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Compassion for Patients.™

Daiichi-Sankyo

Learn about Daiichi Sankyo Pipelines Hosted by JP Morgan

Kazushi Araki
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June 21, 2019

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Today's Contents

- Daiichi Sankyo's ADC
  - Feature 1: High Drug-Antibody Ratio (DAR)
  - Feature 2: High stability linker
  - Feature 3: Selectively cleaved linker
  - Feature 4: Unique and potent payload
  - Feature 5: Bystander effect
  - Feature 6: Short systemic half-life payload
- About ADC Projects
  - DS-8201, U3-1402, DS-1062
- Other Oncology Projects

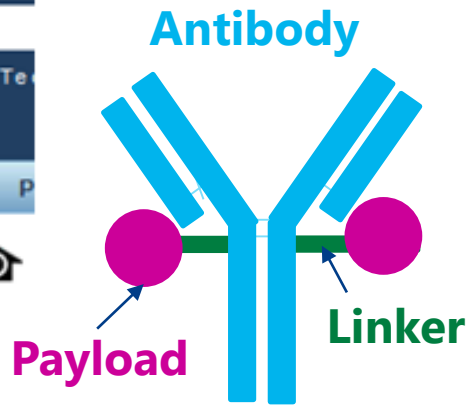
Antibody Drug Conjugate (ADC)

ADC: Marriage of Biologics and Small Molecules

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 Technology*, **2008**, 32 (6)



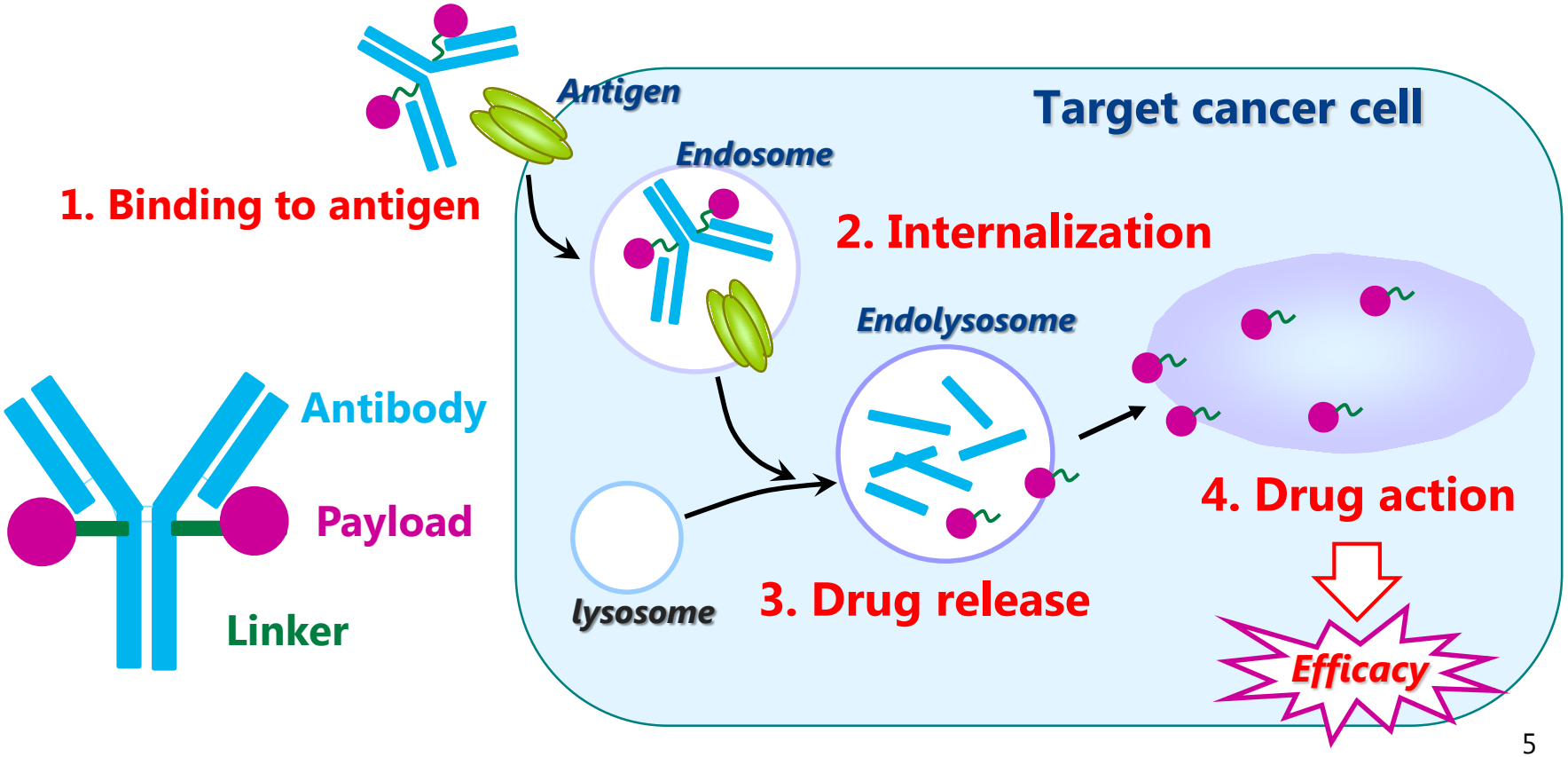
Small molecule	Antibody
✓ Potent efficacy (cytotoxicity)	✓ High selectivity to target
✓ Low selectivity to target	✓ Less adverse events
✓ Issue of adverse events	✓ Efficacy may not be enough

Antibody Drug Conjugate; ADC

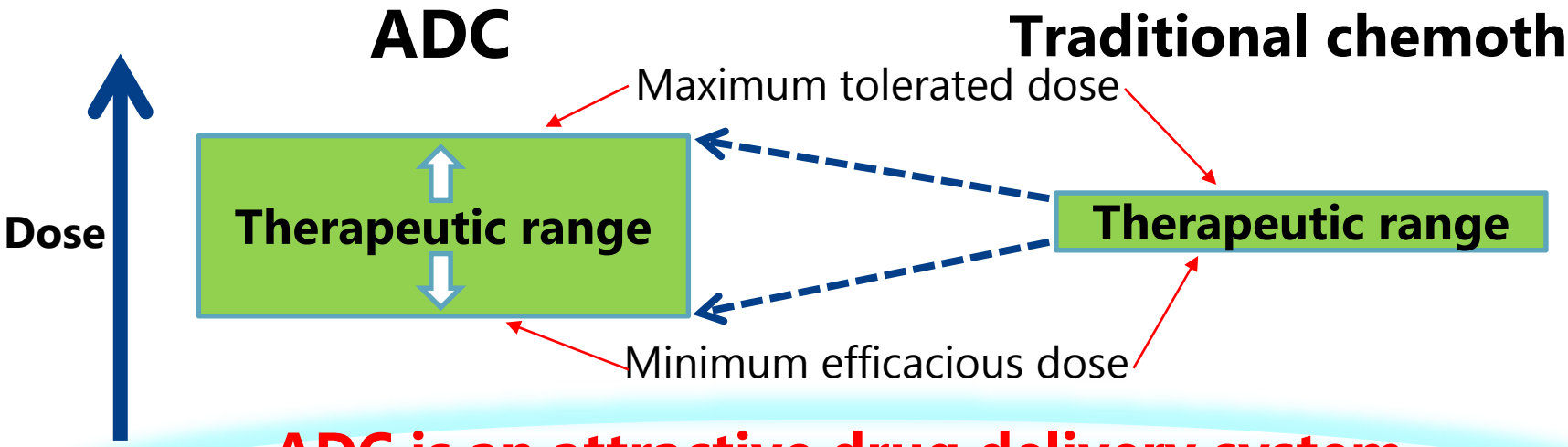
Strength and weakness of low molecule drug and antibody drug are well complemented

MOA of ADC

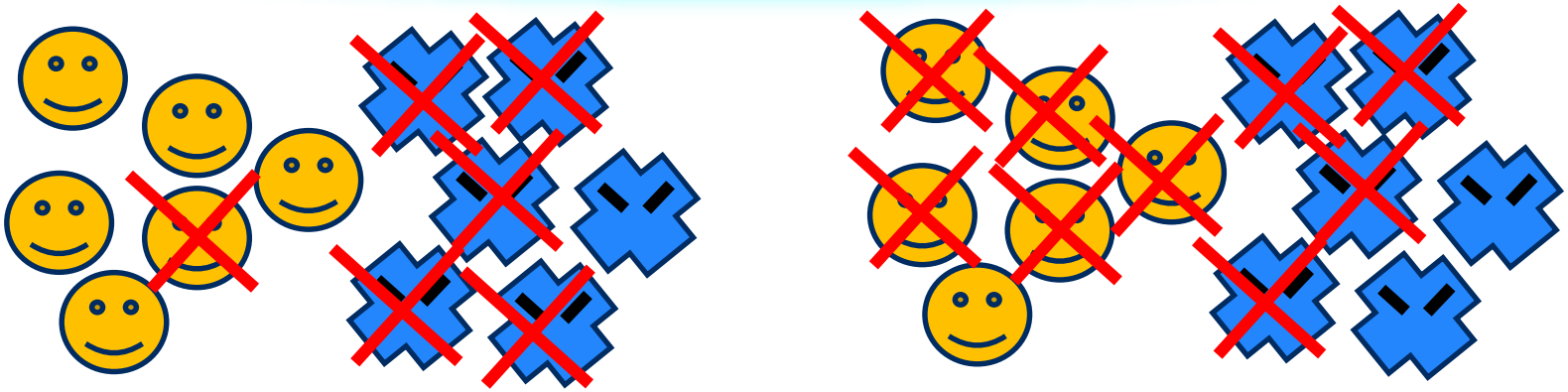
1. ADC bind to antigen on cancer cell surface
2. Internalization (take in ADC into cancer cell)
3. Linker cleaved in cell and release payload (drug)
4. Release payload shows efficacy



Difference between ADC and Traditional Chemotherapy



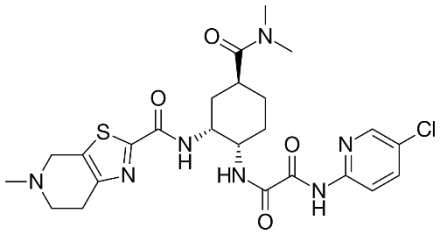
ADC is an attractive drug delivery system with wider therapeutic window

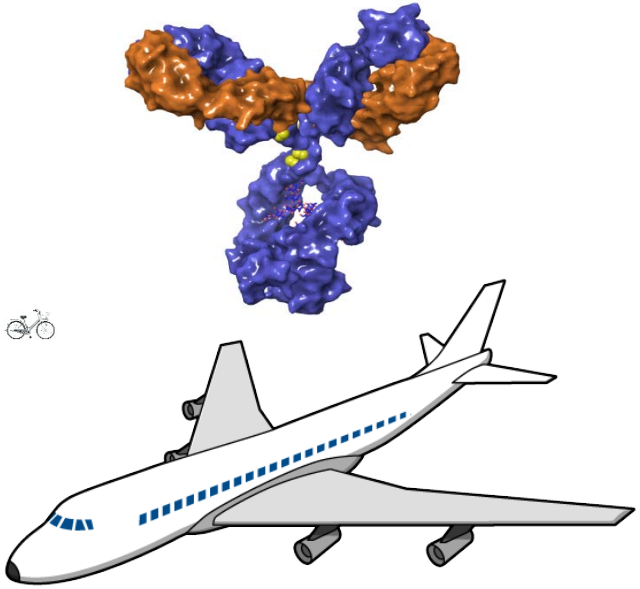


Drug exposure in normal tissue ↓

Drug exposure in cancer tissue ↑

ADC: Needs Expertize of Low Molecule and Antibody Drugs

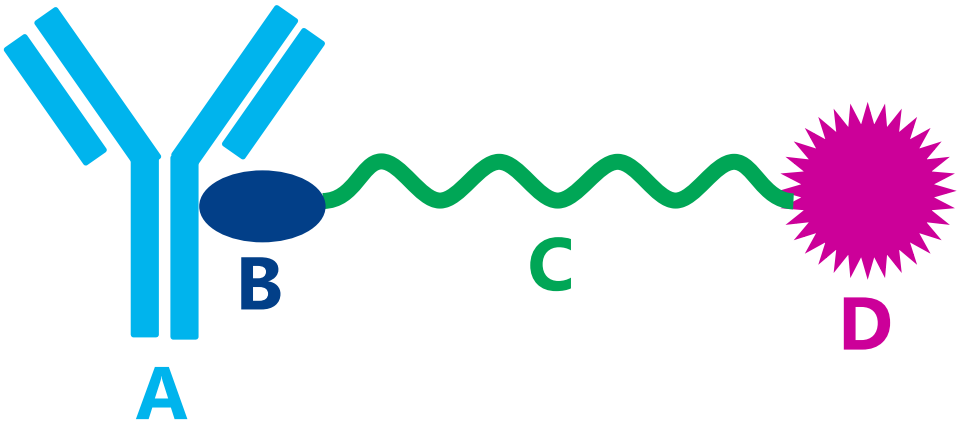




	Low Molecule Drug	Antibody Drug
Molecular weight (size)	Hundreds (small)	About 150,000 (big)
Form	Simple	Complicated
Manufacturing methods	Chemical synthesis	Cell culture
Cost	Low	High

- R&D and manufacturing methods vary widely
- Each needs to improve one's expertise and optimize processes
- Development of ADC technology requires high specialties of both

Component and Requirement of ADC



A: Antibody
- Target antigen which selectively and highly expressed on tumor
- Internalization to target cell with antigen

C: Linker
- Stable until releasing drug

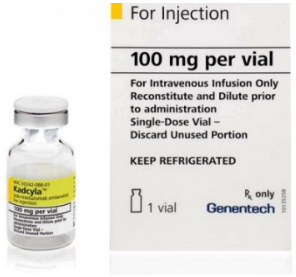
B: Attachment site
- Drug-linker can be attached
- Typically cysteine or lysine residues on antibodies

D: Payload (drug)
- Extremely potent anti-tumor activity
- Availability of linker binding site

ADC of Today and Challenges

Daiichi-Sankyo

- Launched: only 4 products
  - Kadcyla®: anti-HER2 antibody (trastuzumab) ＋DM1*, breast cancer
  - Adcetris®:anti-CD30 antibody＋MMAE*, Hodgkin lymphoma
  - Mylotarg®: anti-CD33 antibody＋Calicheamicin*, AML
  - Besponsa® : anti-CD22 antibody ＋Calicheamicin*, AML



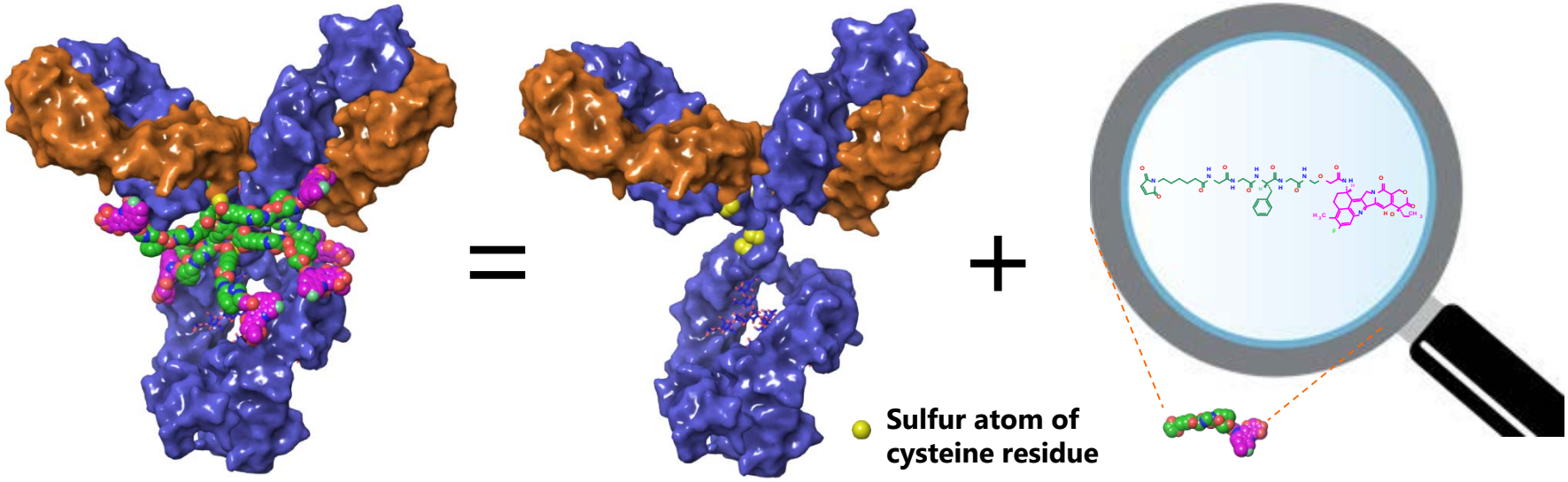
***DM1, MMAE: microtubule inhibitor**
Calicheamicin: DNA cleavage agents

- Anticipated improvements
  - ➢ Limited drug antibody ratio
    - ✓ Average drug antibody ratio (DAR) is limited to 2-4 and thus limitation in efficacy
  - ➢ Instability of linker
    - ✓ Free payloads in blood causes toxicity and also decrease of efficacy occurs by lowered concentration of ADC in blood
  - ➢ Payload
    - ✓ Most payloads are microtubule inhibitors
    - ✓ No treatment is available for patients who failed/tolerant to recent ADCs

DS ADC Technology
Overcoming Challenges

Daiichi Sankyo ADC Structure

ADC = Antibody + Drug-linker



ADC	Antibody（IgG）	Drug-linker
Molecular weight : ca. 156,000	Molecular weight : ca. 148,000	Molecular weight : ca. 1,000

