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Series of "World-leading Technology Seminar" Hosted by Citigroup Global Markets Japan

Daiichi Sankyo ADC*

ADC*, antibody drug conjugate

Daiichi Sankyo Co., Ltd
Biologics & Immuno-Oncology Laboratories
Group Leader
Yuki Abe, Ph.D.

Daiichi Sankyo ADC
Contents

- ✓ Overview: trend of drug development, biologics and cancer treatment, about antibody drugs
- ✓ About antibody drug conjugate (ADC)
- ✓ Discovery of DS-8201a
- ✓ Characteristics and clinical results of DS-8201a
- ✓ Expansion of DXd-ADC technology

Trend of drug development
Recent market of the drugs

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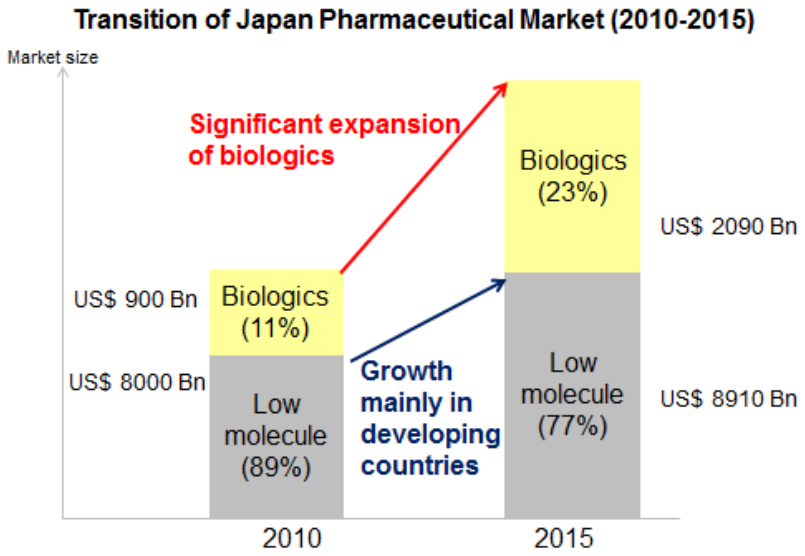
◆ Drugs sales ranking in FY2015 (worldwide)

Rank	Product name (non-proprietary name)	Modality	Therapeutic category	Company (Nationality)	2015 sales (US$M)
1	Humira Adalimumab	Biologics	Antireumatic	Abbvie US	14,012
2	Harvoni Sofosbuvir+ledipasvir	Low molecule		Gilead US	13,864
3	Enbrel Etanercept	Biologics	Antireumatic	Amgen/Pfizer US	8,697
4	Remicade Infliximab	Biologics	Antireumatic/ Crohn disease	Janssen/Merck US	8,355
5	Rituxan Rituximab	Biologics	Anticancer drug	Roche Switzerland	7,321
6	Lantus Insulin	Biologics	Insulin formulation	Sanofi France	7,090
7	Avastin Bevacizumab	Biologics	Anticancer drug	Roche Switzerland	6,945
8	Herceptin Trastuzumab	Biologics	Anticancer drug	Roche Switzerland	6,794
9	Prevnar 13 Pneumococcus vaccine	Biologics	Pneumococcus vaccine, pediatric	Pfizer US	4,464
10	Revlimid Lenalidomide	Low molecule	Anticancer drug	Celgene US	5,801

http://www.medisearch.co.jp/doukou_worldrank.html



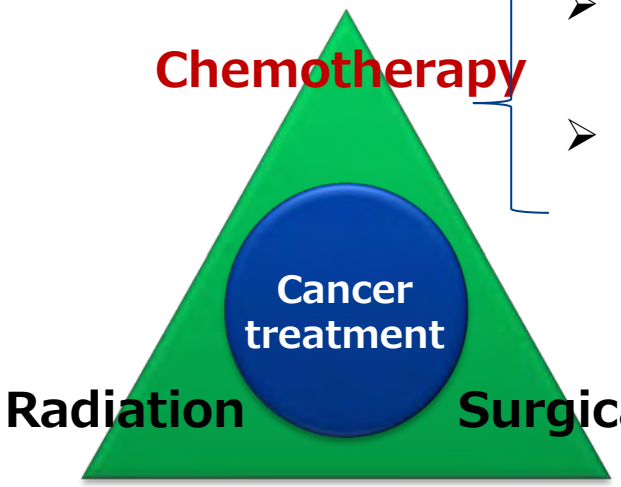
View from Biologics related policy Information from Bio-industry Division of Ministry of Economy, Trade and Industry: May 2015 (citation translated)

- **8 biologics within top 10 of blockbuster drugs***
- **Transition to biologics from small molecule drug is apparent.**
- **Japan companies dedicated to small molecule drugs have fallen behind companies which pursue biologics in US/EU.**

*Blockbuster drugs: drugs with more than $10Bn, 116 drugs in 2015

Biologics and cancer treatment

Antibody drugs as molecular targeted drugs



- **Pros.**
  Effective even to metastatic cancer as long as drug reach due to systemic effect
- **Cons.**
  Deteriorate patient's QOL by long-term therapy and serious adverse events

Unmet medical needs

New drugs with high response with less adverse event is expected

Molecular targeted drugs

Drugs that modulate molecules which are specifically expressed on cancer and/or associate cancer cell growth and metastasis, by identifying difference in molecular basis between cancer and normal cells

Small molecule drugs: tyrosine kinase inhibitor, etc.
Biologics: antibody drugs, etc.

Antibody drugs

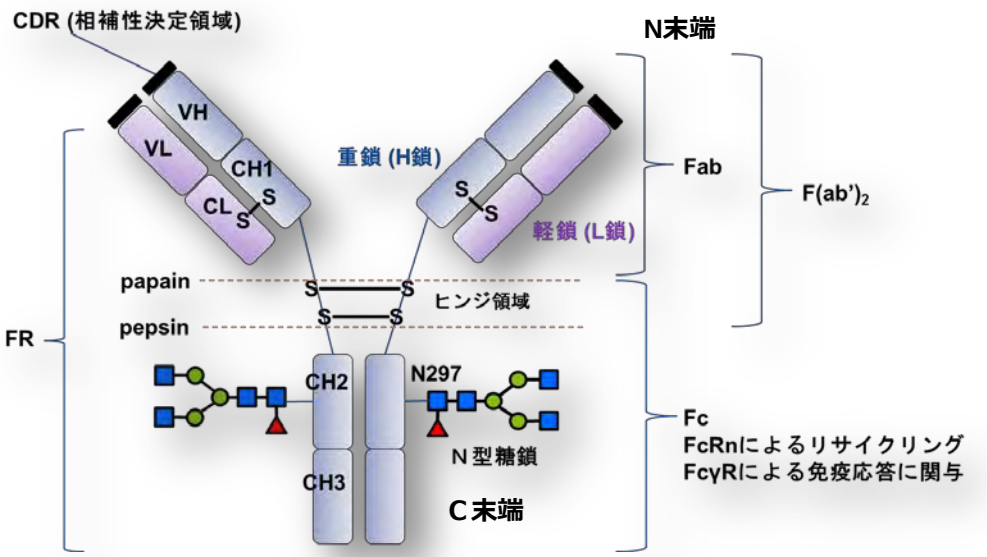
Characteristics of antibody drugs

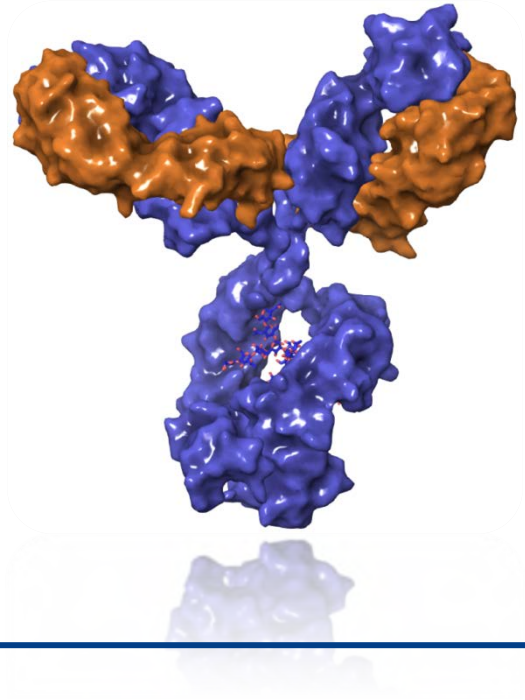
- **High efficacy, less adverse event, favorable drug retention in blood**
  - High specificity to target antigens (drug targets)
  - Better safety profile due to molecular substances produced in a living body
  - From once a week to once in several months administration due to favorable drug retention
- **Applicable to variety of drug discovery targets**
  - Possible to bind to variety of target antigens (drug targets)
  - Variety of binding sites (epitope)
  - Variety of MOA
- **Compatibility to precision medicine**
  - Antigen is candidate for biomarker
  - Antibody itself can be used as a tool of Companion Diagnostics (CDx)

Antibody drugs having potential of blockbuster drugs as new molecular target drugs

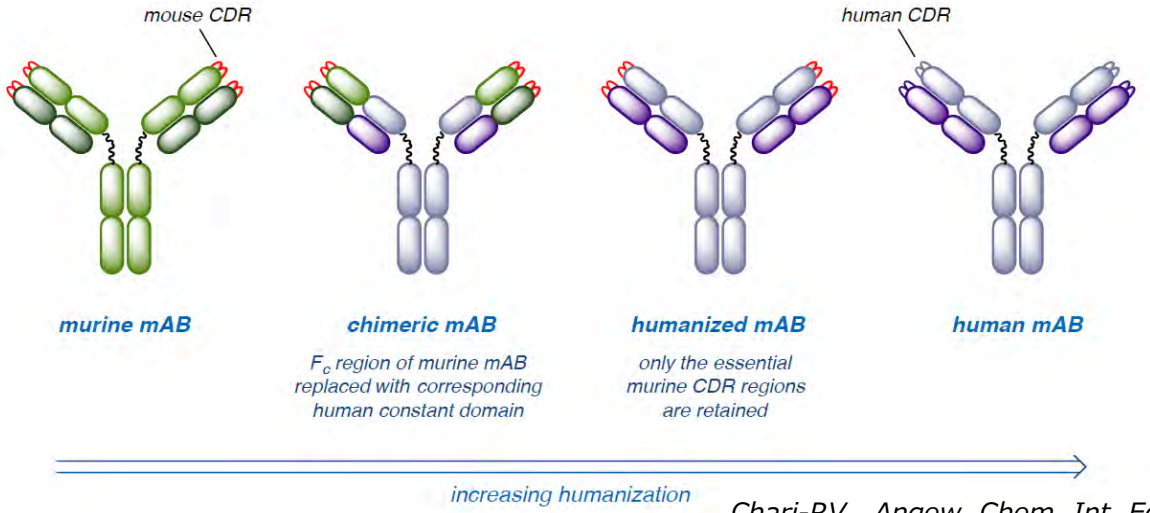
Antibody drugs

ImmunoglobulinG1: IgG1 structure, high specificity and safety





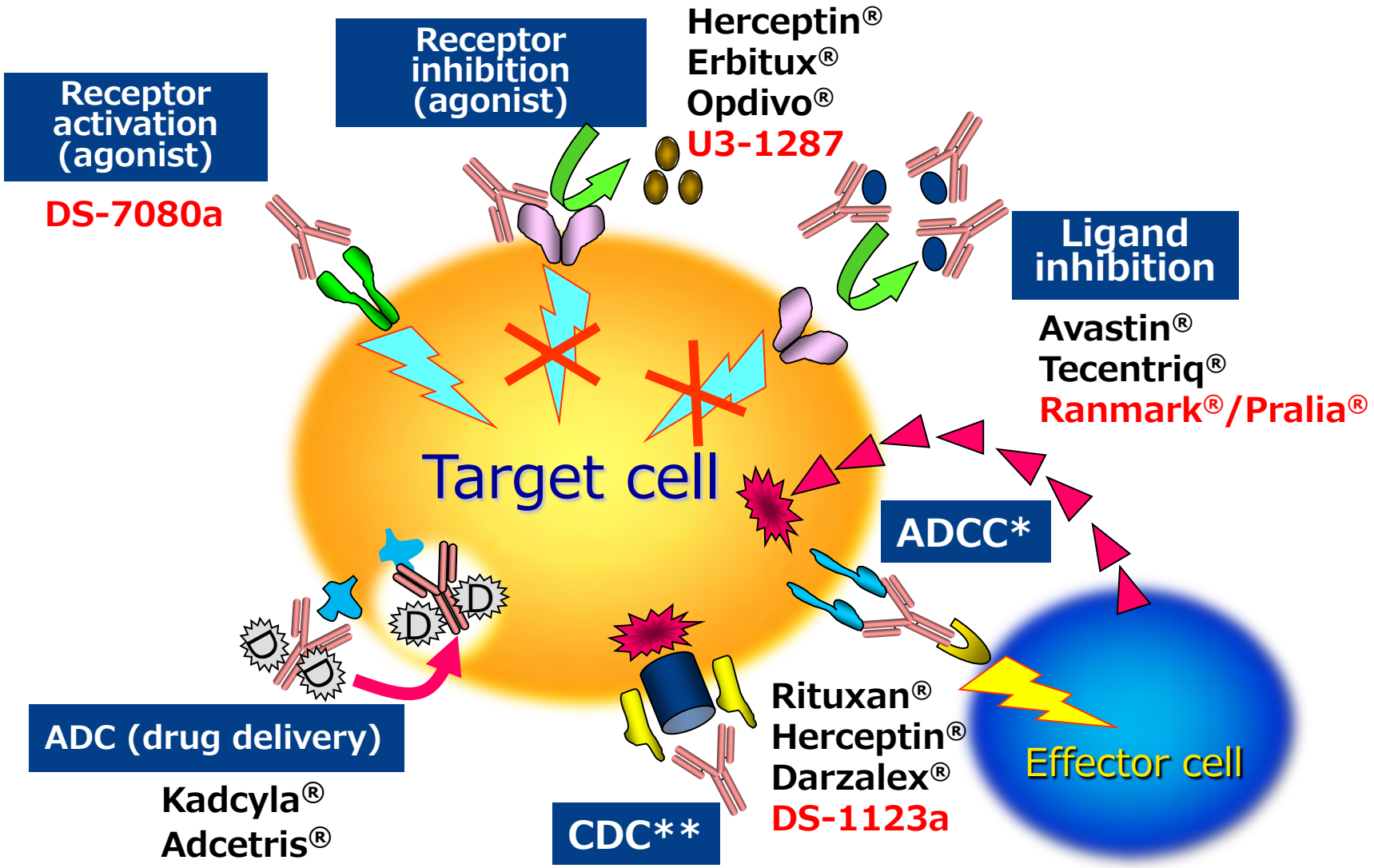
Molecular mass of antibody: about 150 KDa



Murine mAb is considered foreign substance within human body and allergy reaction or anti-antibody may occur, which attenuates efficacy.
Considering safety, chimeric, humanized, or human mAb are widely used as antibody drugs.

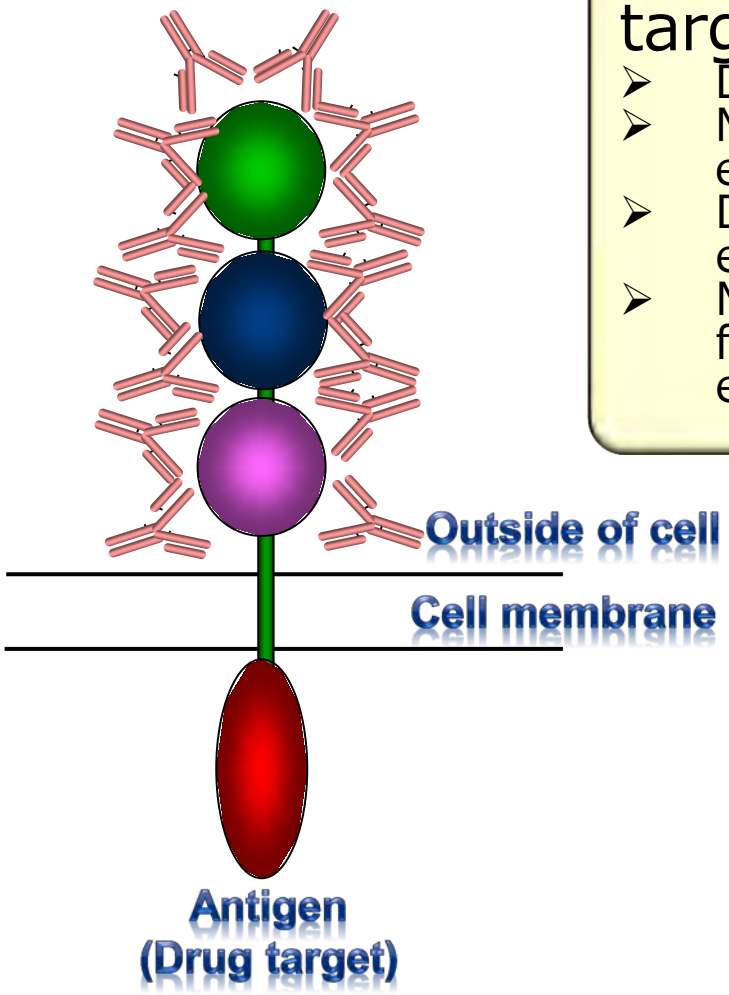
Chari-RV., Angew. Chem. Int. Ed. **2014**, *53*, 3796.

