Daiichi-Sankyo
cancerenterprise

Care. Compassion. Science.
It's Our Obligation.

DS-1062

Yutaka Noguchi DS-1062 Lead
Daiichi Sankyo., CO., LTD.

April 2, 2019

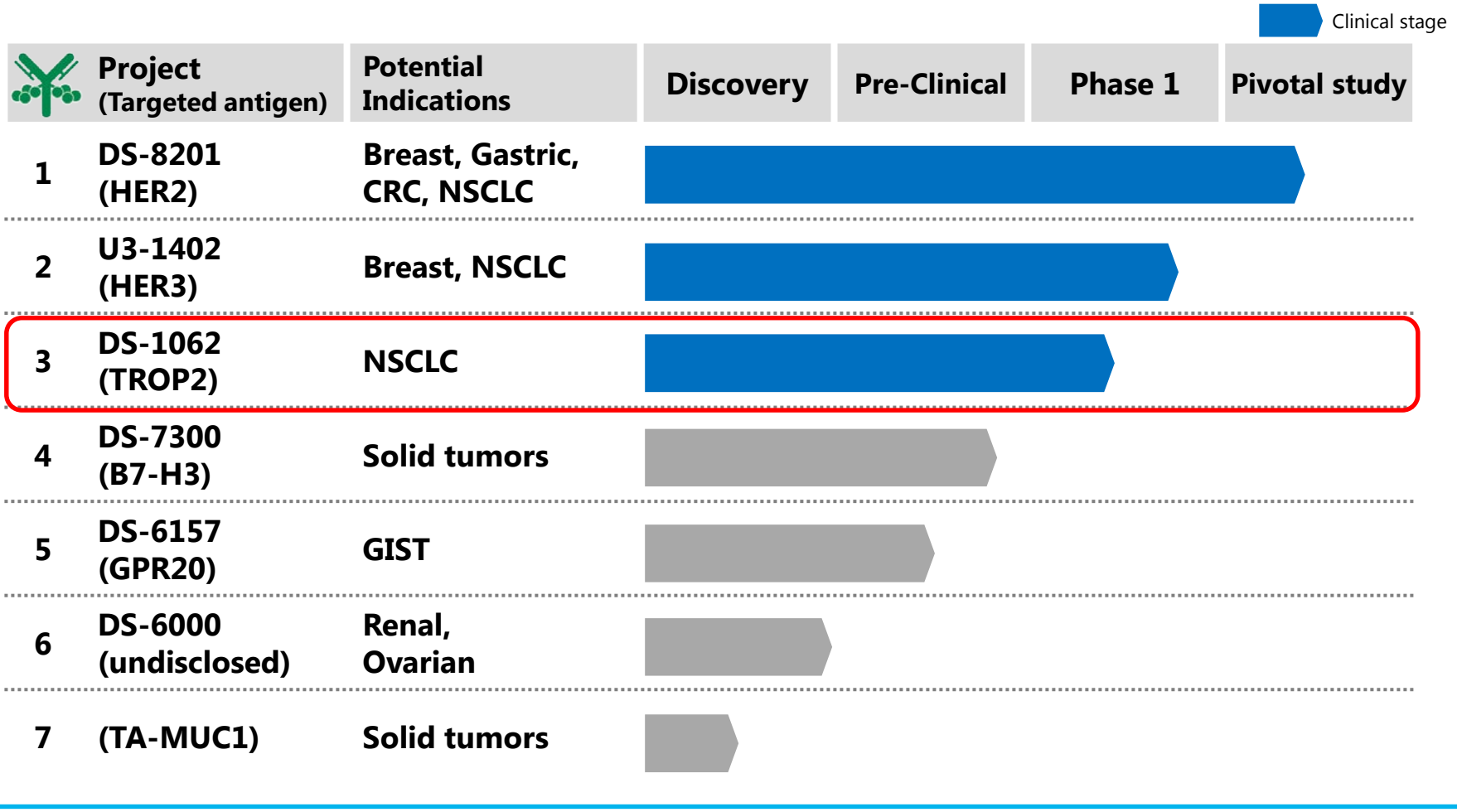
Agenda

- Overview of DXd-ADC Technology
- DS-8201 and U3-1402
- Trophoblast Cell-Surface Antigen 2: TROP-2
- DS-1062 Characteristics
- DS1062 Preclinical data
- DS1062 Phase I study

Daiichi Sankyo ADC Franchise

As of April 2019

ADC Franchise

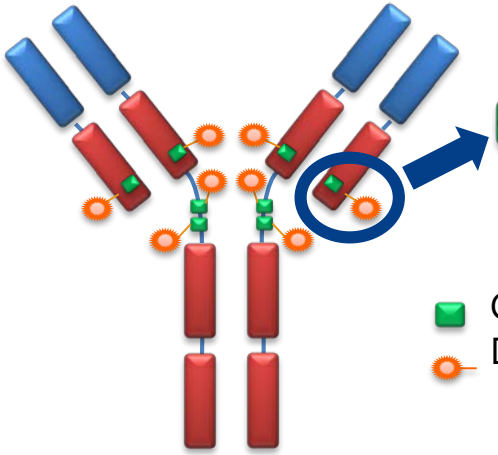


CRC: colorectal cancer, NSCLC: non-small cell lung cancer, GIST: gastrointestinal stromal tumor

Overview of DXd-ADC Technology

Proprietary Daiichi Sankyo ADC Technology: DXd-ADC

DXd-ADC

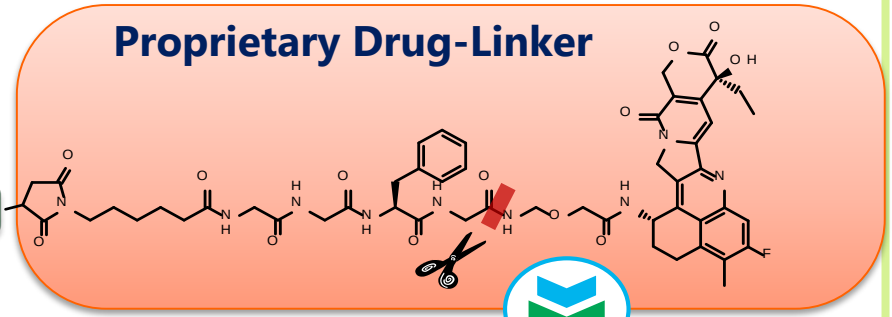


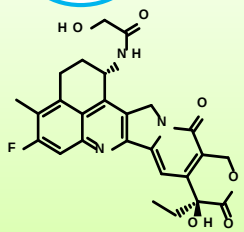
Cysteine residue
Drug-Linker

Conjugation chemistry

The linker is connected to cysteine residue of the antibody

Proprietary Drug-Linker





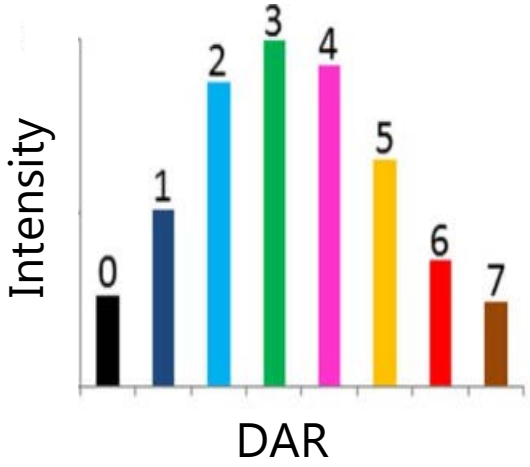
Payload (DXd)
Exatecan derivative

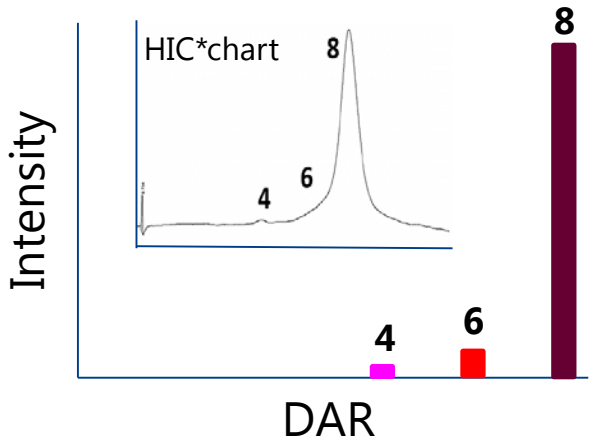
High DAR	**Novel payload**
Stable drug-linker	**High potency**
Tumor-selective cleavable linker	**Bystander effect**
	High clearance of the payload

DXd-ADC: High Drug to Antibody Ratio (DAR)

High drug-to antibody ratio (DAR)

