Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

DS-7300 勉強会

アジェンダ

- DXd-ADCテクノロジーのオーバービュー*
- B7-H3について
  - B7-H3とは？
  - B7-H3の発現および予後との相関
- DS-7300の特徴
  - 薬剤の背景情報
  - in vitroデータ
  - in vivoデータ
  - 競合品の状況について
- Ph1試験
  - 試験デザイン

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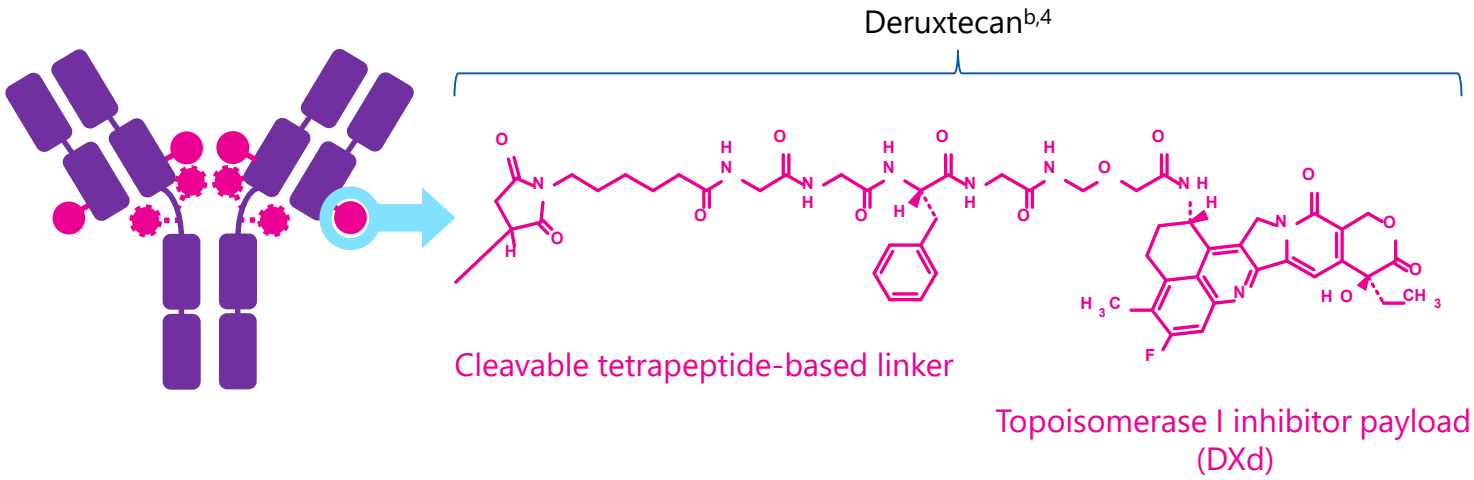
第一三共DXd-ADCの特徴

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]



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]

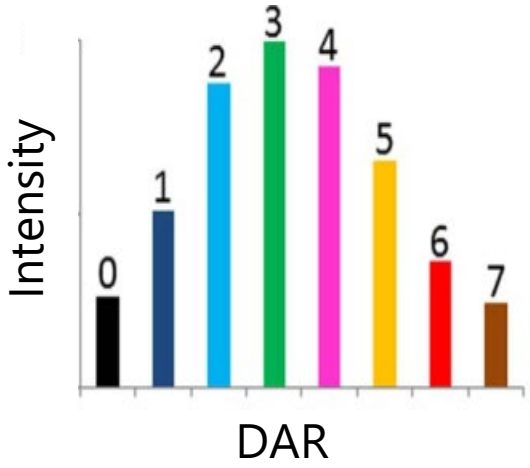
[a] The clinical relevance of these features is under investigation.
[b] Image is for illustrative purposes only; actual drug to antibody ratio and drug positions may vary.
[c] Based on animal data.

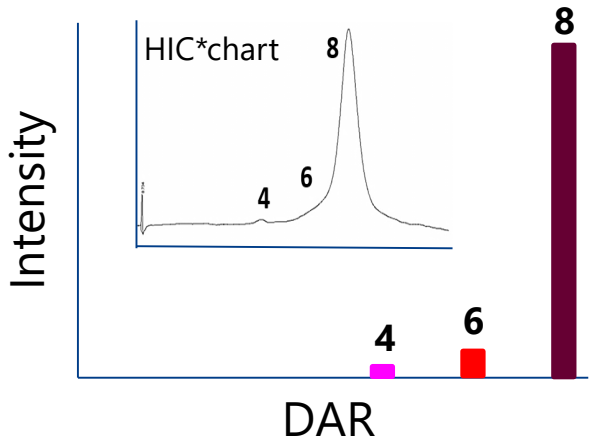
1. Okajima D, et al. Poster presented at: AACR-NCI-EORTC International Conference; October 26-30, 2019; Boston, MA [abstract C026].
2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185.
3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108.
4. Hashimoto Y, et al. *Clin Cancer Res.* 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.