Antibody drugs
Variety of MOA



*ADCC (Antibody-Dependent-Cellular-Cytotoxicity)
**CDC (Complement Dependent Cytotoxicity)
※red: develpe by Daiichi Sankyo

Antibody drugs
Variety of binding sites (epitope)



Antibody and target antigen (drug target)

- Drug target is outside of cell
- Many epitopes regulate molecular function
  e.x. antagonist, agonist, ligand inhibitor, etc.
- Difficult to predict antibody function from epitope
- May have additional activity other than innate function of drug target
  e.g. ADCC, CDC, internalization

Screening by binding activity
Select antibody with high specificity

Screening by antibody function
Select antibody with ideal function

Antibody drugs

Antibody drugs
Next generation

First-generation Antibody drugs
- Difficult to find drug target molecules
- Aggressive competition for same drug targets
- May naked antibodies have less efficacy

Expecting more potent efficacy and expansion of drug targets

Next-generation Antibody drugs
- Optimized and highly functional antibody
- Bispecific antibody, one antibody with two antigen binding sites
- Antibody-Drug Conjugate (ADC), antibody conjugated to anticancer drug

Illustration by D. Simonds from E. Check, 2007, Nature

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ADC
A marriage of biologics and small molecules


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Antibody Drug Conjugates: A Marriage of Biologics and Small Molecules

Antibody drug conjugates offer a niche opportunity in drug development and contract manufacturing.

http://www.pharmtech.com/ *Pharmaceutical Techonology,* **2008**, 32 (6)

Small molecule

- ✓ Drug target is both in and out of the cell
- ✓ Potent efficacy (cytotoxicity)
- ✓ Low selectivity to target
- ✓ Issue of adverse events

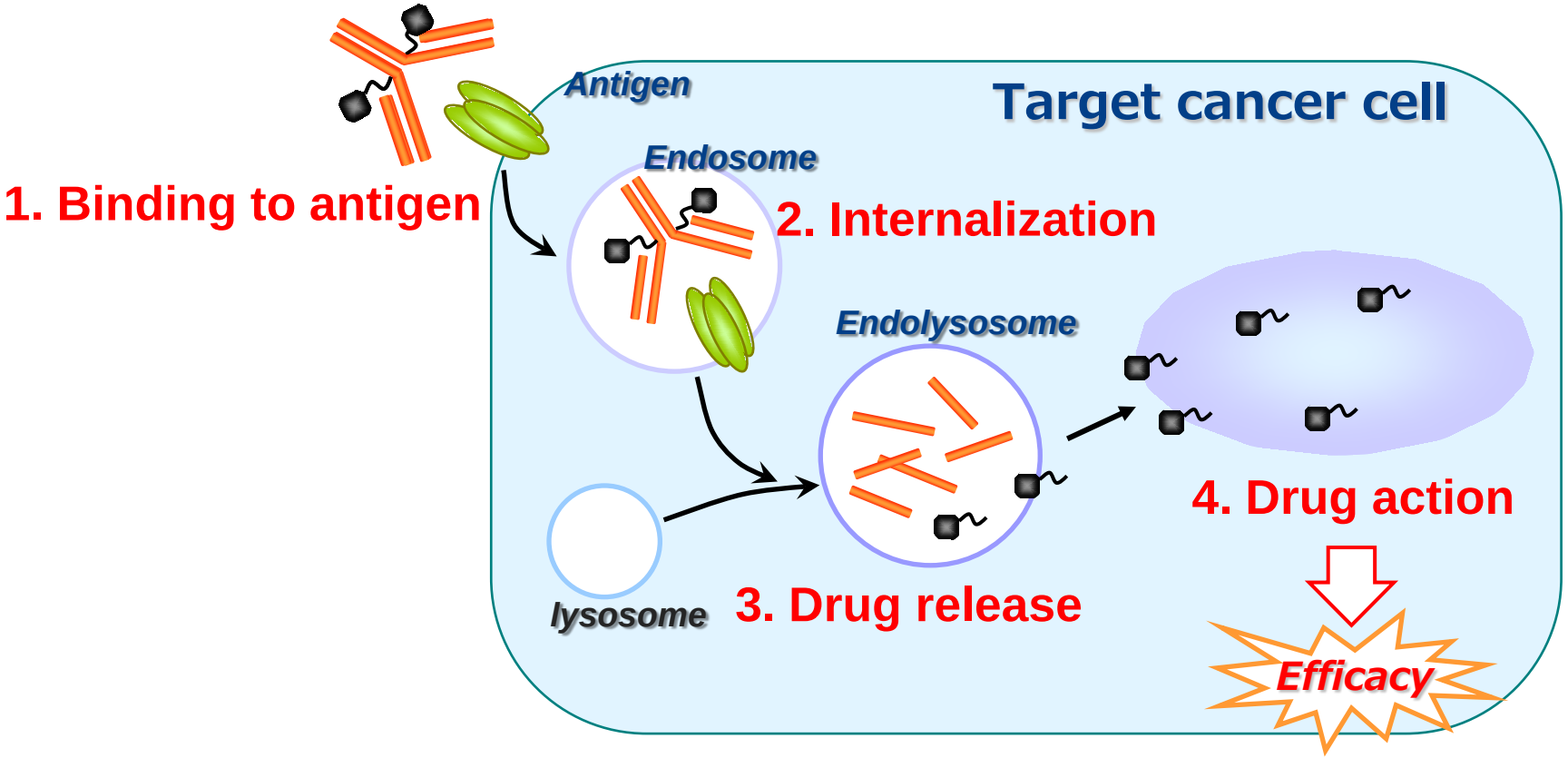
Antibody

- ✓ Drug target is out of the cell
- ✓ Efficacy may not be enough
- ✓ High selectivity to target
- ✓ Less adverse events

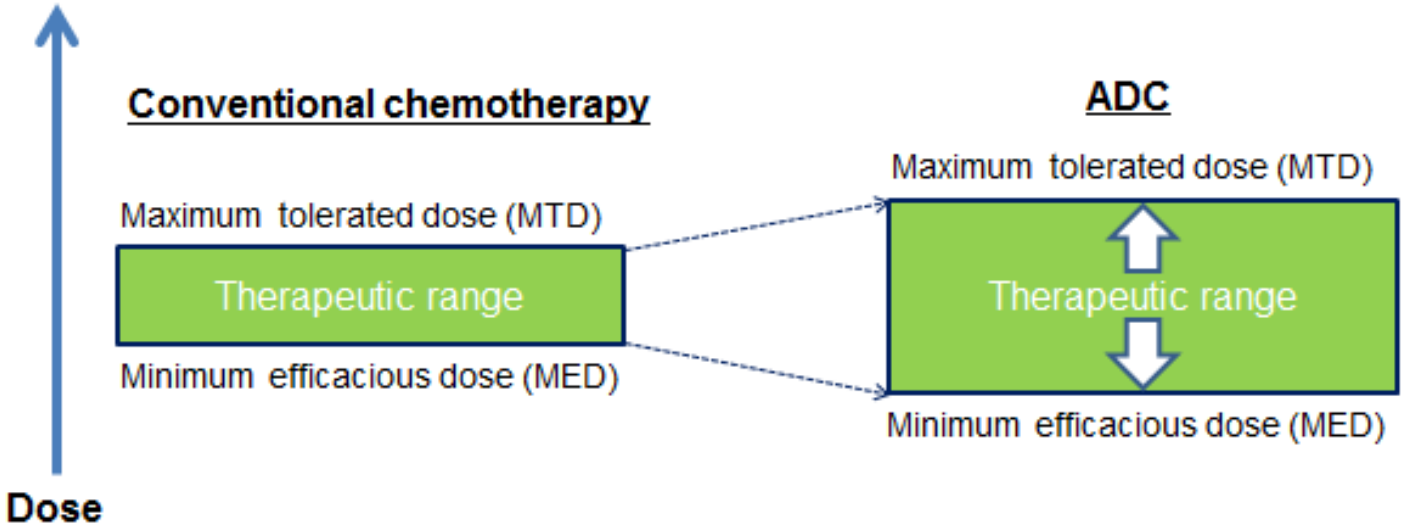
Antibody Drug Conjugate; ADC

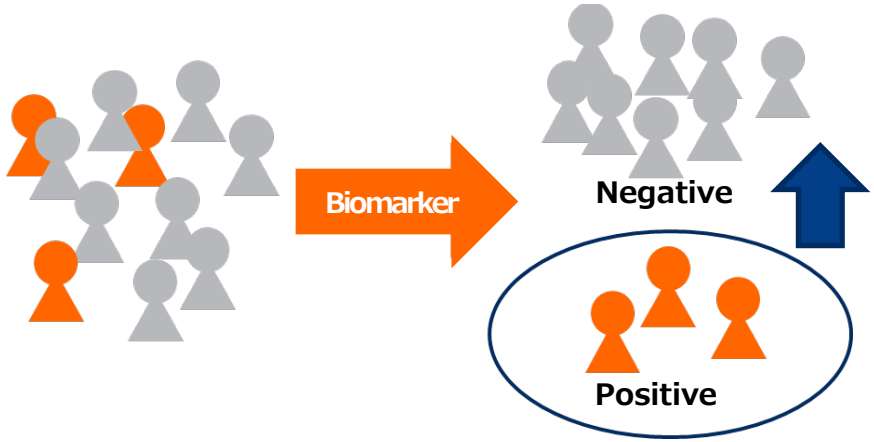
ADC
Antibody Drug Conjugate

- ADC is drug which antibody and small molecule drug are conjugated with appropriate linker
- Armed antibody which antibody is used as target recognition and delivery and small molecule drug is in charge of efficacy



ADC
Difference from existing chemotherapy

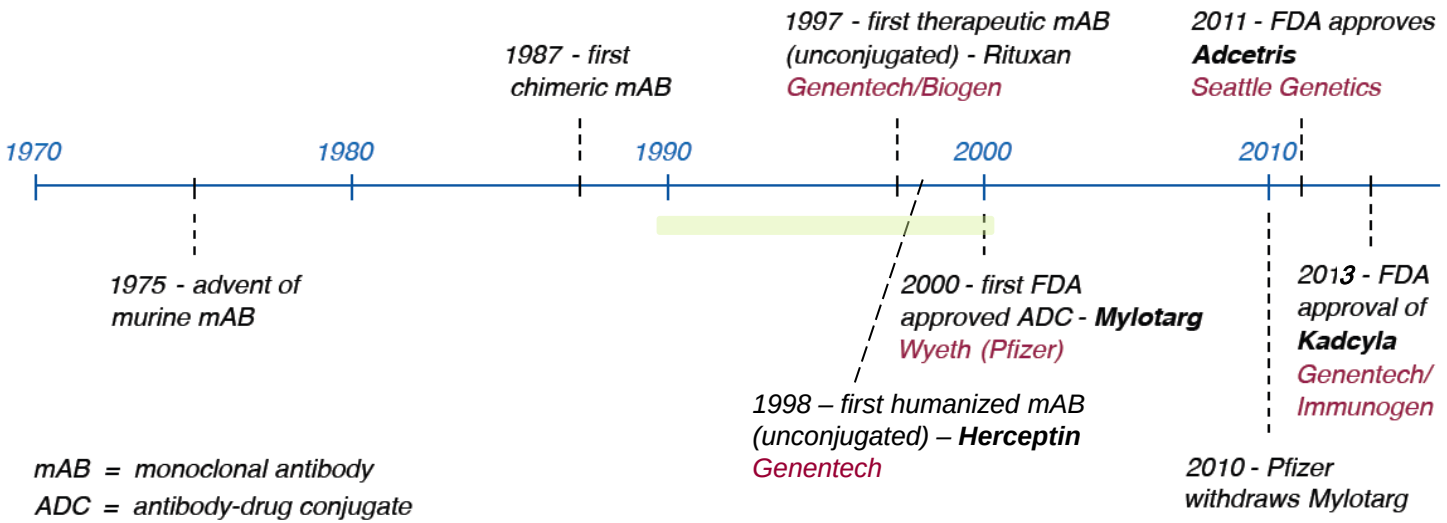




Response rate

ADC is an attractive cancer drug with wider therapeutic window than chemotherapy

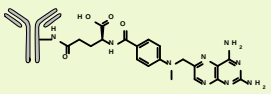
ADC
History of ADC research & development



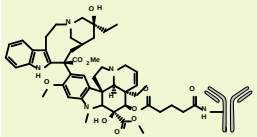
Perez-HL., Drug Discovery Today., **2014**, *19 (7)* , 870.

ADC in 90s

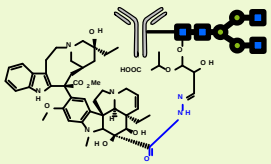
Lilly



KS1/4-methotrexate

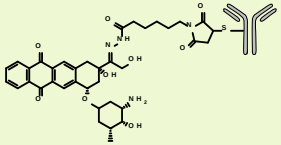


KS1/4-DAVLB



KS1/4-DAVLB HYD

Seattle Genentics / Bristol Myers Squibb



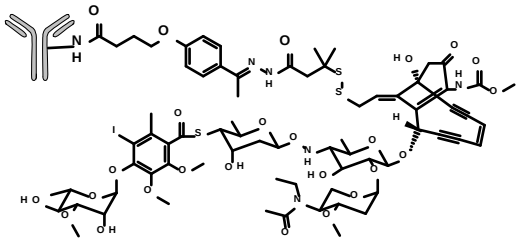
cBR96-doxorubicin

Anti-antibody
Less efficacy
Unstable linker
Serious adverse event

- **Establishment of chimeric and humanized mAb**
- **Maturity of antibody generation technology and production process**
- **Selection of antibody with high drug delivery function**
- **Selection of drug suitable for payload**
- **Designed stable linker in blood**

Elias-DJ., Am. J. Respir. Crit. Care Med., **1994**, *150*, 1114.
Shuneck-D.,Clin. Pharmacol. Ther., **1990**, *47*, 36.
Petersen-BH., Cancer Res., **1991**, *51*, 2286.
Tolcher –AW, J. Clin. Oncol., **1999**, *17*, 478.

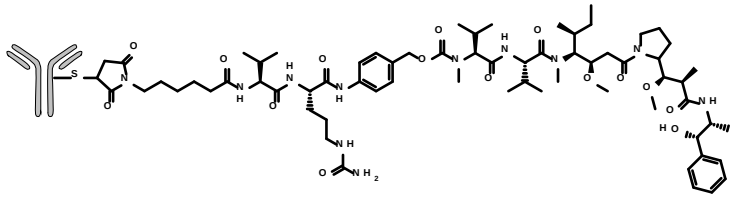
ADC
ADC technology development



Mylotarg® (Gemtuzumab ozogamicin), **DAR*~3**
2000～2010

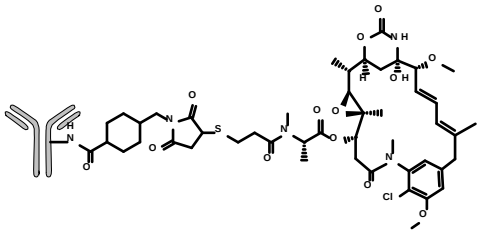
- ✓ **Serious hepatic disorder and fatal cases**
- ✓ **Withdrawn from US market in 2010**

***DAR, Drug to Antibody Ratio**
Average number of drugs on an antibody



Adcetris® (Brentuximab vedotin, SGN-35), **DAR* 4.0**
2012～

- ✓ **Enzyme cleavable type peptide linker**
  Promptly cleaved by cathepsin up-regulated in tumor cell
  Dispatch drug without linker residue from self-cleaved binding site, pABC residue



Kadcyla® (Trastuzumab emtansine, T-DM1), **DAR* 3.5**
2013～

- ✓ **Non cleavable type linker**
- ✓ **Released drug has less membrane permeability**

ADC
ADC of today: approved drugs

- **Launched: only two products**
  - ***Kadcyla***®: anti HER2＋**DM1*** , *breast cancer*
  - ***Adcetris***® :anti CD30＋**MMAE***, *Hodgking lymphoma*

DM1 and MMAE are both potent microtubule inhibitors

*DM1 : *N2'*-deacetyl-*N2'*-(3-Mercapto-1-oxopropyl)-Maytansine
**MMAE : MonoMethyl Auristatin E

- **Under development: about 60 products***
  - **Ph3**: 6 agent, **Ph2**: 18 agents, **Ph1**: 39 agents

Over 60% of ADC have microtubule inhibitors
<u>Due to less efficacy and adverse events,</u>
few projects moves to late stage development

* Overview: The ADC clinical pipeline, 7th World ADC (Oct., 2016, San Diego)

ADC

ADC of today: under development

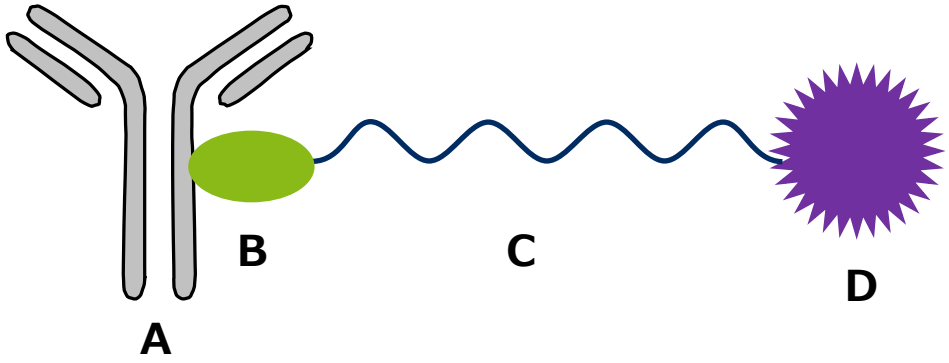
Name	Company	Target	Toxin target	Status
SGN35	Takeda	CD30	Tubulin	Launched
T-DM1	Genentech	HER2	Tubulin	Launched
CMC-544	Pfizer	CD22	DNA	Ph3
SGN-CD33A	Seattle Genetics	CD33A	DNA	Ph3
IMGN853	ImmunoGen	FOLR1	Tubulin	Ph3
CDX-011	Celdex	gpNMD	Tubulin	Ph3
RG7596	Genentech	CD79b	Tubulin	Ph2
SAR3419	Sanofi	CD19	Tubulin	Ph2
PSMA ADC	Progenics	PSMA	Tubulin	Ph2
BT062	Biotest	CD138	Tubulin	Ph2
BAY 94-9343	Bayer	methothelin	Tubulin	Ph2
SGN-CD19A	Seattle Genetics	CD19A	Tubulin	Ph2
IMMU-132	Immunomedics	TROP2	Topoisomerase I (SN38)	Ph2
IMMU-130	Immunomedics	CEACAM5	Topoisomerase I (SN38)	Ph2
AGS-16C3F	Agensys	ENPP3	Tubulin	Ph2
RG7450	Genentech	STEAP1	Tubulin	Ph1
SAR650984	Sanofi	CD38	Tubulin	Ph1
AMG 595	Amgen	EGFRvIII	Tubulin	Ph1
AMG 172	Amgen	CD27L	Tubulin	Ph1
ASG-22ME	Agensys	Nectin-4	Tubulin	Ph1
SGN-LIV1A	Seattle Genetics	LIV1A	Tubulin	Ph1
SGN-CD70A	Seattle Genetics	CD70	DNA	Ph1
DS-8201	Daiichi Sankyo	HER2	Topoisomerase I (DXd)	Ph1
U3-1402	Daiichi Sankyo	HER3	Topoisomerase I (DXd)	Ph1
SYD985	Synthon	HER2	DNA	Ph1
MEDI4276	Astrazeneca	HER2	Tubulin	Ph1
ABBV-838	Abbvie	SLAMF7	Tubulin	Ph1
BAY1187982	Bayer	FGFR2	Tubulin	Ph1