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



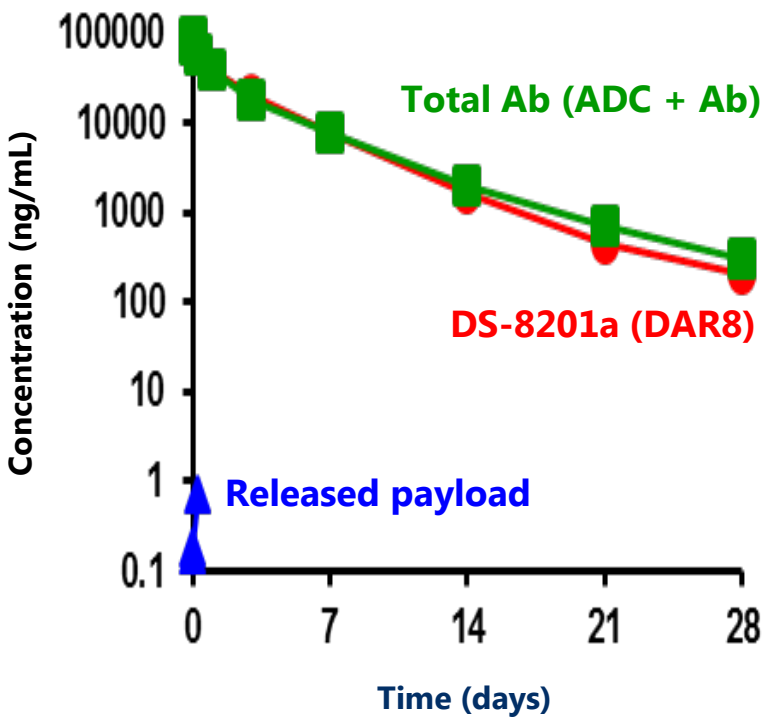


HIC*, Hydrophobic interaction chromatography

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

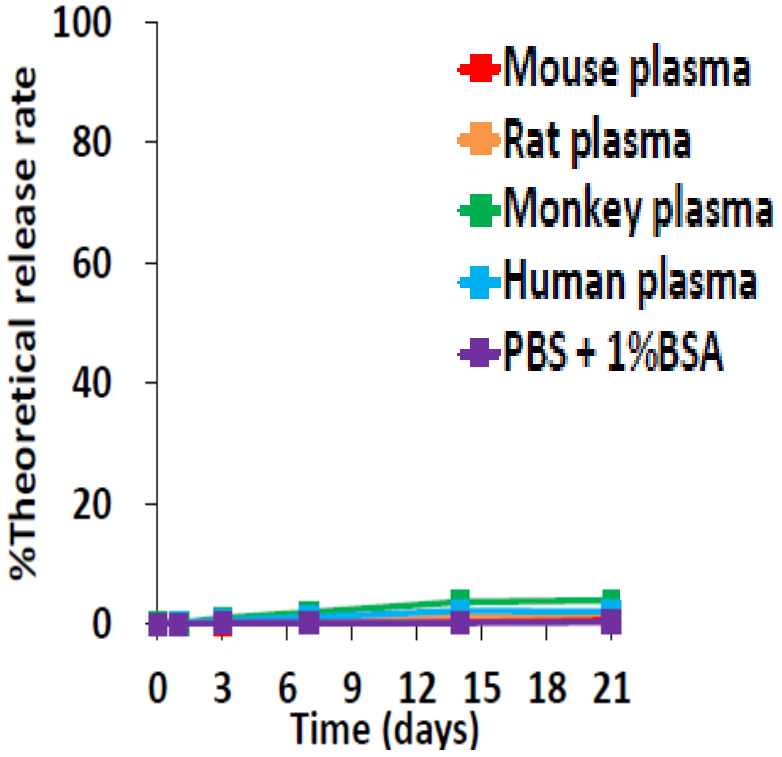
DXd-ADC: Stable Drug-linker in Plasma

Plasma conc. of DS-8201a and payload in monkey



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

Release rates of DXd from DS-8201a in plasma

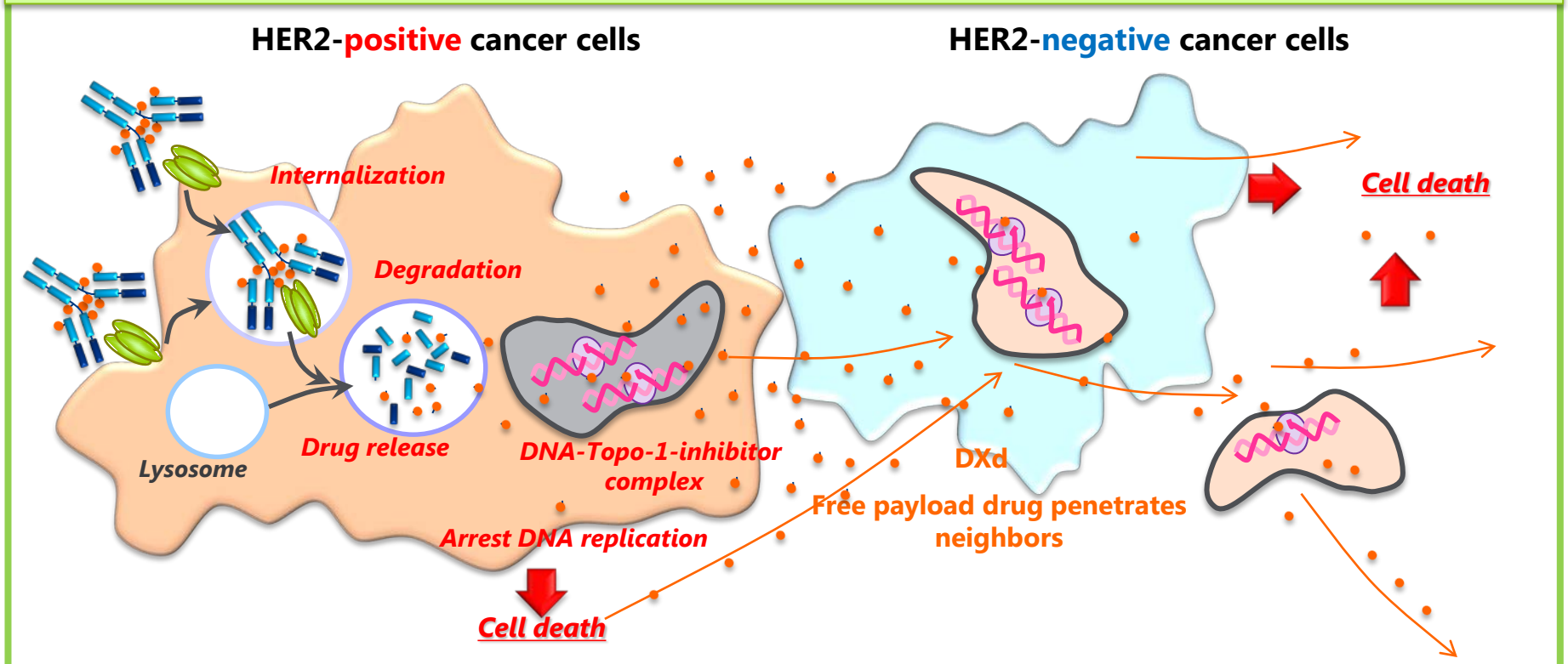


Source: Oitate-M *et al.*, World ADC 2017 San Diego

DXd-ADC: Mode of Action (MOA) of a Bystander Effect

- ADC selectively targets antigen-expressing tumors
- Payload is released by lysosomal enzymes into tumors
- Membrane-permeable free drug attacks neighboring cancer cells which is effective against heterogeneous tumors