DXd-ADC: 高い薬物抗体比率 (例: エンハーツ®)

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



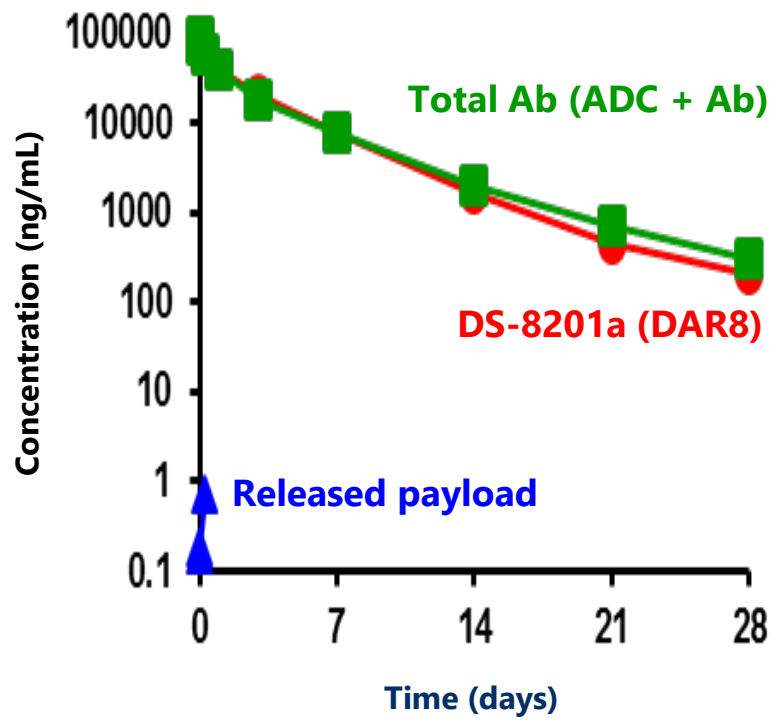


HIC*, Hydrophobic interaction chromatography

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

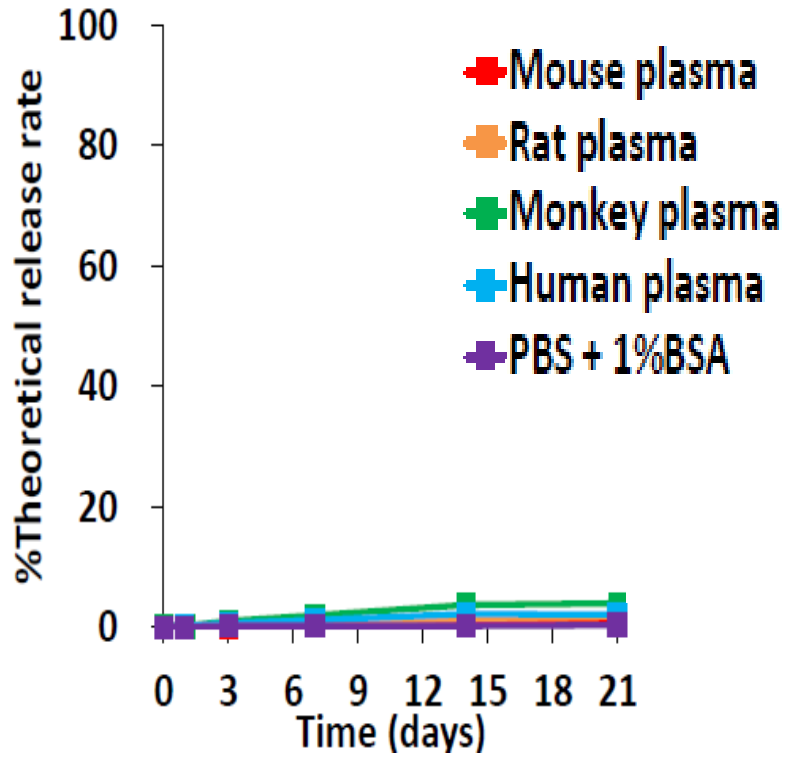
DXd-ADC: 血漿中で安定なリンカー (例:エンハーツ®)