DS ADC: Improved Current Challenges

Previous Generation ADC

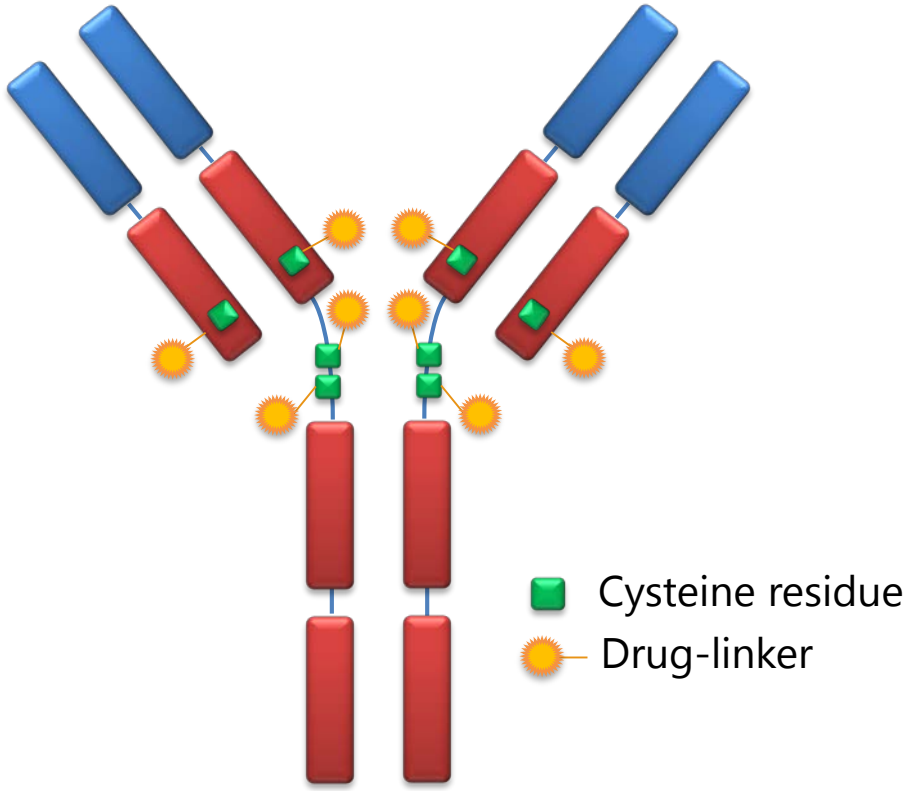
- Limited DAR
  - DAR 2-4
- Instability of linker
  - Free payloads in blood causes toxicity and also decrease of efficacy occurs by lowered concentration of ADC in blood
- Payload
  - Most payloads are microtubule inhibitors
  - No treatment is available for patients who failed/tolerant to recent ADCs

Daiichi Sankyo ADC Technology

- **Feature 1: High DAR**
  - DAR is 2-4 times higher than current ADC
- **Feature 2: High stability linker**
  - Sparing non-cancerous tissue from toxicity by non-cleavable linker
- **Feature 3: Selectively cleaved linker**
  - Cancer-cell selective cleaved linker and release payload
- **Feature 4: Unique and potent payload**
  - DNA topoisomerase I inhibitor
- **Feature 5: Bystander effect**
  - Effective in heterogeneous tumor microenvironment
- **Feature 6: Short systemic half-life**
  - If payload is released, it clear rapidly due to short half-life

Feature 1: High DAR

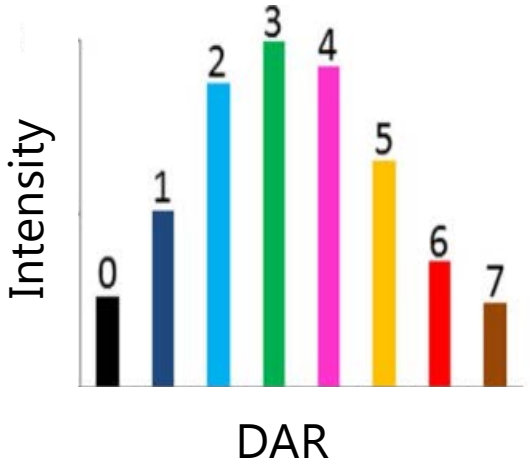
One antibody can load 7-8 payload
= 2-4 times as much as current ADC

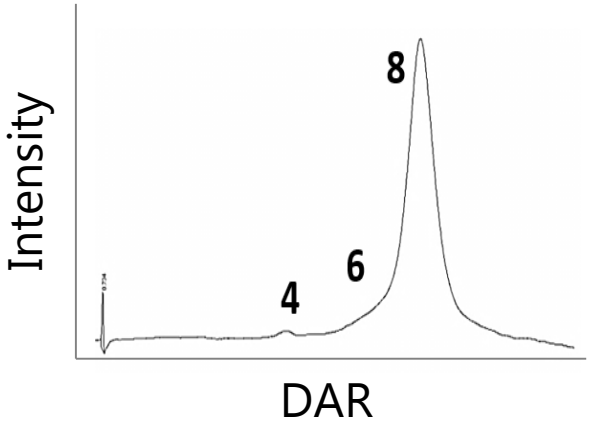


Feature 1: High Drug-to-Antibody Ration (DAR)

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



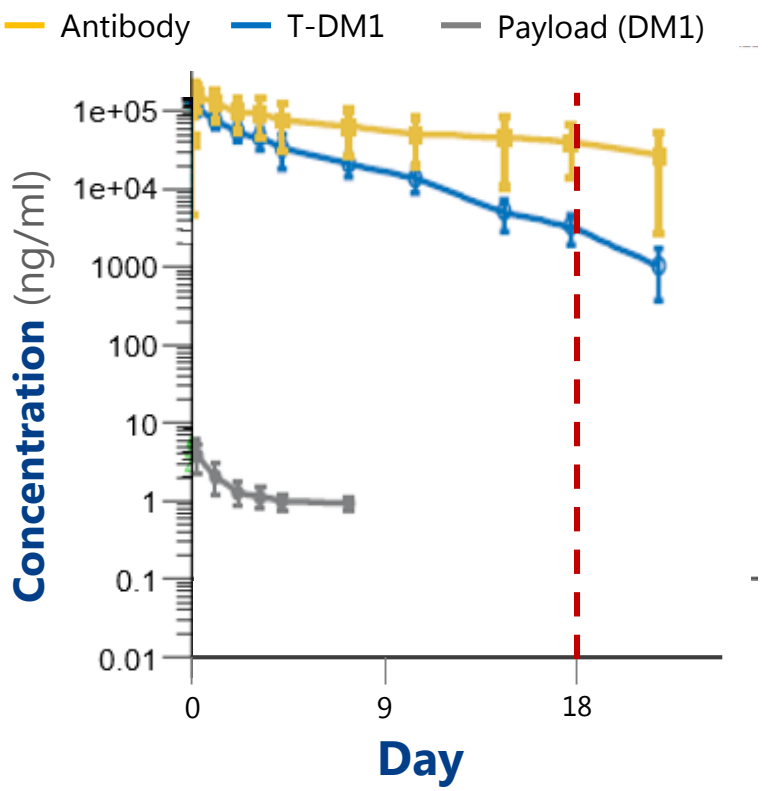


Source: Ogitani-Y *et al.*, Clin. Cancer Res. 2016; 22:5097-5108, Marcoux-J *et al.*, Protein Science 2015; 24:1210-1223

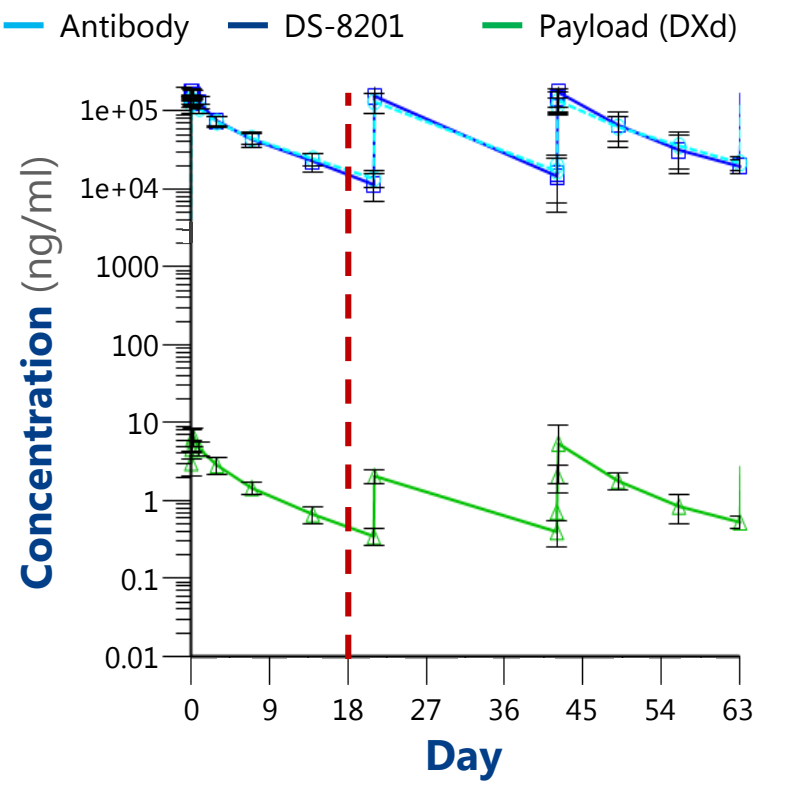
Feature 2: High Stability Linker

Pharmacokinetics profile

T-DM1, 3.6 mg/kg (Phase 1)



DS-8201, 6.4 mg/kg (Phase 1)



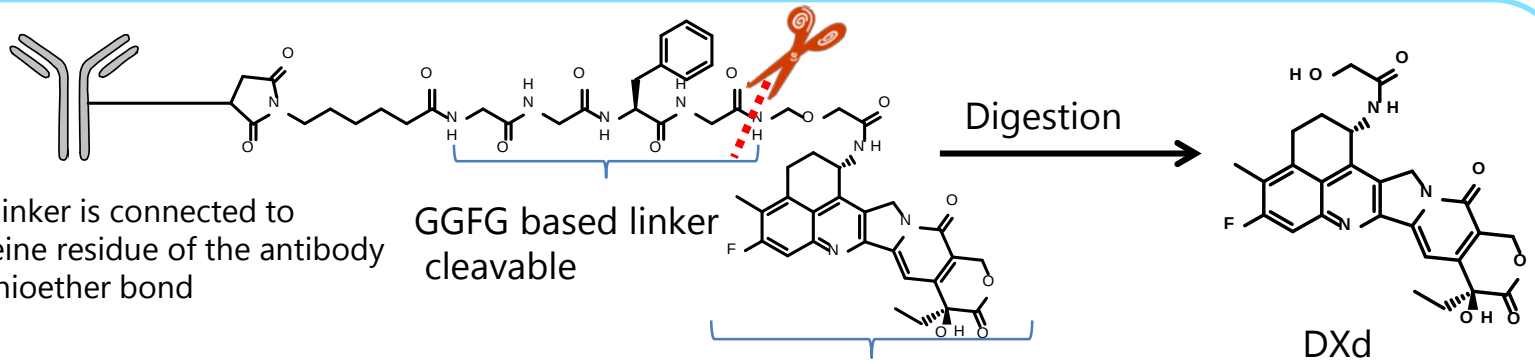
DS-8201: High linker stability and low free payload

Source: Krop-I et al., J. Clin. Oncol. 2010; 28:2698-2704, Tamura-K *et al.*, abstract 4585 (LBA17), ESMO 2016

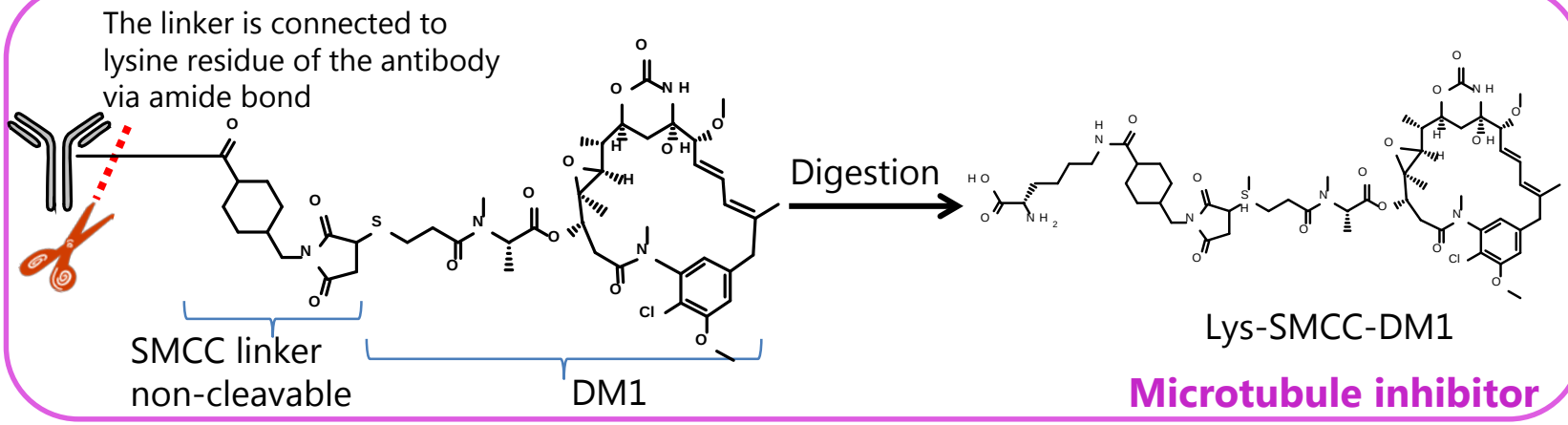
Feature 3: Selectively Cleaved Linker

DS-8201

Cleaved by cathepsin which highly expressed on tumors



Topoisomerase I inhibitor



Microtubule inhibitor

T-DM1

Cleaved by protease in lysosome

Feature 4: Novel MOA and Potent Payload

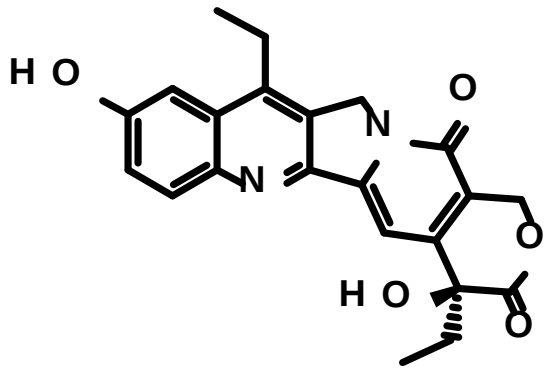
	T-DM1	DS-8201a	SYD-985	XMT-1522	MEDI4276
Company	Genentech	Daiichi Sankyo	Synthon	Mersana	Medimmune
Payload	DM1	DXd	Duocarmicine	AF-HPA	Tubulysin
MOA	Tubulin	**Topoisomerase I**	DNA alkylator	Tubulin	Tubulin
Linker	Undissociated	Dissociated	Dissociated	Dissociated	Dissociated
Attachment site	Lysine residue	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	1.2mg/kg**	0.765mg/kg***	NA

*Yamamoto-H, Jpn J Clin Oncol. 2015 Jan;45(1):12-8
**Aftimos-PG, SABCS, 2016
***Buris-HA, Mersana homepage TPS2606

Feature 4: Novel MOA and Potent Payload

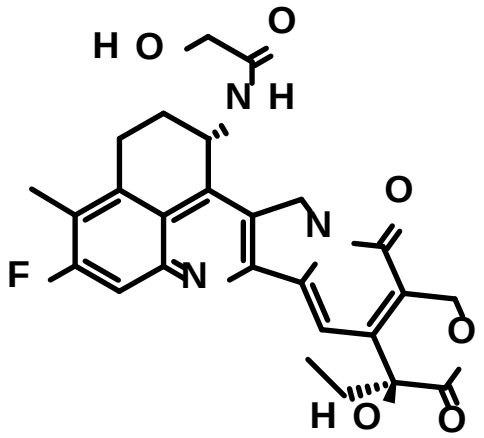
- Novel topoisomerase I inhibitor, DXd
- DXd has 10 times more potent effect than irinotecan

SN-38
(active metabolite of irinotecan)



Topo I IC_{50}: 2.78 μM

DXd
(payload of DS-8201a)



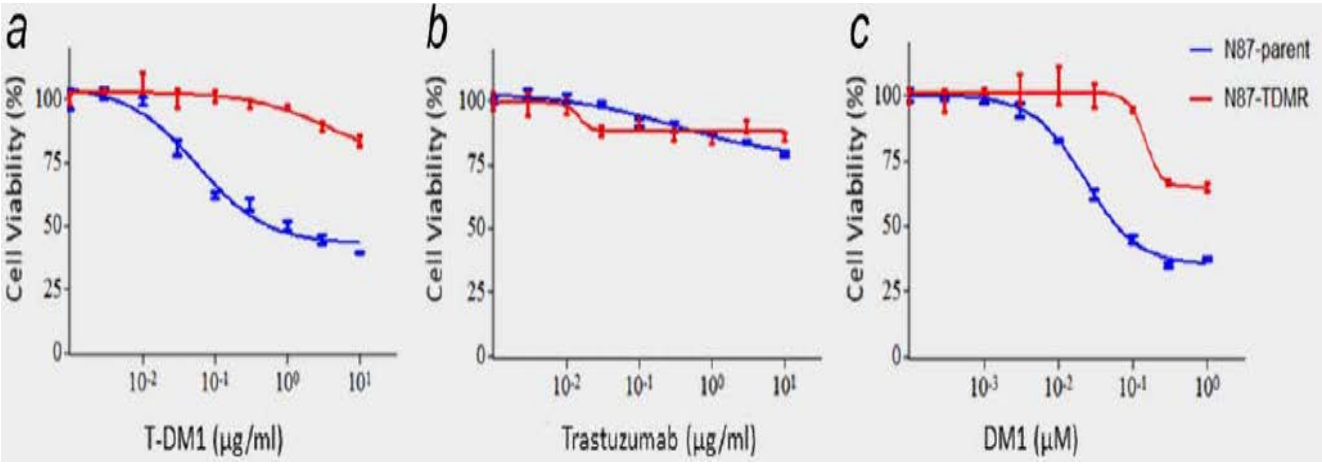
Topo I IC_{50}: 0.31 μM

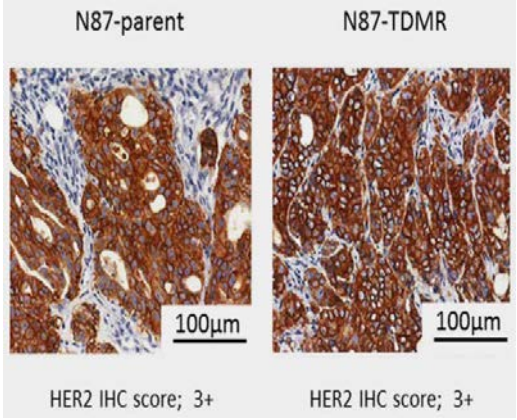
About 1/10 amount is enough
for efficacy