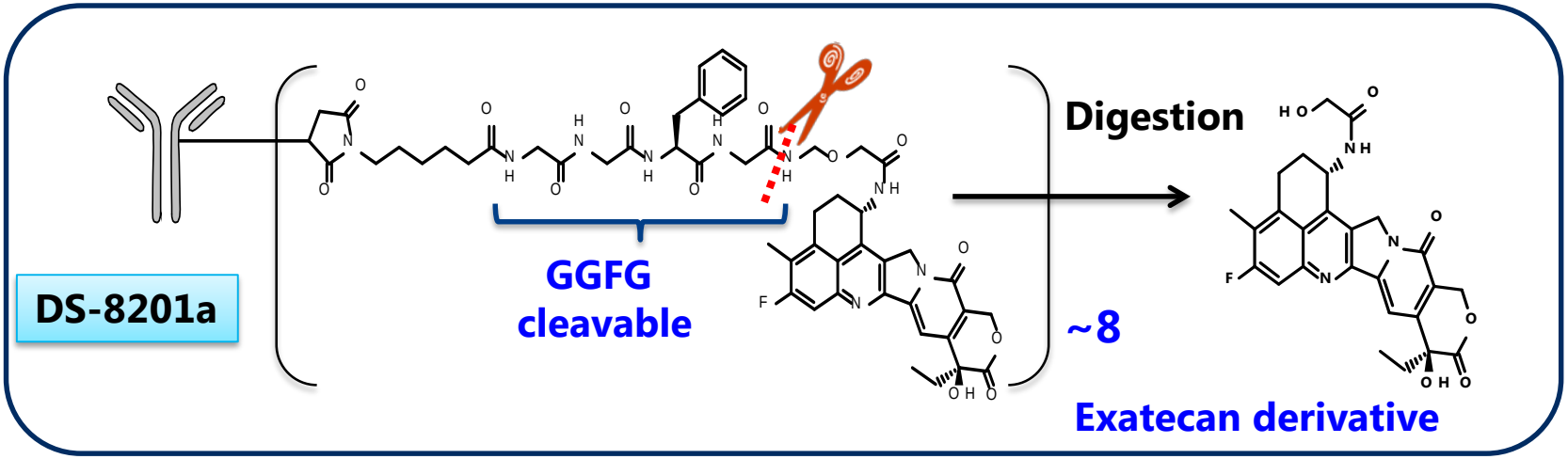
MOA of Bystander Effect

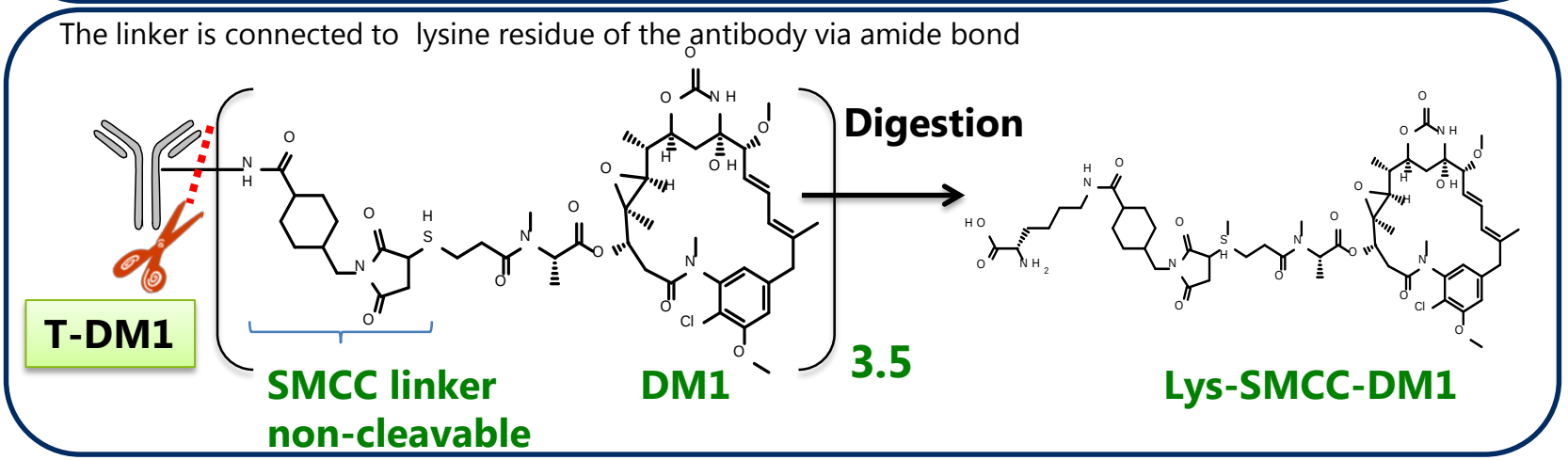


DS-8201 and U3-1402

Structure and Characteristics of DS-8201a Compared to T-DM1

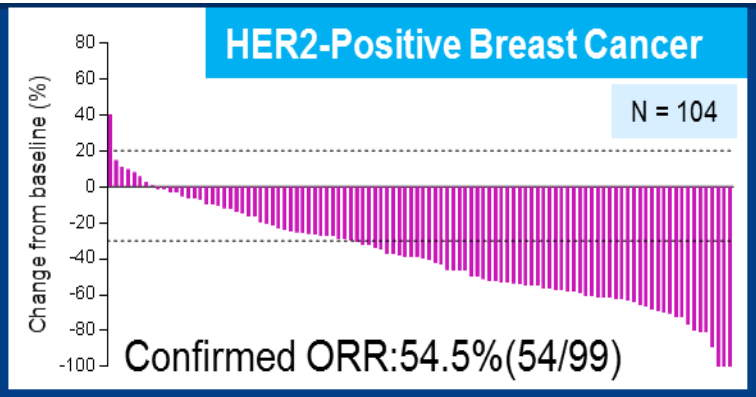
	DS-8201a	T-DM1
Payload	Topoisomerase I inhibitor, Exatecan derivative	Tubulin inhibitor, DM1
Bystander effect	YES	NO
DAR	7-8	3.5

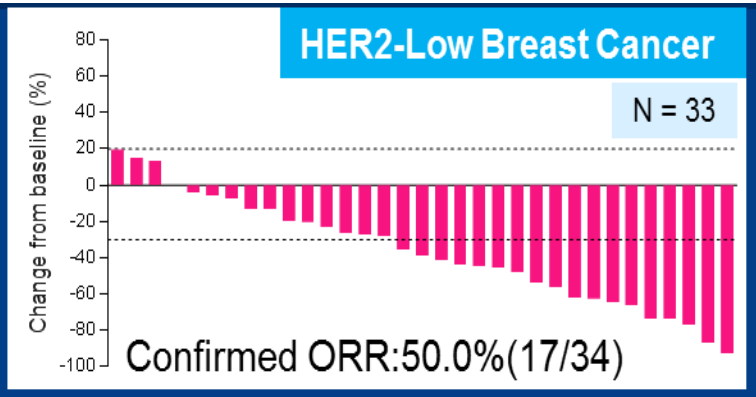


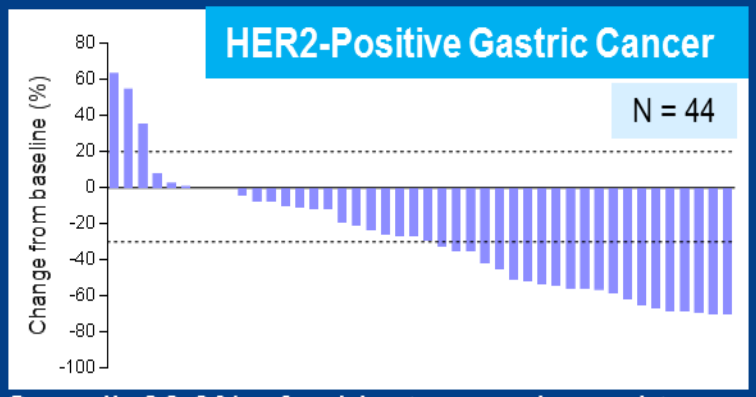


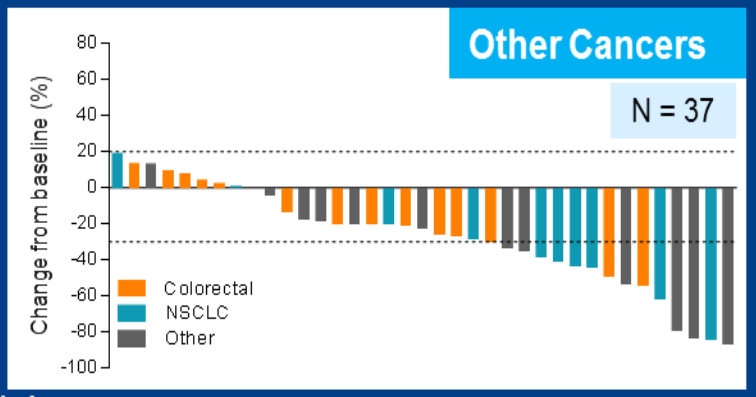
DS-8201a: Clinical Efficacy (5.4 or 6.4 mg/kg)

ClinicalTrials.gov Identifier: NCT02564900









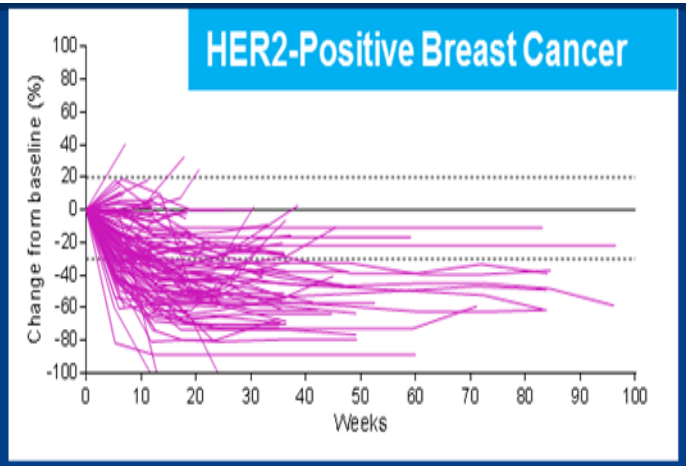
- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR* in the overall population is 49.3%

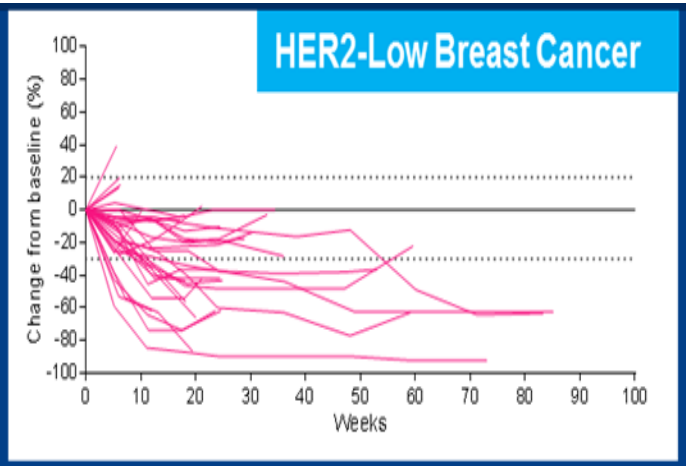
Tumor shrinkage was observed across multiple tumor types.