Plasma conc. of ENHERTU® and payload in monkey



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

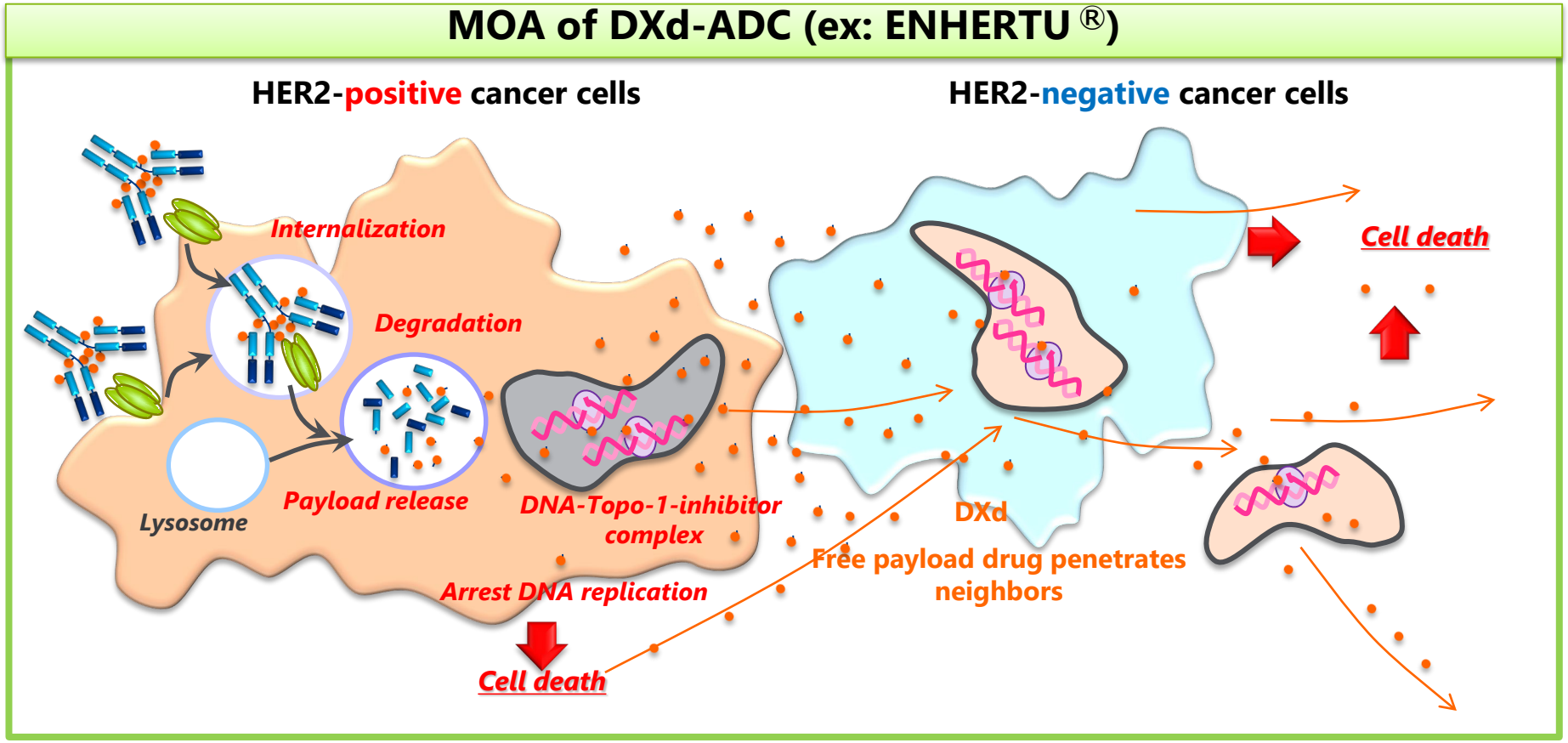
Release rates of DXd from ENHERTU® in plasma



Source: Oitate-M *et al.*, World ADC 2017 San Diego

DXd-ADC: 作用機序 (例:エンハーツ®)

- 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**



第一三共ADCフランチャイズ

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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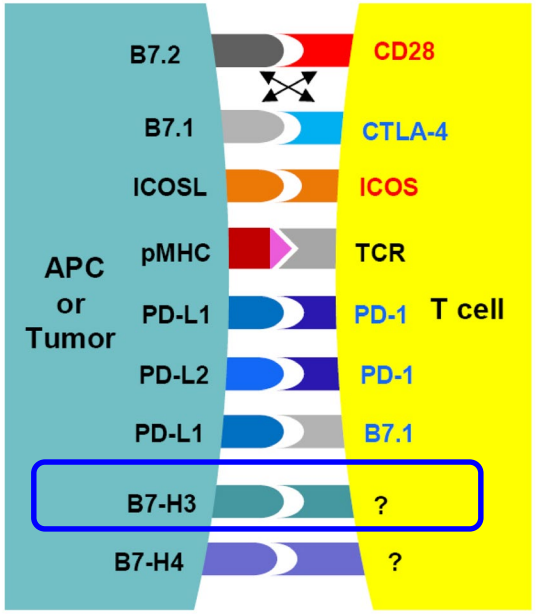
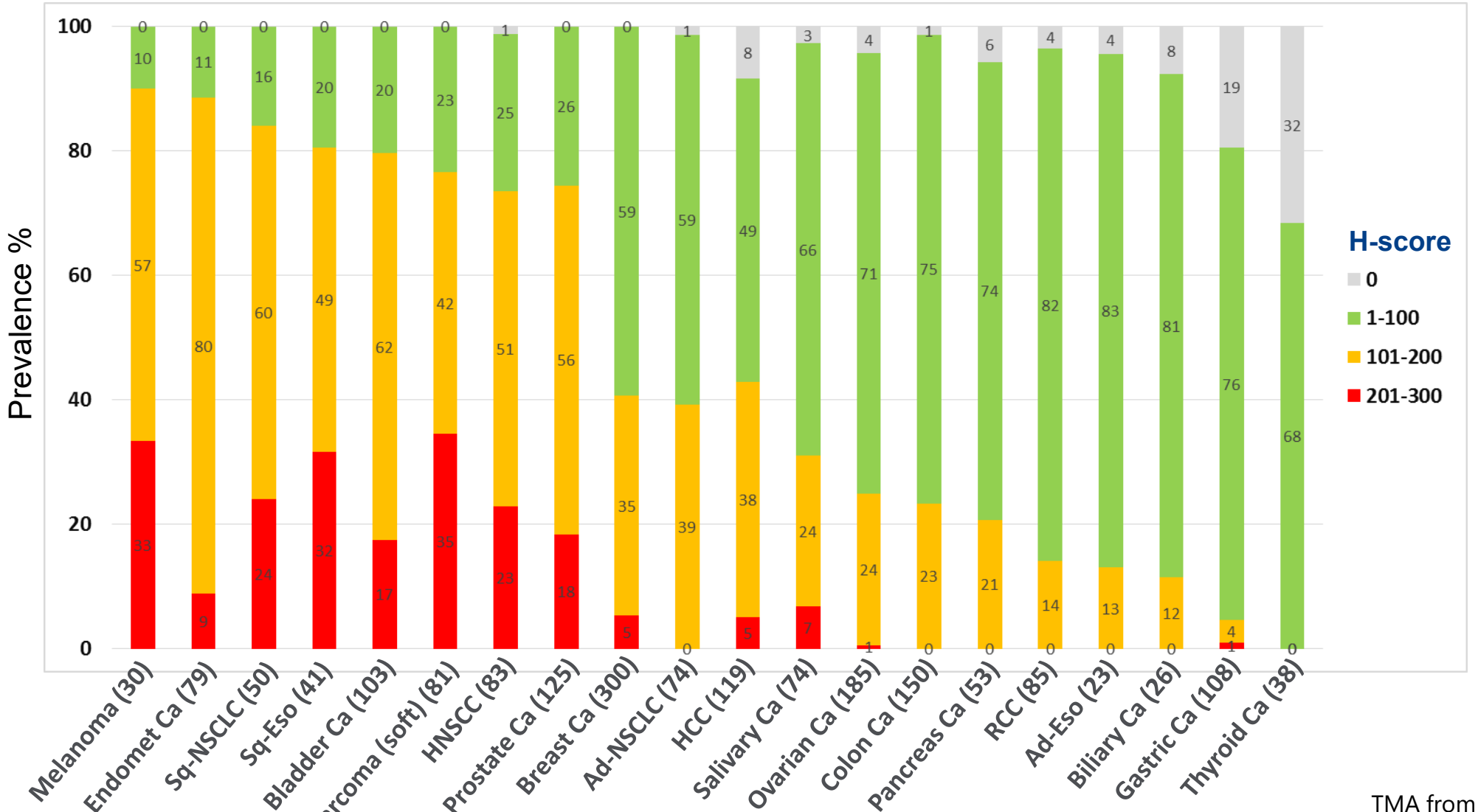
B7-H3 (CD276) バイオロジー: オーバービュー