ADC

ADC of today: discontinued

Name	Company	Discontinued	Targets	Toxins
Mylotarg	Pfizer	Withdrawn	CD33	Calicheamycin
MLN-0246	Seattle Genetics	Ph2	Guanylate cyclase C	MMAE
RG-7599	Roche/Genentech	Ph2	NaPi2b	MMAE
RG-7450	Roche/Genentech	Ph2	STEAP-1	MMAE
SAR3419	ImmunoGen	Ph2	CD19	DM4
IMGN901	ImmunoGen	Ph2	CD56	DM1
DCDT2980S	Roche/Genentech	Ph1	CD22	MMAE
RG-7600	Roche /Genentech	Ph1	Mesothelin	MMAE
RG-7636	Roche /Genentech	Ph1	ETBR	MMAE
PF-06263507	Pfizer	Ph1	5T4	MMAF
MEDI 547	Medimmune	Ph1	EPHA2	MMAF
SGN-75	Seattle Genetics	Ph1	CD70	MMAF
IMGN289	ImmunoGen	Ph1	EGFR	DM1
AMG595	Amgen	Ph1	EGFRvIII	DM1
AMG172	Amgen	Ph1	CD70	DM1
IMMU-110	Immunomedics	Ph1	CD74	doxorubicin
LOP628	Novartis	Ph1	KIT	maitansine

ADC
Component and requirement for ADC



A : Antibody
B : Attachment site
C : Linker
D : Drug

Antibody:
1. Tumor selective and high expression antigens
2. Internalization to target cell
3. Minimized non-specific binding

Linker:
1. Cleavable and non-cleavable
2. Release active substance in target cell

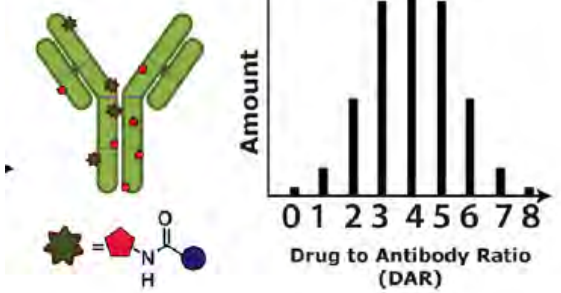
Attachment site:
1. Typically cysteine or lysine residue on antibody
2. Control of drug to antibody ratio
3. Control of drug distribution

Drug:
1. Should have potent efficacy
2. Available linker binding site

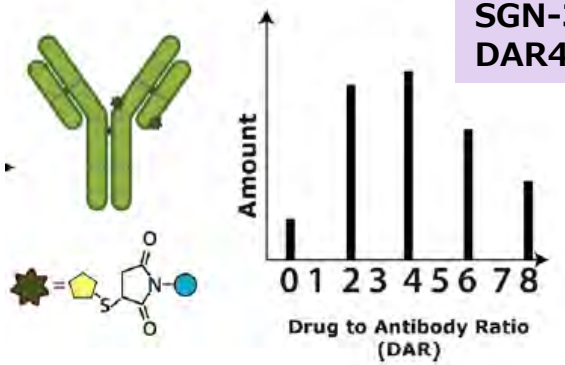
ADC
Issues of existing ADC technology

■Heterogeneity of drug distribution

T-DM1 (KADCYLA®)
DAR3.5 ImmunoGen



SGN-35 (ADCETRIS®)
DAR4 Seattle Genetics

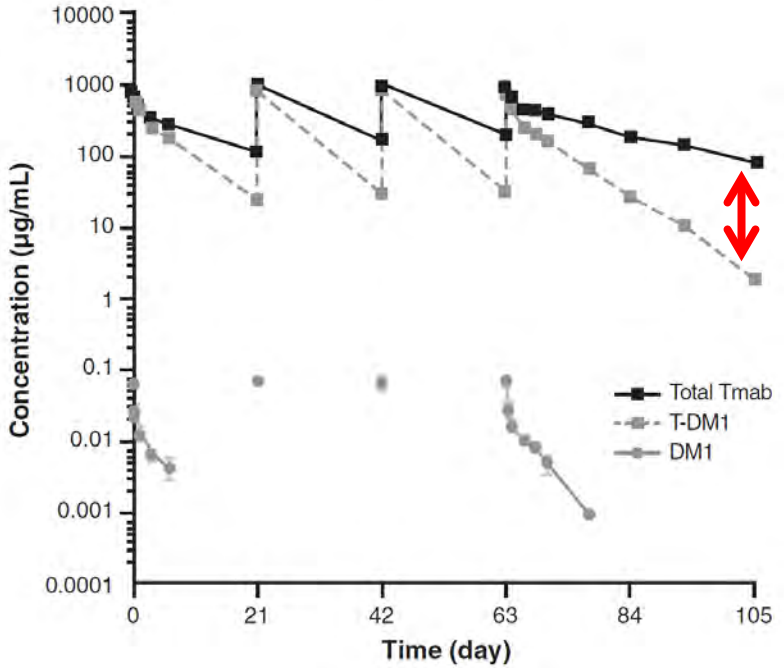


Peters-C, Biosci Rep. 35(4) 2015

A mixture of different DAR* ADCs
→Contains unfavorable DAR* ADCs
DAR*; Drug to Antibody Ratio

■Linker instability

T-DM1 30 mg/kg in monkeys

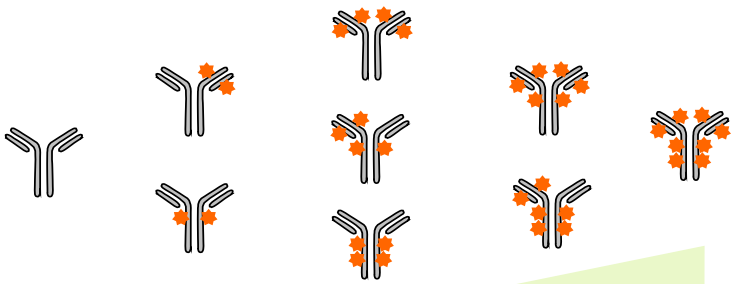


Poon-KA,Toxicol Appl Pharmacol. 273(2) 2013

Free payload release in circulation
→Free payload conc.↑Toxicity↑
→ADC conc. ↓ Efficacy↓

ADC
Issues of existing ADC technology

- **Limited drug loading number**

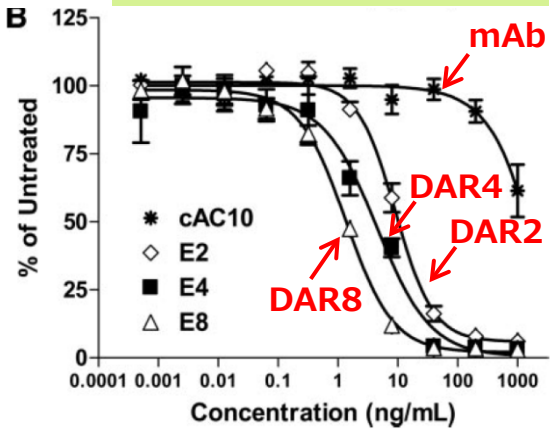


Drug to Antibody Ratio (DAR)
in vitro activity
clearance
aggregation
toxicity

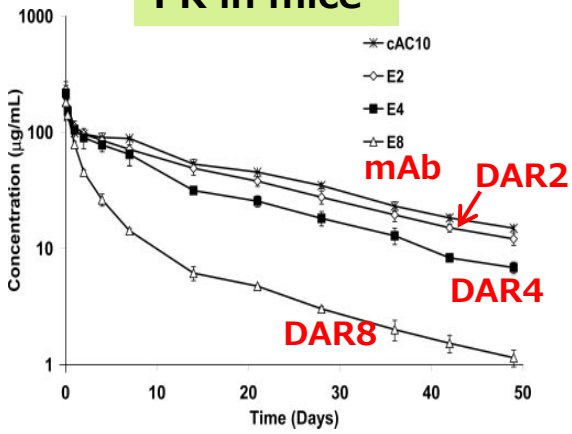
Distribution of payload (DOP)
In vivo activity
Safety margin

Increasing DAR causes decreasing retention time of ADC in the blood
→ Decreasing efficacy

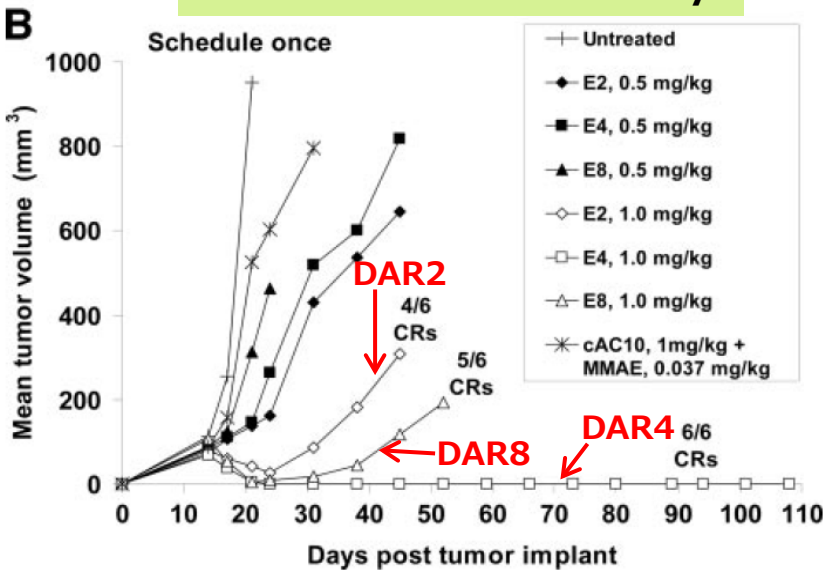
In vitro cytotoxicity



PK in mice



In vivo antitumor efficacy



Hamblett-KJ., Clin. Cancer Res., **2004** *, 10(20),* 7063

ADC
Current issues in the field of ADC

◆ **Limited payload type**
- ➢ No further treatment for resistant/refractory tumors against existing ADCs

◆ **Linker instability**
- ➢ Toxicity derived from the increasing the blood concentration of free payloads
- ➢ Decreased efficacy by decreasing the concentration of ADC

◆ **Limited drug antibody ratio**
- ➢ Increasing DAR causes decreasing retention time of ADC in the blood
- ➢ Heterogenous drug load distribution

Goal of ADC research at Daiichi Sankyo
□ Exploration of Innovative ADC Drugs overcoming these issues

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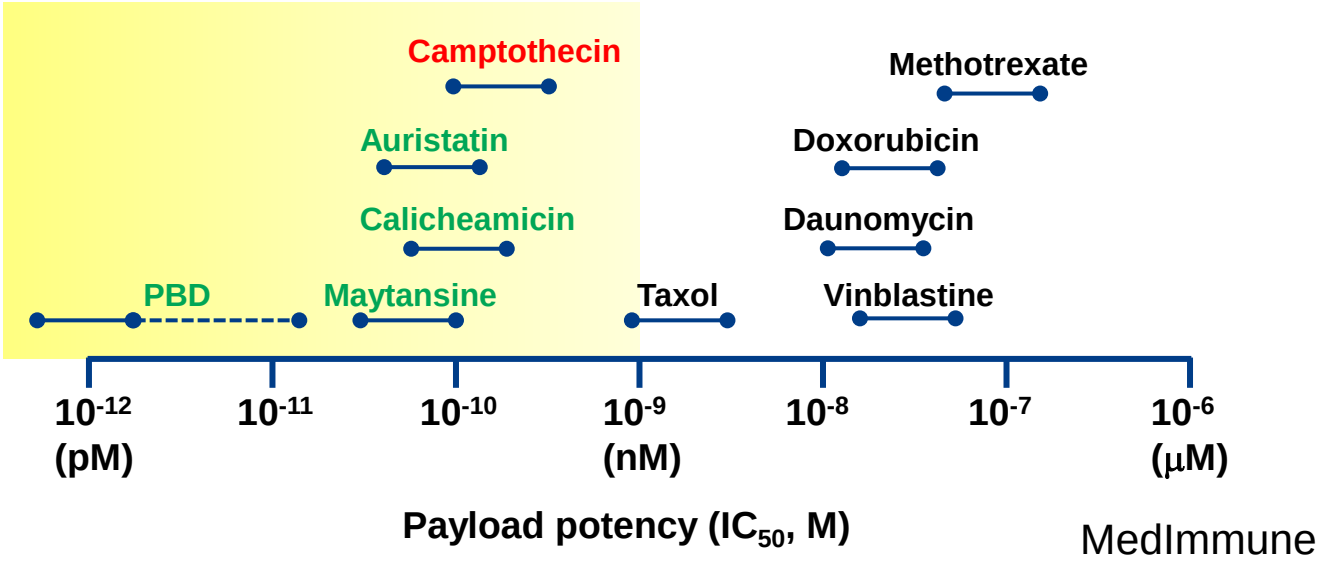
Development of Camptothecin derivatives as payload

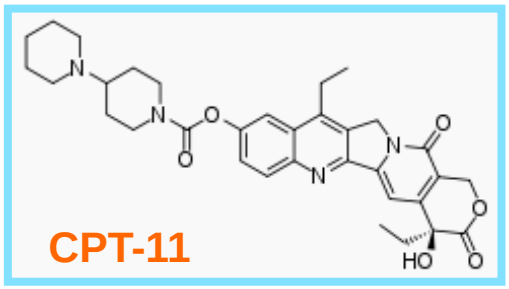
Payloads loaded on ADC and its cytotoxicity

What drug properties are required for the payloads on ADC?

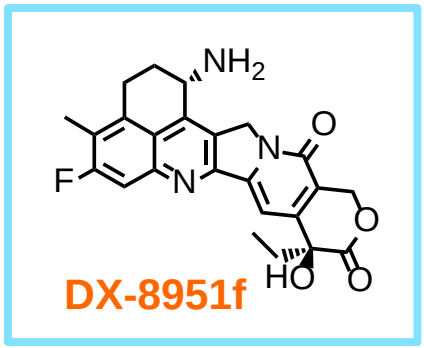
- Potent activity (sub-nM level of GI_{50} for cytotoxicity)
- Elucidated structure activity relationship (SAR)
- Existence of functional groups conjugating with linker
- Enough supply for conducting research



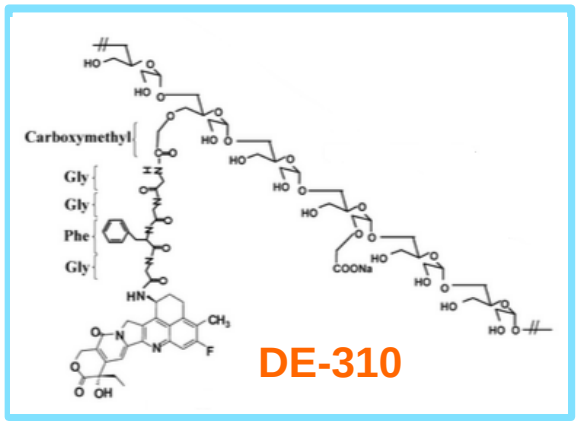
Development of Camptothecin derivatives in Daiichi Sankyo



- DNA topoisomerase I inhibitor irinotecan CPT-11, a prodrug of SN-38, was approved for patients with refractory tumors in 1994.



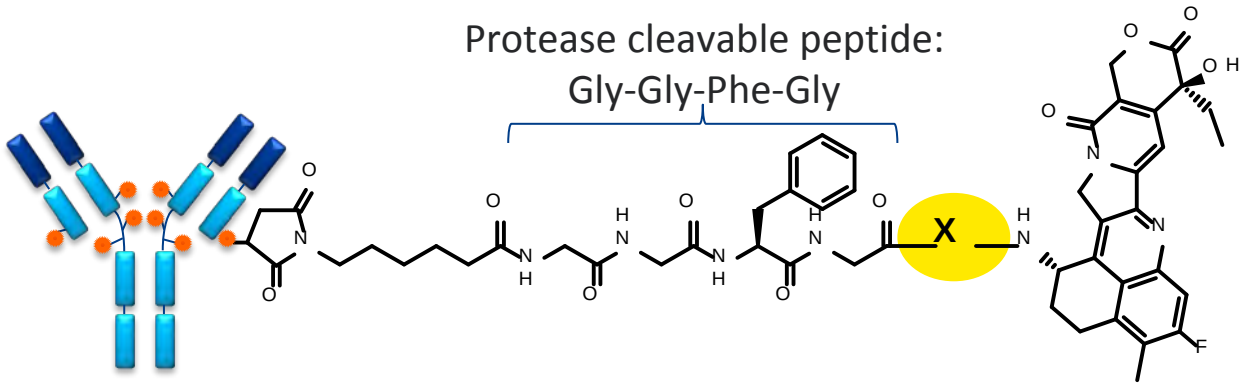
- About 10-fold more potent DX-8951f than SN-38 was developed and clinical study of pancreatic cancer was conducted, but clinical development was discontinued. (Ann N Y Acad Sci (2000) 922, 260-273)



- Macromolecule polymer conjugate DE-310 was synthesized with enzyme cleavable linker and DX-8951f and Enhanced Permeability and Retention (EPR) effect was observed in mouse. Clinical development was discontinued. (Clinical Cancer Research, (2005) 11, 703-711)