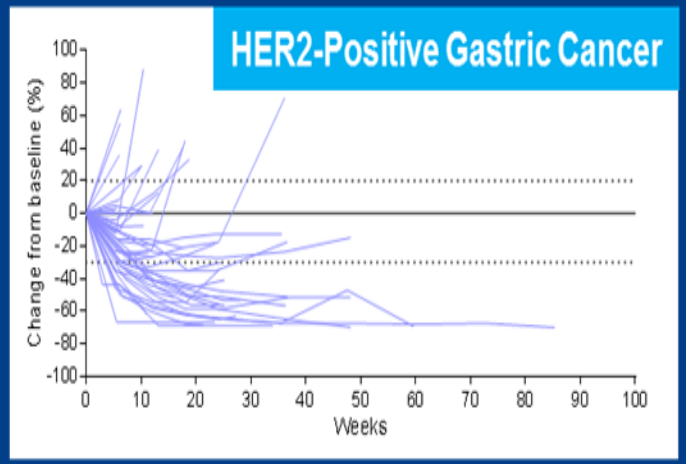
Source: Iwata-H *et al.*, Abstract #2501, ASCO 2018

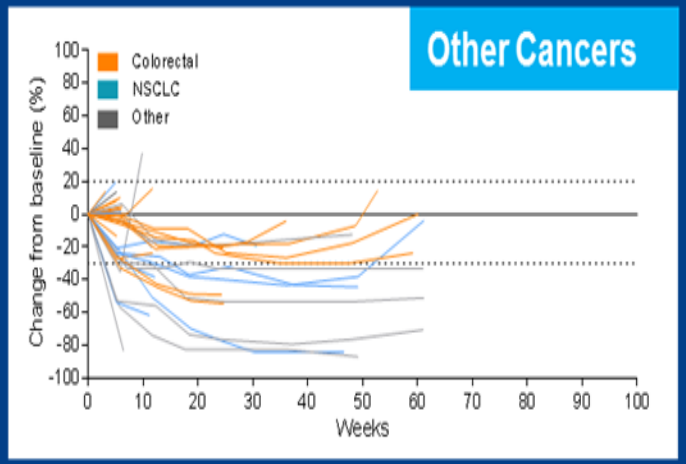
DS-8201a: Tumor Shrinkage Over Time by Tumor Type

ClinicalTrials.gov Identifier: NCT02564900









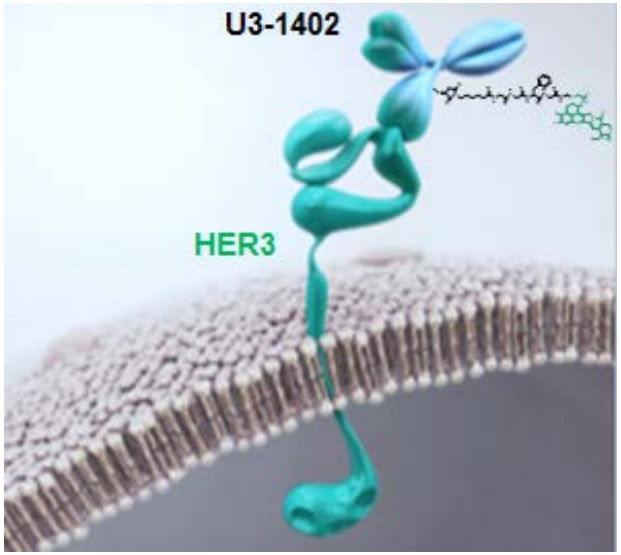
- Overall, 86.3% of subjects experienced tumor shrinkage
- 91.5% of these subjects experienced shrinkage at the time of first imaging assessment at 6 weeks

Includes subjects who had ≥1 postbaseline scan. Dotted lines denote 20% increase and 30% reduction in tumor size, respectively.

Source: Iwata-H *et al.*, Abstract #2501, ASCO 2018

U3-1402 (Anti-HER3 ADC)

HER3 is an important target for ADC Smart-Chemo

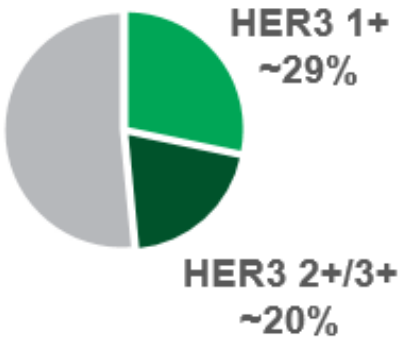


Same ADC Technology
DAR8

+

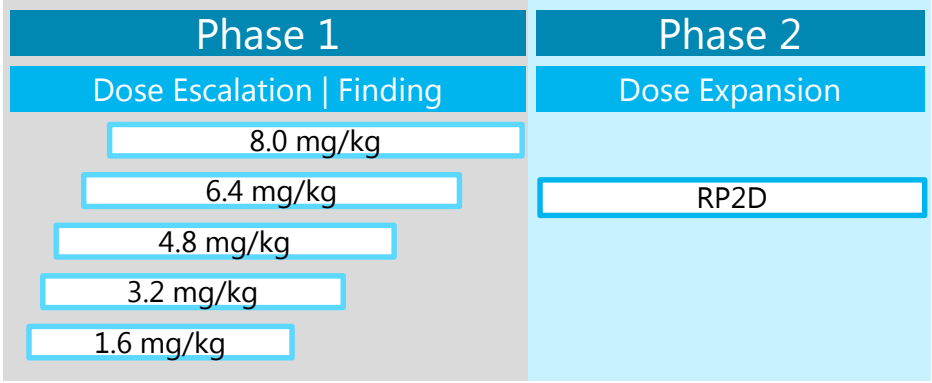
Patritumab
Clinically validated mAb
Acceptable safety & tolerability in >300 subjects

HER3 Expression
In 188 screened breast cancer study patients



Phase 1/2 study in Breast Cancer
ClinicalTrials.gov Identifier: NCT02980341

- HER3 positive (IHC 2+ or 3+) advanced/ unresectable or metastatic breast cancer



Source: LoRusso P, et al., *Clin Cancer Res* 2013; 19:3078-3087; Wakui H, et al., *Cancer Chemother Pharmacol* 2014; 73:511-516.

Clinical Efficacy of U3-1402; HER3-positive (measured by IHC [2+/3+]) Advanced / Unresectable or Metastatic Breast Cancer

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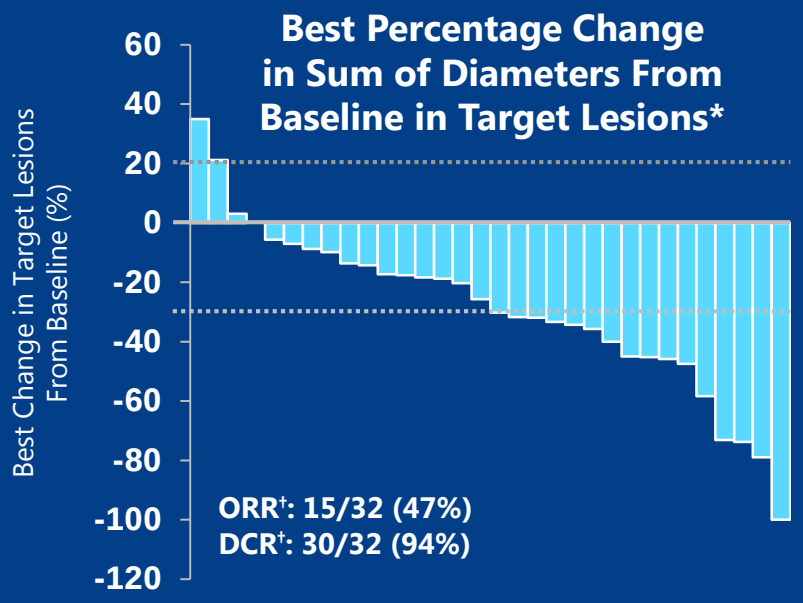
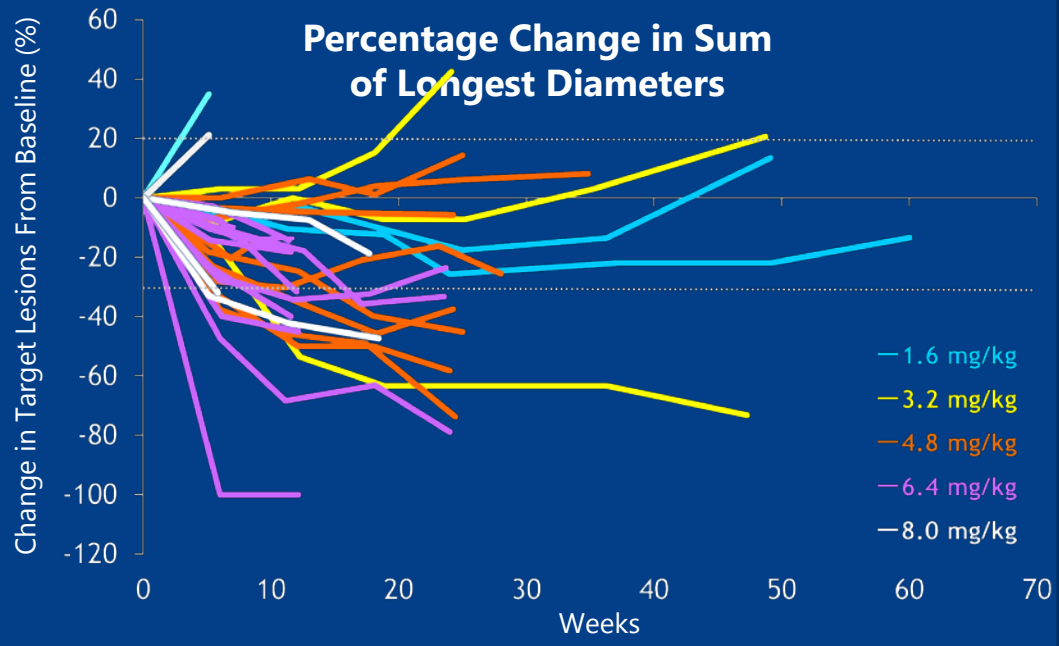
ClinicalTrials.gov Identifier: NCT02980341





Potential against HER3-positive, advanced/unresectable, or metastatic breast cancer

*Analysis set: Efficacy-evaluable patients with at least 1 scan.
Baseline is defined as the last measurement taken before the first dose of study drug.
†Investigator assessment. For each patient, the best percentage change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.
DCR = disease control rate; ORR = objective response rate.

