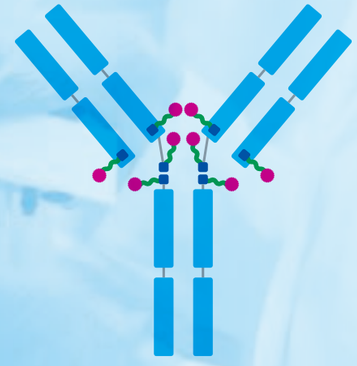
Special Issue

Cancer

(Antibody Drug Conjugate: ADC)



This section of the Special Issue cover the basic knowledge on cancer, basic background on antibody drug conjugate (ADC), characteristics of Daiichi Sankyo's proprietary ADC technology, and data on our clinical stage projects of ADC Franchise such as *DS-8201*, *U3-1402*, and *DS-1062*. This Special Issue will provide an understanding of the characteristics of Daiichi Sankyo's ADC technology and the reasons why we are targeting cancer.

1 Cancer

Cancer is one of the diseases with the high prevalence and mortality both in Japan and worldwide. Every year, approximately 14 million people are newly diagnosed with cancer across the world. In Japan, cancer has been the leading cause of death since 1981, while in 2012, annual cancer deaths reached approximately 380,000 people. Given these statistics, cancer has a devastating impact on human life and health.

▶ Cancer death (all types of cancer) 2012 (Thousands/year)

Worldwide	Japan	U.S.	Europe
8,202	379	617	1,993

Source: GLOBOCAN 2012, "estimated cancer incidencem motarity and prevalence worldwide in 2012"

▶ Number of new patients, number of patients with recurrent disease, 5-year survival (2017)

		Japan	U.S.	5 European countries
Breast cancer	Newly diagnosed cancer (n)	95,000	321,000	259,000
	Recurrent cancer (n)	11,000	34,000	37,000
	5-Year survival (%)	91%	85%	–
Gastric cancer	Newly diagnosed cancer (n)	144,000	26,000	55,000
	Recurrent cancer (n)	25,000	11,000	25,000
	5-Year survival (%)	62%	25%	–
Non-small-cell lung cancer	Newly diagnosed cancer (n)	114,000	191,000	193,000
	Recurrent cancer (n)	41,000	65,000	68,000
	5-Year survival (%)	35%	18%	–
Colorectal cancer	Newly diagnosed cancer (n)	152,000	143,000	235,000
	Recurrent cancer (n)	18,000	32,000	54,000
	5-Year survival (%)	64%	56%	–

Source: CancerMPact (Synix Inc./Kantar Health)

2 Cancer Treatment

(1) Cancer treatment

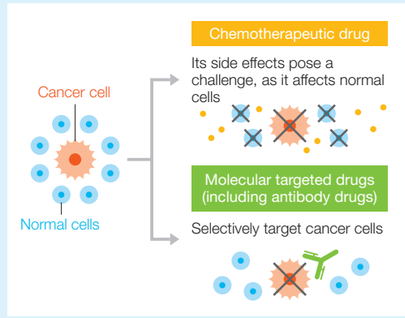
Cancer treatments are divided into two categories: systemic therapy and local therapy. Local therapy consists of surgery and radiotherapy.

	Type	Methodology	Characteristics
Systemic therapy	Drug therapy	Attacks cancer cells with drugs	• A mainstay of treatment if local therapy is inappropriate such as hematological cancer or metastatic disease
Local therapy	Surgery	Removes cancer surgically	• Cancer can be cured if it remains in the primary lesion
	Radiotherapy	Eliminates cancer cells with radiation	• Exerts therapeutic effects without surgically removing organs • Sometimes combined with drug therapy and surgery

(2) Drug therapy (chemotherapeutic drugs and molecular targeted drugs)

Previously, chemotherapeutic drugs played a principal role in drug therapy. Chemotherapeutic drugs are small molecule drugs that produce therapeutic effects on highly proliferative cells. They also affect to maintain function, such as gastrointestinal and bone marrow cells, This impact on normal cells are the cause of most of the chemotherapy-induced side effects.

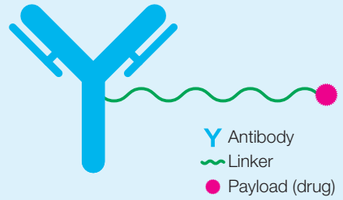
On the other hand, molecular targeted drugs target genes and proteins that are highly expressed in cancer cells. They are less likely to affect rapidly dividing normal cells, Although, molecular targeted drugs have their own unique side effects, they have relatively fewer side effects than conventional chemotherapeutic drugs.