Discovery of DS-8201a

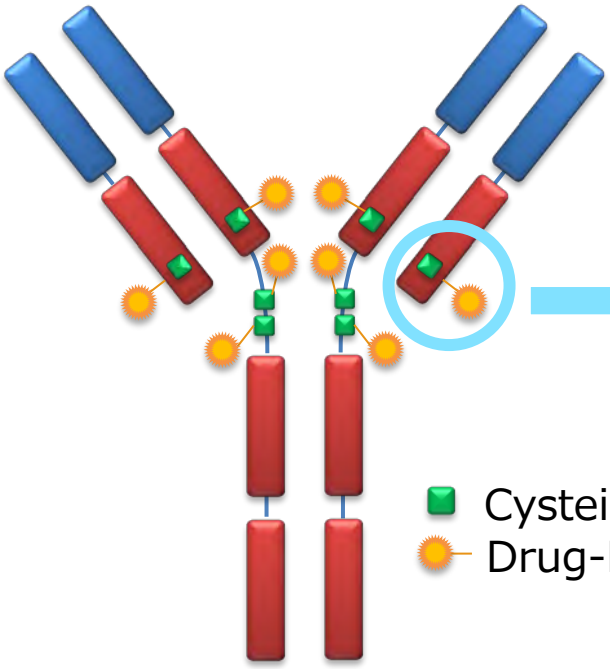
Research on the drug-linker for ADC



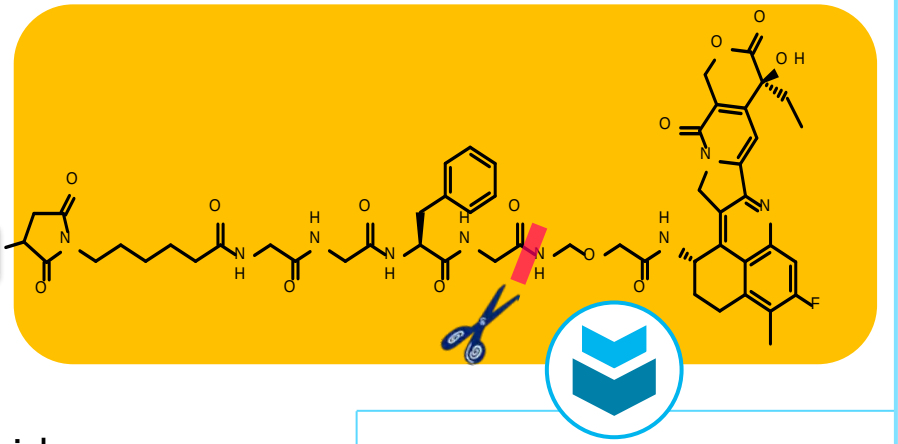
Entry	X	DAR	Aggregate (%)	KPL-4 IC_{50} (nM)
1	None	3.4	26	0.33
2	-NH-CH_2-(C=O)-	3.2	3	0.39
3	-NH-$(CH_2)_2$-(C=O)-	3.8	2	0.07
4	-NH-$(CH_2)_3$-(C=O)-	2.6	3	0.05
5	-NH-$(CH_2)_4$-(C=O)-	3.4	4	0.07
6	-NH-$(CH_2)_5$-(C=O)-	2.5	20	0.11
7	-NH-CH_2OCH_2-C(=O)-	7.7	0.6	0.19

Establishment of smart chemo ADC technology

Structure of DS-8201a

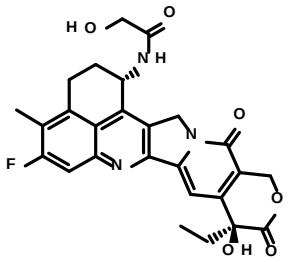


Proprietary Drug-Linker



Conjugation chemistry

The linker is connected to cysteine residue of the antibody

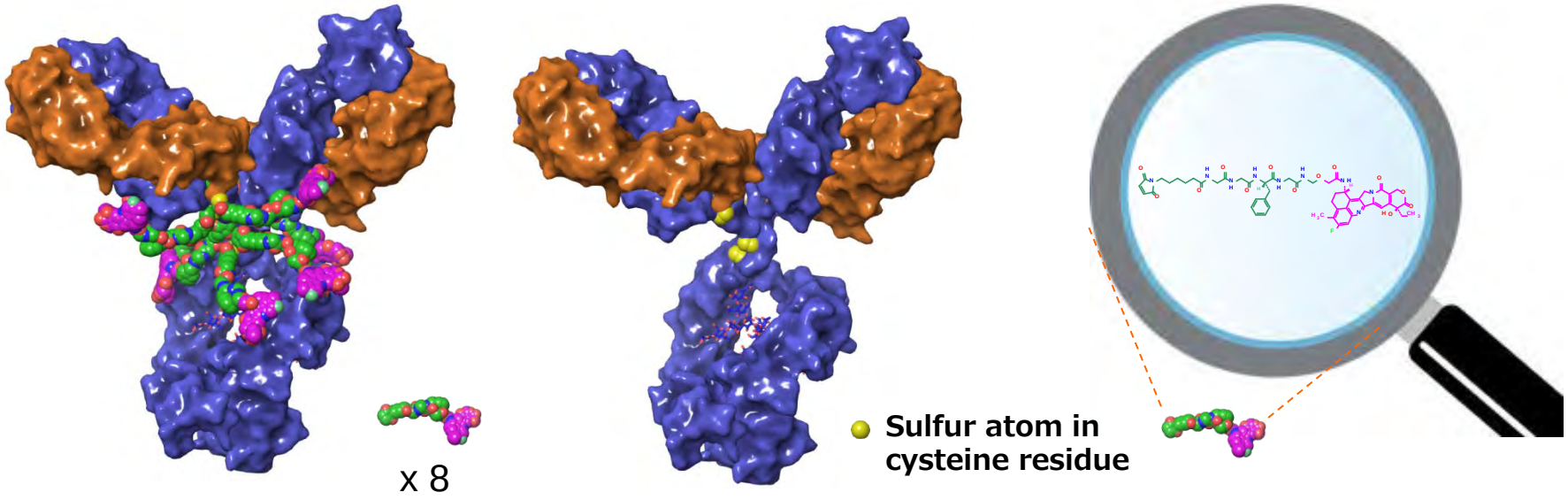


Payload (DXd)

DX-8951 derivative

1. Novel payload
2. High potency
3. Bystander effect
4. High clearance of the payload
5. Stable linker-payload
6. Tumor selective cleavable-linker
7. High DAR and homogeneity

DS-8201a
Three dimensional structure of DS-8201a



ADC	Antibody（IgG）	Drug-Linker
MW*: ca. 156,000	MW: ca. 148,000	MW: ca. 1,000

* : molecular weight

DS-8201a
Comparison with previous generation ADC

Prior generation ADCs

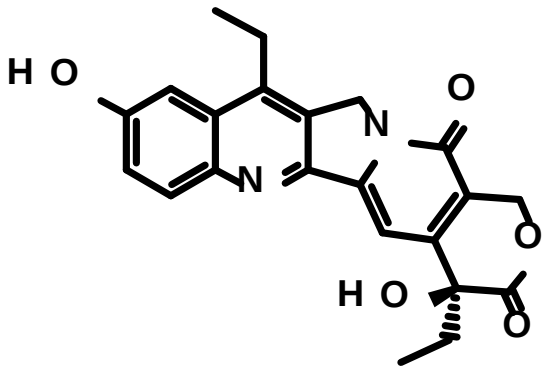
- Limited drug-to-antibody ratio *(3.5-4)*
- Linker instability and lack of tumoral specificity result in toxicity
- Payload related to typical chemotherapy previously received

Our smart chemo ADC technology

- Doubled drug-to-antibody ratio *(7-8)*
- High linker stability and more cancer-cell selective linker release
- Novel differentiated payload
  - Potent DNA topoisomerase I inhibitor
  - Effective in heterogeneous tumor microenvironment (bystander effect)
  - Very short systemic half-life

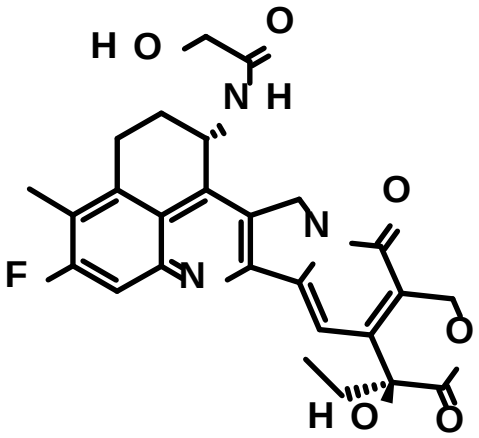
DS-8201a
DXd payload

SN-38
(active metabolite of irinotecan)



Topo I IC_{50}: 2.78 μM

DXd
(active metabolite of DS-8201a)



Topo I IC_{50}: 0.31 μM

- ✓ Novel topoisomerase I inhibitor
- ✓ DXd has more potent effect than irinotecan

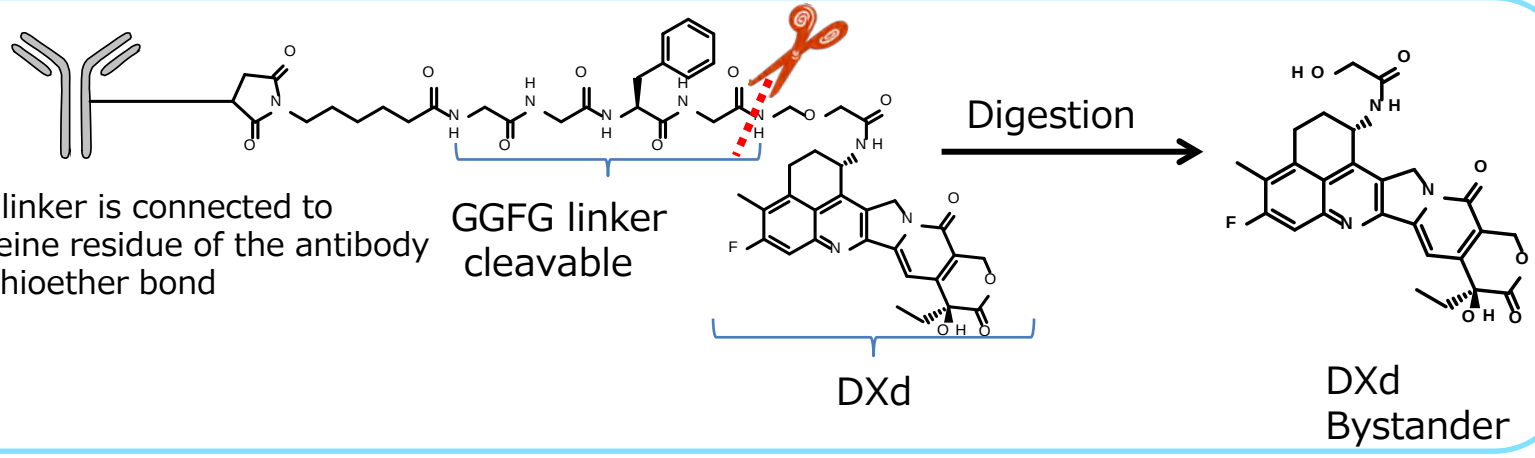
Daiichi Sankyo ADC
Contents

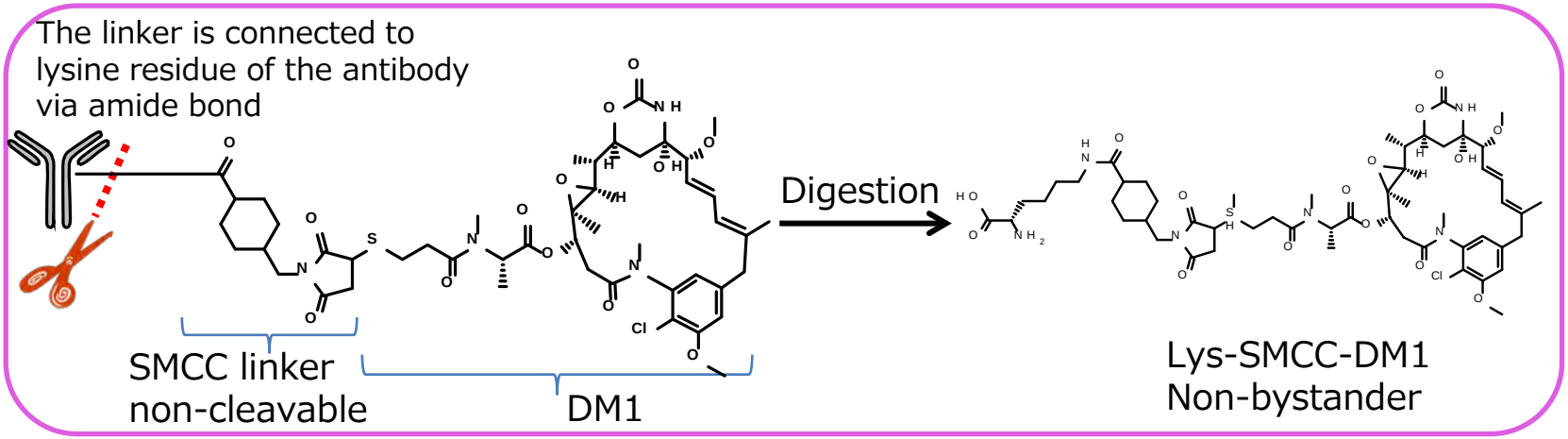
- ✓ Overview: trend of drug development, biologics and cancer treatment, about antibody drugs
- ✓ About antibody drug conjugate (ADC)
- ✓ Discovery of DS-8201a
- ✓ Characteristics and clinical results of DS-8201a
- ✓ Expansion of DXd-ADC technology

DS-8201a

Structures of DS-8201a and T-DM1 (Kadcyla®)

DS-8201a





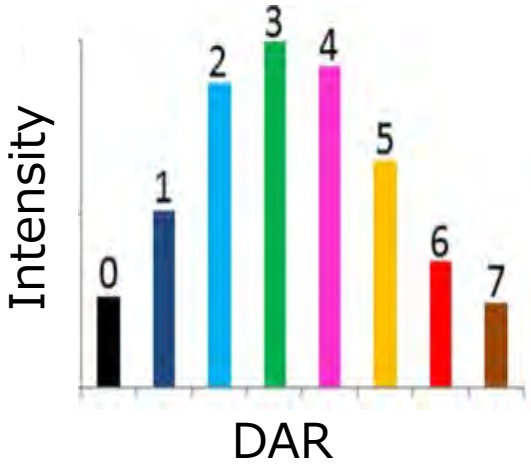
T-DM1

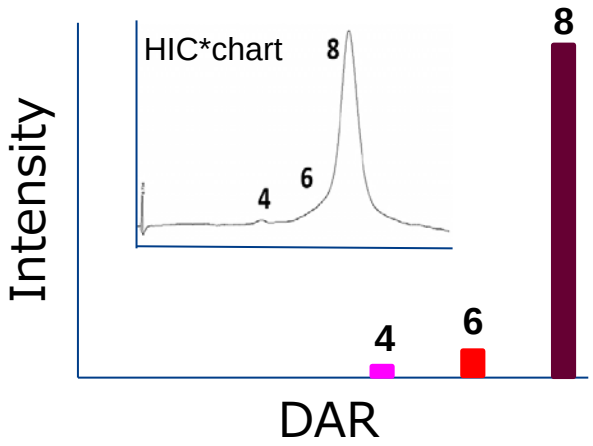
DS-8201a

High drug-to-antibody ratio (DAR)

High drug-to-antibody ratio (DAR)

	T-DM1	DS-8201
Antibody	Trastuzumab	Anti-HER2 Ab
Payload	Tubulin inhibitor (DM1)	DNA Topoisomerase I inhibitor (DXd)
DAR	3.5	7-8





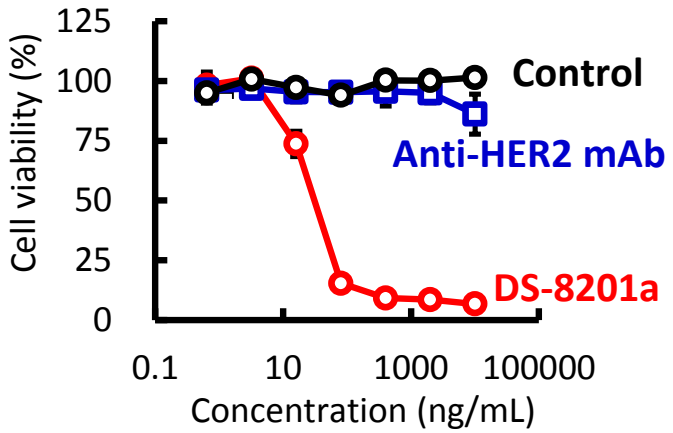
HIC*, Hydrophobic interaction chromatography

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

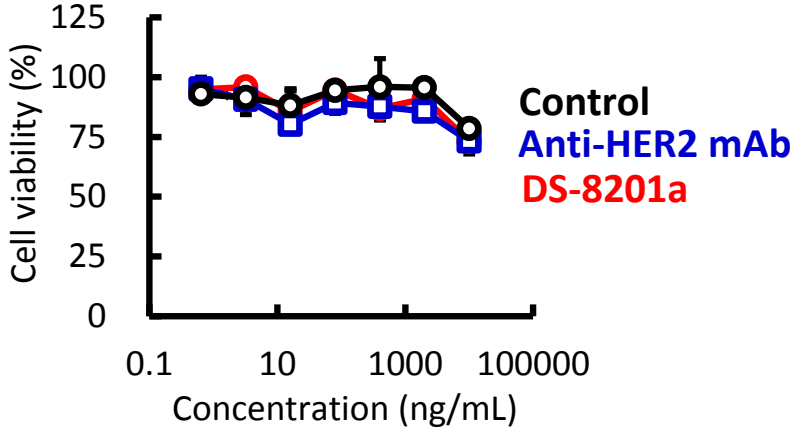
DS-8201a
in vitro assay

Cell killing assay

KPL-4 (Breast, HER2 positive)

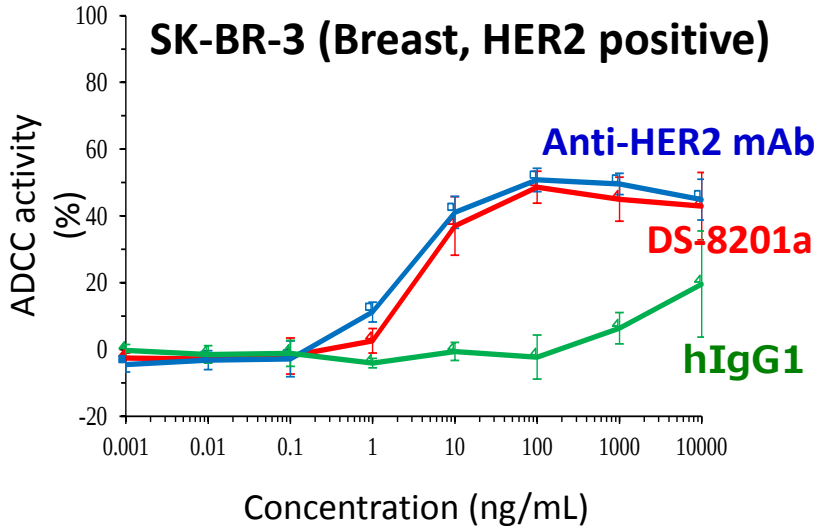


MDA-MB-468 (Breast, HER2 negative)