- 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

様々な固形がんにおけるB7-H3の発現



TMA from University Basel

B7-H3の発現とがんの予後/治療反応性との相関

- High B7-H3 protein level was associated with poor overall survival in NSCLC
  Altan M, et al. *Clin Cancer Res.* 2017;23(17): 5202–5209
- Higher B7-H3 expression was associated with poorer survival outcomes in ESCC
  Song J et al. *Onco Targets Ther.* 2016;9:6257-6263
- High B7-H3 expression was significantly associated with decreased OS and PFS in bladder cancer
  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 endometrial cancer
  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 prostate cancer
  Zhan X, et al. *Proc Natl Acad Sci U S A.* 2007;104(49):19458-19463
- B7-H3 expression was correlated critically with nonresponsiveness to anti-PD-1 immunotherapy in NSCLC
  Yonesaka K, et al. *Clin Cancer Res.* 2018;24(11):2653-2664

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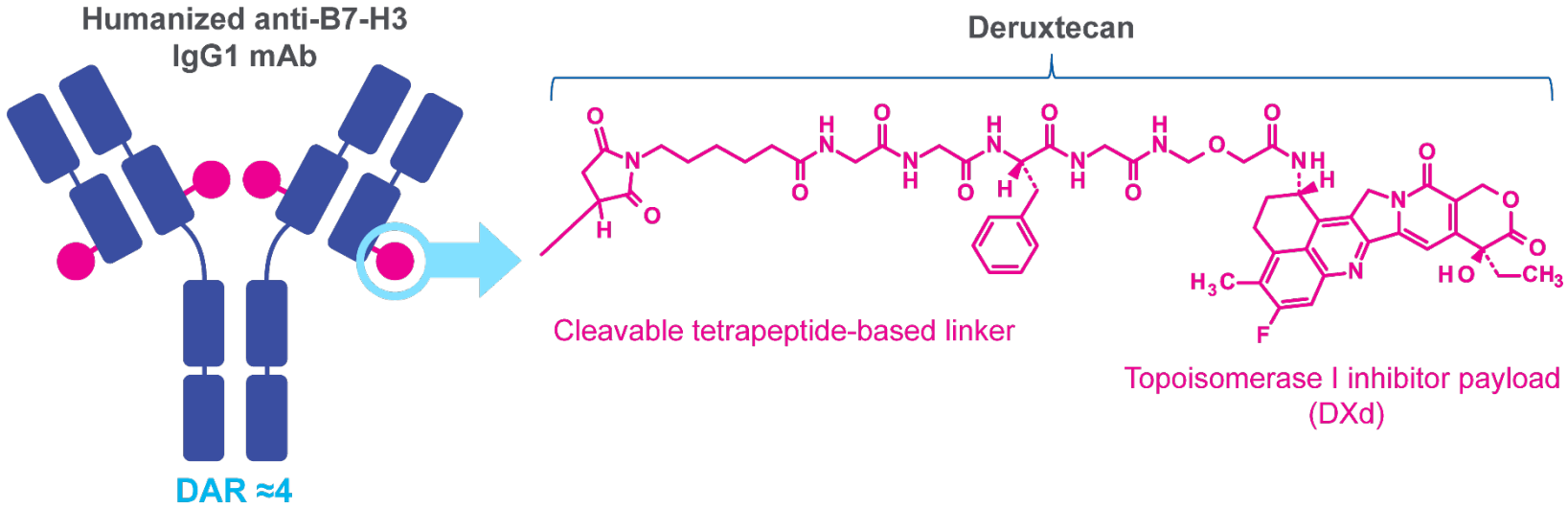
DS-7300の作用機序

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



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**

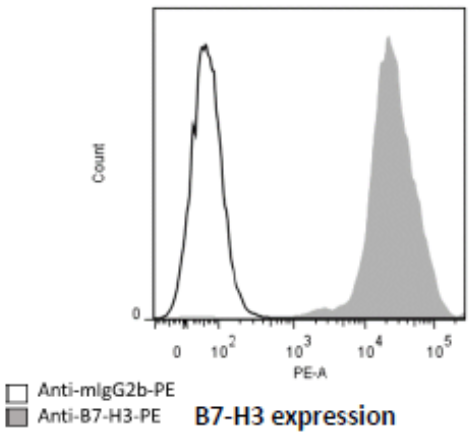
[a]The clinical relevance of these features is under investigation.