3 What are Antibody Drug Conjugates (ADCs)?

(1) What are ADCs?

ADC, which is short for Antibody Drug Conjugate, is an agent that covalently combines an antibody with a payload, chemotherapeutic drug, through a molecule called linker. Chemotherapeutic drugs and antibody drugs each have their own advantages and disadvantages, but ADCs have the potential to skillfully compensate for the disadvantages of both drugs.



Chemotherapeutic drug
- Potent effects (cytocidal activity)
- Low target selectivity
- Problem of side effects

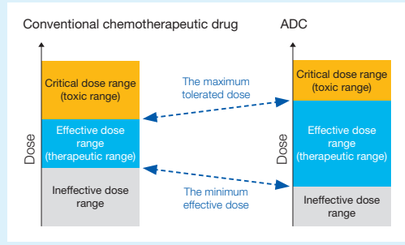
+

Antibody (molecular targeted drug)
- High target selectivity
- Relatively fewer side effects
- Sometimes insufficient efficacy

↓

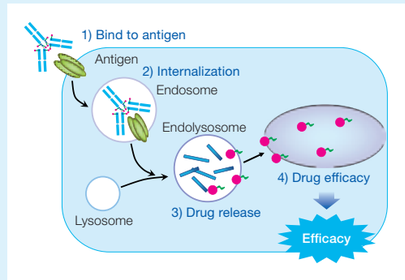
Antibody Drug Conjugate

With conventional chemotherapeutic drugs, the minimum effective dose required for killing cancer cells is high, whereas the maximum tolerated dose is low, because their toxicity hampers substantial dose escalation. Thus, a narrow therapeutic range is a problem for these drugs. By employing ADC technologies, the chemotherapeutic agent can be delivered more to cancer cells. As a result, the drug exerts its therapeutic effects at a lower dose, and because the amount of chemotherapeutic drug reaching normal cells is decreased, the maximum tolerated dose is higher, so that the therapeutic range becomes wider.



(2) Mechanism of action

1) ADC binds to an antigen on the surface of a cancer cell
2) Subsequently, ADC is taken up into the cancer cell by internalization
3) Lysosomes in the cancer cell play a role in cleaving linker in the cancer cell, resulting in release of payload (drug)
4) The released payload exerts its therapeutic effects



4 Characteristics of Daiichi Sankyo's ADCs

As of July 2018, 4 ADCs have been approved for marketing. Daiichi Sankyo scientists pursued the goal of developing ADC technology which overcomes difficulties of preceding ADCs.

Existing ADCs	Daiichi Sankyo's ADC technology
Linker issues • Drug-antibody ratio (DAR)*: 2 to 4 • Toxicity and/or reduced efficacy due to released payloads in the blood	Characteristic 1: high drug-antibody ratio (DAR) • 8 at the maximum
	Characteristic 2: highly stable linker • Payloads are less likely to be detached in the blood, which reduces the risk of exposing normal tissue to toxicity.
	Characteristic 3: selective linker cleavage • Linkers are selectively cleaved in cancer cells to release the payload.
Payload issues • Most of the ADCs use tubulin polymerization inhibitors • No treatment option for tumors unresponsive/ resistant to existing ADCs. • Concern for relatively long half-life which may affect normal cells.	Characteristic 4: unique and potent payload • Newly developed DNA topoisomerase I inhibitor
	Characteristic 5: bystander effect • The drug can exert its therapeutic effects even in an environment where various cancer cells are mixed.
	Characteristic 6: payload with a short half-life in the blood • The payload, even if released, is quickly eliminated because of its short half-life in the blood

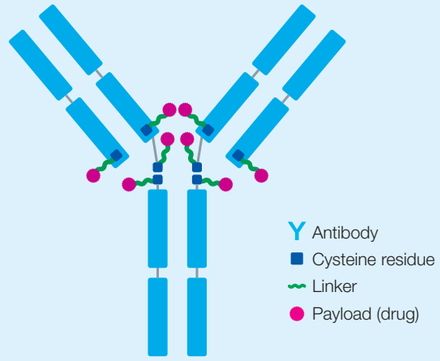
* Average number of drugs linked to each antibody

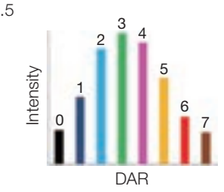
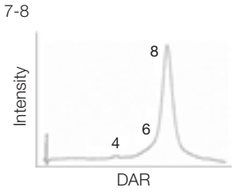
(1) Characteristic 1: high drug-antibody ratio (DAR)

The drug-antibody ratios (DARs) for currently approved ADCs range between 2 and 4, whereas Daiichi Sankyo's ADCs can load a maximum number of payloads of 8. Historically, ADCs bearing more payloads per antibody cause aggregation. But Daiichi Sankyo's ADC causes no aggregation, even though it has high payload loading. Furthermore, we have technology to control DAR according to antigen expression and internalization rates.