TOPO I IC_{50}: concentration which inhibit 50% of topoisomerase I enzyme

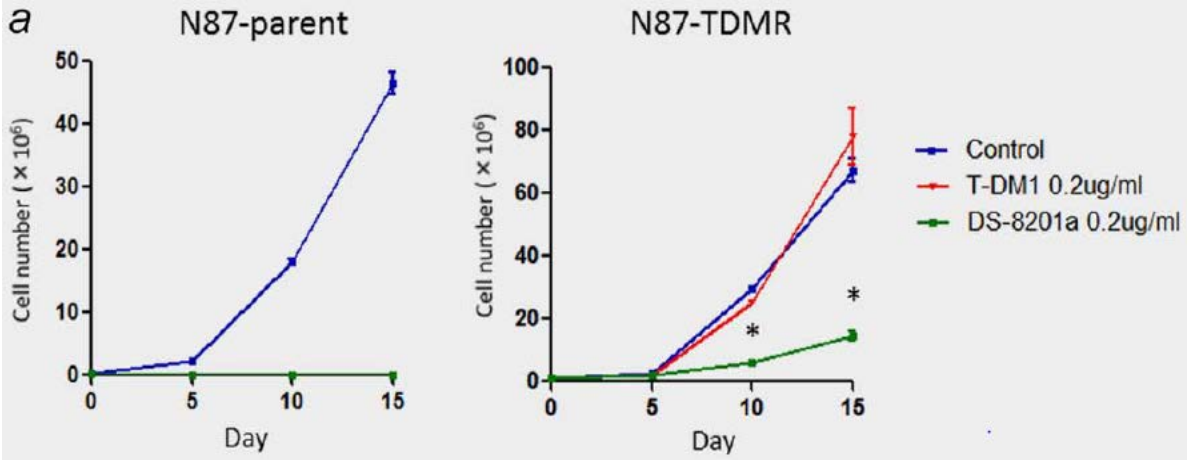
Feature 4: Unique and Potent Payload

- T-DM1 resistant cell (N87-TDMR) has HER2 expression but low sensitivity to free payload, DM-1





- MOA of DS-8201 payload is different and therefore has superior efficacy to N87-TDMR

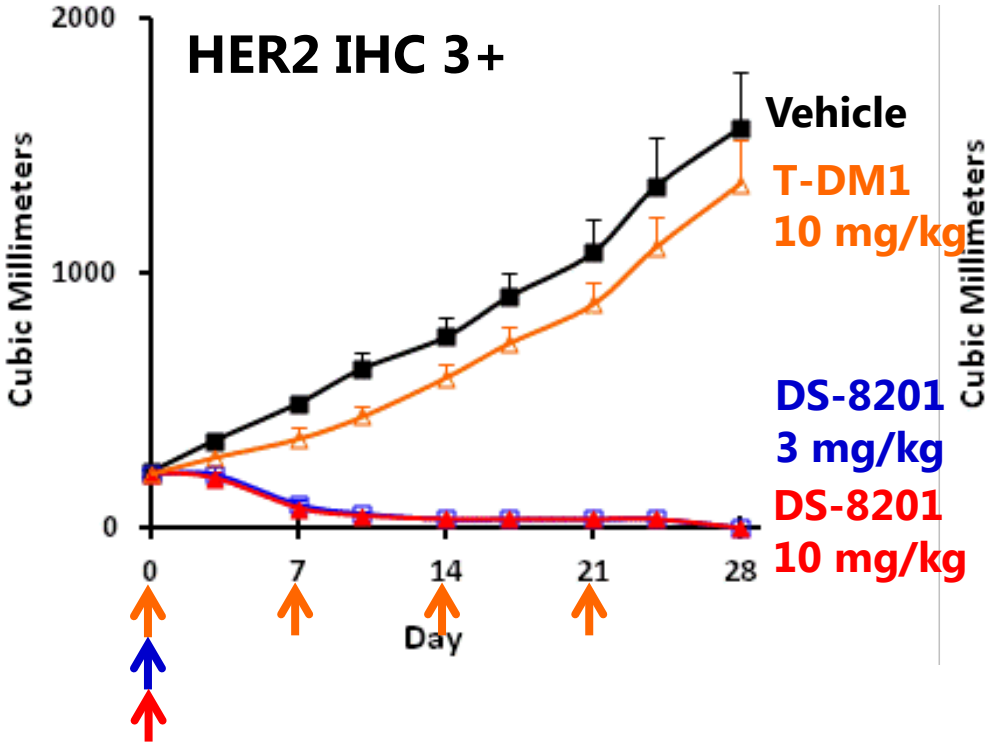


Takegawa-N et al., Int J Cancer 2017

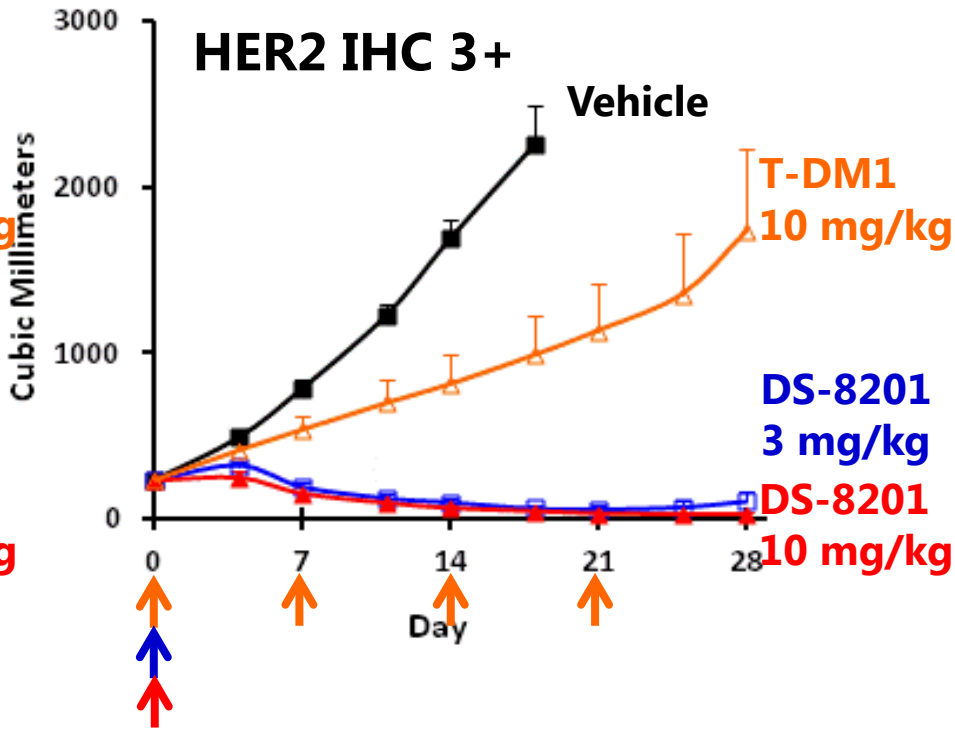
Feature 4: Unique and Potent Payload

T-DM1 treated patient's cancer tissue xenograft model

Cancer tissue from patients who are treated by T-DM1 for 13 months



Cancer tissue from patients who are treated by T-DM1 for 3 months

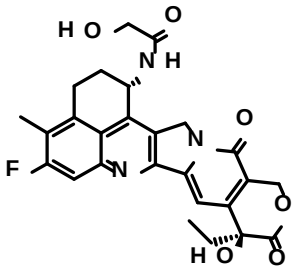


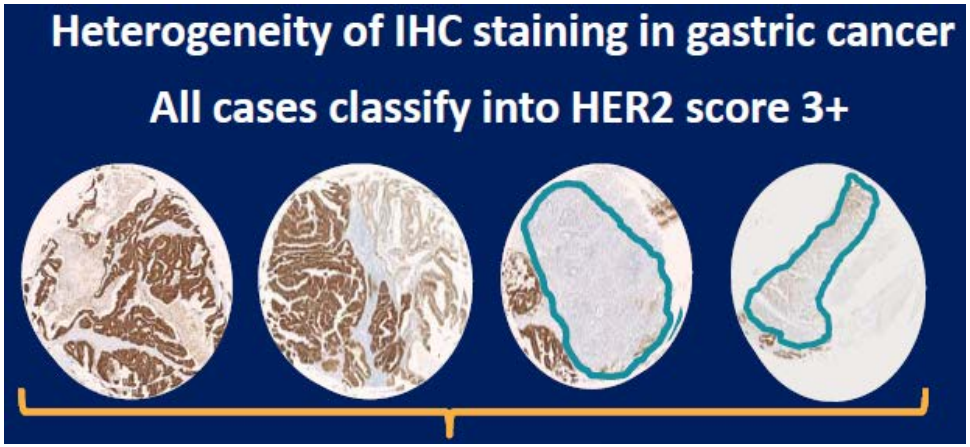
Source: Tamura-K *et al.*, abstract 4585 (LBA17), ESMO 2016

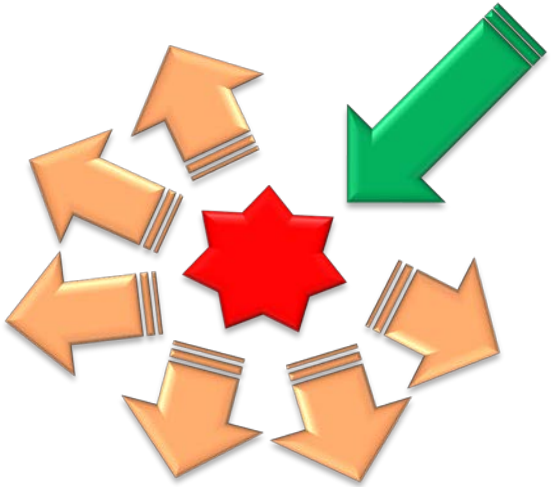
Remarkable efficacy of DS-8201 was seen in T-DM1 resistant or low-resonse cancer patient-derived xenograft model

Feature 5: Bystander Effect

Released drug is designed to have high cell membrane cross-penetration







- Cancer tissues are group of heterogeneity
- Target expression is sometimes uneven

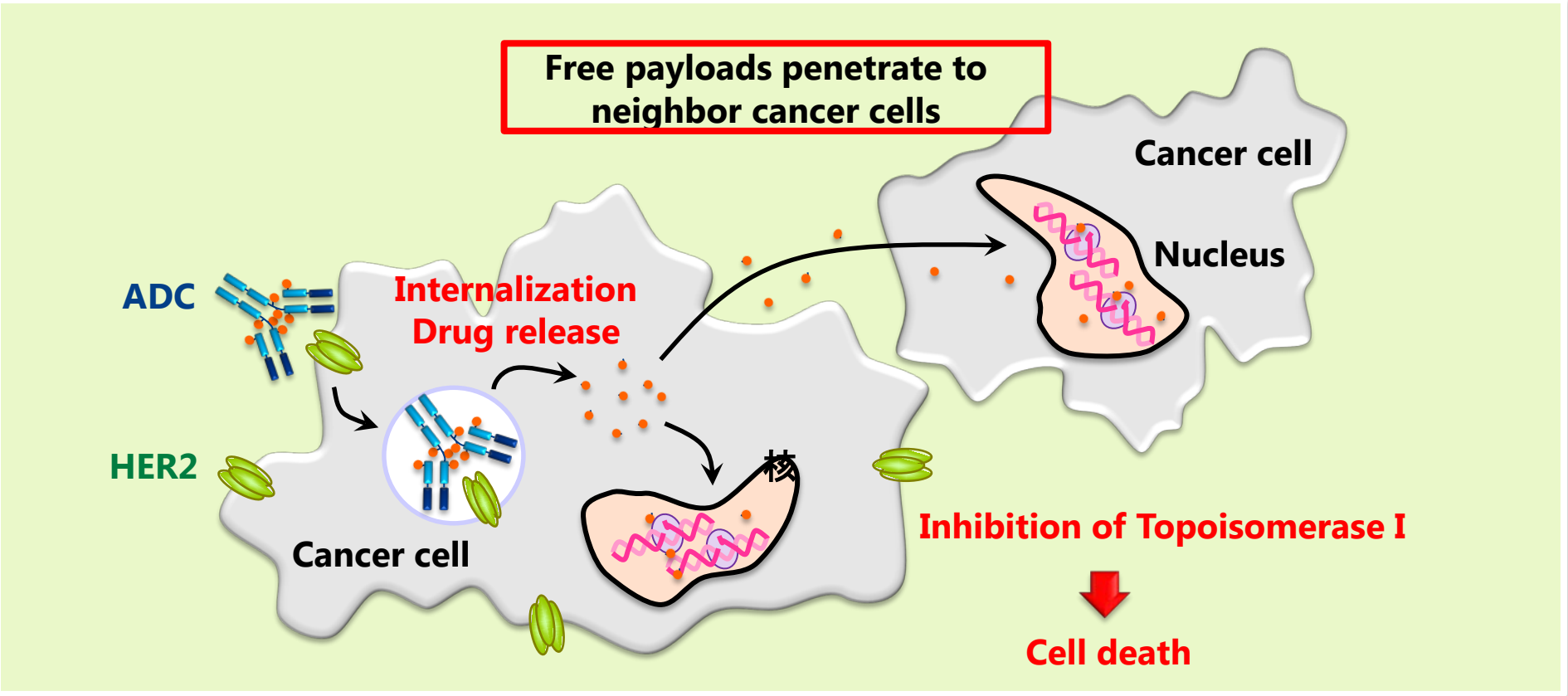
- Free payloads penetrate to neighbor cancer cells and have anti-cancerous effect
- Effective in heterogeneous tumor microenvironment

Doi-T et al., abstract 108, ASCO 2017

Feature 5: Bystander Effect

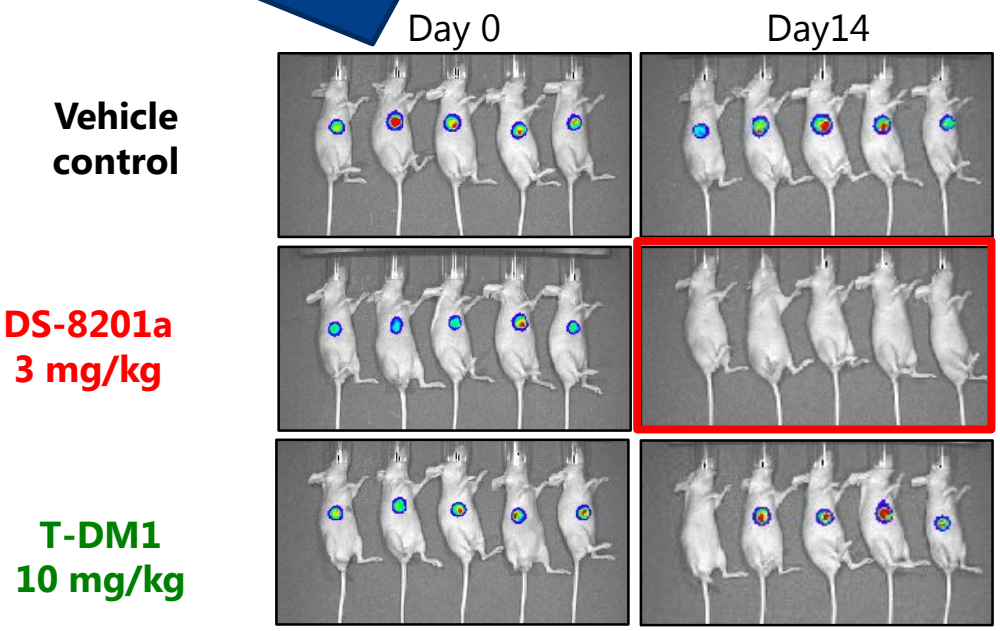
Bystander effect of ADC:

- 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

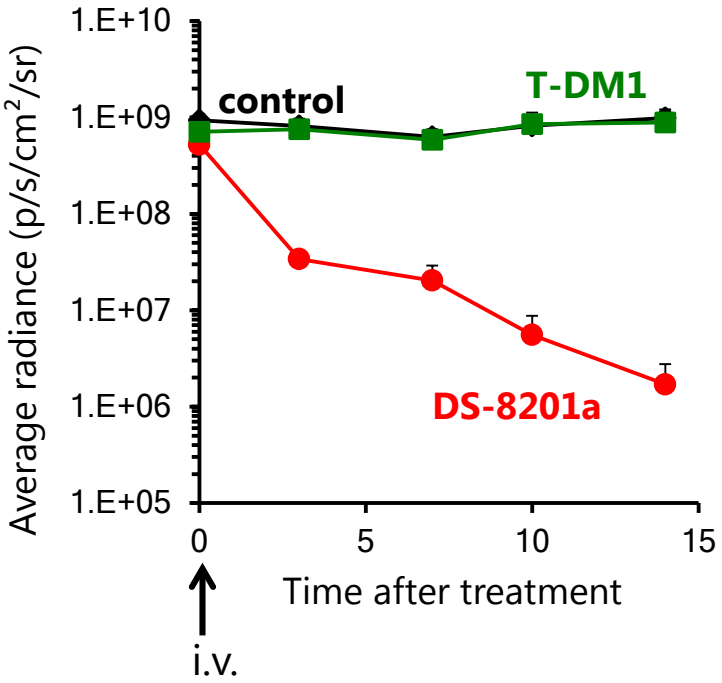


Feature 5: Bystander Effect in vivo Study

Co-inoculate HER2 positive cells and HER2 negative cells (Luc tagged) to right flank of mice



Luciferase activity



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

- DS-8201a treatment clearly decreased luciferase signal

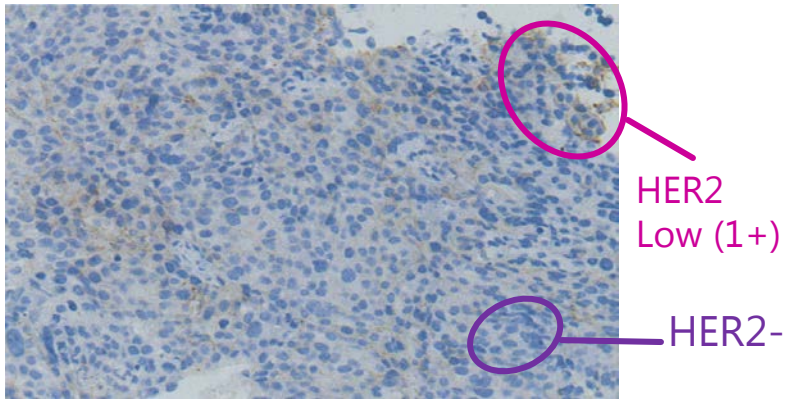
→ **Luc-gene transfected HER2-negative cells was eliminated**