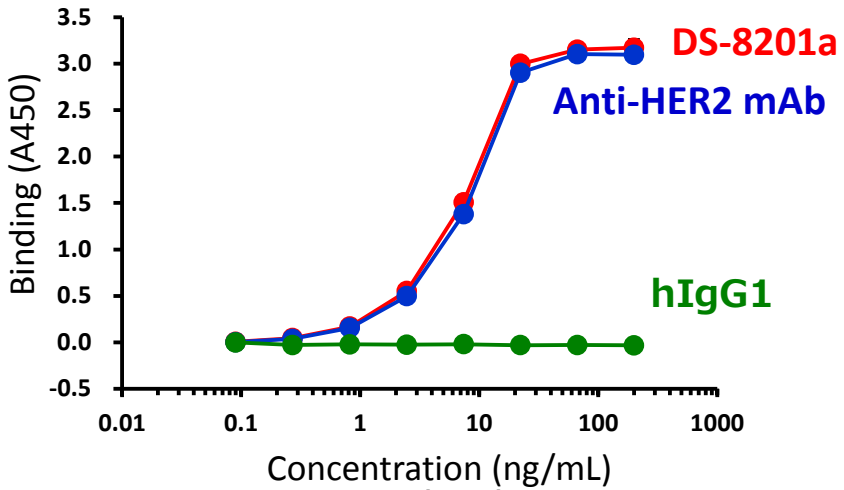


ADCC

SK-BR-3 (Breast, HER2 positive)



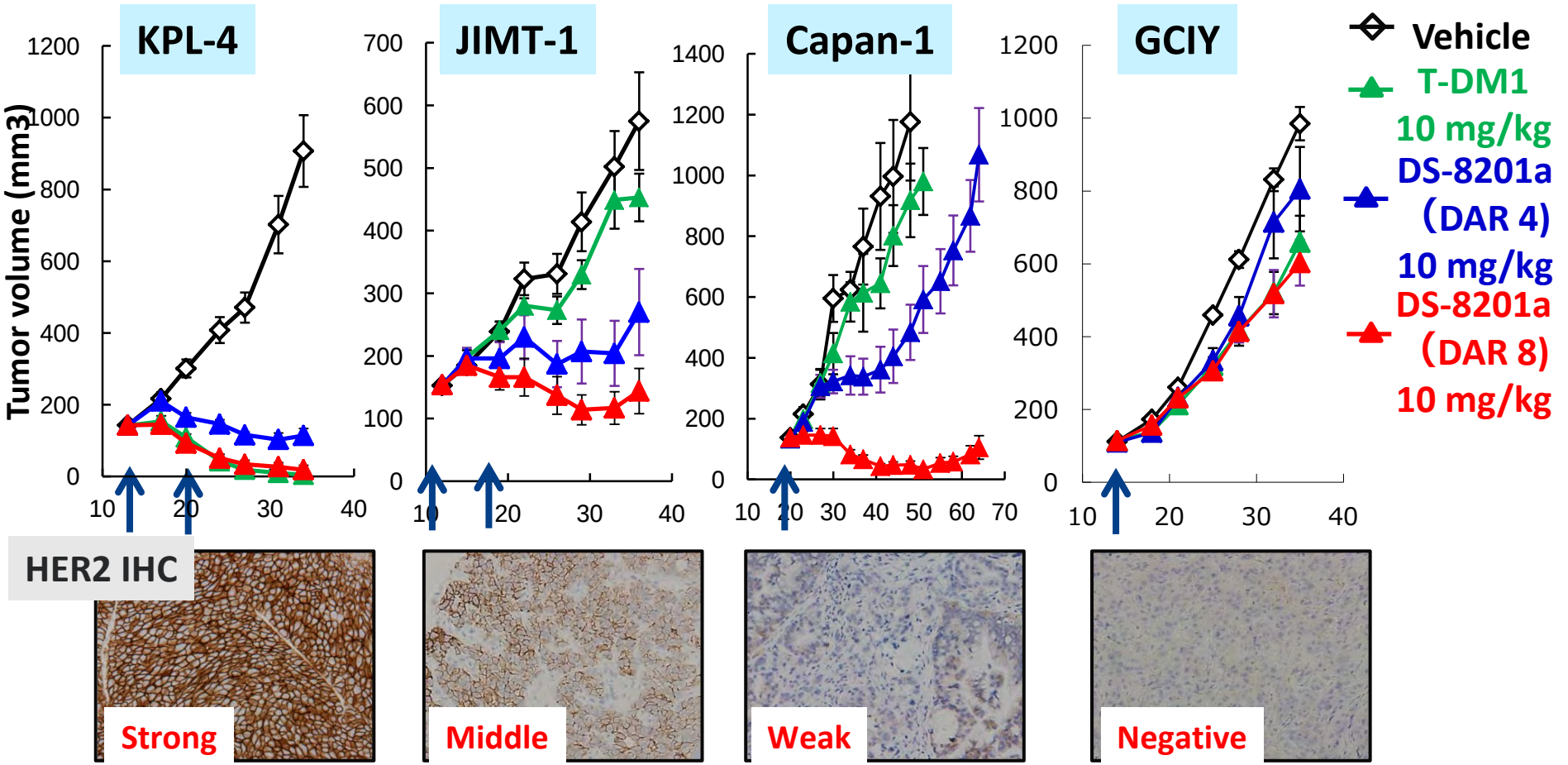
HER2 binding (ELISA)



Ogitani-Y et al., Clin Cancer Res 2016

DS-8201a
DS-8201a vs T-DM1 antitumor effect（non-clinical study）

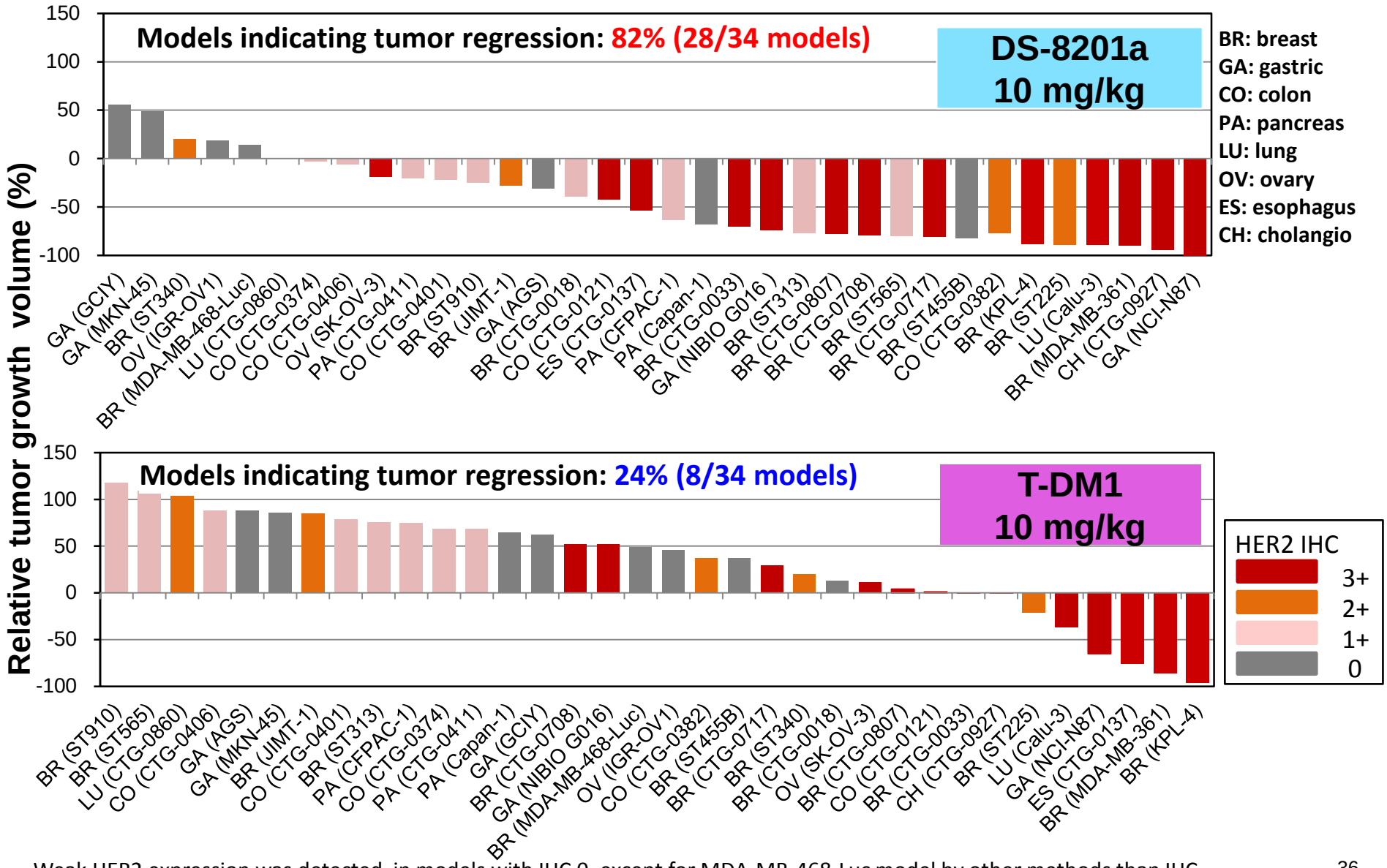
- **T-DM1 and DS-8201a (DAR8) showed efficacy against HER2 high models.**
- **DS-8201a (DAR8) showed more potent efficacy against HER2 low models.**



Ogitani-Y et al., Clin Cancer Res 2016

DS-8201a

DS-8201a vs T-DM1 antitumor effect (non-clinical study)



Weak HER2 expression was detected in models with IHC 0, except for MDA-MB-468-Luc model by other methods than IHC.

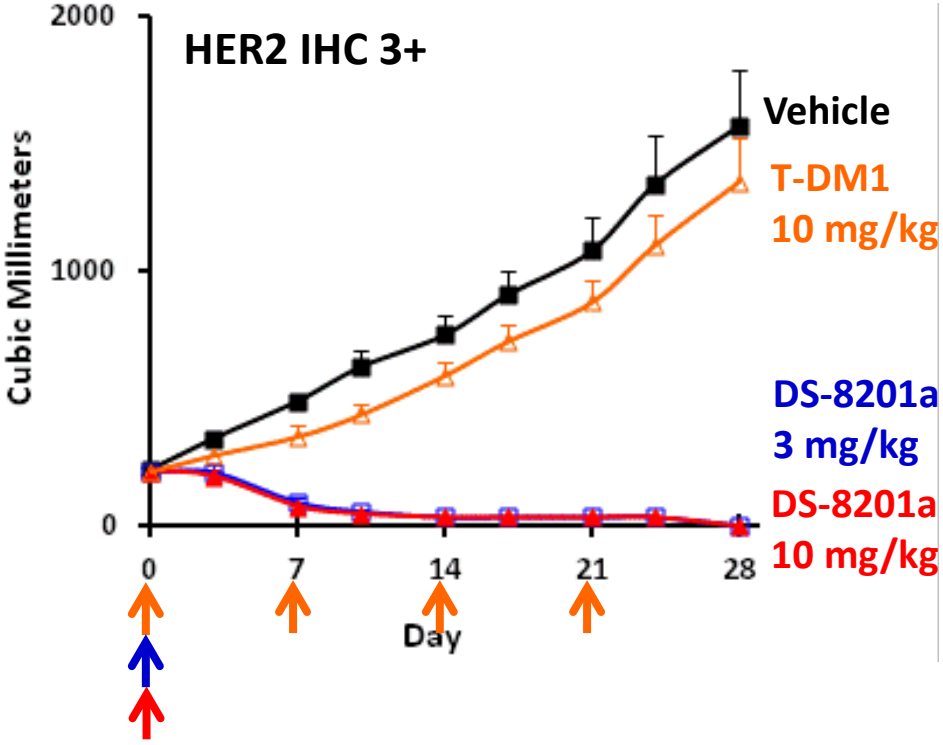
Source: Yuki Abe *et al.*, Bioconjugate 2016

DS-8201a

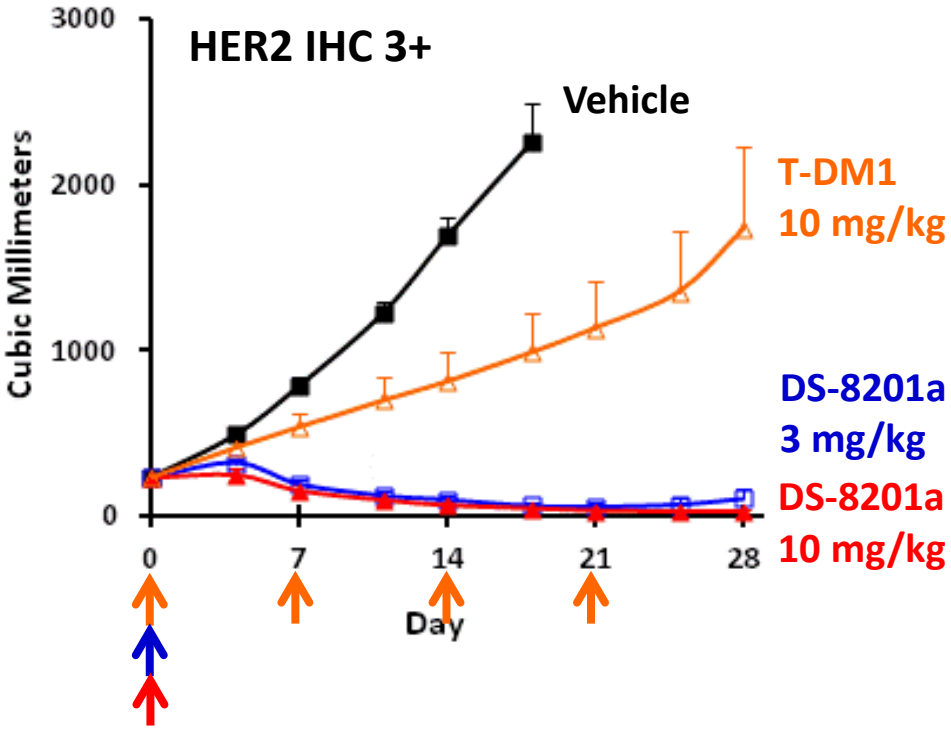
DS-8201a vs T-DM1 antitumor effect（non-clinical study）

PDX, Patient Derived Xenograft

ST1616B/TDR
(from 13-mo T-DM1 treated Pt)



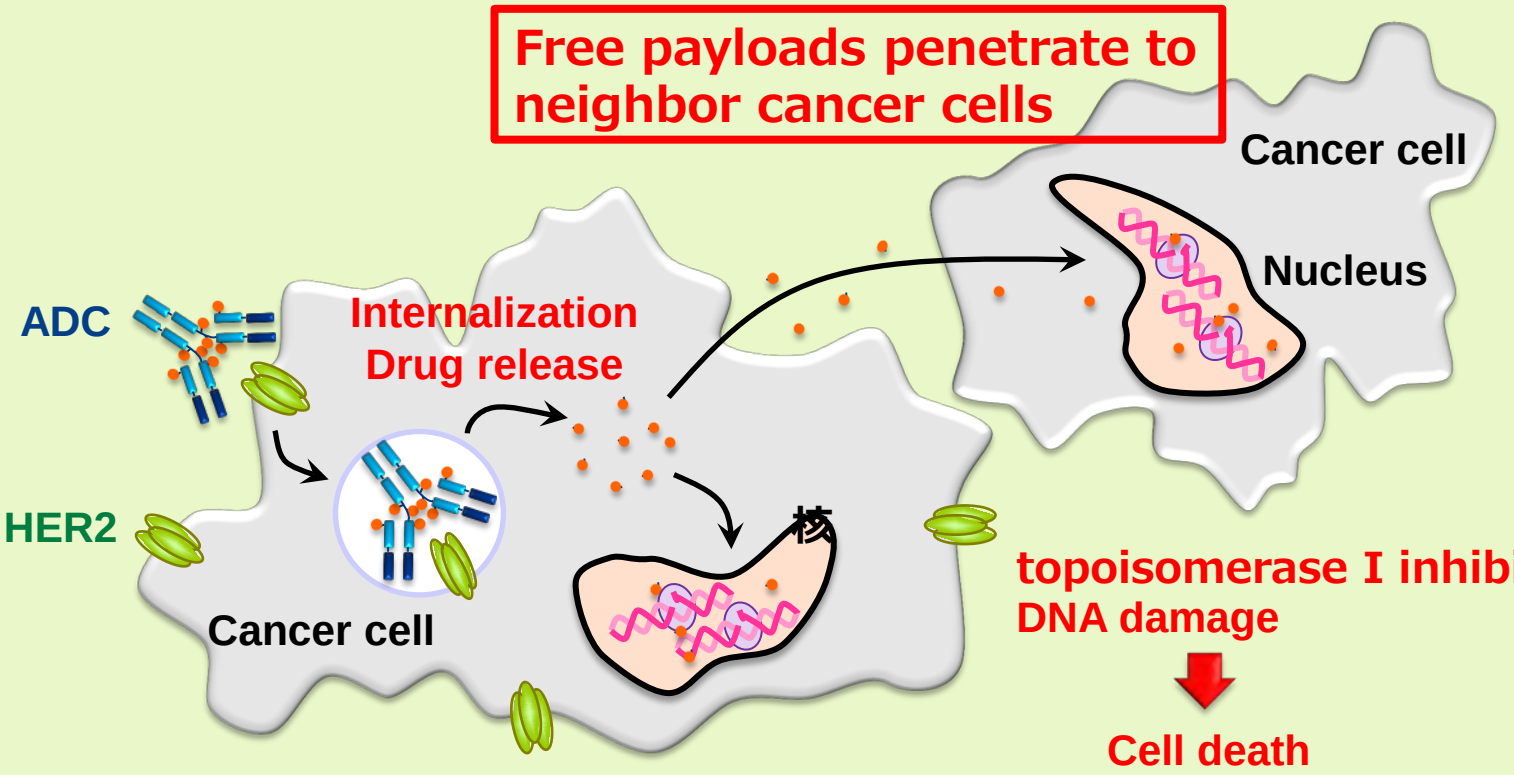
ST1360B/TDR
(from 3-mo T-DM1 treated Pt)



Source: Tamura-K *et al.*, abstract 4585 (LBA17), ESMO 2016

DS-8201a

Bystander effect by DXd payload



Bystander effect of ADC;
An effect that released payloads in cancer cells penetrate the cell membrane and show activity on neighboring dividing cancer cells.
Through this effect, activity against target antigen-negative cancer cells, in other words, activity against tumors with antigen heterogeneity is observed.