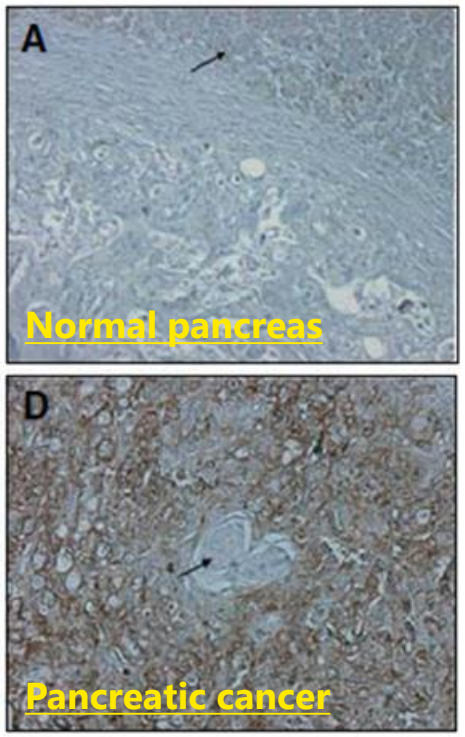
Source: Kogawa-T *et al.*, Abstract #2512, ASCO 2018

Trophoblast Cell-Surface Antigen 2: TROP2

TROP2

- A 36-kDa single pass transmembrane glycoprotein
- TROP2 is overexpressed in a variety of human carcinomas including lung, breast, pancreatic, cervical, ovarian, colorectal and gastric cancers
  - ✓ Some overlap with Irinotecan indications
  - ✓ TROP2 correlates with poor prognosis

    (Clin. Cancer Res. 2006, Br. J. Cancer 2008)
- TROP2 is effectively internalized with binding antibody
- TROP2 is expressed in the epithelium of normal tissues including skin, esophagus and lung
  - ✓ Normal cell turnover is slower than tumor cells
  - ✓ High expression in non-target tissues requires careful determination of risk/benefit profile



TROP2 immunostaining in pancreatic cancer

(Br. J. Cancer 2008)

TROP2 is an attractive target for ADC therapy

TROP2 and Poor Prognosis

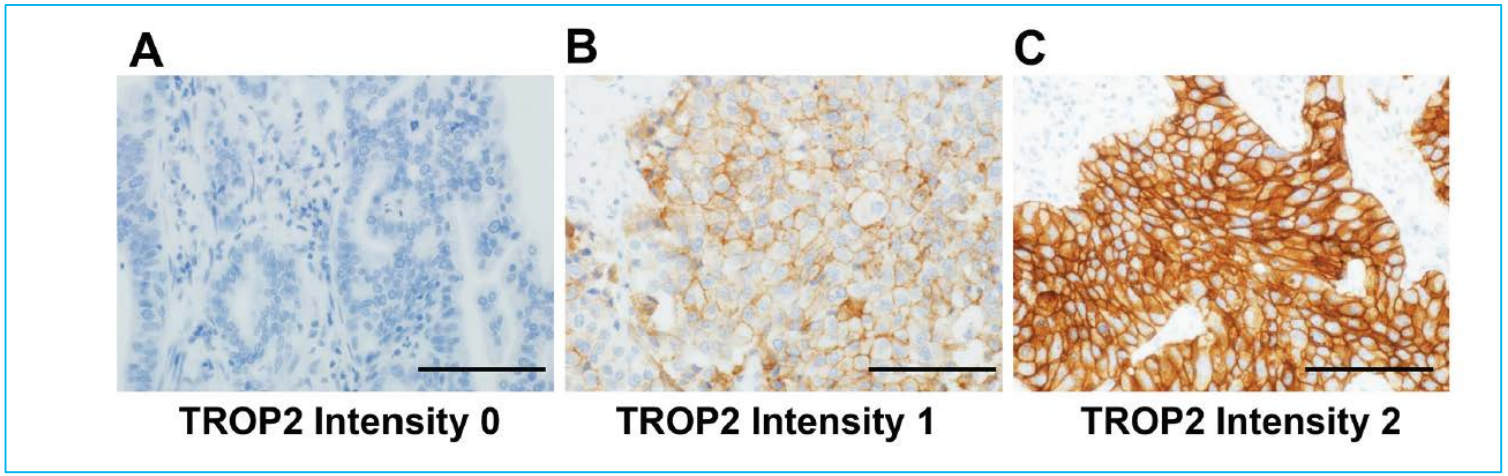
1. High expression of TACSTD2 correlates with poor prognosis in Invasive Ductal Breast Cancer
   - Exp Mol Pathol. 2013 Feb;94(1):73-8.

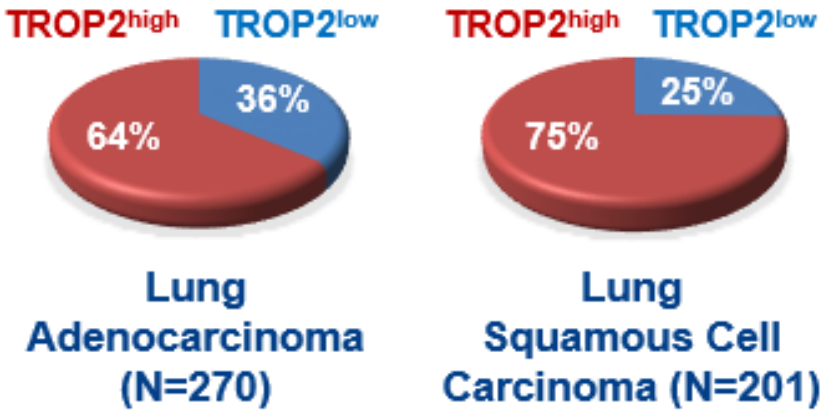
2. TROP2 overexpression was associated with poor OS in solid tumors
   - Sci Rep. 2016 Sep 20;6:33658.

3. TROP2 tended to be expressed in cases with an unfavorable outcome, and was significantly associated with an unfavorable outcome in nonlepidic-type adenocarcinomas in pulmonary adenocarcinoma
   - Virchows Arch. 2010 Jul;457(1):69-76.

4. High expression of TROP2 correlates with poor prognosis in pancreatic cancer
   - Br J Cancer. 2008 Oct 21;99(8):1290-5.

TROP2 Expression in Lung





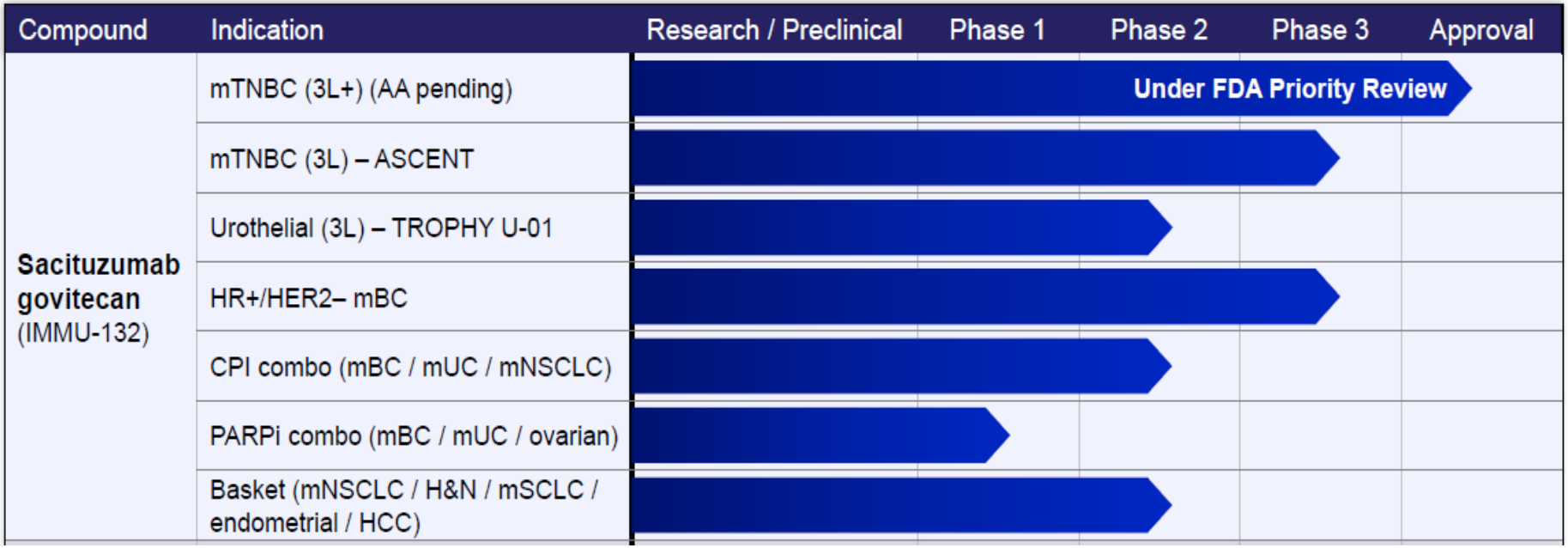
NSCLC is a good indication for DS-1062 because of its high TROP2 expression in both adeno and squamous cell carcinoma