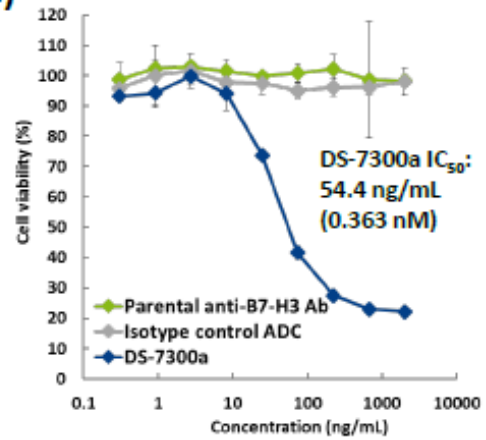
Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185., Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108., Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142., Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

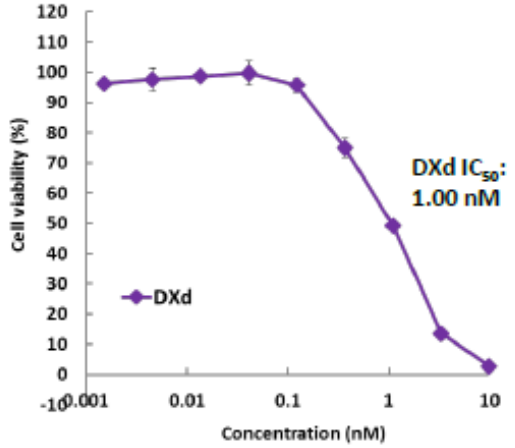
DS-7300aはB7-H3を発現するがん細胞の増殖を阻害する (*in vitro*)

B7-H3 expression of human cancer cells and *in vitro* cell growth inhibition by DS-7300a

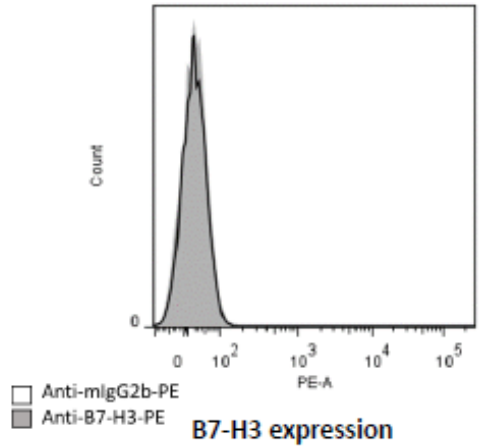
RH-41 (Rhabdomyosarcoma)

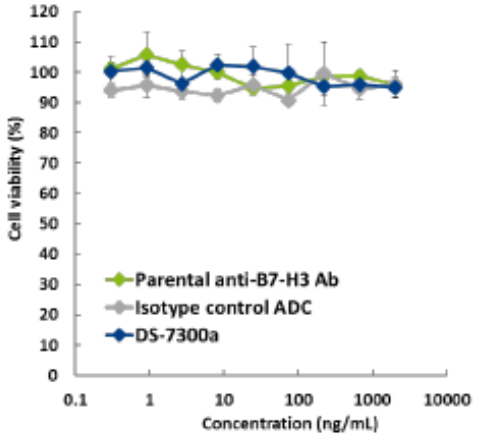


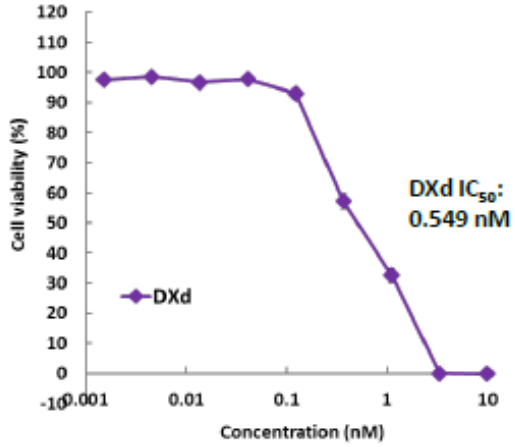




CCRF-CEM (ALL)