Feature 5: Bystander Effect

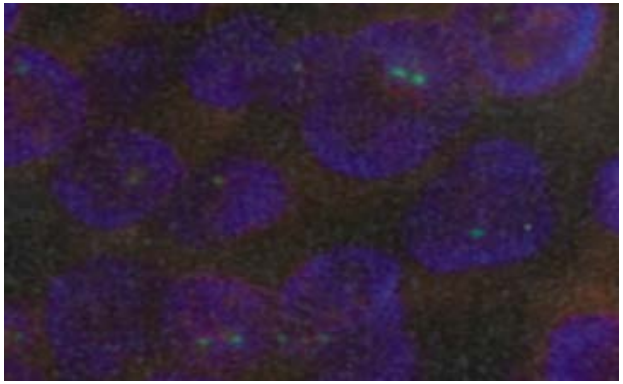
- DS-8201 bystander effect on Low HER2 (non-clin study)

Breast HER2 Low

Patient-derived xenograft ST565
(IHC 1+, FISH -)

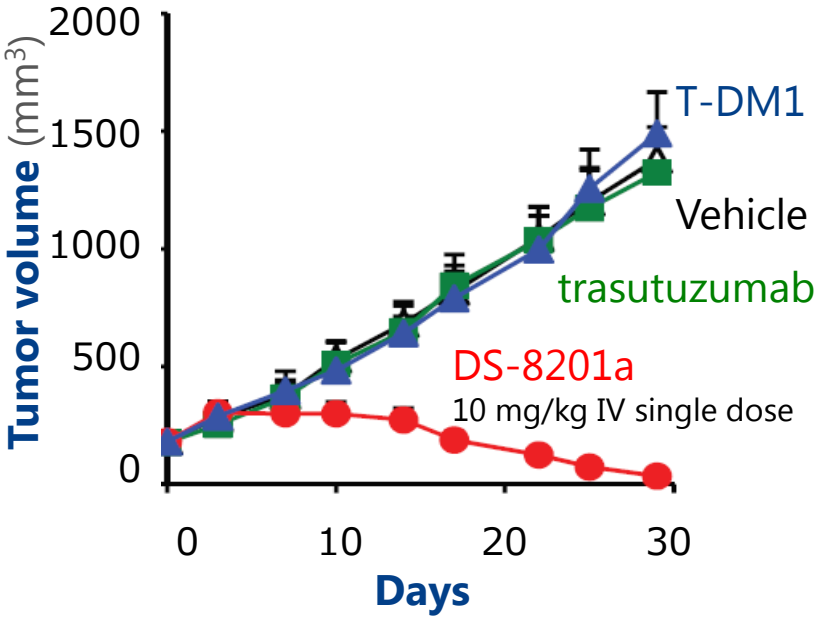


FISH negative (signal ratio 1.3)



Change in tumor volume (mm^3)

Patient-derived xenograft ST565



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

Feature 6: Short Systemic Half-Life

- High concentration of free payload in blood is one of the reason of adverse events
- Released payload is designed to be excreted immediately which results in lowering occurrence of adverse events

Payload	$T_{1/2}$ in Rat (hour)
DXd* (payload of DXd-ADC)	0.9
DM1** (payload of T-DM1)	3.3-10
MMAE*** (payload of Adcetris)	5.7-11

** In-house report*
*** KADCYLA BLA*
**** ADCETRIS BLA*

DS ADC: Improved Current Challenges

Previous Generation ADC

- Limited DAR
  - DAR 2-4
- Instability of linker
  - Free payloads in blood causes toxicity and also decrease of efficacy occurs by lowered concentration of ADC in blood
- Payload
  - Most payloads are microtubule inhibitors
  - No treatment is available for patients who failed/tolerant to recent ADCs

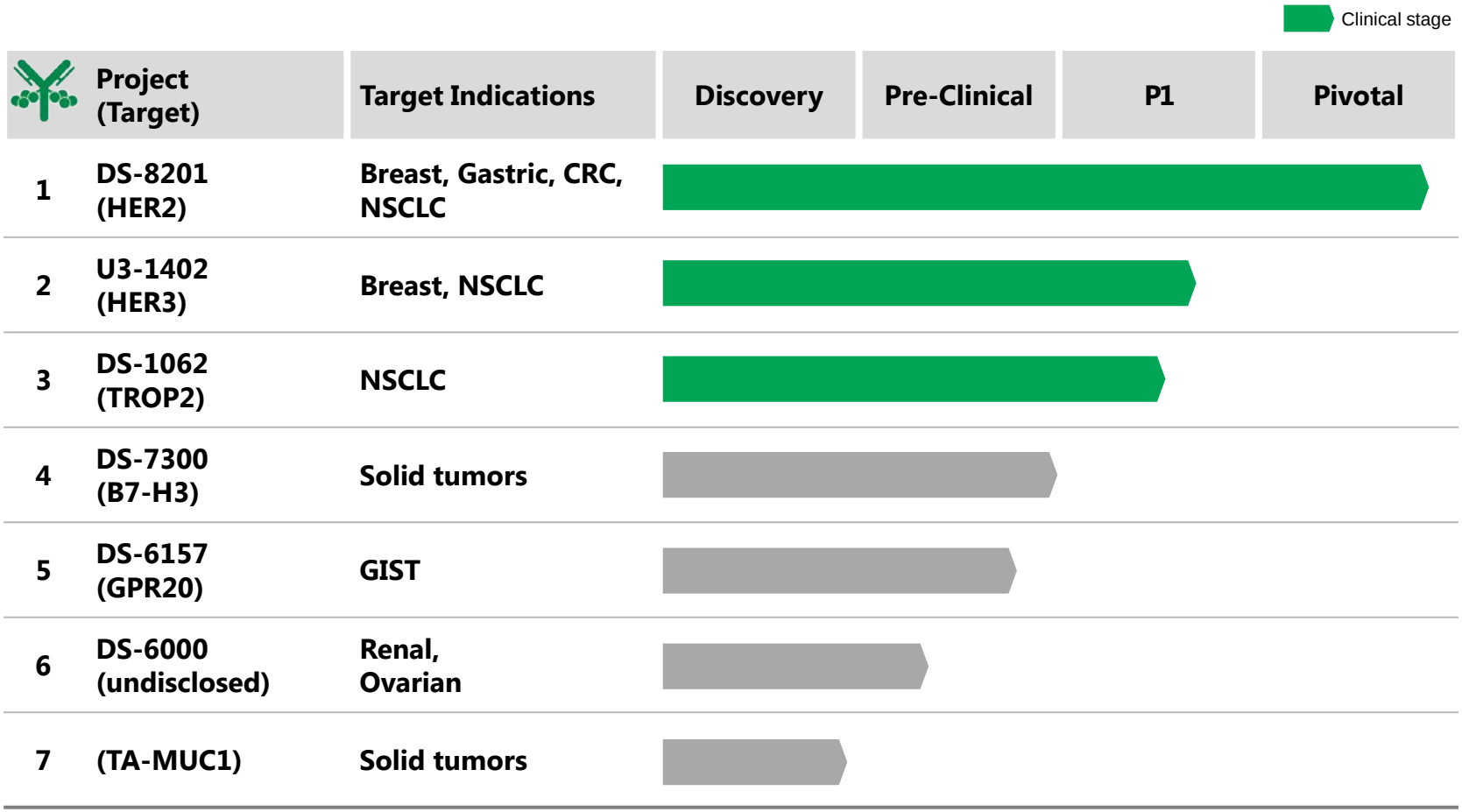
Daiichi Sankyo ADC Technology

- **Feature 1: High DAR**
  - DAR is 2-4 times higher than current ADC
- **Feature 2: High stability linker**
  - Sparing non-cancerous tissue from toxicity by non-cleavable linker
- **Feature 3: Selectively cleaved linker**
  - Cancer-cell selective cleaved linker and release payload
- **Feature 4: Unique and potent payload**
  - DNA topoisomerase I inhibitor
- **Feature 5: Bystander effect**
  - Effective in heterogeneous tumor microenvironment
- **Feature 6: Short systemic half-life**
  - If payload is released, it clear rapidly due to short half-life

Daiichi Sankyo ADC Franchise

(as of June 2019)

ADC Franchise

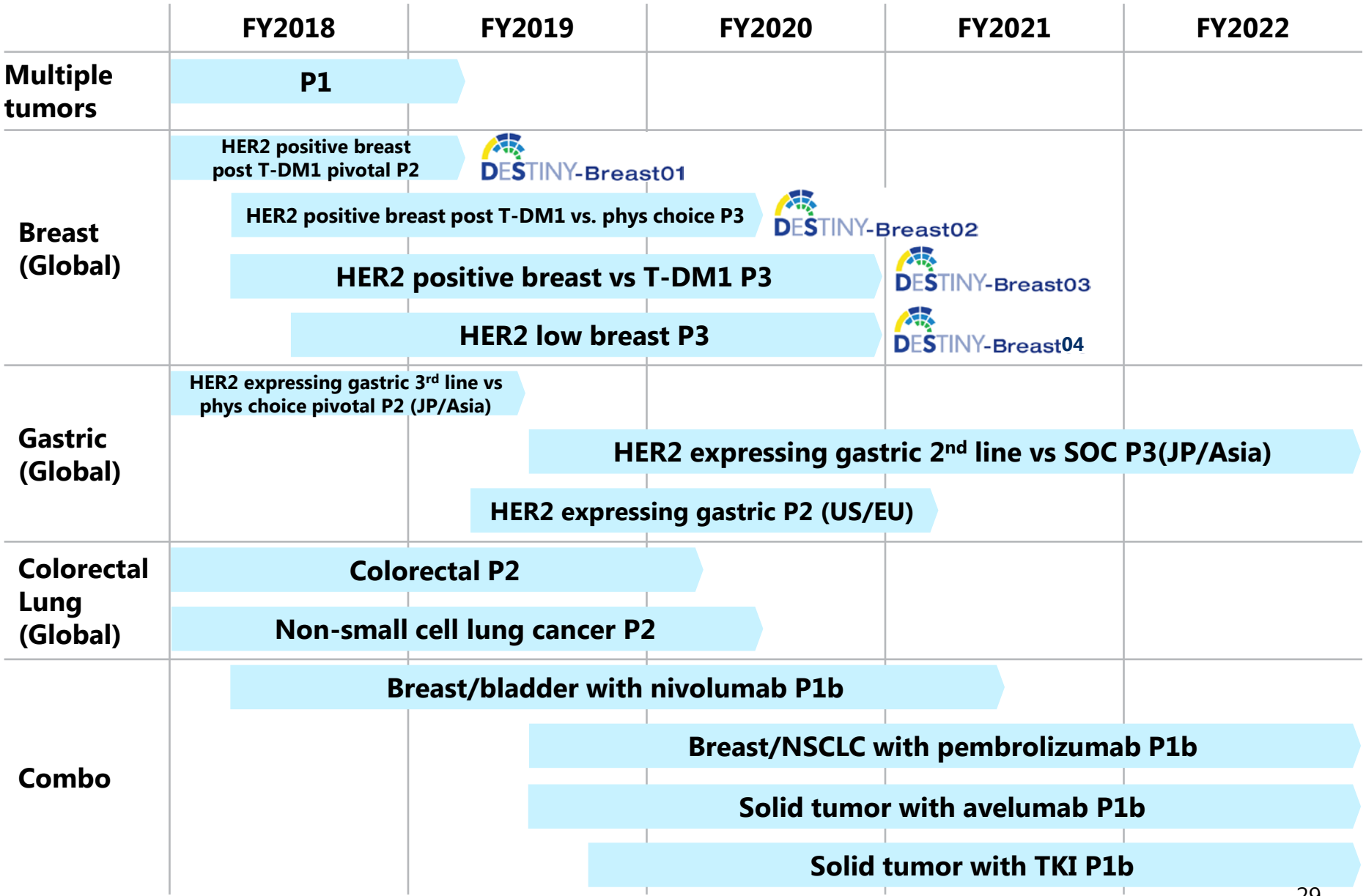


CRC: colorectal cancer, NSCLC: non-small cell lung cancer, GIST: gastrointestinal stromal tumor

DS-8201

DS-8201: Study Plan

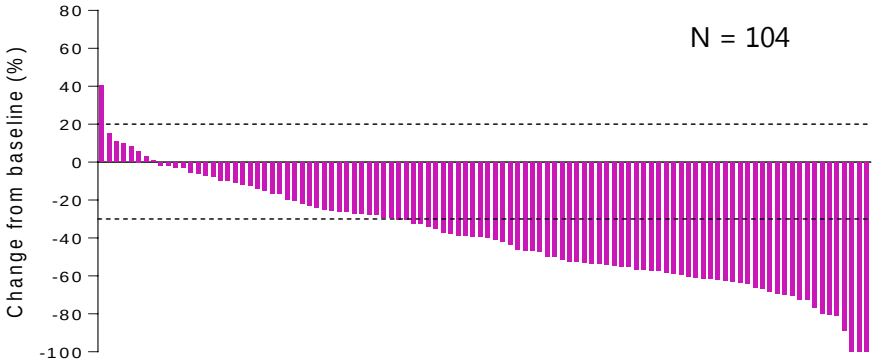
As of April 2019

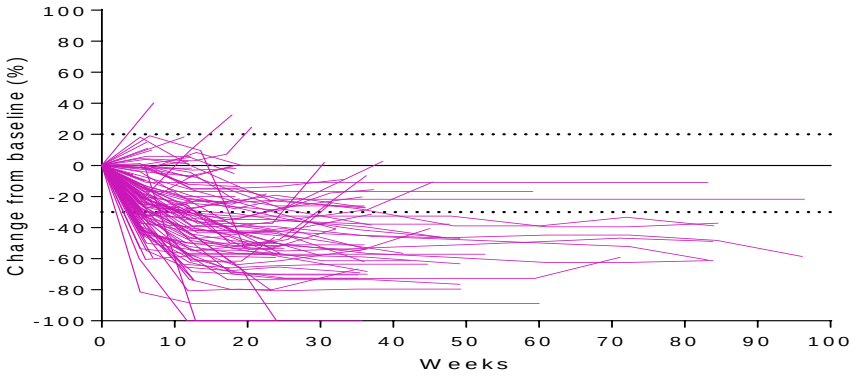


Explanation of Terms

CR (complete response)	Cancer disappears completely
PR (partial response)	The size of the cancer has shrunk by more than 30% and lasted for more than 4 weeks
ORR (overall response rate)	Percentage of patients who had a therapeutic effect. Expressed by the sum of CR and PR
DCR (disease control rate)	Percentage of patients whose symptoms are controlled
DOR (duration of response)	Duration of effect lasting
PFS (progression-free survival)	Period of survival without cancer progression
PD (progressive disease)	Cancer progression
SD (stable disease)	Size (long diameter) of the cancer has not changed substantially before and after treatment

DS-8201: P1 Study HER2 Positive Breast Cancer



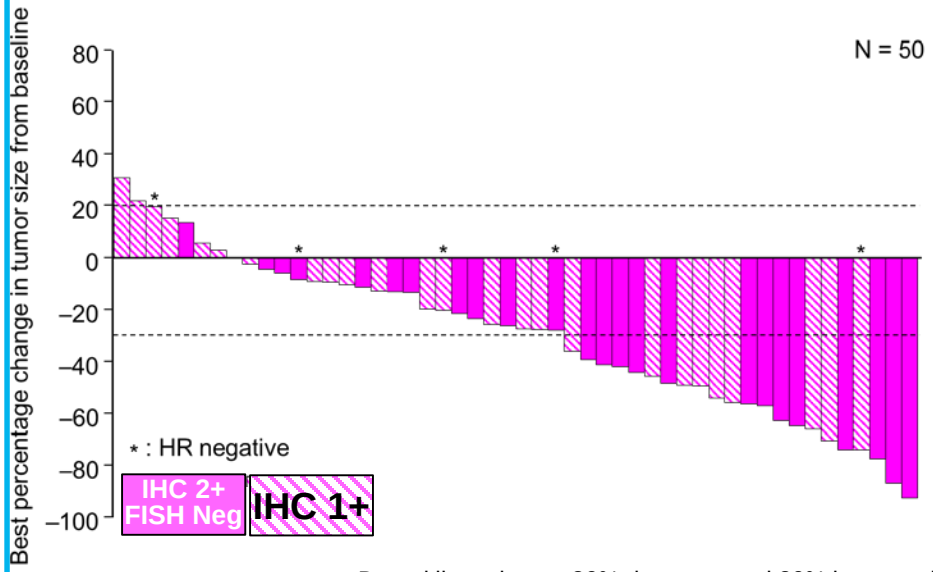


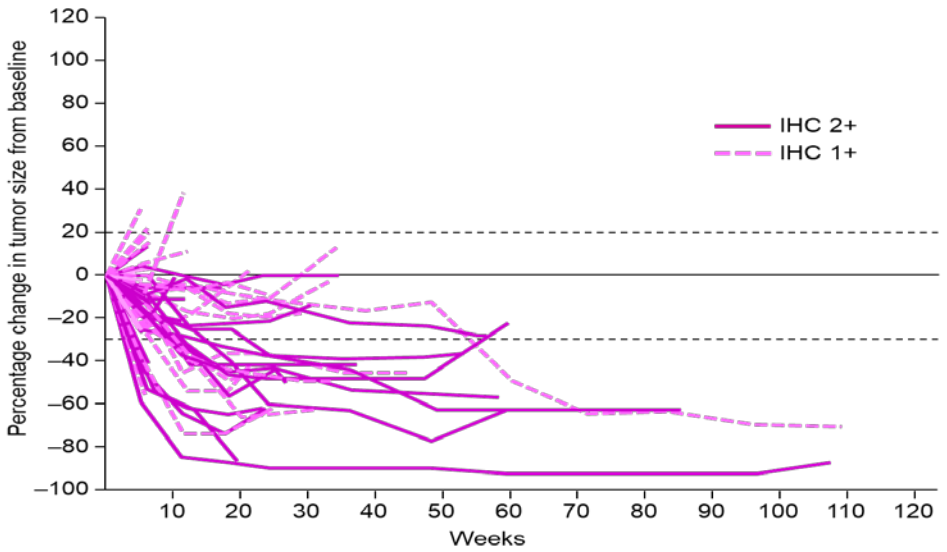
Data cutoff for this analysis is April 18, 2018
Iwata et al, ASCO2018 Presentation

	Confirmed ORR (n/N) (95% CI)	DCR % (n/N)	DOR, median (95% CI), month	PFS	
				Median, (95% CI)	Min, max
HER2 positive breast cancer N=114	59.5% (66/111) (49.7, 68.7)	93.7% (104/111)	20.7 (NE)	22.1ヶ月 (NE)	0.8, 27.9