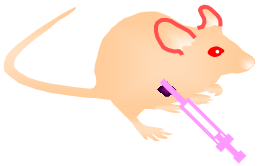
DS-8201a

Bystander effect in vivo experiment 1

HER2 positive cells (NCI-N87)

HER2negative cells (MDA-MB-468-Luc)

Co-inoculate to right flank



Nude mice

Day -7

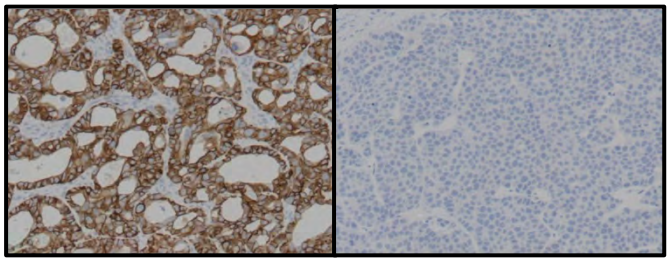
Day 0

ADC injection (i.v.)

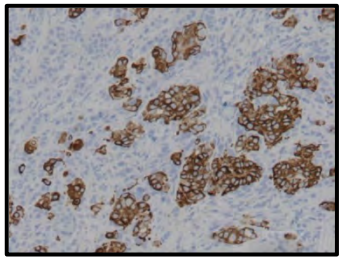
Day 14

HER2 expression in tumor (Immunohistochemistry, IHC method)

NCI-N87 **MDA-MB-468-Luc**



Co-inoculation



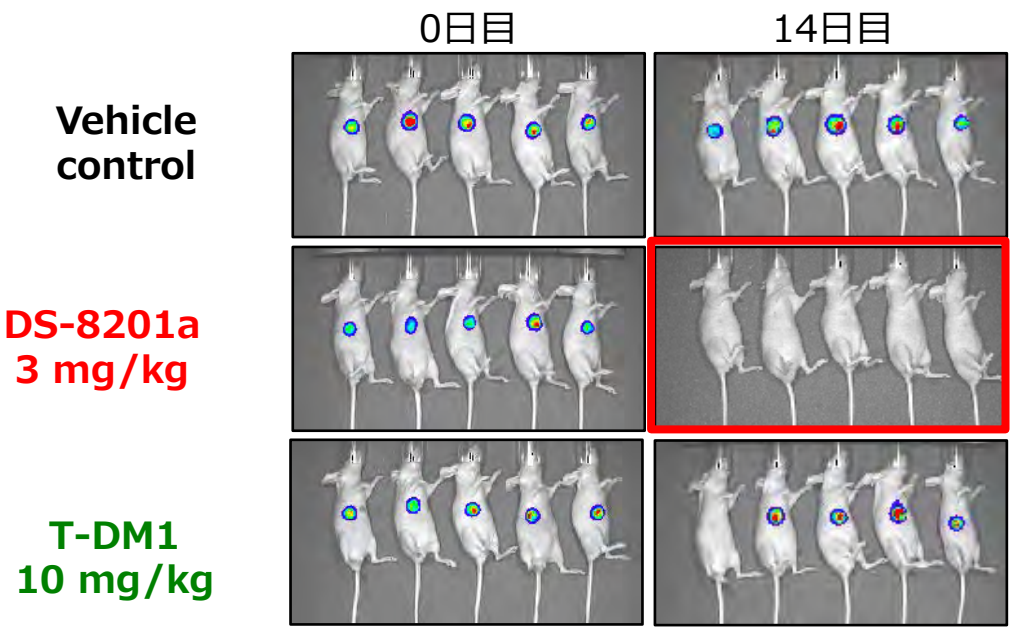
Measure luciferase activity
Measure HER2 negative tumor

HER2 immunostaining (IHC method)
Measure HER2 positive tumor

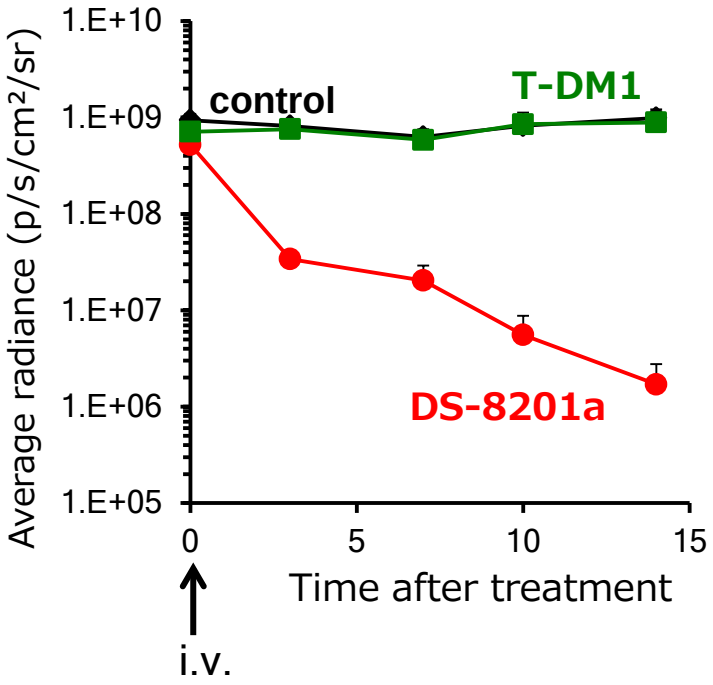
DS-8201a

Bystander effect in vivo experiment 1

Luciferase imaging (= MDA-MB-468-Luc)



Luciferase activity



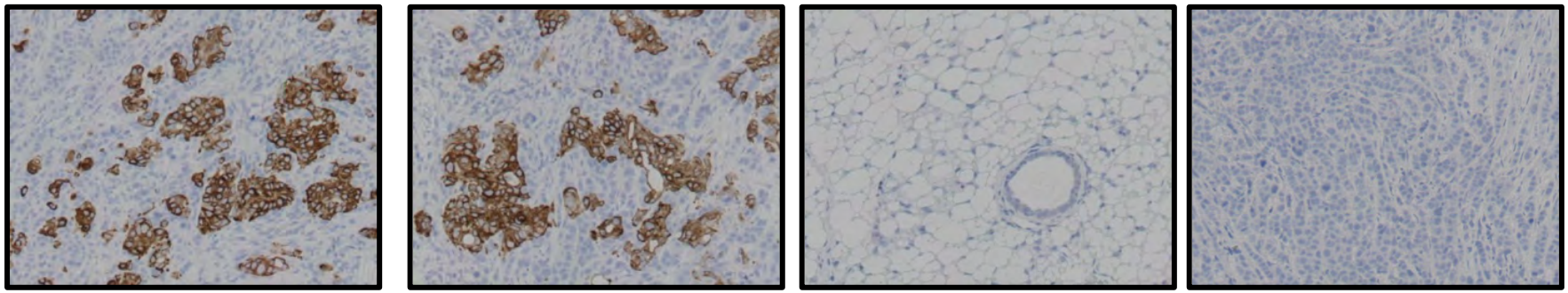
Ogitani-Y et al., Clin Cancer Res 2016; 22:5097

- DS-8201a treatment clearly decreased luciferase signal
- **→ Luc-gene transfected MDA-MB-468-Luc (HER2-negative) cells was eliminated**

DS-8201a

Bystander effect in vivo experiment 1

HER2 immunostaining (= NCI-N87)



HER2 positive tumors and HER2 negative tumor cells

Tumors eradicated

HER2 negative tumor cells alive

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

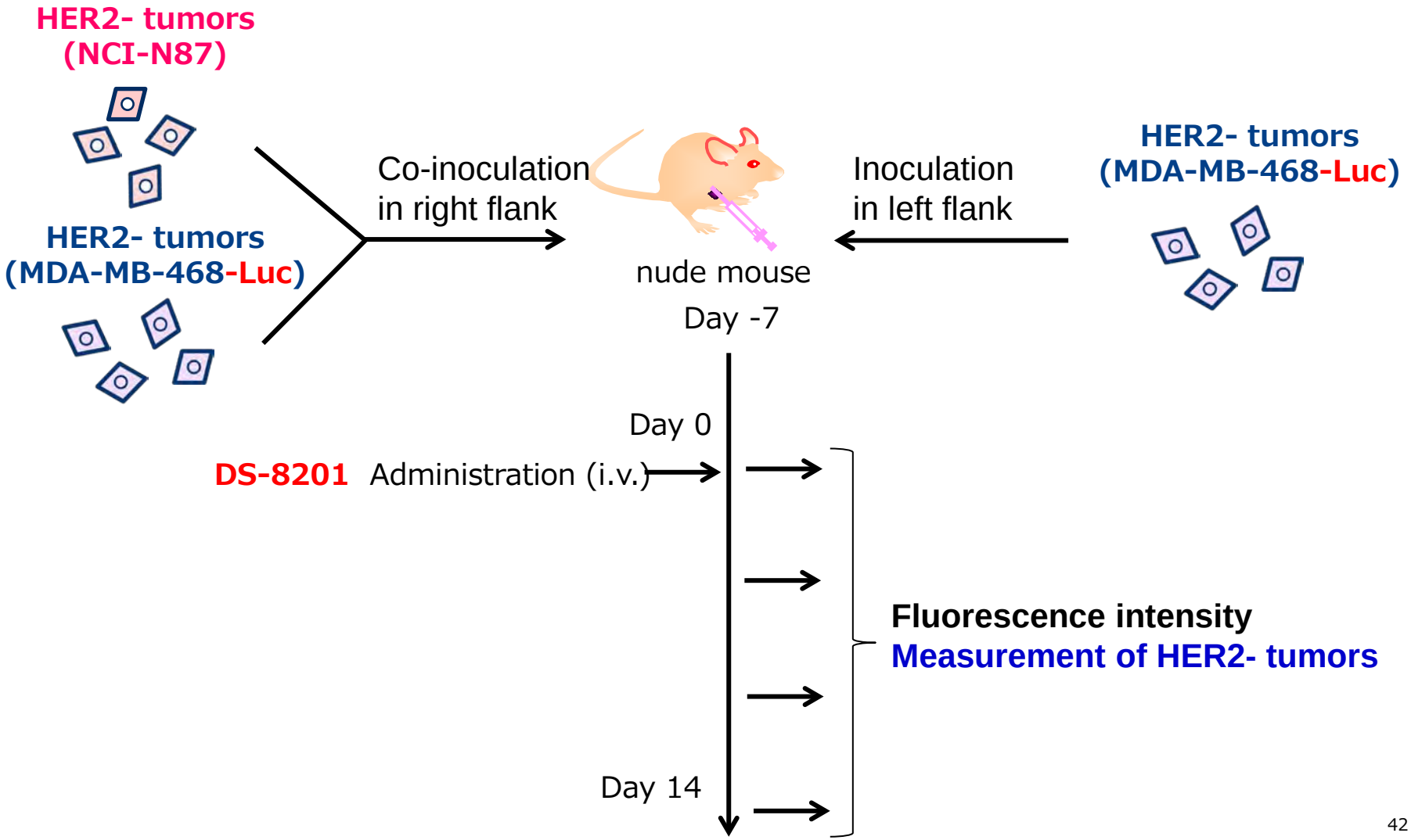
- HER2 positive tumor cells were almost eradicated after given T-DM1 and HER2 negative tumor cell is alive.
- Both HER2 positive and HER2 negative cells eradicated after given DS-8201a.

→Under the co-inoculated condition, DS-8201a showed antitumor activity against not only HER2 positive tumors, but also HER2 negative tumors.

DS-8201a

Bystander effect in vivo experiment 2

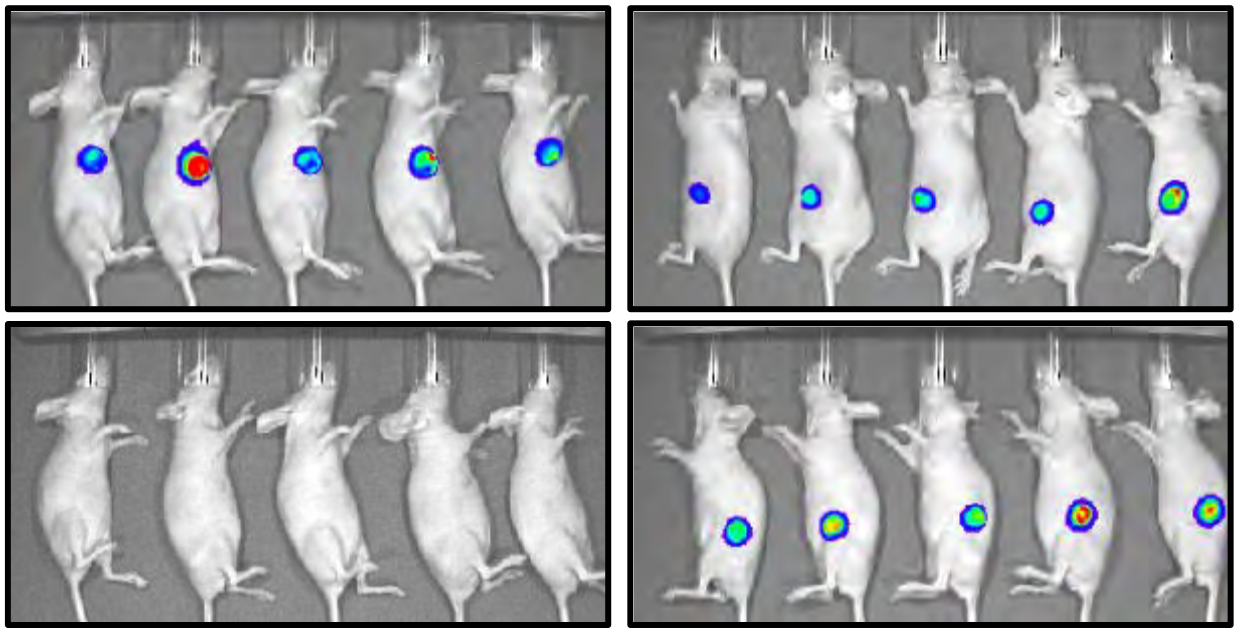
Effect on HER2 negative tumor cells distant from HER2 positive tumor cells was evaluated



DS-8201a

Bystander effect in vivo experiment 2

Day14 after ADC injection	Right flank	Left flank
Inoculated cells:	NCI-N87 MDA-MB-468-Luc	- MDA-MB-468-Luc



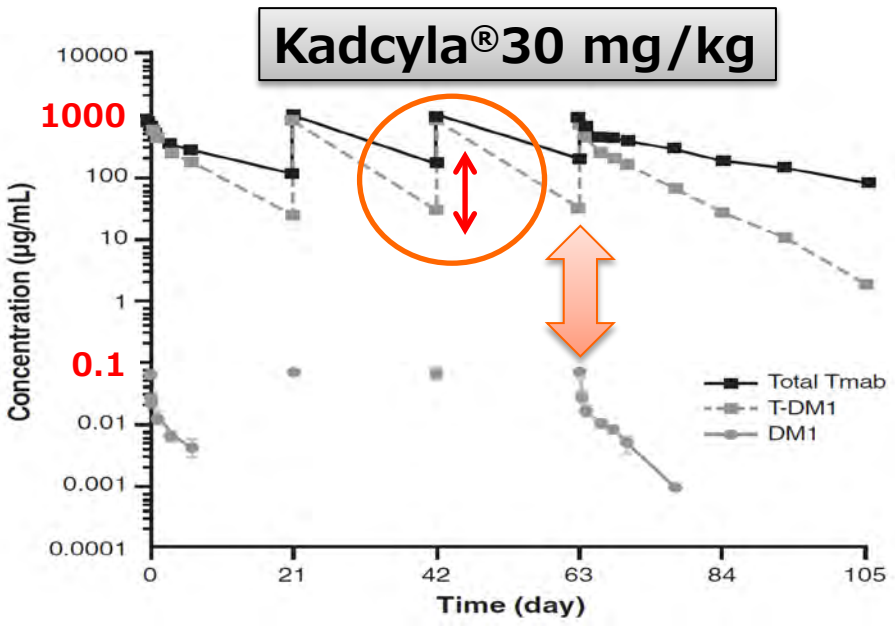
Ogitani-Y et al., Clin Cancer Res 2016; 22:5097

- By giving DS-8201a, MDA-MB-468-Luc cell adjacent to NCI-N87 cell eradicated, but no effect to distant MDA MB-468-Luc cell.

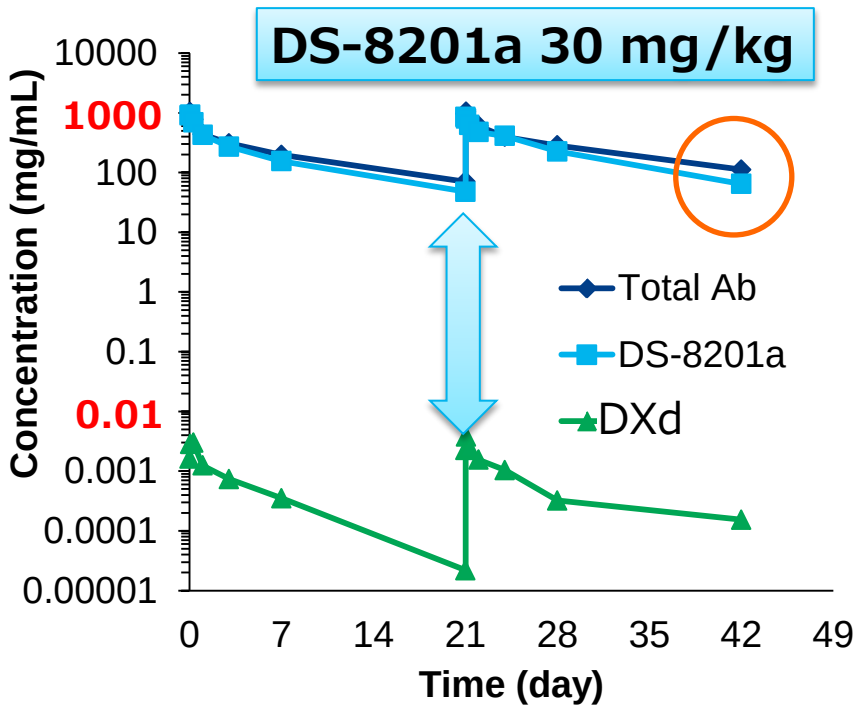
→Bystander effect is observed only in the case of cancer cells adjacent to HER2 positive cell.