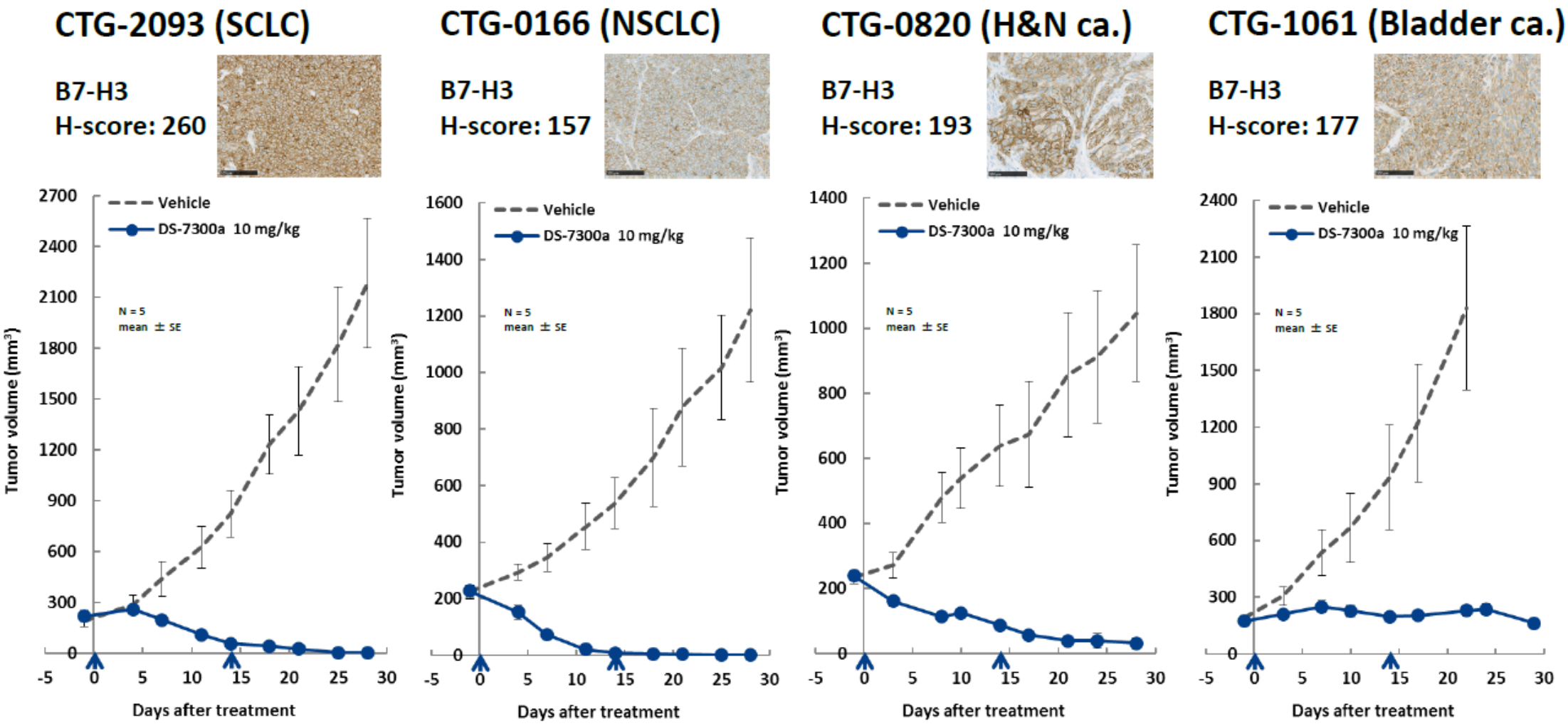






Yamato M, et al. EORTC-NCI-AACR 2020. Abstract 28.

DS-7300aはB7-H3を高発現する種々のがん細胞の患者由来ゼノグラフト(patient-derived xenograft: PDX)モデルで抗腫瘍効果を示している

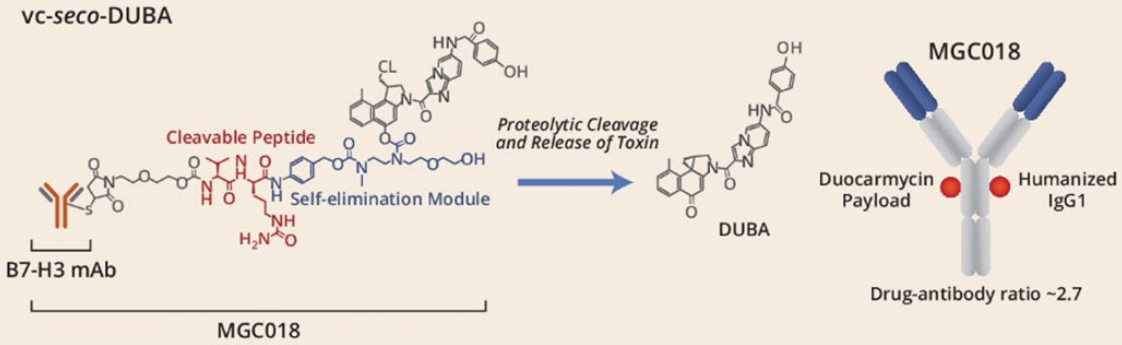


Yamato M, et al. EORTC-NCI-AACR 2020. Abstract 28.

