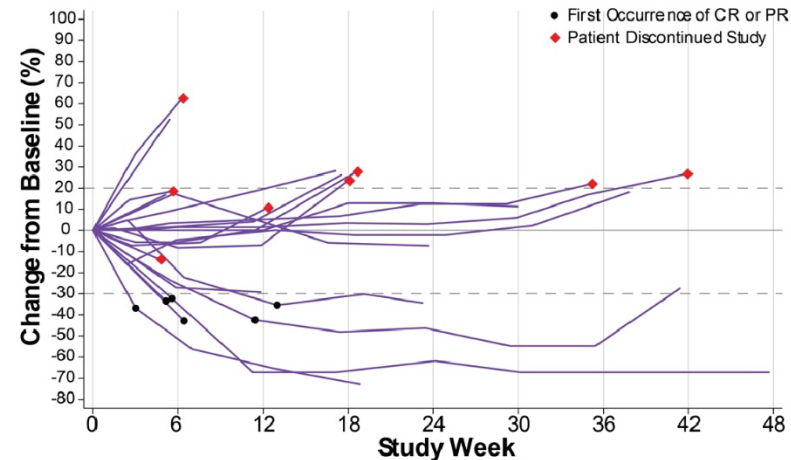
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J101 study design

Part 1: Dose Escalation
DS-7300a IV Q3W Monotherapy
in Advanced Solid Tumors[a]

RDE →

Part 2: Dose Expansion[c]
DS-7300a IV Q3W Monotherapy
Selected Advanced Solid Tumors

8.0[b] mg/kg

6.4[b] mg/kg

4.8[b] mg/kg

3.2 mg/kg

1.6 mg/kg

0.8 mg/kg

Cohort 1: Tumor type will be updated at ESMO

Cohort 2: Tumor type will be updated at ESMO

Cohort 3: Tumor type will be updated at ESMO
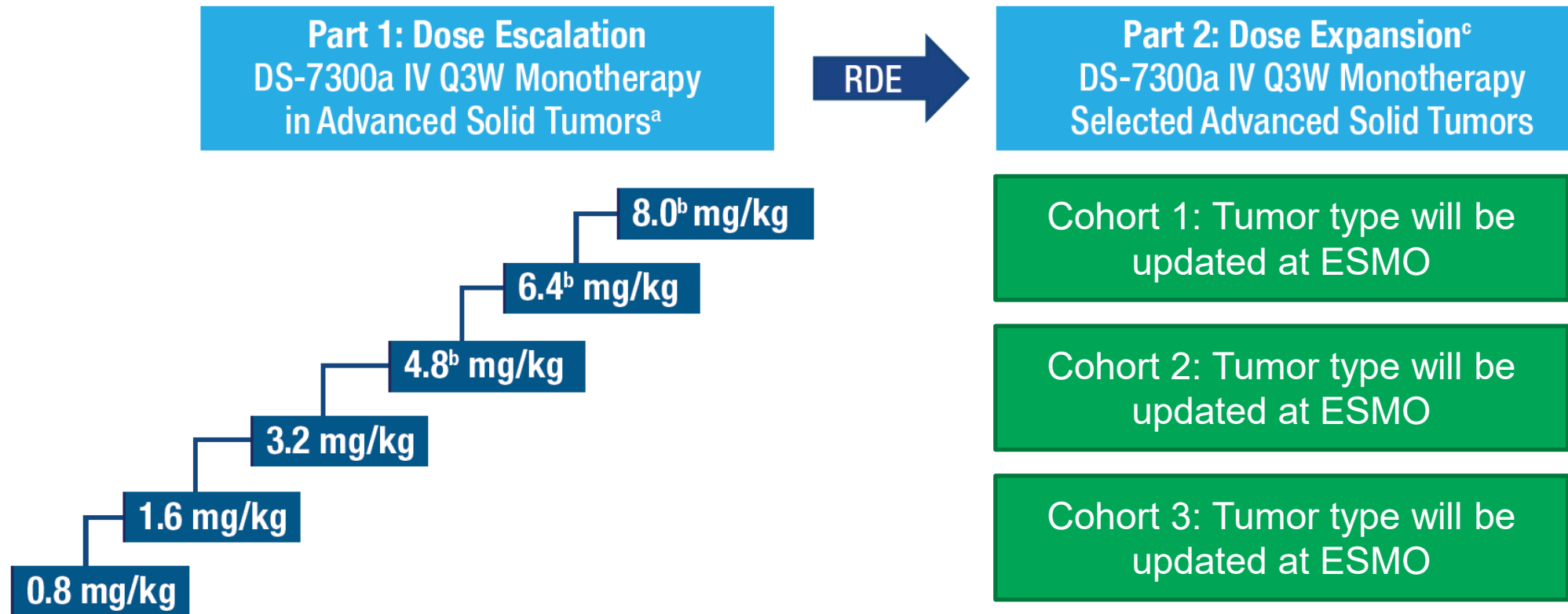
IV, intravenous; Q3W, once every 3 weeks.

[a] Advanced/unresectable or metastatic HNSCC, esophageal squamous cell carcinoma, squamous and adenocarcinoma NSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, prostate cancer, breast cancer

[b] These are planned doses. Actual dose levels will be determined by clinical toxicity findings in each dose cohort. Higher or intermediate doses may also be considered. In order to refine the RDE, additional patients may be enrolled into selected dose levels

End of presentation