DS-8201a

High linker stability and low free payload, preclinical



Poon-KA., Toxicol Appl Pharmacol. 2013 273(2):298



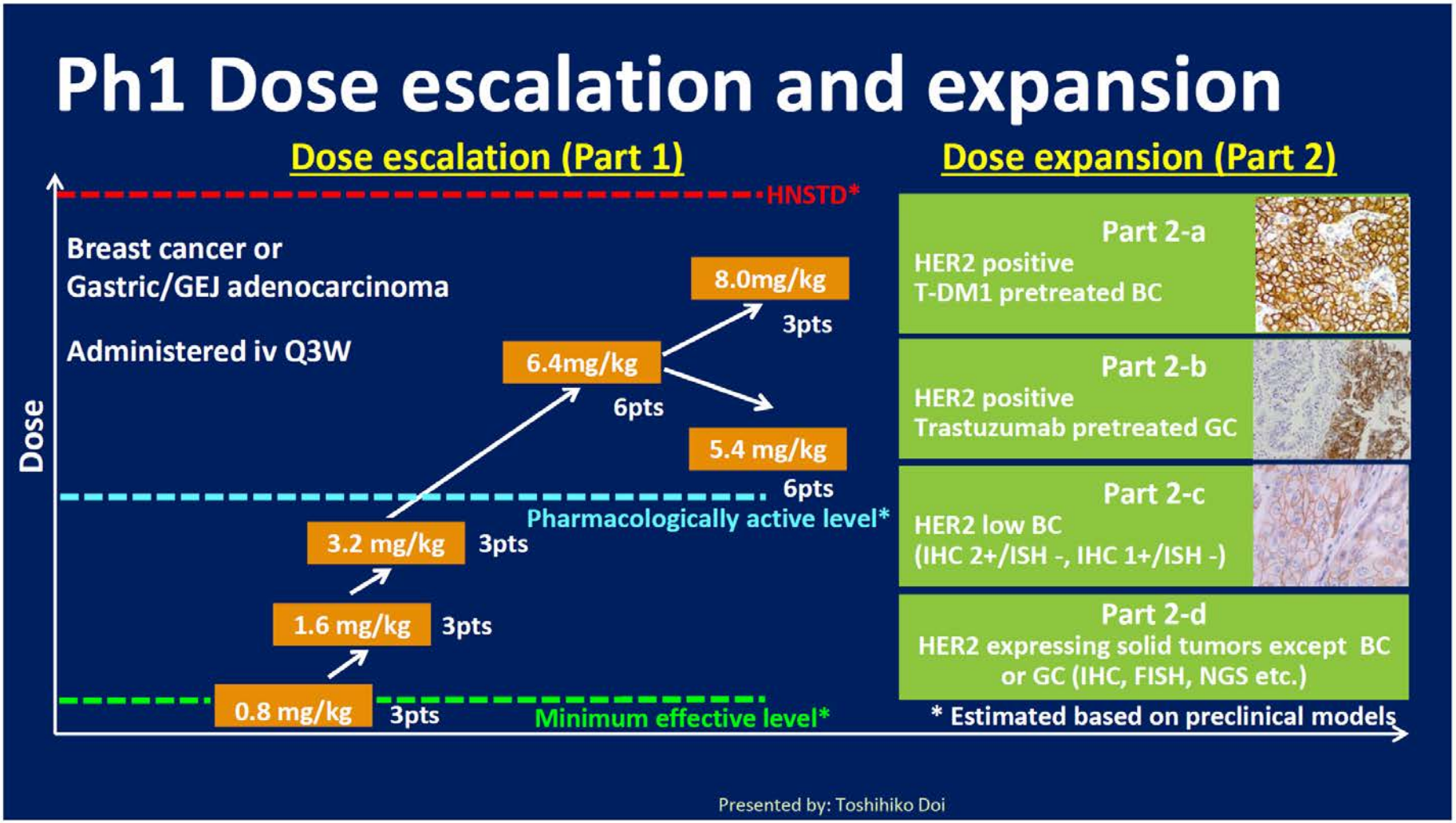
	Kadcyla®	DS-8201a
Dose	0, 3, 10, 30 mg/kg	0, 10, 30, 78.8 mg/kg
Regimen	i.v., q3w×4	i.v., q3W×3
Target Organ	≥3: liver, lymph, skin, lung ≥10: kidney, thrombocytopenia, axonal degeneration	≥10: intestine, ≥30: lung, skin, testicle 78.8: bone marrow, kidney
HNSTD*	**10 mg/kg**	**30 mg/kg**

*** HNSTD: highest non-severely toxic dose**

Tox profile cited in Kadcyla [pharmacology review(s)]. South San Francisco, CA: Genentech, Inc., 2013.

DS-8201a

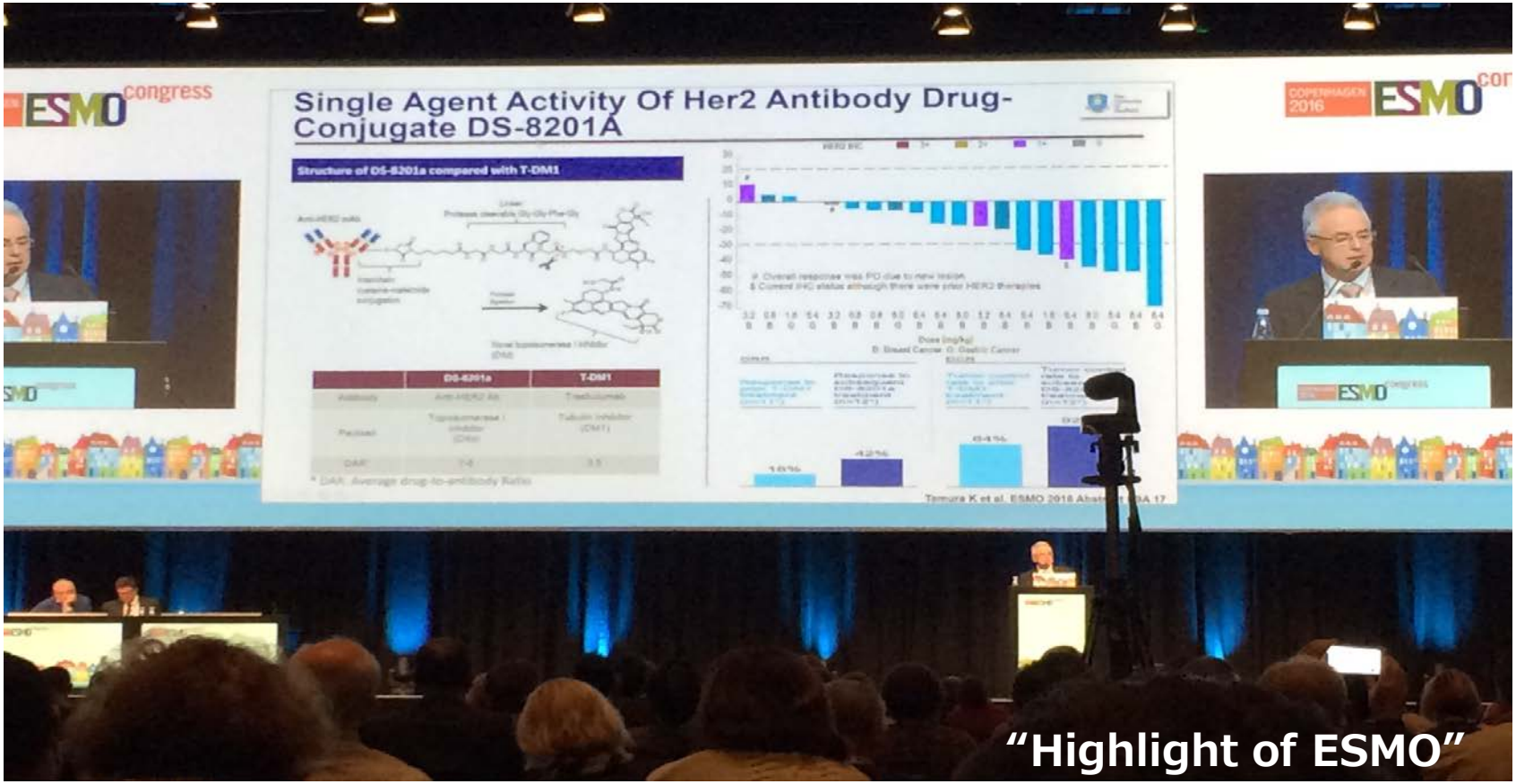
Ph1 study design



Source: Toshihiko Doi, et al., abstract No. 108, ASCO 2017

DS-8201a
Fast track designation

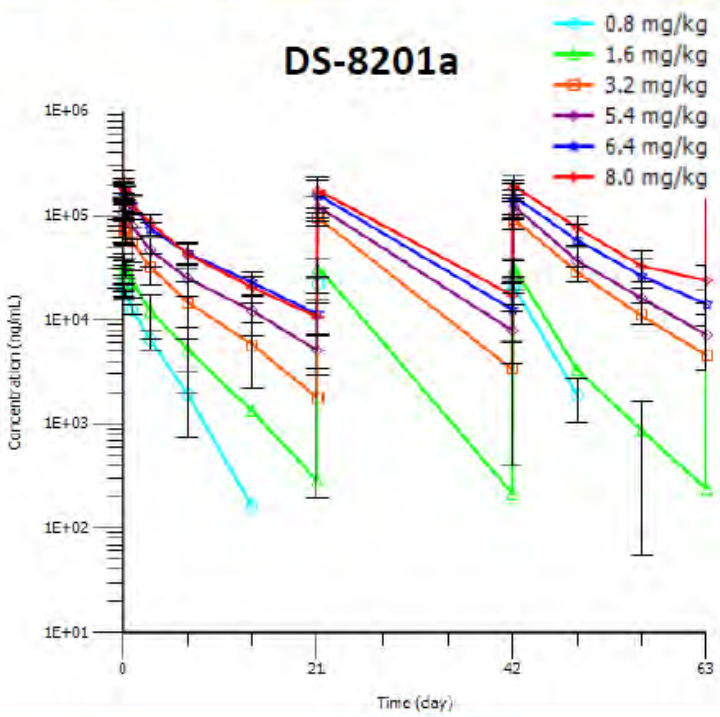
- Presented data in Late breaking session of European Society for Medical Oncology (ESMO) (Oct 2016)
- Fast track designation by FDA for HER2 positive metastatic breast cancer (Nov 2016)

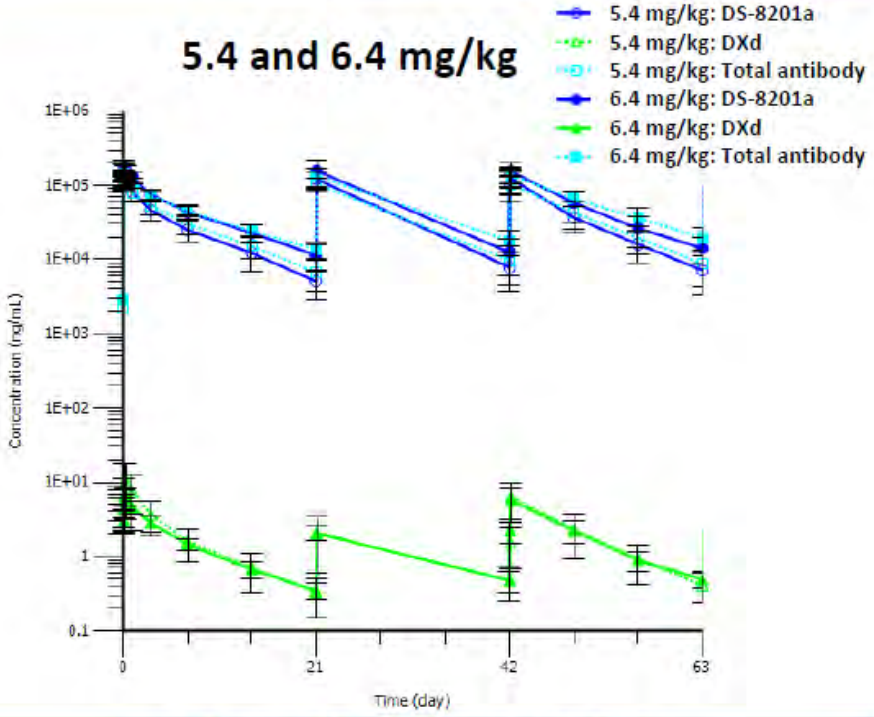


DS-8201a

Ph1 PK data

Pharmacokinetics





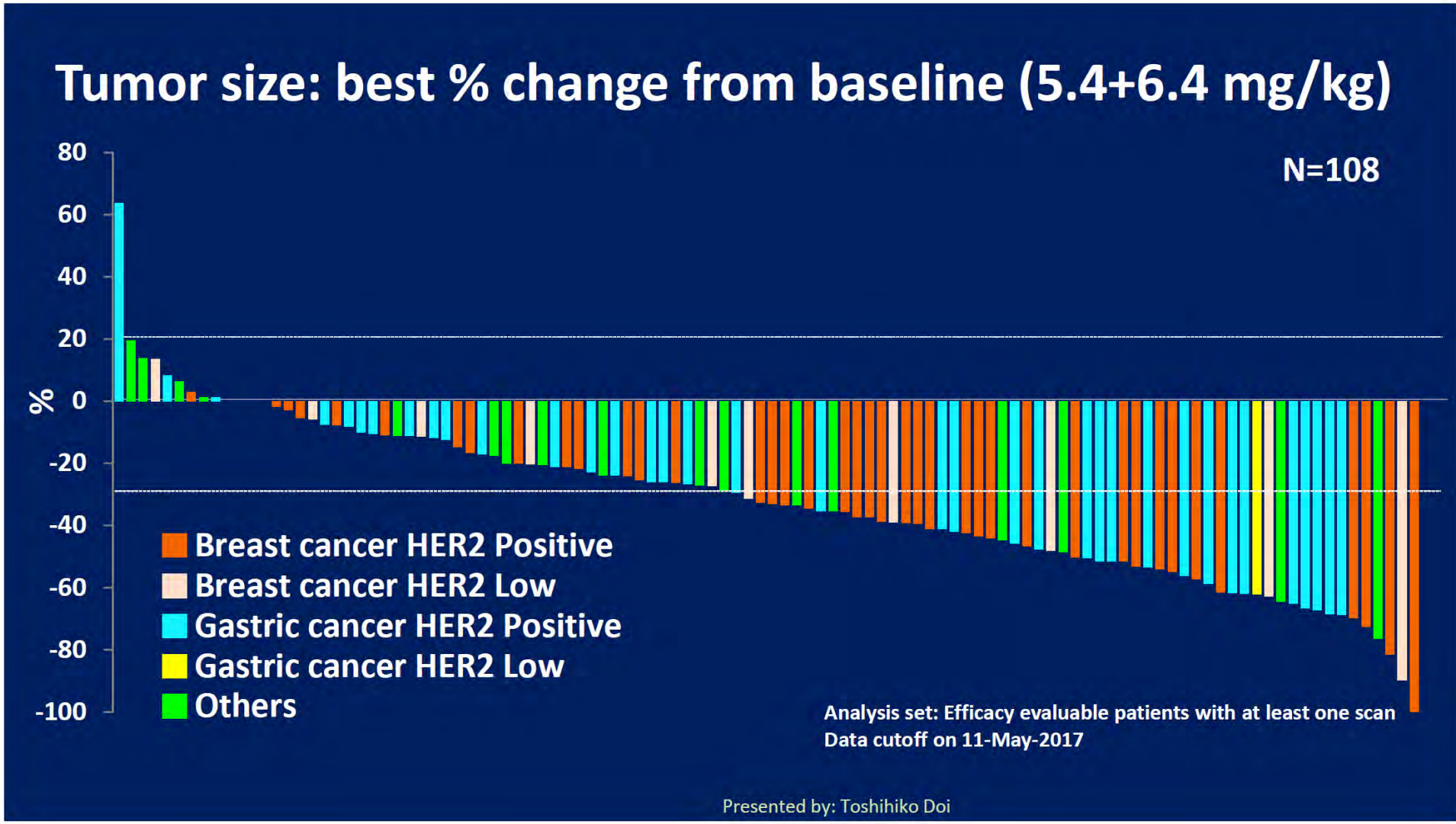
Analysis set: PK evaluable patients in Part1
Data cutoff on 11-May-2017

Presented by: Toshihiko Doi

Source: Toshihiko Doi, et al., abstract No. 108, ASCO 2017

DS-8201a

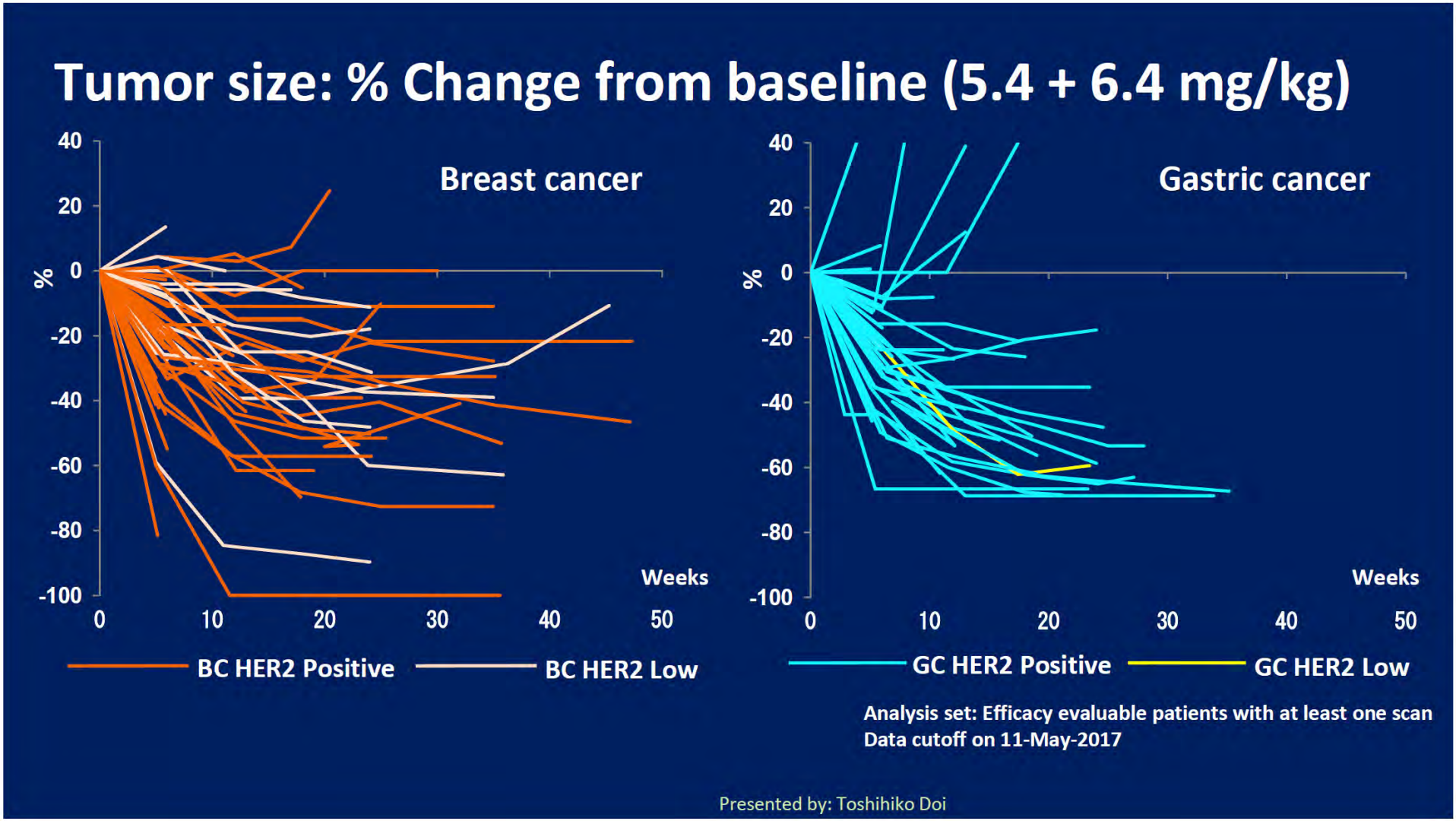
Ph1 Efficacy data（5.4+6.4mg/kg）



Source: Toshihiko Doi, et al., abstract No. 108, ASCO 2017

DS-8201a

Ph1 Efficacy data（5.4+6.4mg/kg）



Source: Toshihiko Doi, et al., abstract No. 108, ASCO 2017

DS-8201a

Ph1 Efficacy data（5.4+6.4mg/kg）

Daiichi-Sankyo cancerenterprise

Confirmed overall response rate (5.4+6.4 mg/kg)