競合品状況-1: MGC-018

J. Clin. Oncol., 39, no. 15_suppl (May 20, 2021) 2631-2631.

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



- 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

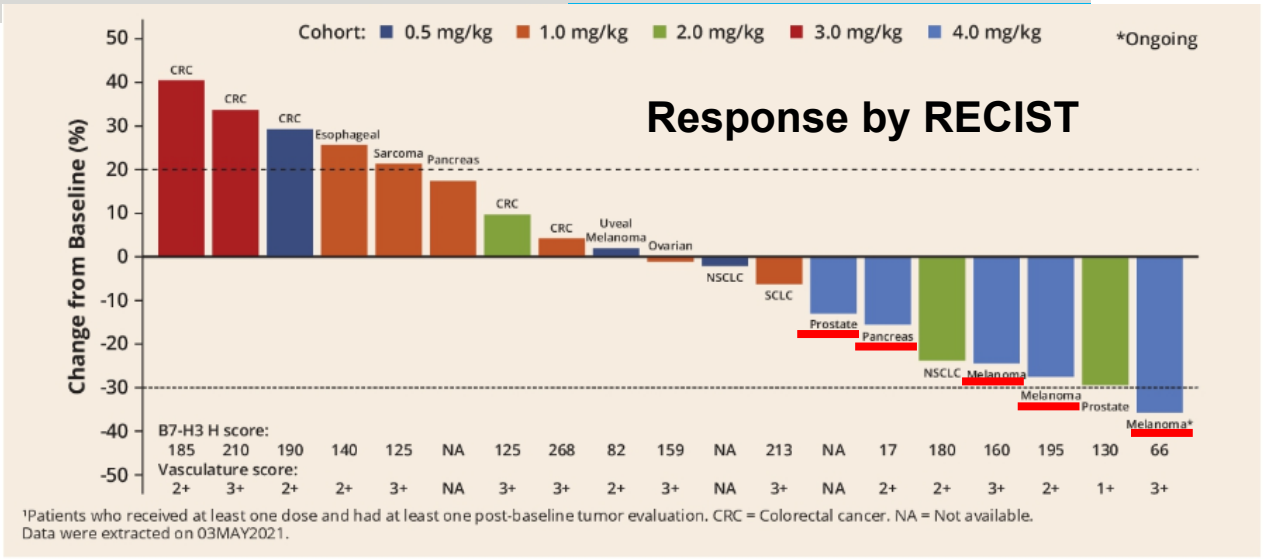
DUBA Linker Payload provided and conjugated by *Byondis*.

Treatment-Emergent Adverse Events

Manageable Safety Profile

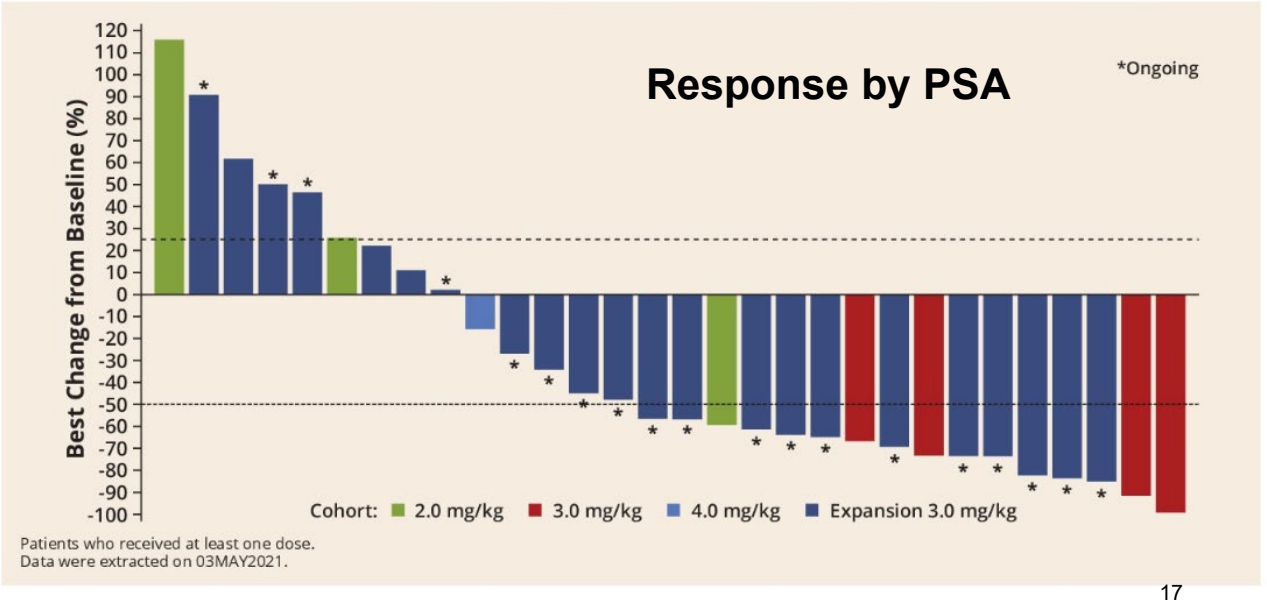
Patients Experiencing at Least One Adverse Event	0.5 mg/kg (N=3)	1.0 mg/kg (N=6)	2.0 mg/kg (N=7)	3.0 mg/kg* (N=7)	4.0 mg/kg (N=6)	All (N=29)
Adverse Event	3 (100%)	6 (100%)	7 (100%)	7 (100%)	6 (100%)	29 (100%)
Treatment-Related Adverse Event[1]	3 (100)	5 (83.3)	6 (85.7)	7 (100)	6 (100)	27 (93.1)
Adverse 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.