Source: Inamura K et al., *Oncotarget* 2017; 8:28725-28735

TROP2-ADC Competitor: Immunomedics

Product	Stage	Conjugated drug	DAR	Linker
IMMU-132/ Sacituzumab govitecan-hziy	**Phase 3 (TNBC)**	**SN-38 (Topo1 inhibitor)**	**7.6**	**Proteolytic & PH- dependent cleavage**

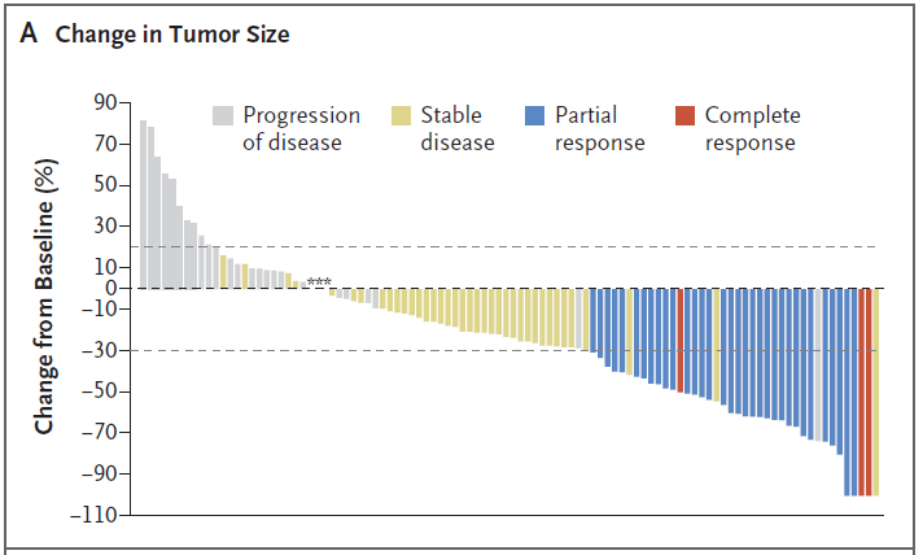
- TNBC: FDA Breakthrough Designation granted.
  - ➢ Confirmatory Phase 3 study is on-going.
  - ➢ Failed to win accelerated approval due to CMC issues.
- NSCLC & SCLC: FDA Fast Track Designation granted.



JPMorgan 2019

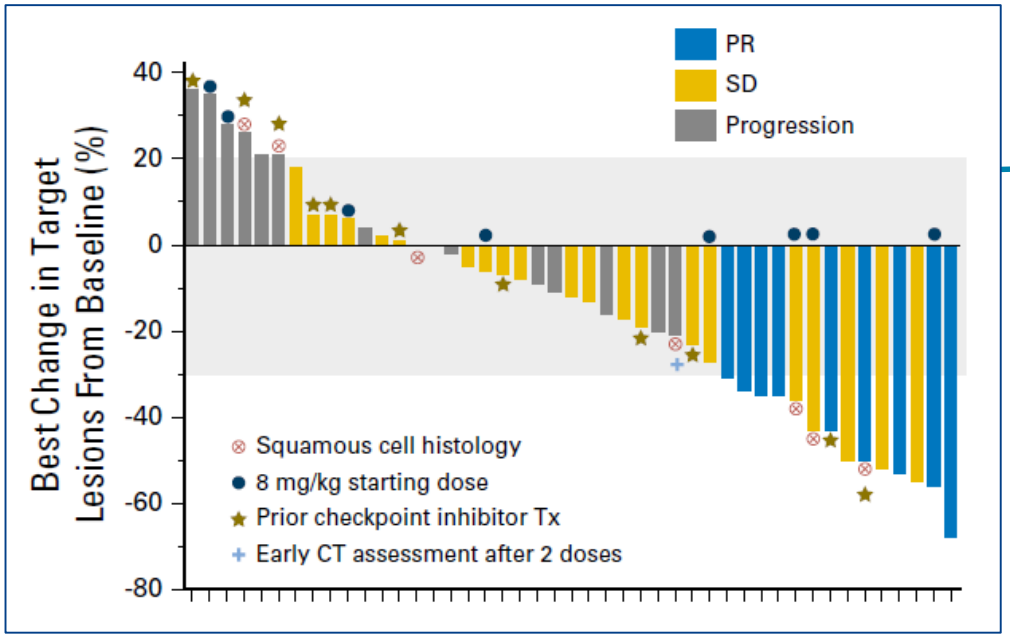
Sacituzumab Govitecan in TNBC

- Phase 1/2, basket design, open-label, single-group, multicenter trial involving patients with various types of advanced solid cancers who have received at least one previous therapy for metastatic disease.
- **Efficacy**:
  - ✓ ORR= 33.3%
  - ✓ mPFS= 5.5mo (n=108)
- **Safety**:
  - ✓ The most common adverse events are: nausea, diarrhea, fatigue, neutropenia, and anemia,
  - ✓ The most common adverse events of grade 3 or higher (>5% incidence): neutropenia, anemia, and a decreased white-cell count.



N Engl J Med 2019;380:741-51.

Sacituzumab Govitecan in NSCLC



FDA Fast Track Designation

Response Rate:19%
Response Duration: 6.0 months
Median PFS: 5.2 months
Median OS: 9.5 months

Journal of Clinical Oncology 35, no. 24 (August 20 2017) 2790-2797

Table 2. Frequency of Adverse Events Regardless of Causality

	All Grades, No. (%)			Grade ≥ 3, No. (%)		
Adverse Event	All Patients	8 mg/kg Dose	10 mg/kg Dose	All Patients	8 mg/kg Dose	10 mg/kg Dose
No. of patients	54	8	46	54	8	46
Nausea	43 (80)	7 (88)	36 (78)	4 (7)	0 (0)	4 (9)
Diarrhea	33 (61)	5 (63)	28 (61)	4 (7)	1 (13)	3 (7)
Fatigue	25 (46)	3 (38)	22 (48)	3 (6)	0 (0)	3 (7)
Alopecia	21 (39)	3 (38)	18 (39)	NA	NA	NA
Neutropenia	20 (37)	2 (25)	18 (39)	15 (28)	1 (13)	14 (30)
Vomiting	19 (35)	4 (50)	15 (33)	2 (4)	1 (13)	1 (2)
Anemia	17 (31)	1 (13)	16 (35)	2 (4)	0 (0)	2 (4)
Constipation	17 (31)	3 (38)	14 (30)	0 (0)	0 (0)	0 (0)
Anorexia	13 (28)	0 (0)	13 (28)	1 (2)	0 (0)	1 (2)
Hypophosphatemia	12 (22)	1 (13)	11 (24)	1 (2)	0 (0)	1 (2)
Dehydration	10 (19)	0 (0)	10 (22)	2 (4)	0 (0)	2 (4)
Weight decrease	10 (19)	0 (0)	10 (22)	0 (0)	0 (0)	0 (0)
Leukopenia	10 (19)	2 (25)	8 (17)	5 (9)	1 (13)	4 (9)
Hypomagnesemia	9 (17)	0 (0)	9 (20)	0 (0)	0 (0)	0 (0)
Dyspnea	8 (15)	2 (25)	6 (13)	2 (4)	1 (13)	1 (2)
Pneumonia	7 (13)	1 (12)	6 (13)	5 (9)	0 (0)	5 (11)

Abbreviation: NA, not applicable.

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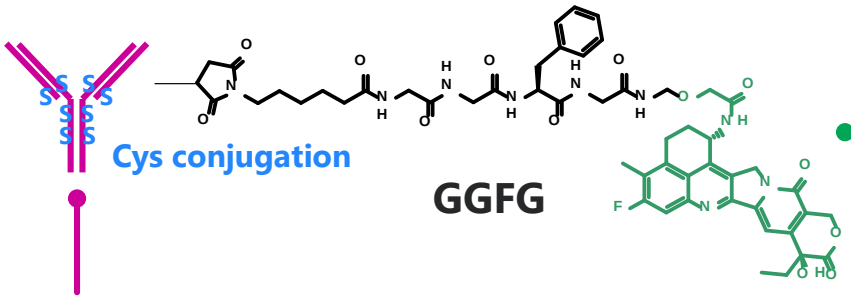
TROP2 ADC is designed to be best in class



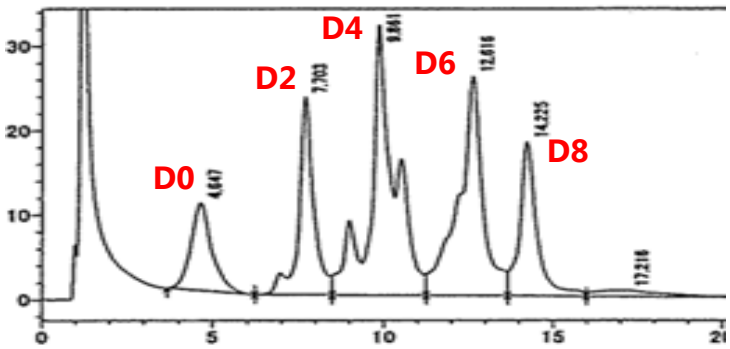
Antibody
Humanized anti-TROP2 monoclonal antibody (hIgG1)