Also,for currently approved ADCs, the number of payloads varies. There are antibodies with no payload loaded, or those with only one or two payloads, leading to insufficient drug efficacy.

Daiichi Sankyo's ADC technology enables maximum of eight payloads per antibody homogeneously.



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

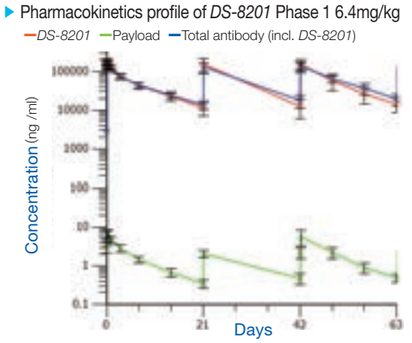
* *Kadcyla* BLA

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

(2) Characteristic 2: highly stable linker

ADC technology is currently characterized by its cancer cell-specific efficacy, in which the linker plays an important role. If the linker is unstable, ADC is degraded and the payloads are released in the human blood plasma, thereby reducing efficacy and potentially causing side effects. As shown in the graph below, the pre-clinical study has confirmed the long-term stability of Daiichi Sankyo's ADCs. Moreover, pharmacokinetic analysis of the phase 1 study has confirmed in vivo stability of ADCs as well. The graph on the right shows that the linker is stable by indicating that the blue line representing the blood concentration of the antibody closely overlaps with the red line representing the blood concentration of *DS-8201*. If the unstable linker releases the payload, the red line and the blue line diverge extremely from each other.

▶ Pharmacokinetics profile of *DS-8201* Phase 1 6.4mg/kg



▶ In vitro Plasma Stability of *DS-8201*

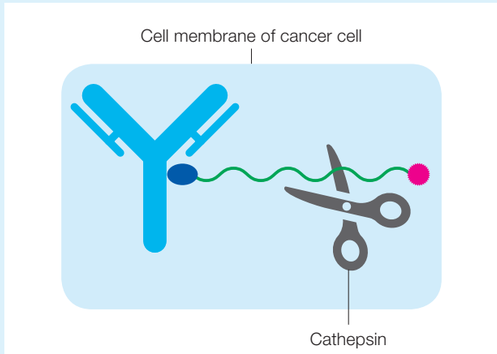
Reference information

	Days	Theoretical release rate
*T-DM1**	4	–20
DS-8201	7	1.1

* *Kadcyla* BLA

(3) Characteristic 3: selective linker cleavage

The linker must be stable in the blood, and readily release its payload once internalized into the cancer cell after it binds to the cancer-cell antigen. Some existing ADCs have linkers that are cleaved by proteinases in lysosomes found not only in cancer cells but also in other parts. In this case, the linkers may also be cleaved in extracellular environment. On the other hand, to release the payload, the linker of Daiichi Sankyo's ADCs is cleaved by cathepsins, which are highly expressed in cancer cells; therefore, the possibility of the linker being cleaved in parts other than cancer cells is extremely low. Concerning the cleavage site of ADC, the linker of some existing ADCs does not have the cleavage site on linker, whereas *DS-8201* has the cleavage site at appropriate location of linker, which efficiently releases payload in cancer cells.



(4) Characteristic 4: unique and potent payload

The payload of Daiichi Sankyo's ADCs is *DXd*, a topoisomerase I inhibitor. Daiichi Sankyo has an experience of developing *irinotecan*, which has been launched for the treatment of cancers including colorectal cancer and lung cancer. As the in vitro activity of *DXd* is approximately 10 times as potent as that of SN-38 (active metabolite of irinotecan), *DXd* exerts potent effects at a relatively low dose.

Furthermore, the pre-clinical pharmacology study has demonstrated that *DXd* is effective in cancer cells less sensitive or resistant to payload of *T-DM1*, the standard of care for breast cancer.