[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)



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

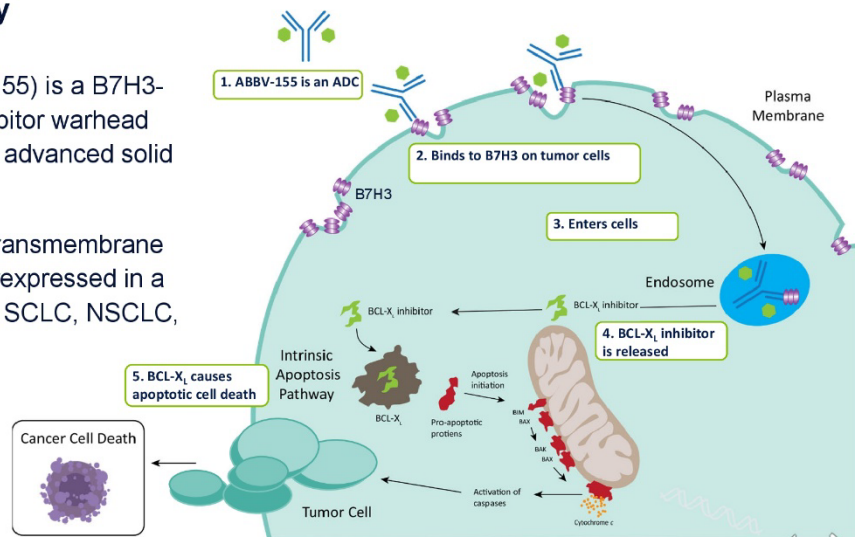
競合品状況-2: ABBV-155

J. Clin. Oncol., 39, no. 15_suppl (May 20, 2021) 3015-3015

Daiichi-Sankyo

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

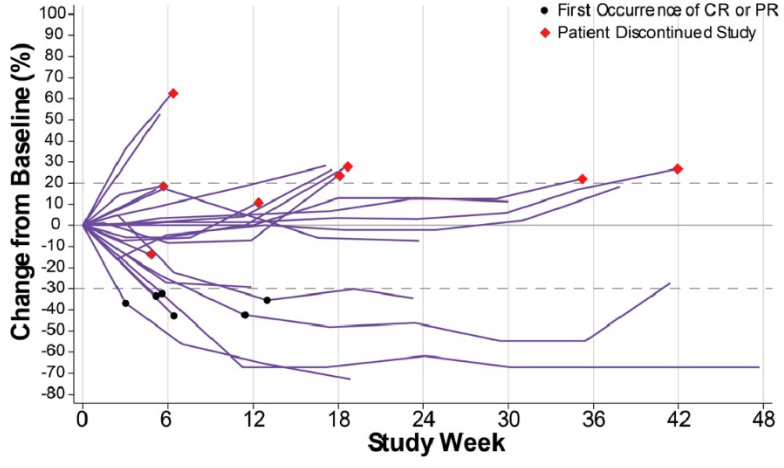
- Two DLTs related to cytopenias for combination therapy

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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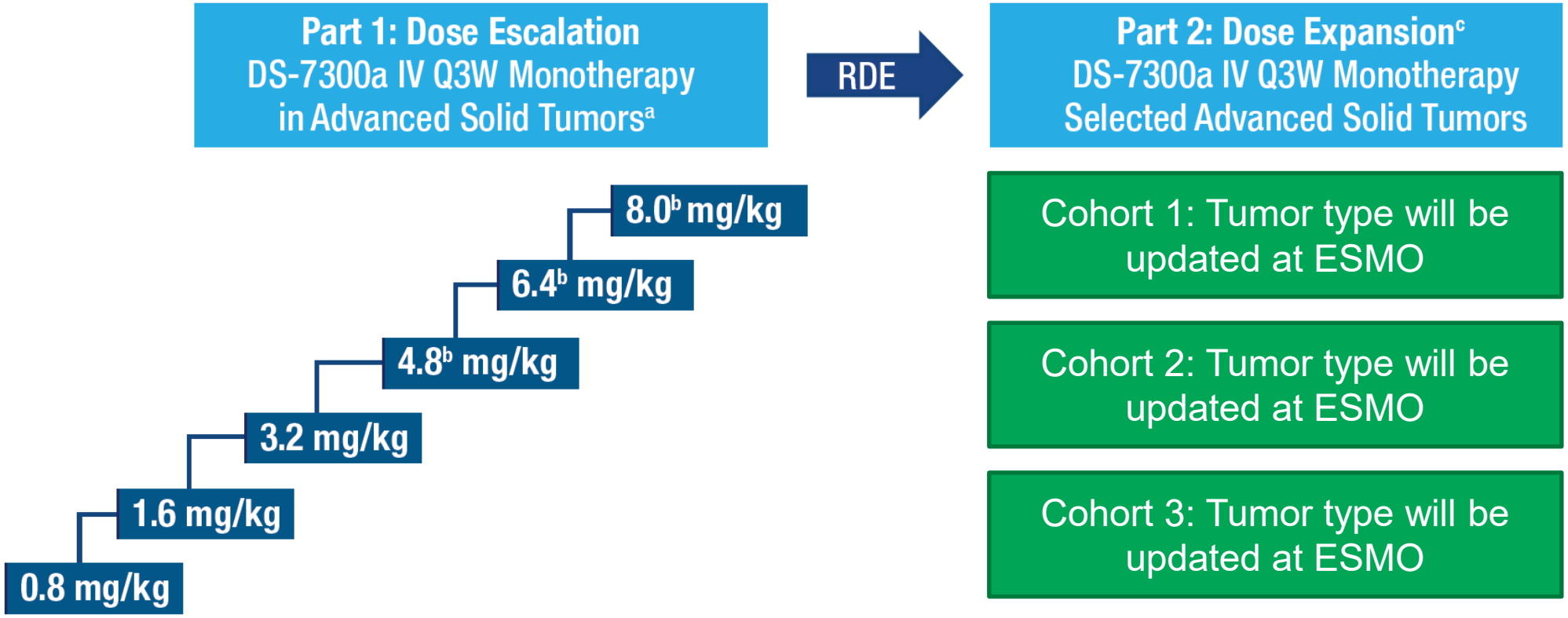
J101試験デザイン



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