Payload
Topoisomerase I inhibitor

Selective-DAR4 to protect safety margin

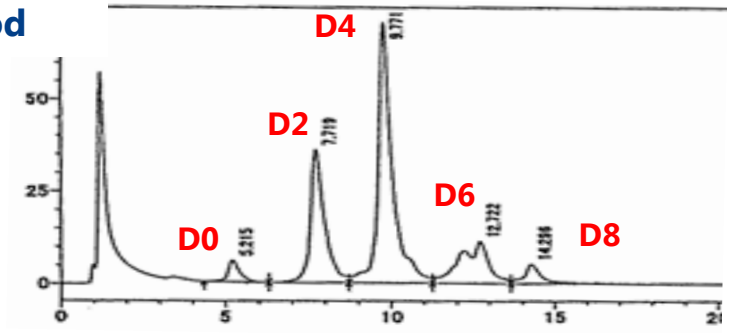
Non-selective DAR*4

HIC



Optimized conjugation method

Selective DAR4



*drug-antibody ratio

In vitro Cell Growth Inhibitory Activity of DS-1062a

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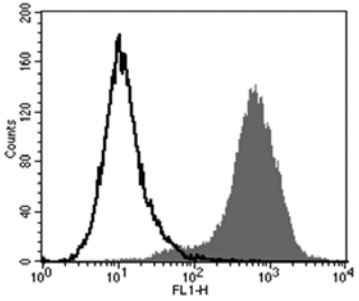
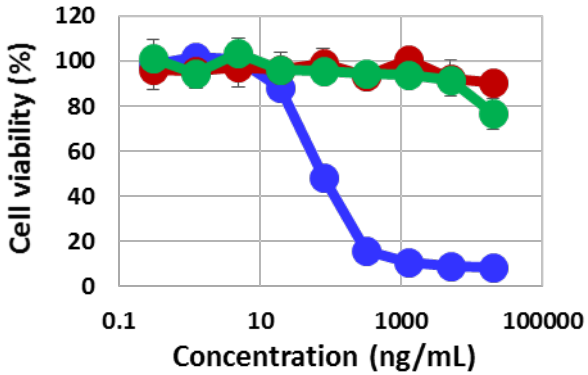
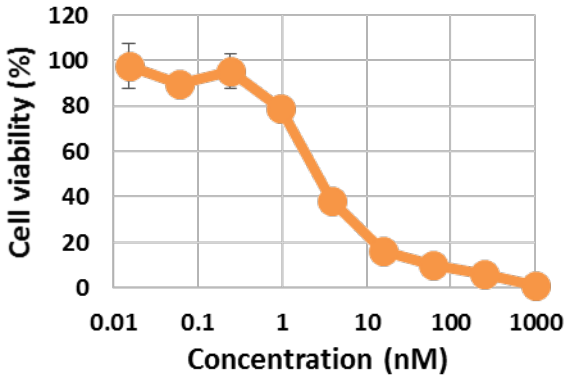
DS-1062a
Anti-TROP2 antibody
Isotype control ADC
DXd

BxPC3 (TROP2 positive)

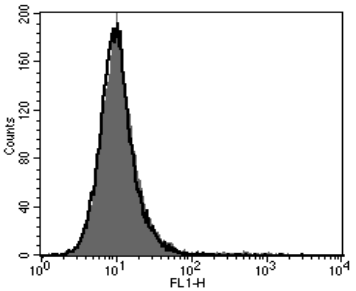


TROP2 expression

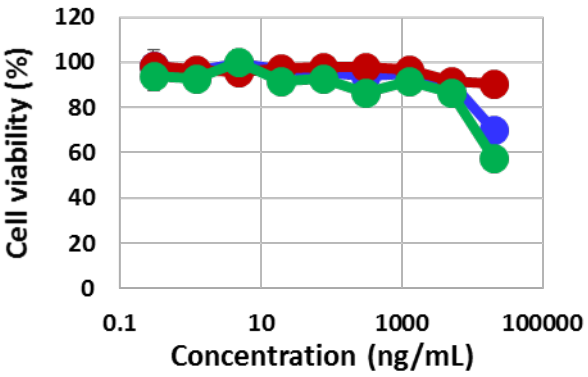


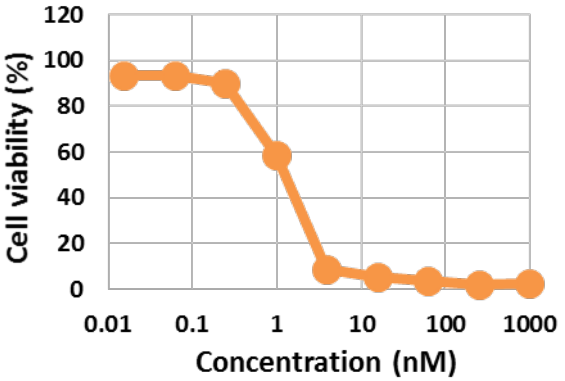


Calu-6 (TROP2 negative)



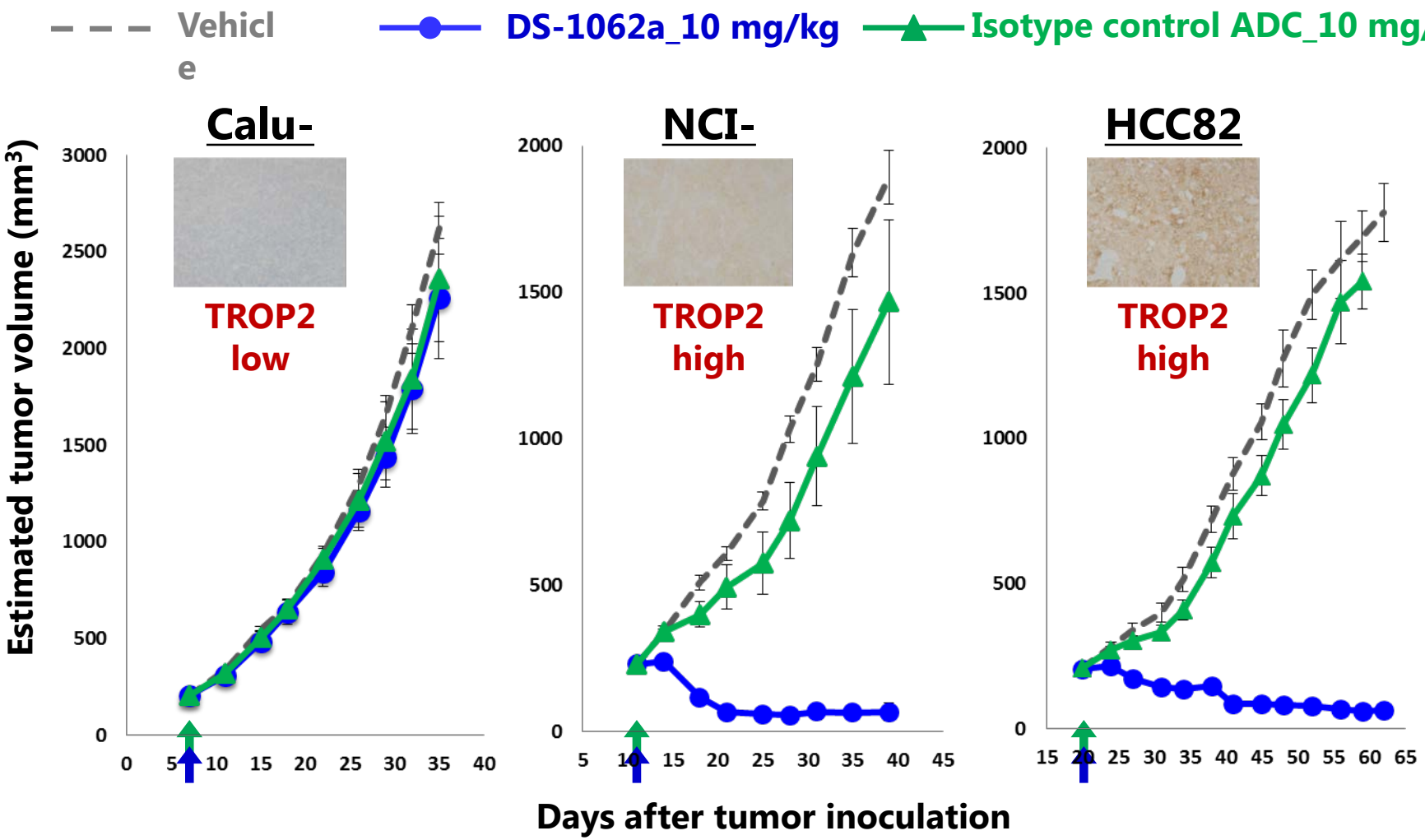
TROP2 expression





DS-1062a demonstrated specific cell growth inhibitory activity to TROP2-positive cells, but not to TROP2-negative cells

Anti-Tumor Activity of DS-1062a in Xenograft Mice Models



DS-1062a demonstrated stronger anti-tumor activity in TROP2-high tumor models compared to in TROP2-low tumor models

Comparison of DS-1062 and Sacituzumab Govitecan-hziy

	DS-1062a (Daiichi Sankyo)	Sacituzumab Govitecan-hziy (Immunomedics)
Antibody	MAAP-9001a (humanized IgG1)	hRS7 (humanized IgG1)
Payload	DXd (TopoI inhibitor)	SN38 (TopoI inhibitor)
DAR	4	7.6
Linker cleavage	Enzymatic	pH-dependent and enzymatic
Human PK ($T_{1/2}$)	TBD	11.7 h at 10 mg/kg dosing*
Dosing	q3w regimen	10 mg/kg at day1 and 8 of 3 weeks
Dose Limiting Toxicity in Human	TBD	Neutropenia, MTD=12mg/kg**
Stage	Phase I NSCLC	Phase 3