SN-38 Active metabolite of *irinotecan*	*DXd* Payload on *DS-8201*
TOPO1 IC_{50}*1 2.78μM*2	TOPO1 IC_{50} 0.31μM

Effective at approximately one-tenth of the dose

*1 TOPO1 IC_{50}: A concentration required for 50% inhibition of topoisomerase Inhibition of topoisomerase prevents DNA synthesis and division of cancer cells

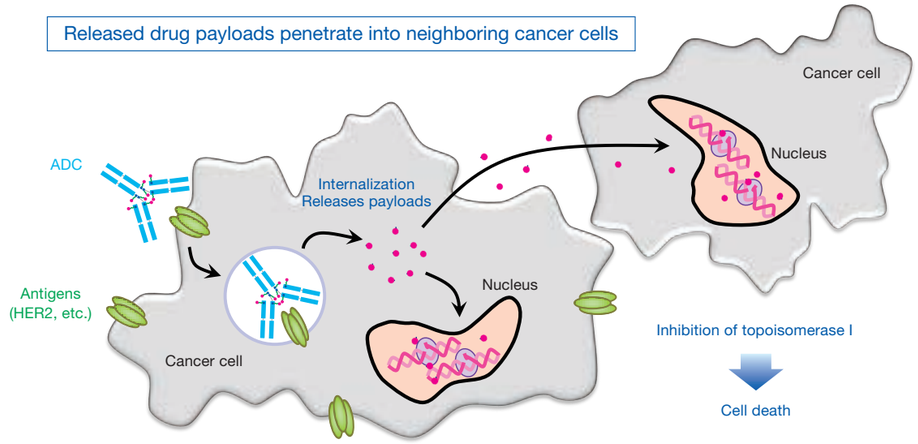
*2 μM: micromolar, a unit of concentration

(5) Characteristic 5: bystander effect

The *DXd* payload is designed to have higher lipophilicity and membrane permeability than the payload of *T-DM1*. The payload is released from the ADC in cancer cells, penetrates the membrane and exerts effects on the neighboring cancer cells. This is known as Daiichi Sankyo ADC's "bystander effect". In a cancer lesion, antigen expression-positive cancer cells and antigen expression-negative cancer cells are present concomitantly. By this bystander effect, the drug is also expected to exert an efficacy on tumors with a large number of cancer cells of negative expressing of antigen.

To validate the clinical relevance of this proposed effect, we are currently conducting translational research.*

* Translational research: the research, method, and process of deepening the understanding of diseases and drug interaction mechanisms through the mutual use of information and samples in clinical and non-clinical studies.



(6) Characteristic 6: payload with a short half-life in the blood

In general, the increased blood concentration of free drug payloads released from ADC has potential to cause side effects. Although, Daiichi Sankyo's drug payload is less likely to be released because of stable linker compared to other ADCs, that the drug payload is designed to be eliminated quickly from the blood (a short half-life in the blood) even when released.

Payloads	Half-life in rats (time)
*DXd**1 (payload of Daiichi Sankyo's ADCs)	0.9
*DM1**2 (payload of *T-DM1*)	3.3-10

*1 In-house report
*2 *KADCYLA* BLA

5 Daiichi Sankyo's ADC Projects

At present, Daiichi Sankyo has seven ADC projects for different antibody targets with the same linker and payload.

The compounds at the clinical stage are *DS-8201*, *U3-1402*, and *DS-1062*, and those at the pre-clinical stage are *DS-7300*, *DS-6157*, and *DS-6000*.

Among these compounds, *DS-8201* and *U3-1402* have achieved a certain level of effects at the clinical stage, and we will provide detailed information mainly on the results.

▶ ADC Franchise

Clinical stage

Project (target)	Preceded indications	Discovery	Pre-clinical	Phase 1	Pivotal
DS-8201 (HER2)	Breast cancer, Gastric cancer, Colorectal cancer, Non-small-cell lung cancer				
U3-1402 (HER3)	Breast cancer Non-small-cell lung cancer				
DS-1062 (TROP2)	Non-small-cell lung cancer				
DS-7300 (B7-H3)	Solid tumors				
DS-6157 (undisclosed)	Gastrointestinal stromal tumor (GIST)				
DS-6000 (undisclosed)	Kidney cancer Ovarian cancer				
TA-MUC1	Solid tumor				

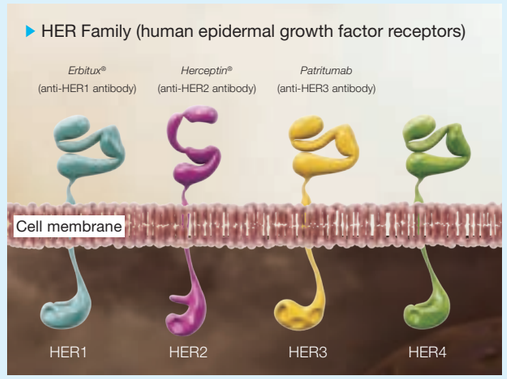
(1) *DS-8201 (anti-HER2-ADC)*

DS-8201 is an anti-HER2 antibody conjugate using our proprietary ADC technologies, which is our first and flagship ADC that has proceeded to the clinical phase.

a) What is HER2?