	ORR n (%)	DCR n (%)
Total	39/97 (40.2)	89/97 (91.8)
Breast Cancer	19/45 (42.2)	44/45 (97.8)
BC Prior T-DM1	16/35 (45.7)	35/35 (100.0)
BC Prior T-DM1+Pertuzumab	14/30 (46.7)	30/30 (100.0)
Gastric Cancer	16/36 (44.4)	32/36 (88.9)
GC Prior CPT-11	8/18 (44.4)	17/18 (94.4)

Analysis set: Efficacy evaluable patients for confirmed overall response
Data cutoff on 11-May-2017

Presented by: Toshihiko Doi

Source: Toshihiko Doi, et al., abstract No. 108, ASCO 2017

DS-8201a

Ph1 Safety data（5.4+6.4mg/kg）

Daiichi-Sankyo cancerenterprise

TEAE, any grade, >20% (No DLT observed)

Preferred Term (N=133)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	All (%)
Hematologic					
Platelet count decreased	13.5	9.0	8.3	3.8	34.6
Anaemia	3.0	12.0	14.3	1.5	30.8
Neutrophil count decreased	0.8	9.8	12.0	3.0	25.6
White blood cell count decreased	0.8	12.8	9.0	1.5	24.1
Gastrointestinal disorders					
Nausea	51.9	13.5	1.5	0.0	66.9
Decreased appetite	33.8	20.3	3.8	0.0	57.9
Vomiting	31.6	3.8	1.5	0.0	36.8
Diarrhoea	19.5	5.3	0.8	0.0	25.6
Constipation	18.8	3.0	0.0	0.0	21.8
Others					
Alopecia	21.1	6.0	0.0	0.0	27.1
Malaise	18.0	4.5	0.8	0.0	24.1

Any Grade 3/4 – 43.6%

Analysis set: Safety evaluable patients who received at least one dose of DS-8201a
Data cutoff on 11-May-2017

Presented by: Toshihiko Doi

Source: Toshihiko Doi, et al., abstract No. 108, ASCO 2017

DS-8201a
Comparison with other HER2 ADCs

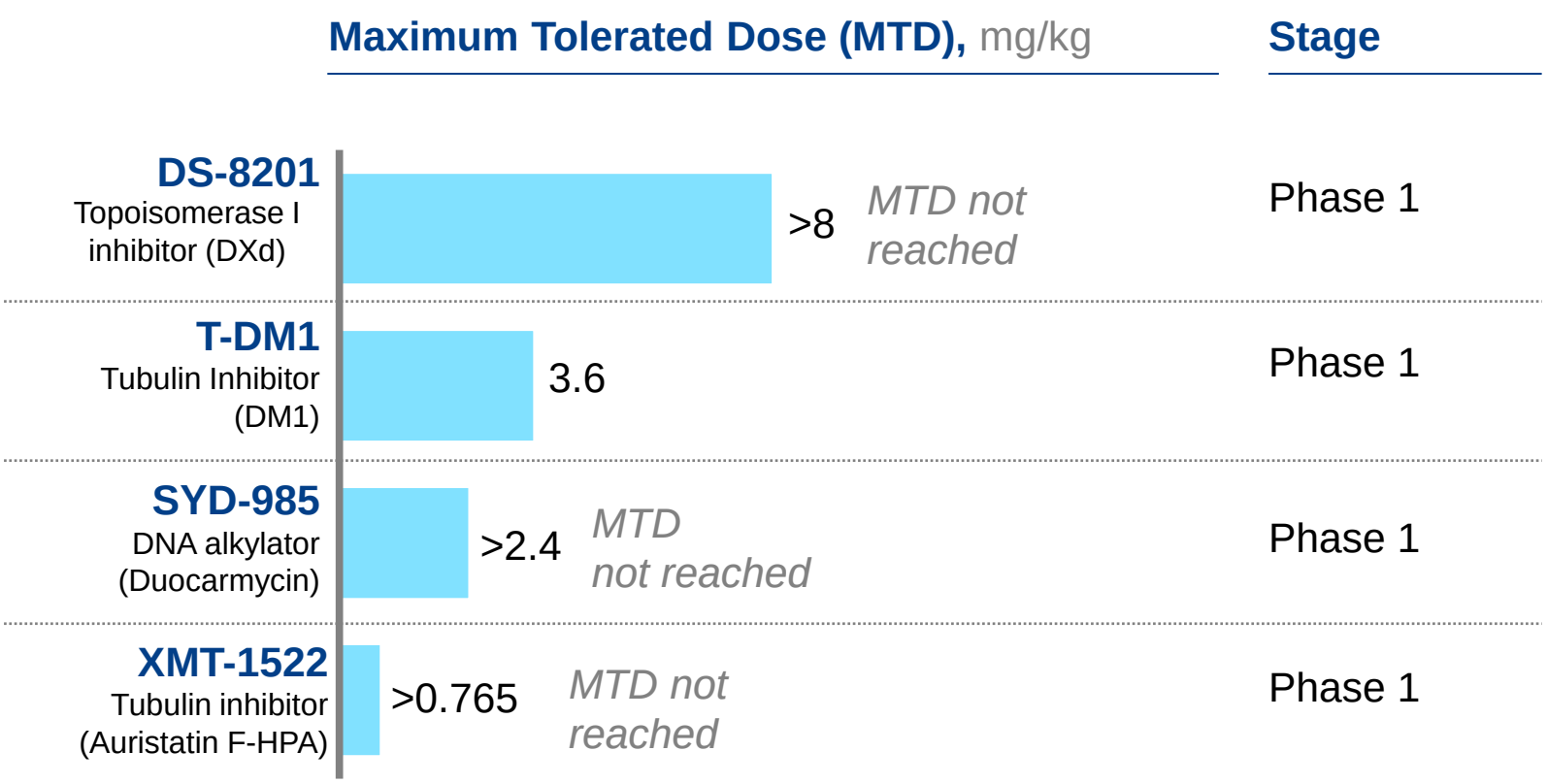
	T-DM1	DS-8201a	SYD-985	XMT-1522	MEDI4276
Company	Genentech	Daiichi Sankyo	Synthon	Mersana	Medimmune
Payload	DM1	DXd	Duocarmicine	AF-HPA	Tubulysin
MOA	Tubulin	Topoisomerase I	DNA alkylator	Tubulin	Tubulin
Linker	Undissociated	Dissociated	Dissociated	Dissociated	Dissociated
Attachment site	Lysine residue	Cysteine residue	Cysteine residue	Cysteine residue	Engineered cysteine
Drug-to-antibody ratio (average)	3.5	7-8	2	12-15	4
Human Dose (Ph1)	3.6mg/kg*	6.4mg/kg	1.8mg/kg**	0.765mg/kg***	NA

*Yamamoto-H, Jpn J Clin Oncol. 2015 Jan;45(1):12-8
**Herpen-CML, ESMO poster 333
***Buris-HA, Mersana homepage TPS2606

DS-8201a

MTD comparison with other HER2 ADC projects

Safety profile of various HER2 ADCs (clinical)



DS-8201: MTD not reached

Source: Krop-I *et. al.*, J. Clin. Oncol. 2010; 28:2698-2704, Bergstrom-DA *et al.*, AACR LBA-231 2015, Herpen-CML *et al.*, ESMO Poster 333 2015, Tamura-K *et al*. abstract 4585 (LBA17), ESMO 2016, Mersana homepage

Daiichi Sankyo ADC
Contents

- ✓ Overview: trend of drug development, biologics and cancer treatment, about antibody drugs
- ✓ About antibody drug conjugate (ADC)
- ✓ Discovery of DS-8201a
- ✓ Characteristics and clinical results of DS-8201a
- ✓ Expansion of DXd-ADC technology

DXd-ADC: Our pipeline

Clinical stage

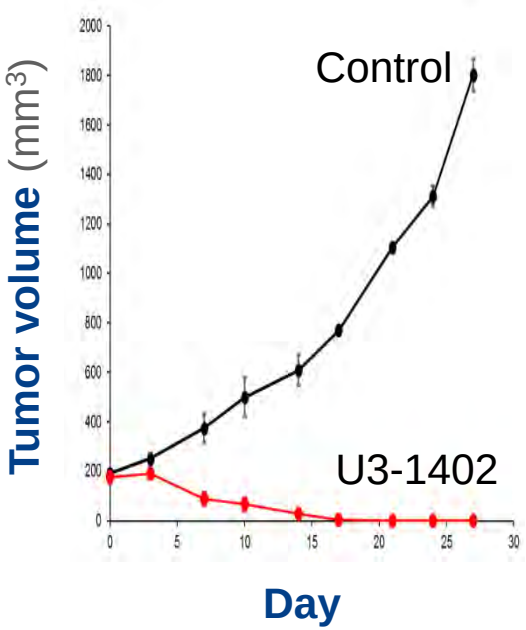
Antibody target	Potential indications	Discovery	Preclinical	Phase1
HER2 (DS-8201)	Breast, Gastric			
HER3 (U3-1402)	Breast, NSCLC			
TROP2 (DS-1062)	Solid Tumors			
B7-H3 (DS-7300)	Solid Tumors			
Project 5	Solid Tumors			
Project 6	Solid Tumors			

Note: Compounds under discussion are investigational agents and are not approved by the FDA or any other regulatory agency worldwide as a treatment for indications under investigation. Efficacy and safety have not been established in areas under investigation. There are no guarantee that these compounds will become commercially available in indications under investigation.

DXd-ADC: Our Pipeline, Preclinical data

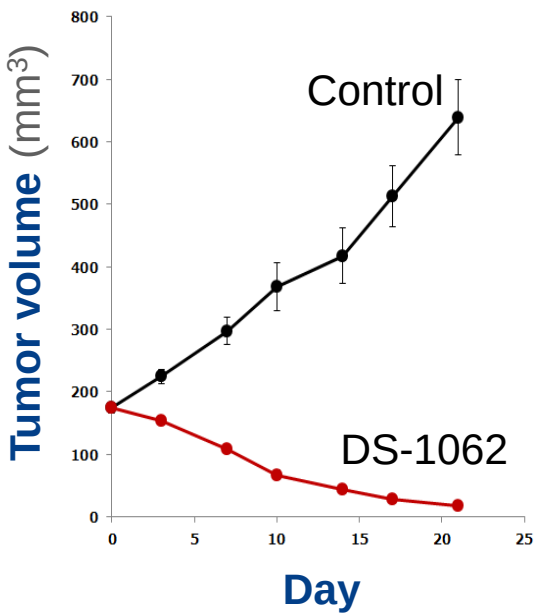
Triple negative breast cancer

HER3-ADC



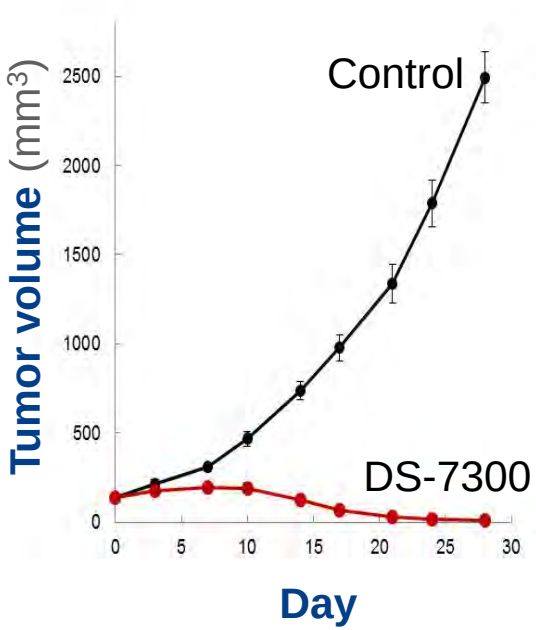
Pancreatic cancer

TROP2-ADC



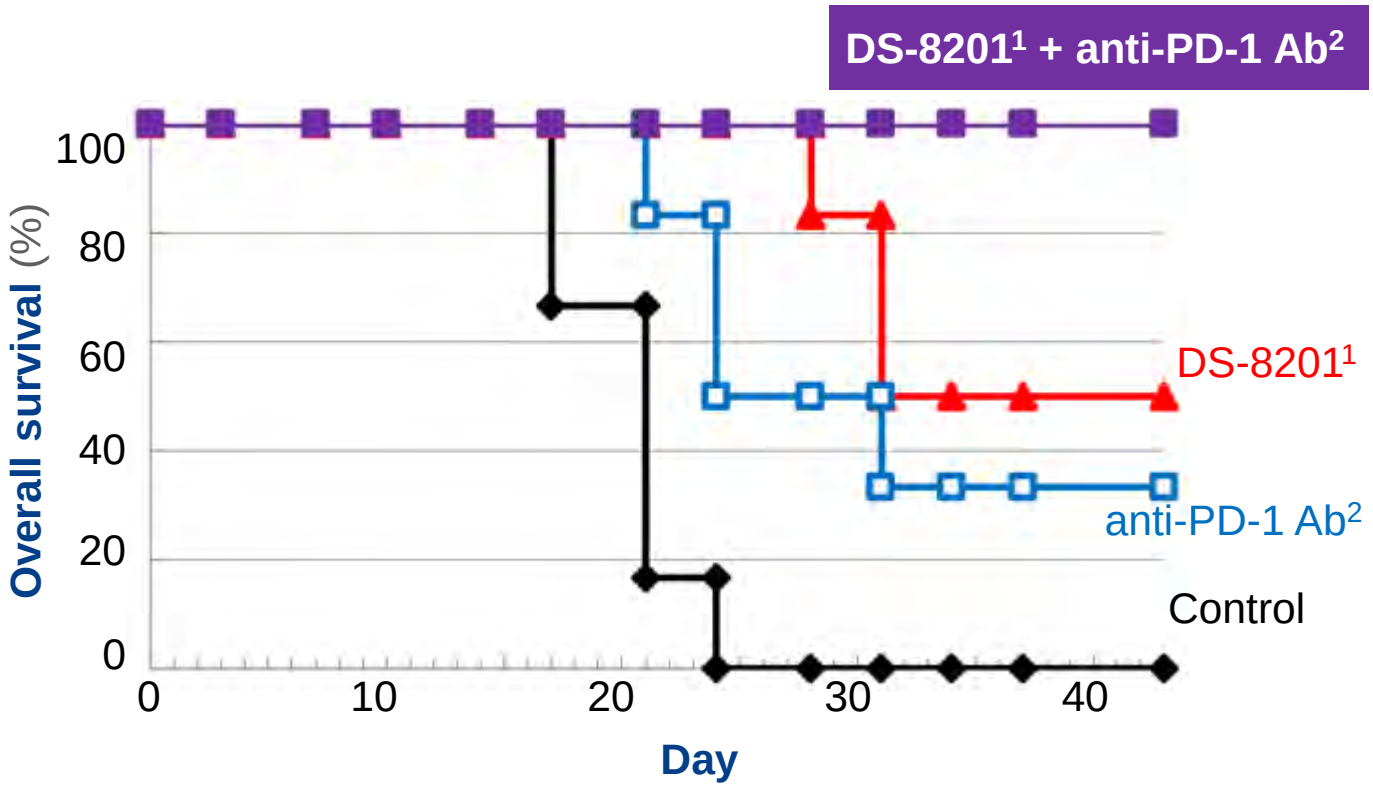
NSCLC

B7-H3-ADC



DS-8201–I/O: Potential I/O benefit, Preclinical data

Survival of mouse with human HER2-expressing tumor cells (Preclinical)



1. 10 mg/kg 2. 2.5mg/kg

DXd-ADC: Partnerships

Immuno-Oncology partnerships with our existing ADC assets

HER2-ADC

HER3-ADC

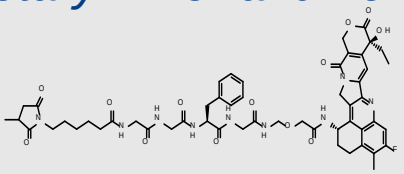
TROP2-ADC

B7-H3-ADC

I/O mechanisms (e.g., checkpoint inhibitors)

Partnerships to apply our ADC technology to **new antibodies and targets**

Our proprietary linker and novel payload



Additional targets

Summary

- Developed new ADC technology with the derivative of DX-8951 which is a novel potent DNA topoisomerase I inhibitor.
- Our smart chemo ADC technology has seven unique features such as novel payload, high potency, bystander effect, high clearance of the payload, stable linker, tumor selective cleavage and high DAR.
- DS-8201a with promising antitumor activity and favorable safety profile in patients was granted First Track Designation treatment for HER2 positive metastasis breast cancer by FDA.
- Actively looking for partnerships with our ADC technology.

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Q & A