NE: not estimable
Lancet Oncology, April 29, 2019

DS-8201: P1 Study HER2 Low Breast Cancer



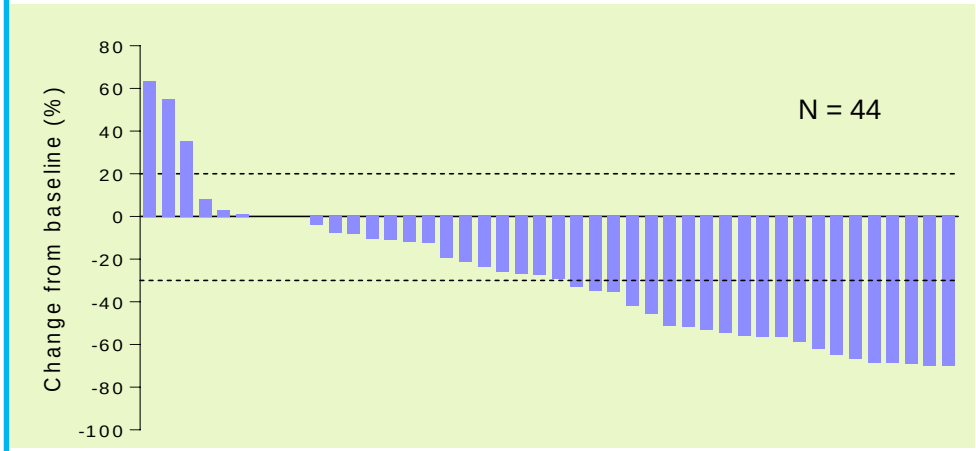


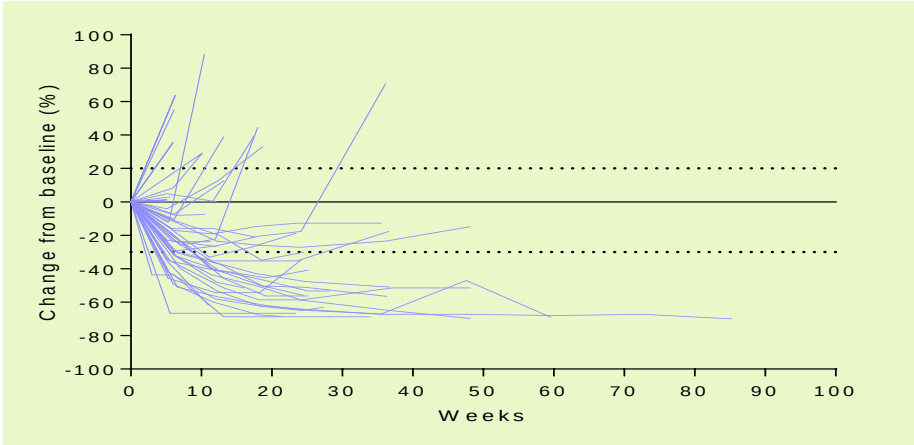
Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
HR, hormone receptor; IHC, immunohistochemistry.

	Confirmed ORR, n/N (%)	Confirmed DCR, n/N (%)	Duration of Response, median (range), mo	PFS, median (95% CI), mo
All (N = 51)	**19/43 (44.2)**	**34/43 (79.1)**	**9.4 (1.5+, 23.6+)**	**7.6 (4.9, 13.7)**
Subgroups				
IHC 1+ (n = 27)	7/21 (33.3)	14/21 (66.7)	7.9 (2.1+, 11.3)	5.7 (1.4, 7.9)
IHC 2+ (n = 24)	12/22 (54.5)	20/22 (90.9)	11.0 (1.5+, 23.6+)	13.6 (NA)
HR+ (n = 45)	18/38 (47.4)	31/38 (81.6)	11.0 (1.5+, 23.6+)	7.9 (4.4, 13.7)
Prior CDK4/6 inhibitor (n = 15)	4/12 (33.3)	9/12 (75.0)	NR	7.1 (NA)

Modi et al, SABCS, 2018; Poster # P6-17-02, Abstract #486

DS-8201: P1 Study HER2 Positive Gastric Cancer



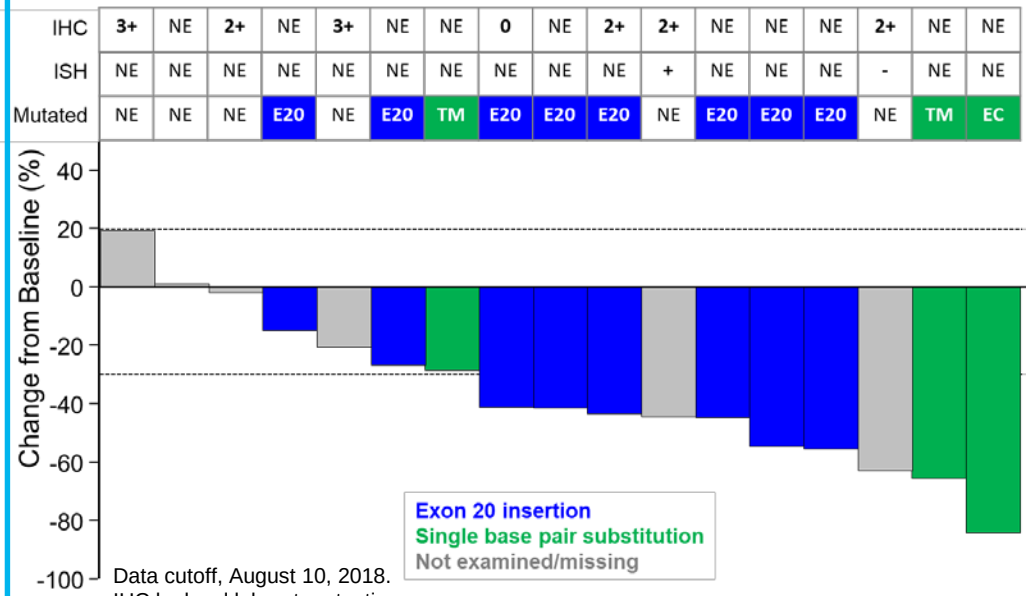


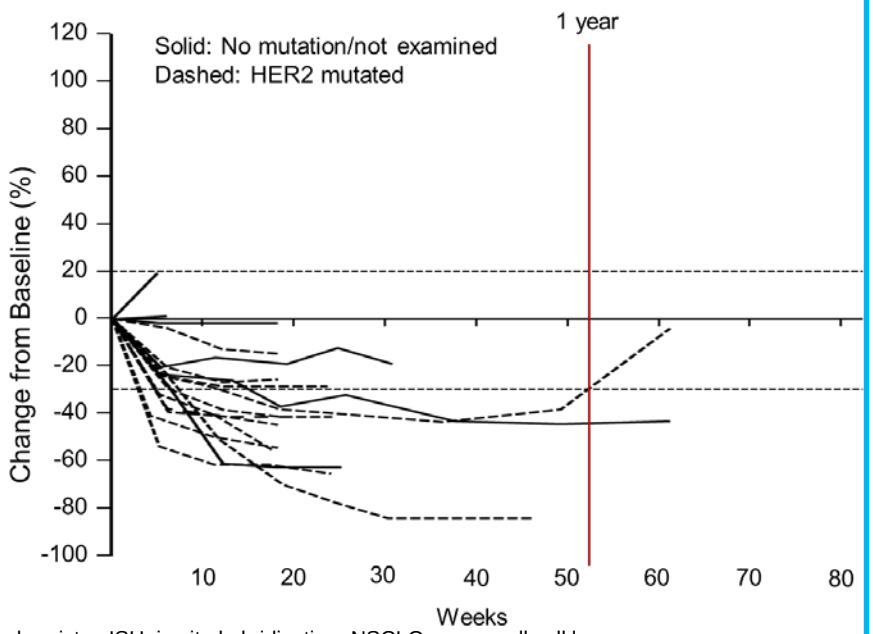
Includes subjects who had ≥1 postbaseline scan. Dotted lines denote 20% increase and 30% reduction in tumor size, respectively.
*Confirmed response includes subjects who had ≥2 postbaseline scans, progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.
Data cutoff is April 18, 2018.

	Confirmed ORR (n/N) (95% CI)	DCR % (n/N)	DOR, Median (95% CI), months	PFS	
				Median, (95% CI)	Min, max
HER2 Positive Gastric Cancer N = 44	43.2% (19/44) (28.3, 59.0)	79.5% (35/44)	7.0 (NA)	5.6 months (3.0, 8.3)	1.2, 19.6+

Iwata et al. ASCO 2018. Abstract # 2501

DS-8201: P1 Study HER2 Mutated or Expressing NSCLC





Data cutoff, August 10, 2018.
IHC by local laboratory testing.
E20, exon 20 insertion; EC, single base pair substitution at extracellular domain; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small cell lung cancer; NE, not examined or missing; TM, single base pair substitution in transmembrane domain.

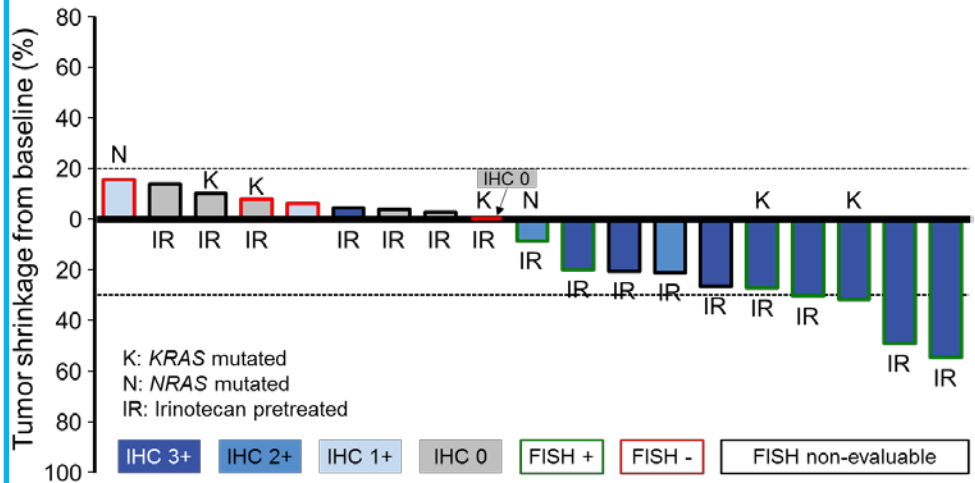
	Comfirmed ORR, % (n/N)	Comfirmed DCR, % (n/N)	DOR, median (range), months	PFS, median (range), months
HER2-expressing or HER2-mutated NSCLC N = 18	58.8% (10/17)	88.2% (15/17)	9.9 (0.0+, 11.5)	14.1 (0.9, 14.1)
HER2-mutated NSCLC N = 11	72.7% (8/11)	100% (11/11)	11.5 (0.03+, 11.5)	14.1 (4.0+, 14.1)

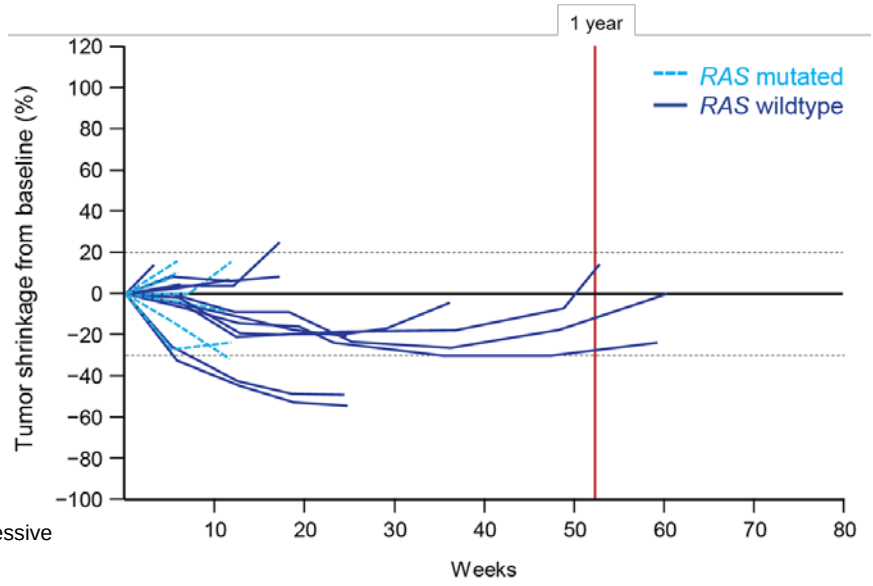
Tsurutani et al, WCLC, 2018; Abstract #13325

DS-8201: P1 Study CRC by HER2 Status IHC/FISH

Daiichi-Sankyo

- ORR 27.3% (3/11) in HER2 (IHC 2+, 3+)





HER2 status based on centrally assessed retrospective analysis of archival samples.
Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IR, irinotecan pretreated; K, *KRAS* mutation; N, *NRAS* mutation.

	Confirmed ORR, % (n/N)	Confirmed DCR, % (n/N)	DOR, median (range), months	PFS, median (range), months	OS, median (range), months
CRC N=19*	15.8% (3/19)	84.2% (16/19)	NR (0.0+, 5.5+)	3.9 (2.1,8.3)	NR (1.0+, 17.9+)

* Evaluable patients (one IHC 0 patient was not evaluable out of 20 enrolled)

Yoshino et al, ESMO 2018; Poster #563P

HER2 mBreast Cancer Post T-DM1 Submissions Plan

- Preparation for BLA/NDA submissions is progressing to plan

US

BLA submission
1H FY2019

Estimated Review Period:
6M after acceptance of the application by FDA

- Fast-track status
- Breakthrough therapy designation

Japan

NDA submission
2H FY2019

Estimated Review Period:
Maximum 12M after application

EU

MAA submission
1H FY2020

Estimated Review Period:
12M after application

HER2 Gastric Cancer Submission Plan

- Preparation for JNDA submission is progressing steadily

Japan

NDA submission
1H FY2020

Estimated Review Period:
6M after application

SAKIGAKE designation

DS-8201: P1 Study *The Lancet Oncology* Breast Cancer

	Pertuzumab + trastuzumab + docetaxel (1L)[1]	T-DM1 (1L, failed study)[2]	T-DM1 (2L)[3]	T-DM1 (3L+)[4]	DS-8201[5]
mPFS	18.5m	14.1m	9.6m	6.2m	**22.1m**
DoR	20.2m	20.7m	12.6m	9.7m	20.7m
OS	56.5m	53.7m	30.9m	22.7m	NR
ORR	80%	60%	43.6%	31%	59.5%
Median prior Rx for adv. disease	0	0	1	4	7 100% prior T-DM1 88% prior pertuzumab

[1]CLEOPATRA (NEJM 2012), [2]MARIANNE (J Clin Oncol 2017), [3]EMILIA (NEJM 2012), [4]TH3RESA (Lancet Oncol 2017), [5]Lancet Oncology, April 29, 2019, m: Month, NR:Not Reached

DS-8201: P1 Study *The Lancet Oncology* Gastric Cancer

	Trastuzumab + chemo (1L)[1]	Ramucirumab + chemo (2L)[2]	T-DM1 (failed study; 3+L)[3]	DS-8201[4]
mPFS	6.7m	4.4m	2.7m	5.6m
DoR	6.9m	4.4m	4.3m	**7.0m**
OS	13.8m	9.6m	7.9m	**12.8m**
ORR	47%	28%	21%	43.2%
Median prior LoT[5]	0	1	1	3

[1]ToGA (Lancet 2010), [2]RAINBOW (Lancet Oncol. 2014), [3]GATSBY (Lancet Oncol. 2017), [4]Lancet Oncology, published April 29, 2019
m: Month, [5]Line of Therapy

DS-8201: Safety Interstitial Lung Disease (ILD)

Daiichi-Sankyo

Investigator-Reported and Adjudicated Cases of ILD

- Median duration of treatment 108 days; 29.5% subjects on treatment for ≥180 days
  - Median time to onset of ILD 149 days

Population	Adjudication status	Grade					Total
		1	2	3	4	5	
All subjects All doses, N = 665	Investigator reported, n (%)	30 (4.5)	23 (3.5)	6 (0.9)	2 (0.3)	5 (0.8)	66 (9.9)
	Cases adjudicated, n	16	13	4	0	5	38
	Adjudicated as drug-related ILD, n	11	12	3	0	4	30

Data cutoff: October 15, 2018

- **March 2018: ILD recognized as DS-8201 risk: key actions implemented**
  - Proactive awareness of subjects thru consent, to report signs or symptoms of possible ILD
  - Active training of investigational sites on monitoring for, evaluation and treatment of suspected ILD cases

Spring 2019: Proactive "Safe Use Campaign"

"DS-8201: have you screened for and mitigated against ILD today?"