* Reported in ASCO 2015 and AACR 2017

** Clin Cancer Res; 21(17) September 1, 2015

DS1062-A-J101 Study

DS-1062a Phase 1 Study Design

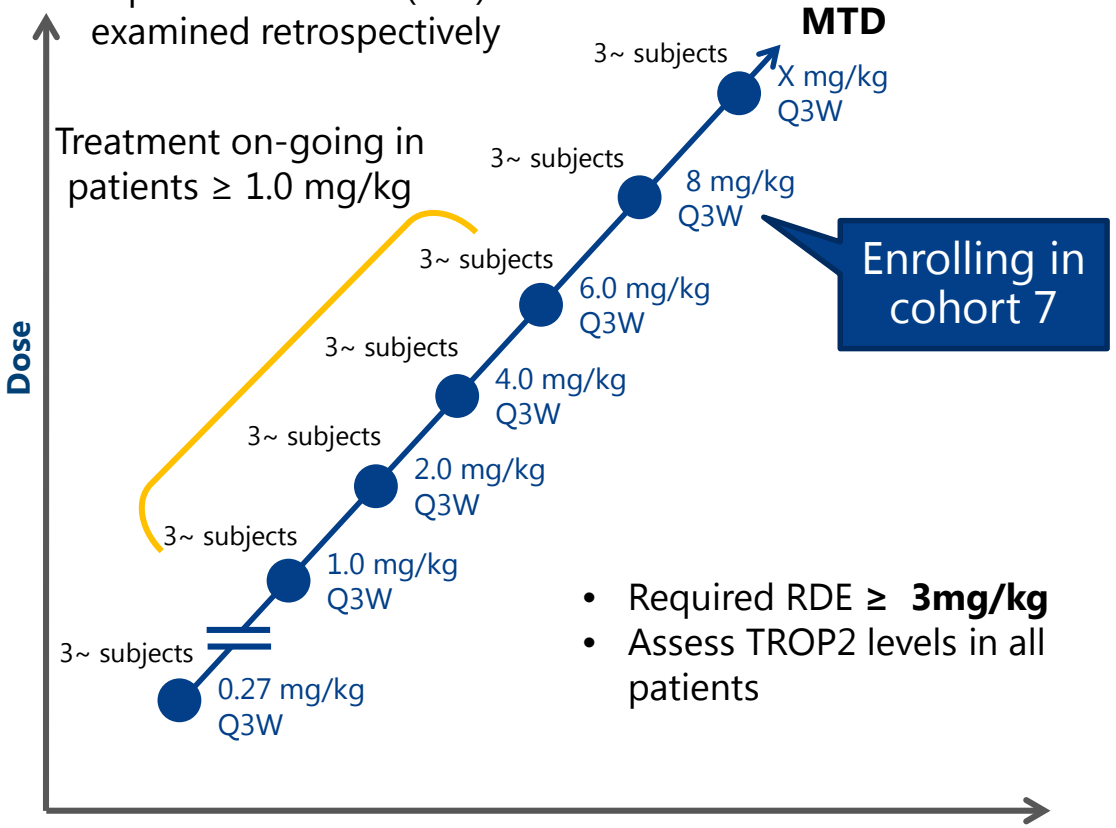
Daiichi-Sankyo

NSCLC ≥ 3rd line

Dose Escalation

No selection based on TROP2 expression. TROP2 (IHC) is examined retrospectively

Treatment on-going in patients ≥ 1.0 mg/kg



Enrolling in cohort 7

- Required RDE ≥ **3mg/kg**
- Assess TROP2 levels in all patients

Dose Expansion

n=40 in RDE* → POC

Assess efficacy and safety for GO/NO-GO decision

Following NSCLC POC

- Open 2 other expansion cohorts for other TROP2 positive tumors

POC → **Expansion Indication A n=40**

Expansion Indication B n=40

* RDE: Recommended Dose for Expansion

Safety and tolerability of DS-1062 up to 6.0mg/kg warrants further evaluation in higher dose exposure
Dose escalation data to be presented at ASCO 2019

POC: Proof of Concept

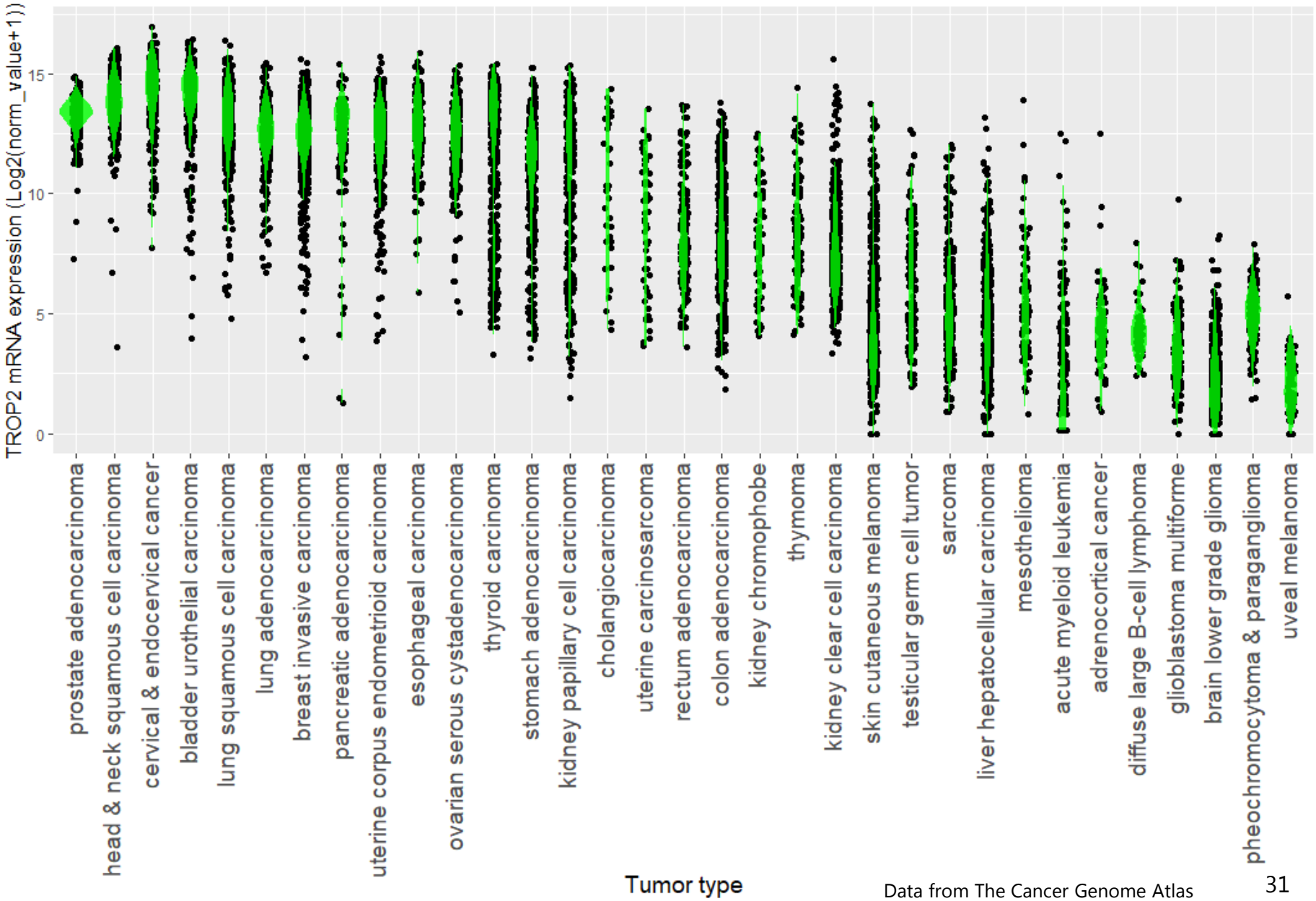
Phase I Study Sites

- IND/CTN approved: Dec2017
- First Patient Dosed: 07Feb2018 @ National Cancer Center Hospital

Study Site	Investigator
National Cancer Center Hospital (JP)	Toshio Shimizu, MD, PhD
National Cancer Center Hospital East (JP)	Kiyotaka Yoh, MD
Virginia Cancer Specialists (US)	Alexander Spira, MD, PhD, FACP
Dana-Farber Cancer Institute (US)	Jacob Sands, MD
Massachusetts General Hospital (US)	Rebecca Suk Heist, MD, MPH
UCLA Medical Center (US)	Aaron Lisberg, MD
MD Anderson Cancer Center (US)	Funda Meric-Berstam, MD
Sarah Cannon Research Institute (US)	Melissa Johnson, MD

Future prospects

TROP2 Expression in Various Cancers



Data from The Cancer Genome Atlas

DS-1062 Landscape

POC in NSCLC

NSCL
C

Other TROP2 Positive Cancers

TNBC
Pancreatic cancer
Esophageal cancer
Cholangiocarcinoma
Gastric cancer
Colorectal cancer
Bladder, Head & Neck, Ovarian cancer, Breast Cancer (HER2+, ER/PR+)

Fast-to-Market in Salvage line

Monotherapy
- Expedited pathway for accelerated approval

Earlier Lines

Combination
- Immunotherapy (PD-1/PD-L1)
- Antibody/Chemotherapies

Expand development after confirming BIC potential.

Take Home Message

TROP2 is an attractive target for DXd-ADC:

- Overexpressed in a variety of cancers
- Effectively internalized with binding antibody

DS-1062 has great potential:

- Preclinical anti-tumor efficacy and clinical evidence of Sacituzumab govitecan in TNBC
- Fulfill unmet medical needs in multiple cancers
- First-in-human study is ongoing

Phase I data will be presented at ASCO2019