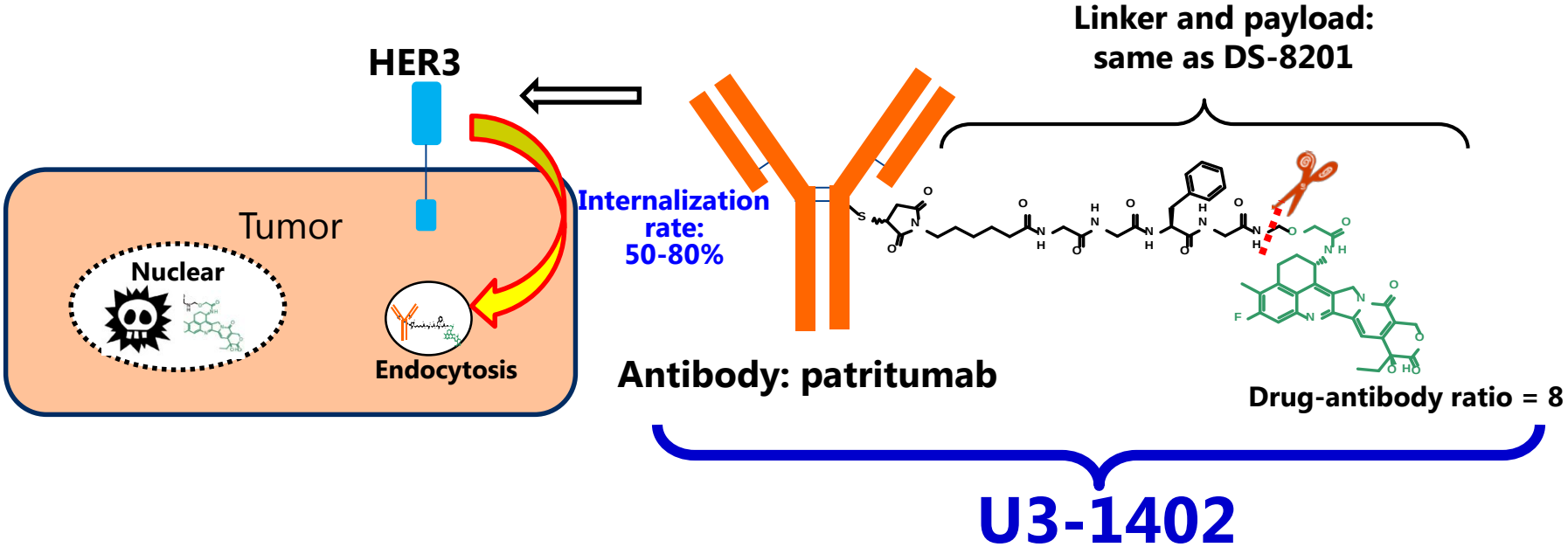
U3-1402

U3-1402: HER3 Targeted ADC

Product concept

Highly-internalized ADC:

Patritumab (anti-HER3 mAb) armed with topoisomerase I inhibitor, to target HER3 expressing tumors

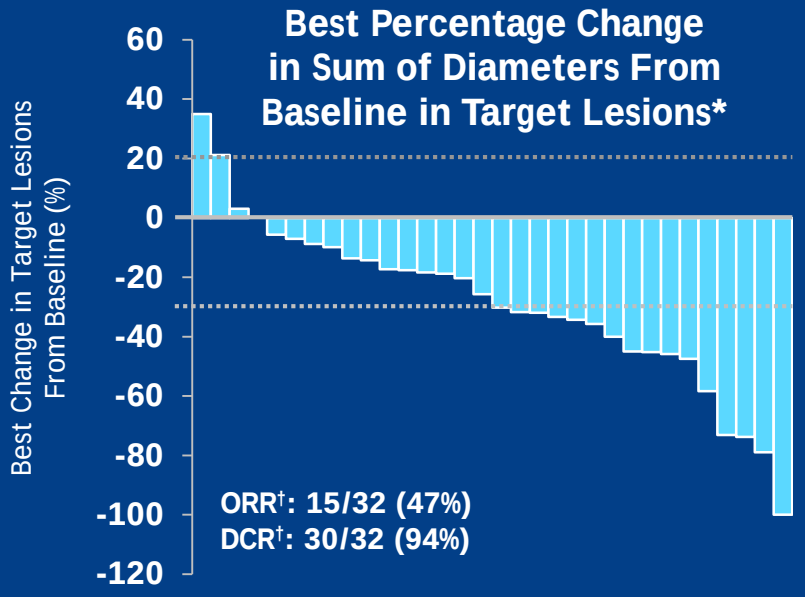


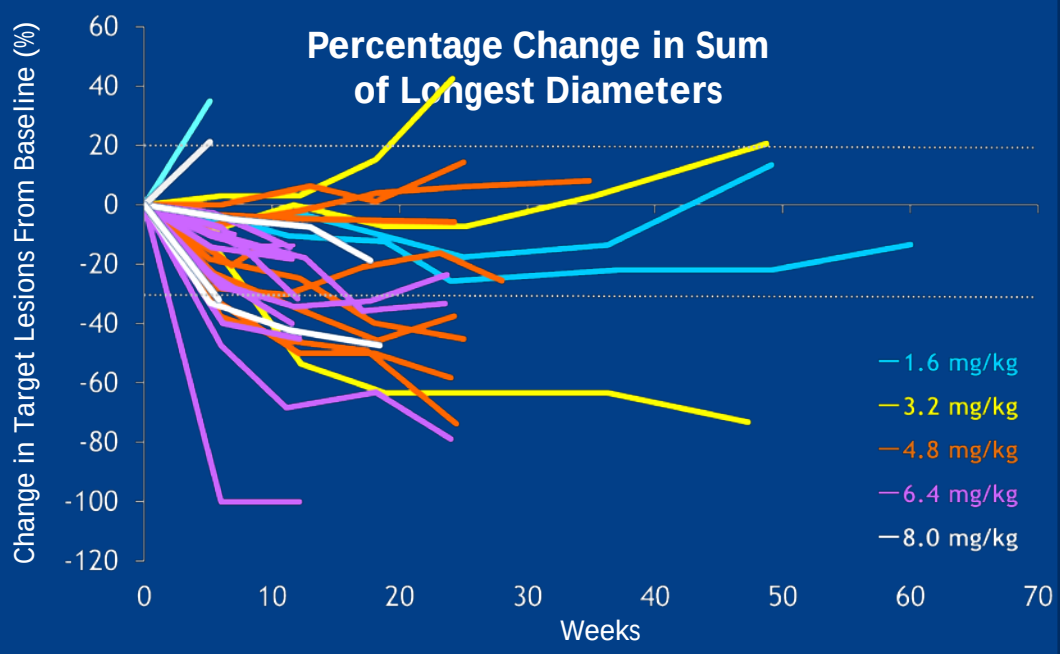
Potential first-in-class drug

U3-1402: HER3 Positive Refractory/Metastatic Breast Cancer Efficacy

Daiichi-Sankyo

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

Safety Summary of Patients Treated with U3-1402

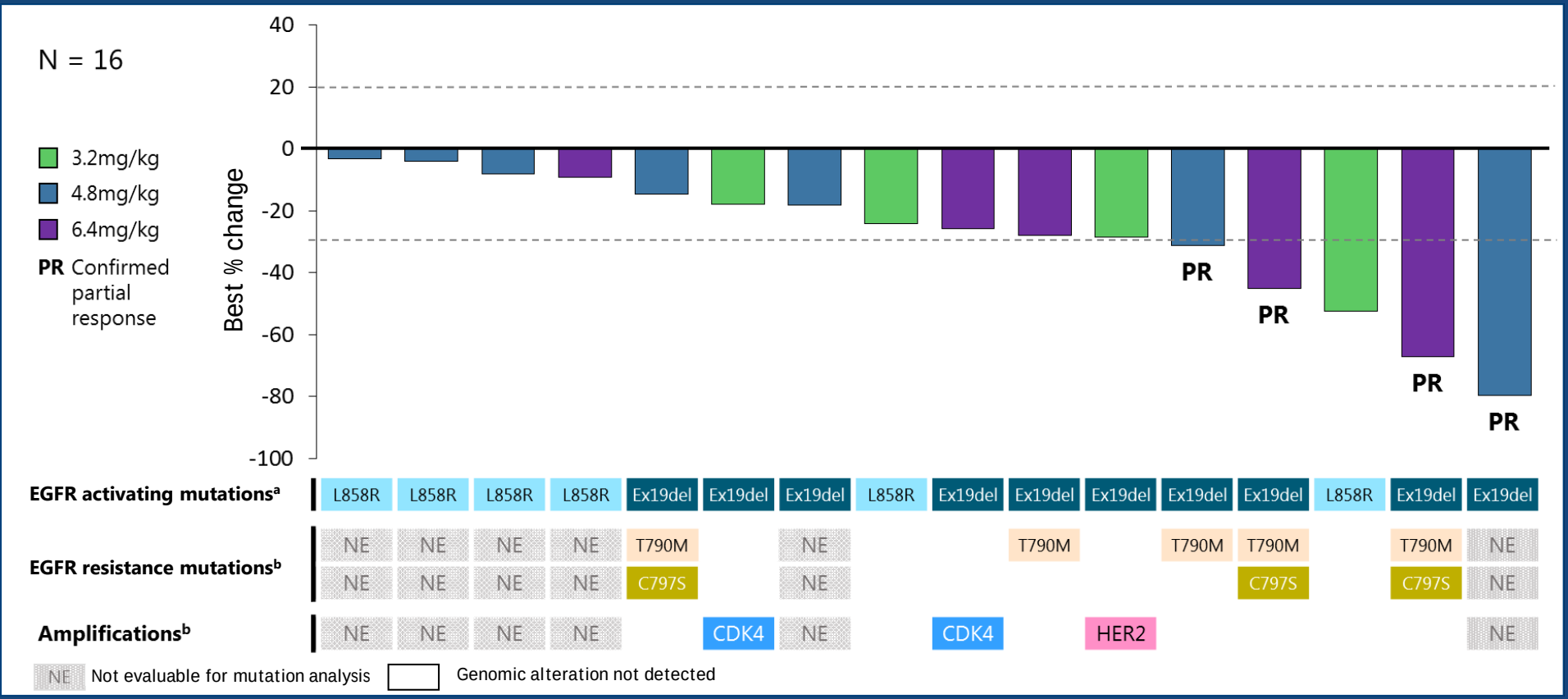
Median duration of exposure was 105 days (range: 21–336)

Summary	Dose escalation, n (%) (N = 23)[a]
TEAEs regardless of causality	23 (100.0)
Drug-related	22 (95.7)
Treatment-emergent SAEs regardless of causality	6 (26.1)
Drug-related	3 (13.0)
TEAEs leading to drug withdrawal/discontinuation	1 (4.3)
TEAEs leading to dose reduction	7 (30.4)
TEAEs leading to dose interruption	6 (26.1)
TEAEs leading to death	0

Data cutoff date of February 25, 2019. [a] Safety analysis set included all patients who received ≥1 dose of U3-1402. SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Jänne-P *et al.*, Abstract #9010, ASCO 2019

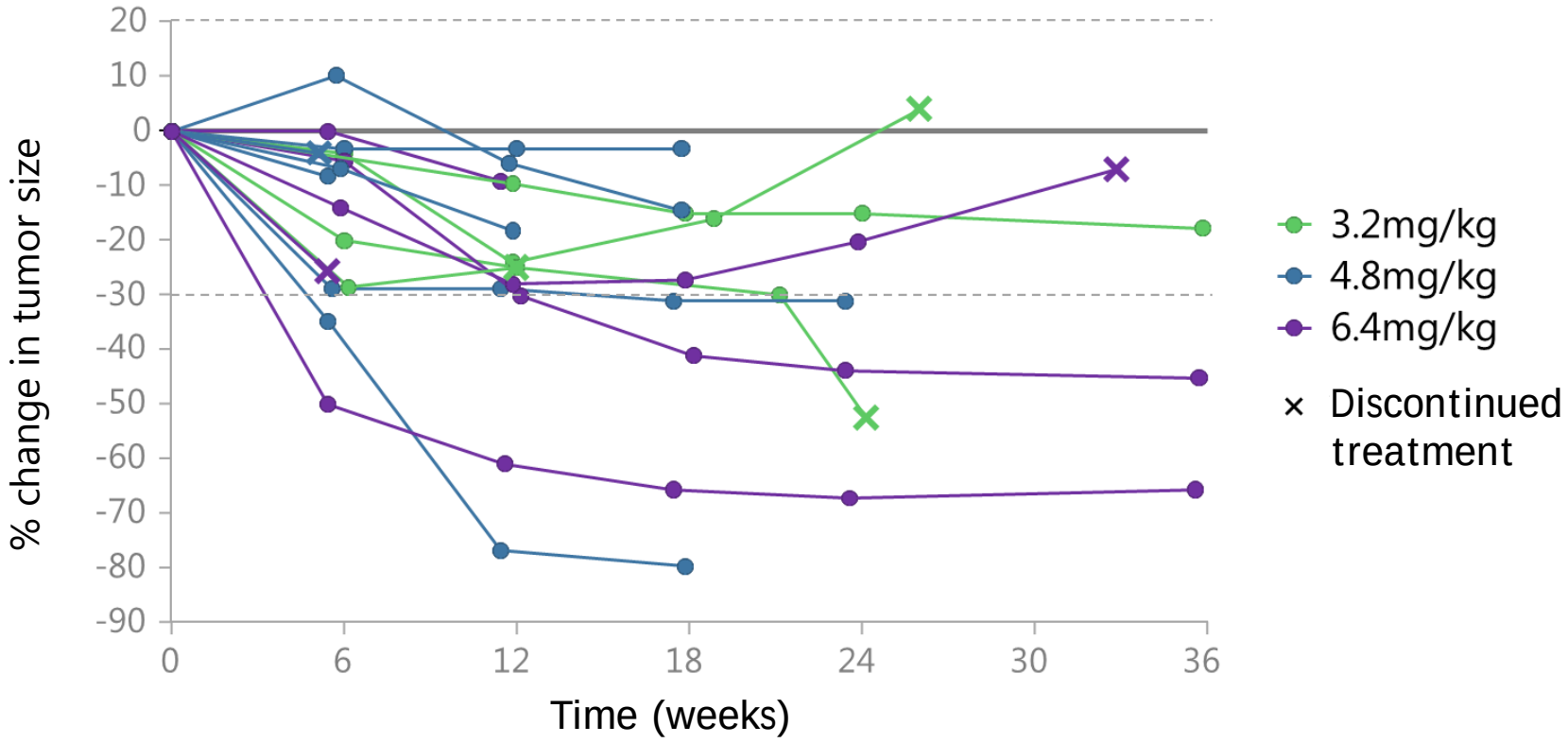
U3-1402 Antitumor Activity Across Diverse EGFR-TKI Resistance Mechanisms



Data cutoff date of February 25, 2019. Dotted lines denote 20% increase and 30% decrease in tumor size. Sixteen patients received ≥1 dose of U3-1402 and had pre- and post-treatment evaluable tumor assessments.
[a]Local testing as reported by the investigator. [b]Performed centrally using Oncomine Comprehensive assay v3 from formalin-fixed, paraffin-embedded tumor tissue.

Source: Jänne-P *et al.*, Abstract #9010, ASCO 2019

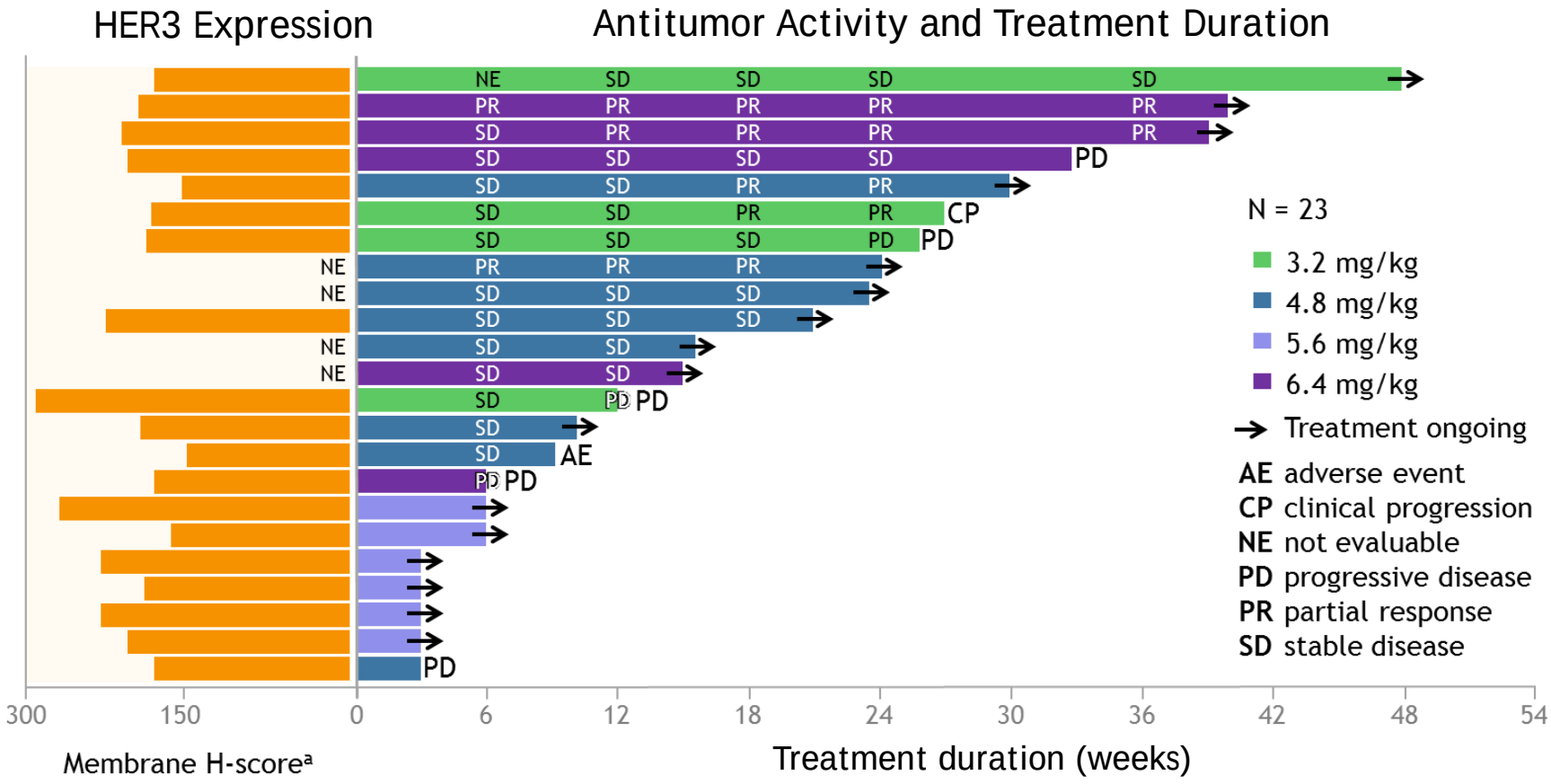
U3-1402 Antitumor Activity Over Time



Data cutoff date of February 25, 2019. Sixteen patients received ≥1 dose of U3-1402 and had pre- and post-treatment evaluable tumor assessments.
Dotted lines denote 20% increase and 30% decrease from baseline in tumor size over time.

Source: Jänne-P *et al.*, Abstract #9010, ASCO 2019

U3-1402 Treatment Duration

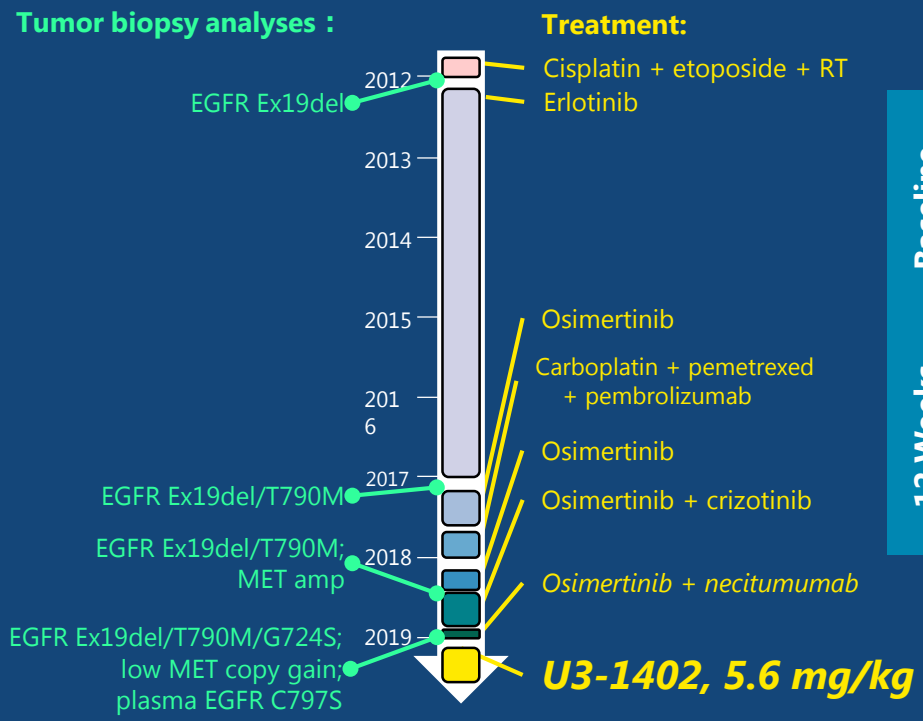


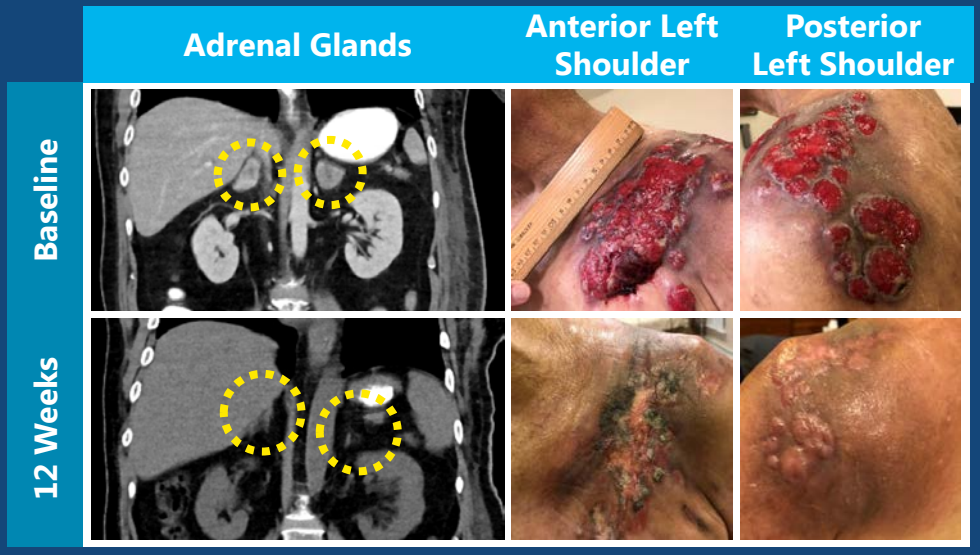
Data cutoff date of February 25, 2019. Safety analysis set included all patients who received ≥1 dose of U3-1402. [a]Membrane H-score is a composite of percentage of positively staining cells and intensity of individual cell staining. Scores range from 0–300. For patients with multiple H-scores, the highest number was used.

Source: Jänne-P *et al.*, Abstract #9010, ASCO 2019

U3-1402 Patient Case

65-year-old male NSCLC patient





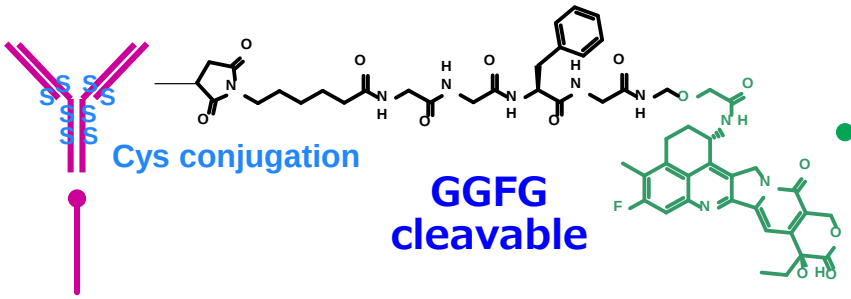
Patient of Dr. Mark Awad, DFCI

Source: Jänne-P *et al.*, Abstract #9010, ASCO 2019

DS-1062

DS-1062: Efficacy and Safety Balanced by Selecting DAR4

TROP2 ADC is designed to be best in class



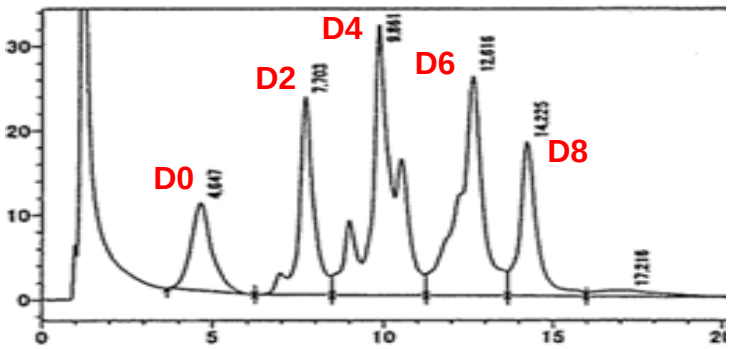
Antibody
Humanized anti-TROP2 monoclonal antibody (hIgG1)

Payload
Topoisomerase I inhibitor

Selective-DAR4 to protect safety margin

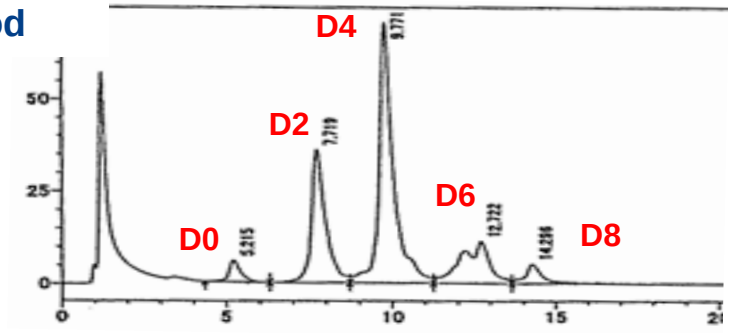
Non-selective DAR*4

HIC



Optimized conjugation method

Selective DAR4



*drug-antibody ratio

DS-1062: Comparison to Sacituzumab Govitecan

	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

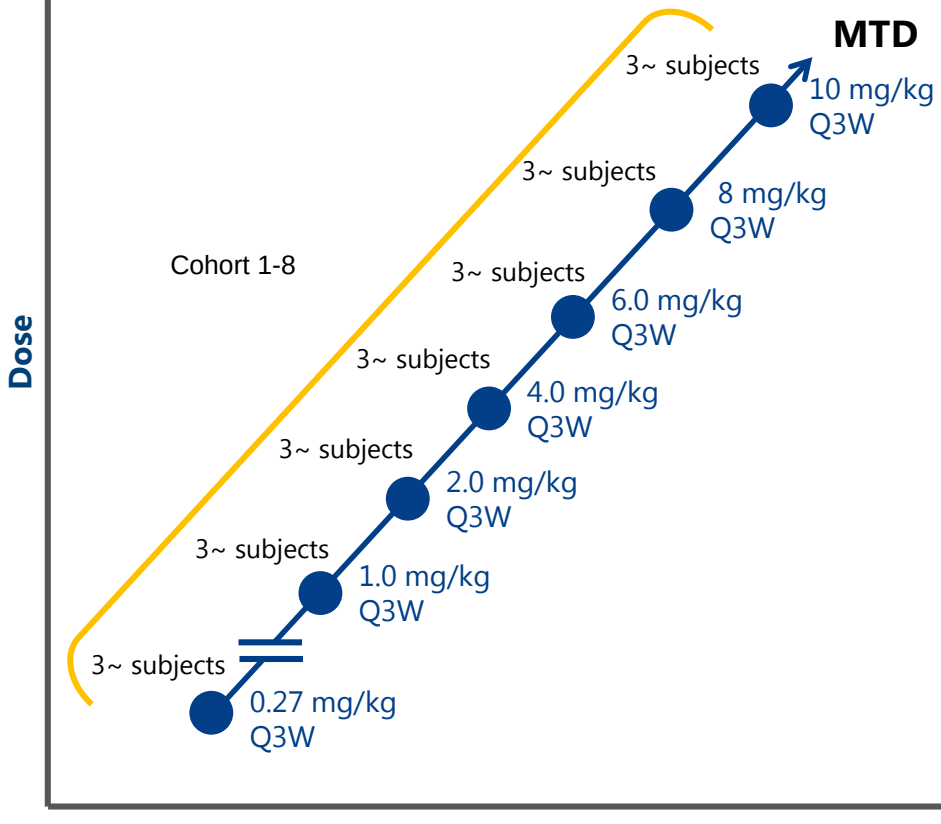
** Clin Cancer Res; 21(17) September 1, 2015

DS-1062: Relapsed NSCLC P1 Study Design

NSCLC ≥ 3rd line

Dose Escalation

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



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

IHC : immunohistochemistry, RDE: Recommended Dose for Expansion, POC : Proof of Concept, Q3W: every 3 weeks

DS-1062: TROP2 Targeted ADC, MTD Not Reached

- Safety Summary: number of patients with TEAEs (in ≥10% of patients), regardless of causality

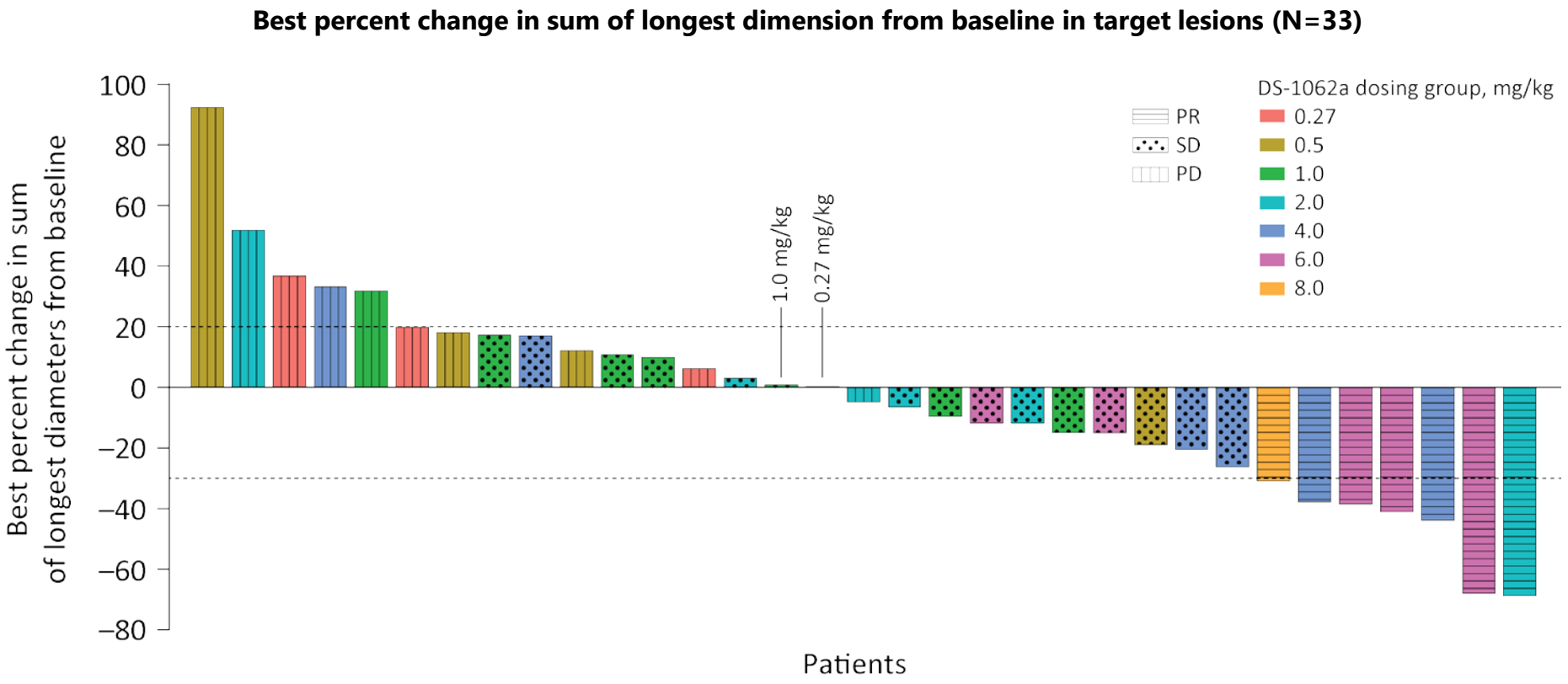
TEAE, n (%)	N=39	
	All grades	Grade ≥3[a,b]
Any TEAE	34 (87.2)	16 (41.0)
TEAE, by preferred term (in ≥10% of patients)		
Fatigue	13 (33.3)	2 (5.1)
Nausea	12 (30.8)	0
Anemia	9 (23.1)	0
Decreased appetite	9 (23.1)	0
Alopecia	8 (20.5)	0
Infusion related reaction	8 (20.5)	0
Constipation	6 (15.4)	0
Vomiting	6 (15.4)	0
Cough	5 (12.8)	0
Dyspnea	5 (12.8)	1 (2.6)
Rash	5 (12.8)	0
Diarrhea	4 (10.3)	0
Pain	4 (10.3)	1 (2.6)
Weight decreased	4 (10.3)	0

[a]TEAEs include 'uncoded (all grades: n=5, 12.8%; grade ≥3, n=1, 2.6%); [b]The majority of TEAEs were grade 3 (n=8; 20.5%), except for one grade 2 and 1 grade 5 TEAE (grade 5 sepsis; 6.0 mg/kg treatment group).
TEAE, treatment-emergent adverse event.

DS-1062: TROP2 Targeted ADC Anti-tumor Activity

Daiichi-Sankyo

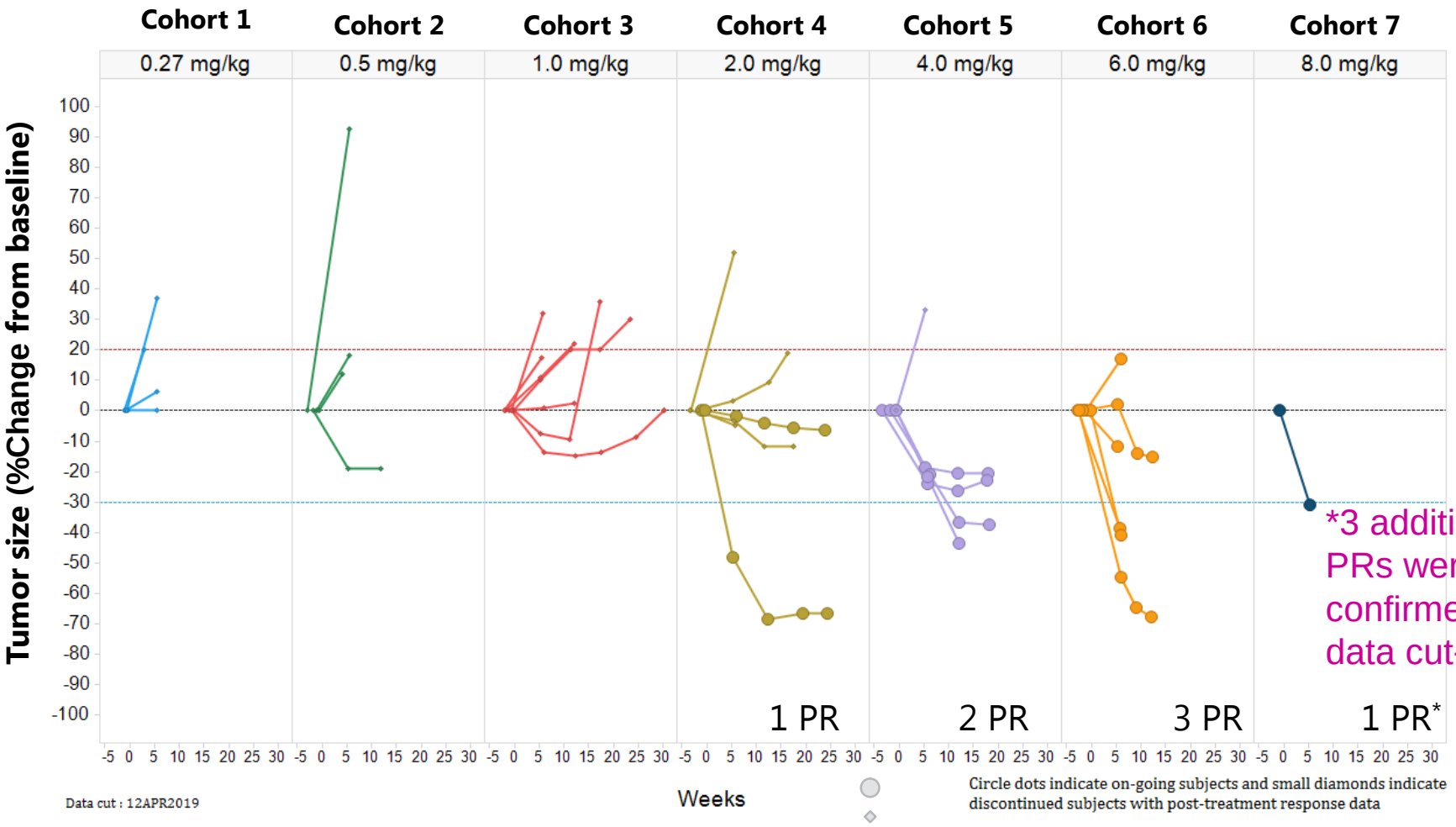
◆ Objective responses emerging at >2mg/kg dose



ASCO 2019 Abstract #9051

DS-1062: TROP2 Targeted ADC

- Dose / Effect Spider Plot (preliminary data April 12, 2019)



*3 additional PRs were confirmed after data cut-off

ASCO 2019 Abstract #9051

DS-3201

DS-1001

AML / HEM Franchise Progress

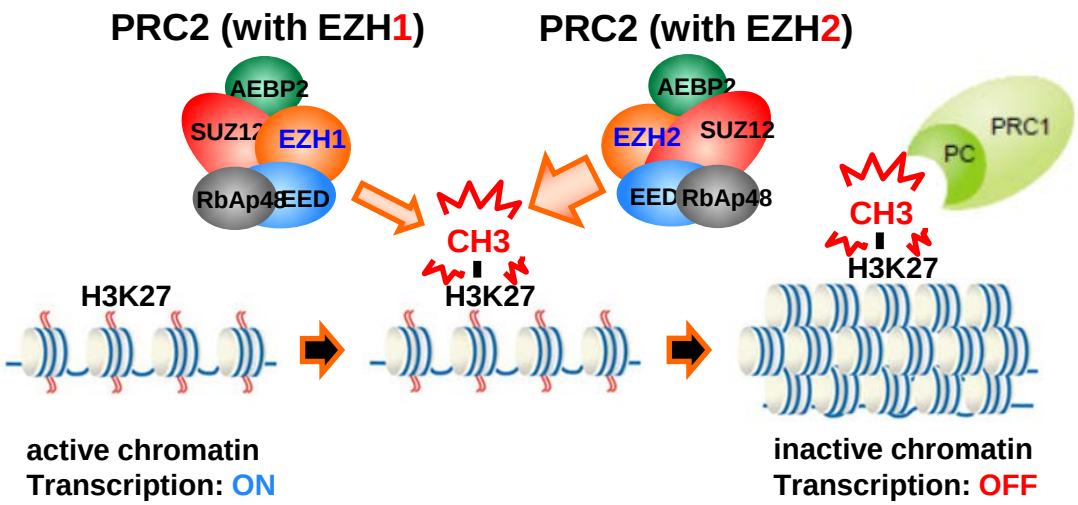
Quizartinib	• QuANTUM-First study (Newly Diagnosed FLT3-ITD AML) continues to accrue ahead of expectations; >90% enrolled
DS-3201 EZH1/2 inhibitor	• Granted SAKIGAKE designation for PTCL in Japan in April 2019 • Small-Cell Lung Cancer (SCLC) Phase 1 study initiated
DS-1001 IDH1m inhibitor	• Phase 1 results reported at ASCO (Abstract # 2004)
DS-3032 MDM2 inhibitor (milademetan)	• Dose escalation of P1 combination studies with quizartinib and azacitidine have started

DS-3201 (valemetostat): Dual EZH 1/2 Inhibitor

DS-3201

Potent and selective dual inhibitor of the histone methyltransferases (histone-modifying enzymes) EZH1 and EZH2 at histone H3 (H3K27)

A promising new epigenetic approach

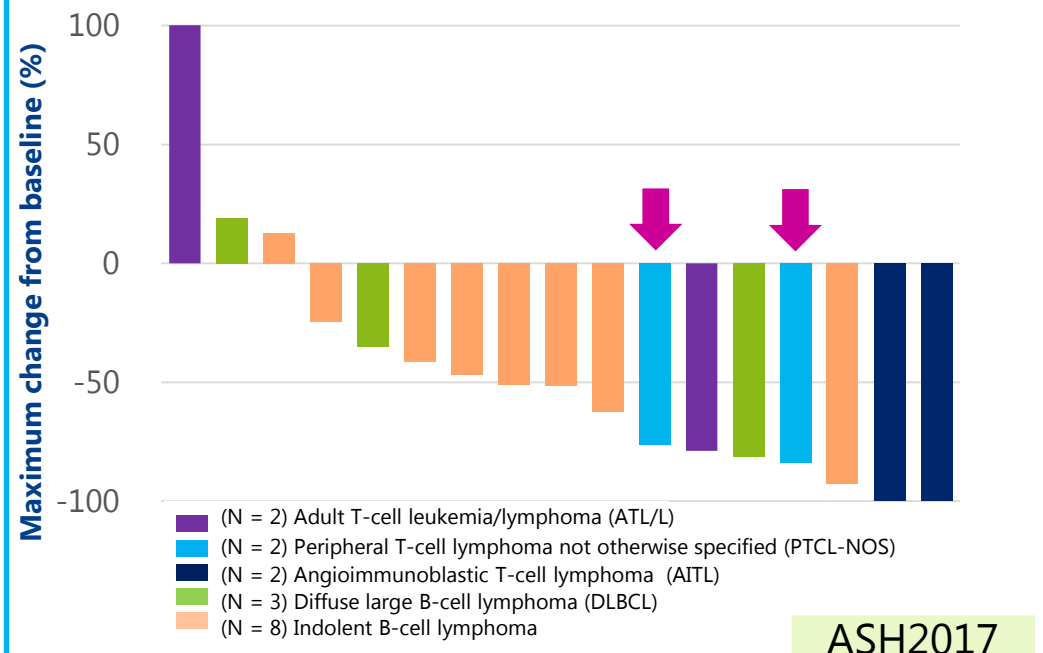


- Tri-methylation of H3K27 (H3K27me3) is negative regulator of tumor suppressor genes or cell differentiation genes
- **Dual inhibition of EZH1 and EZH2** is hypothesized to allow more potent blockade of hyper methylation of H3K27 and overcome compensatory mechanism between EZH1 and EZH2

SAKIGAKE Designation: DS-3201 PTCL

- Potential first-in-class **EZH1/2 dual inhibitor**
- Received **SAKIGAKE Designation** for **relapsed/refractory peripheral T-cell lymphoma (PTCL)** treatment based on the preliminary result of Phase 1 Non-Hodgkin lymphomas trial including PTCLs

Preliminary results in relapsed or refractory Non-Hodgkin Lymphoma



ASH2017

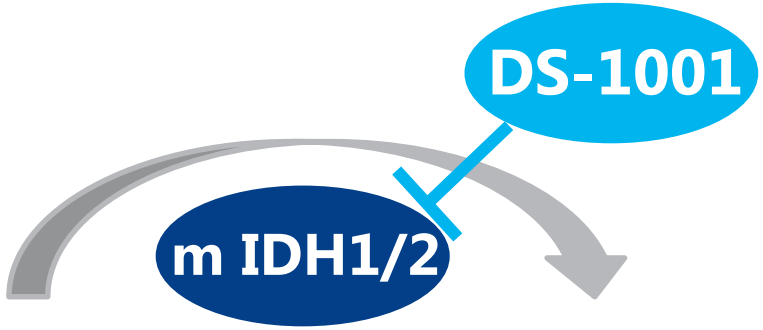
PTCL

- Non-Hodgkin lymphoma arising from T cells
- Tend to be aggressive and associated with poor prognosis, particularly for relapsed disease
- **High unmet medical needs** (very few treatment options)

Maruyama D, et al. ASH 2017. Abstract 4070

DS-1001：Mutant IDH1 Inhibitors

MOA



α-ketoglutarate
(α-KG)

(R)-2-hydroxyglutarate
(2-HG)

Annual incidence of diseases with IDH1 mutation

AML / Myelodysplastic syndrome
7500/yr
5-10% in total

Cholangio-carcinoma
1500/yr
15% in total

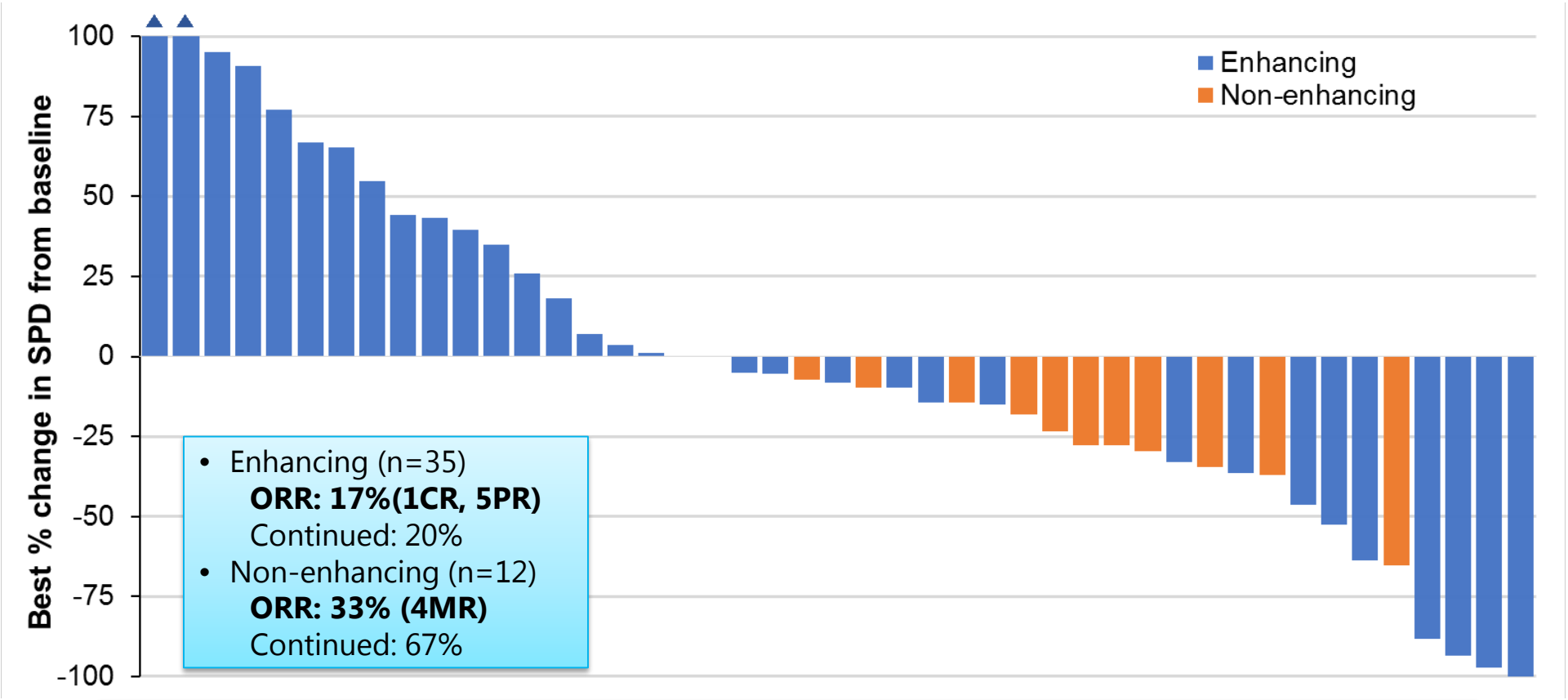
Glioma
11000/yr
~50% in total glioma

85% in low-gr glioma and secondary GBM

Chondro-sarcoma
4600/yr
70% in total

Numbers and circle siz3es indicate the estimated number of patients with IDH1m (annual incidence/year in JP/US/EU: our estimates)

DS-1001: Efficacy Best Percentage Change



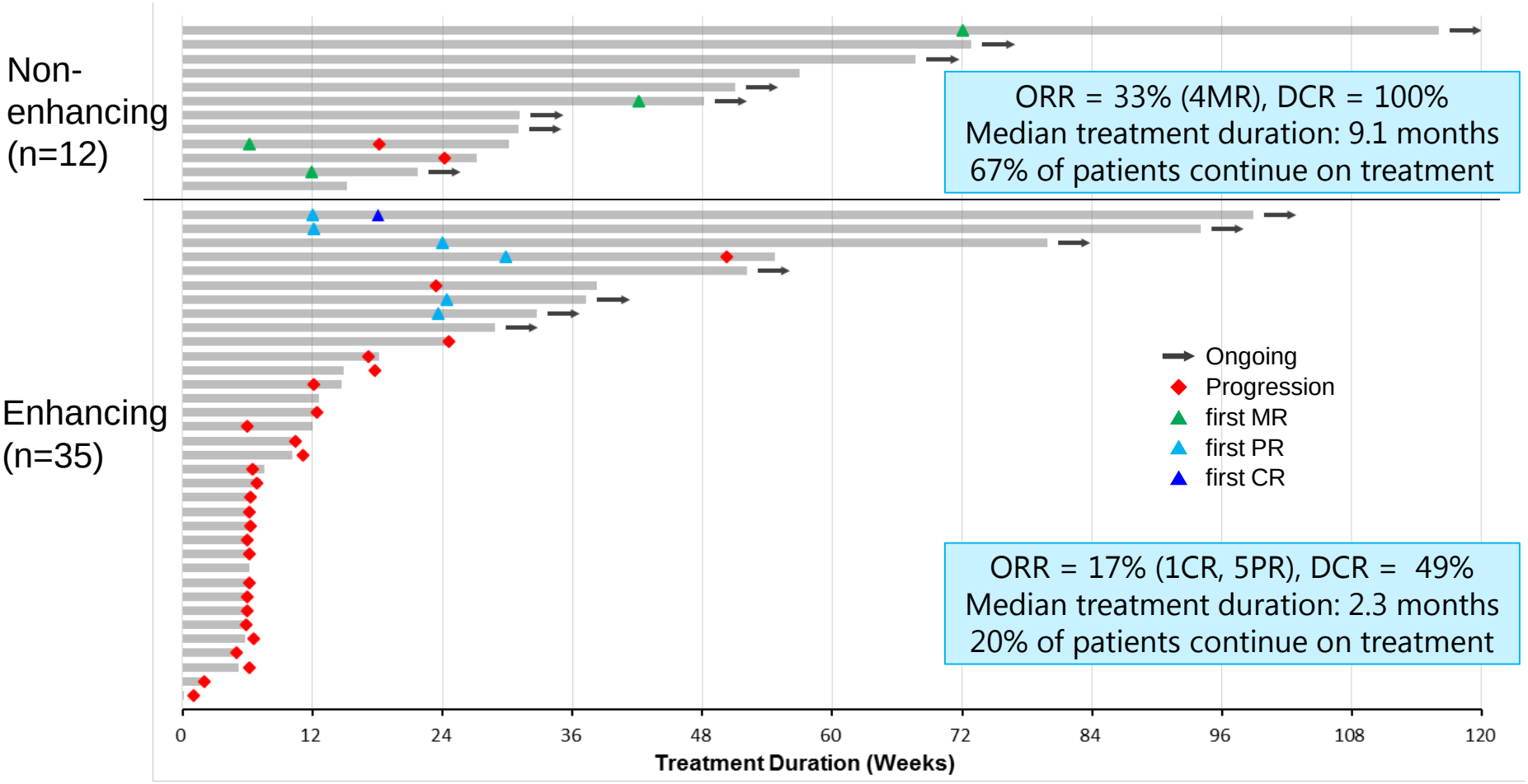
- Antitumor activity was observed in recurrent gliomas
- High response rates were also observed in contrast-enhanced and non-contrast-enhanced tumors

Source: Natsume-A *et al.*, Abstract #2004, ASCO 2019

DS-1001: Efficacy Treatment Duration and Time to Response

As of May 7, 2019

Daiichi-Sankyo



- Extended disease control was observed in the non-enhancing glioma (median treatment period 9.1 months, 67% of patients continued)
- Once responded, the duration of the reaction was quite long

Source: Natsume-A *et al.*, Abstract #2004, ASCO 2019

Summary

Major R&D Pipeline (Oncology)

As of June 2019

Daiichi-Sankyo

	Generic name/Project number (drug efficacy/mechanism of action)	Target Indication	Region	Stage
				Phase 1 / Phase 2 / Phase 3 / NDA/BLA
ADC Franchise	DS-8201 (anti-HER2 ADC)	BC (HER2 positive post T-DM1)	JP/US/EU/Asia	★ → 🏅 → ▶
		BC (HER2 positive vs T-DM1)	JP/US/EU/Asia	▶
		BC (HER2 low)	JP/US/EU/Asia	▶
		GC (HER2 expressing post trastuzumab)	JP/Asia	★ → 🏅
		CRC	JP/US/EU	▶
		NSCLC	JP/US/EU	▶
		BC and bladder cancer (with nivolumab)	US/EU	▶
	U3-1402 (anti-HER3 ADC)	BC	JP/US	▶
		NSCLC	US	▶
	DS-1062 (anti-TROP2 ADC)	NSCLC	JP/US	▶
AML/HEM Franchise	Quizartinib/AC220 (FLT3 inhibitor)	AML (relapsed/refractory)	JP/US/EU/Asia	▶ → 🏅
		AML (1st line)	JP/US/EU/Asia	▶
	DS-3032 (MDM2 inhibitor)	Solid tumor	JP/US	▶
		AML	JP/US	▶
	DS-3201 (EZH1/2 inhibitor)	PTCL	JP	▶ → 🏅
		ATL/L	JP	▶
		AML, ALL	US	▶
		SCLC	US	▶
	PLX2853 (BRD4 inhibitor)	AML, solid cancer	US	▶
	DS-1001 (IDH1m inhibitor)	Glioma	JP	▶
	Axi-Cel® (anti-CD19 CAR-T cells)	BCL	JP	★ → ▶
Breakthrough Science	Pexidartinib (CSF-1/KIT/FLT3 inhibitor)	TGCT	US/EU	▶ → 🏅
	DS-1647 (G47Δ virus)	Glioblastoma multiforme	JP	★ → 🏅
	DS-1205 (AXL inhibitor)	NSCLC [with osimertinib (Asia) gefitinib (JP)]	JP/Asia	▶

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, ATL/L: adult T-cell leukemia/lymphoma, BCL: B-cell lymphoma, NSCLC: non-small cell lung cancer, PTCL: peripheral T-cell lymphoma, TGCT: tenosynovial giant cell tumor

★: Projects in the field of oncology which are planned for registration application based on the results of P2 studies, 🏅 designated as breakthrough therapy (FDA)/SAKIGAKE (JP)

Upcoming Milestones

DS-8201

Breast — DESTINY-Breast01

Pivotal Phase 2 in HER2 positive mBC
- US: BLA submission in 1H FY2019
- JP: NDA submission in 2H FY2019

Gastric — DESTINY-Gastric01

Pivotal Phase 2 in HER2 positive mGC
- JP: NDA submission 1H FY2020

Quizartinib

AML — QUANTUM-R

Relapsed/Refractory *FLT3*-ITD AML
- US: FDA PDUFA August 25, 2019
- JP: expecting approval in June 2019
- EU:review on track for 2H FY2019 approval

Pexidartinib

TGCT — ENLIVEN

Tenosynovial Giant Cell Tumor
- US: FDA PDUFA August 3, 2019
- EU: review on track 1H FY2020

DS-1647 (G47Δ)

GBM

Glioblastoma multiforme
- JP: NDA submission in 1H FY2019

Thank you for listening

Daiichi Sankyo / DS Cancer Enterprise is a Global Pharma Innovator with strengths in Science and Technology, and will have a pipeline to meet various UMNs of patients

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