HER2 is a glycoprotein found on the cell surface. It has a structure similar to the epidermal growth factor receptor (HER1). It is a receptor tyrosine kinase associated with cell proliferation. HER2, which is overexpressed on the surface of cancer cells, such as those of breast cancer, gastric cancer, colorectal cancer, lung cancer, and bladder cancer, activates signal transmission and induces cancer cell proliferation.

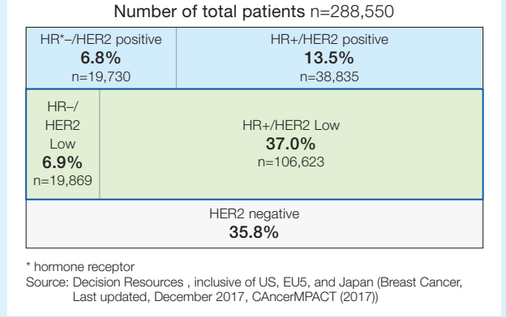
▶ HER Family (human epidermal growth factor receptors)



b) HER2 low expression

To date, cancers have been classified into two types by immunostaining that detects HER2 expression: HER2-positive and HER2-negative. However, it has been revealed that HER2 is expressed in some types of breast cancers classified as HER2-negative (IHC2+/ISH-, IHC1+). These are called HER2 low expression (HER2 Low) by us. It is said that approximately 44% of breast cancer patients have HER2-low tumors, and at the moment, no medications are approved for the indication of HER2-low tumors.

The phase 3 study in patients with HER2 low breast cancer, which will be started in fiscal 2018, aims to address this part of unmet medical needs.



* hormone receptor
Source: Decision Resources , inclusive of US, EU5, and Japan (Breast Cancer, Last updated, December 2017, CAncerMPACT (2017))

▶ What are IHC and ISH?

Staining methods used in pathology.
- Captures antigens detected such as proteins and nucleic acids in tissues and cells using a probe.
- A technique that enables microscopic observation through staining using pigments and enzymes bound to the probe.

IHC: abbreviation of immunohistochemistry
- Observes protein expression levels including HER2 (surface of cancer cell)

ISH: abbreviation of in situ Hybridization
- Observes amplification levels of HER2 gene (DNA), etc. (nuclear of cancer cell)

Furthermore, it has also been revealed that HER2-negative cancer cells classified as IHC0 by immunostaining show HER2 expression that is not completely zero, but at a certain level (below 10%). We will perform further translational research including a companion diagnostics (CDx) to increase the HER2 measurement sensitivity so that *DS-8201* can be a treatment option for such patients.

Commonly Used	HER2 Status	DS terminology for Future Use
HER2 positive or HER2 overexpressing	IHC 3+	HER2 positive (HER2 overexpressing)
	IHC 2+/ISH +	
HER2 negative	IHC 2+/ISH -	HER2 low
	IHC 1+/ISH -	
	IHC 0	HER2 negative

c) *DS-8201* development plan and clinical studies started in fiscal 2017

In the phase 1 study, which was started in September 2015, *DS-8201* was administered to approximately 250 patients with HER2-expressing breast cancer, gastric cancer, colorectal cancer, and lung cancer. Although they have a history of treatment with multiple drugs, many of them showed a complete response irrespective of cancer types.

Based on the interim results from the phase 1 study, *DS-8201* was granted Breakthrough Therapy Designation for the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have been

treated with *trastuzumab* and *pertuzumab* and have disease progression after *ado-trastuzumab* (*T-DM1*) by the U.S. FDA in August 2017.

Since autumn in 2017, a number of new studies have been started.

For breast cancer, a pivotal phase 2 study in patients with HER2-positive breast cancer who had already received treatment with the existing therapeutic agent of *T-DM1* was started in October 2017.

For gastric cancer, a pivotal phase 2 study in patients with HER2-overexpressing gastric cancer after treatment with the existing therapeutic agent of *trastuzumab* was started in November 2017. Concerning gastric cancer, *DS-8201* was granted SAKIGAKE Designation for unresectable advanced and relapsed gastric cancer with HER2-overexpression by the Ministry of Health, Labour and Welfare in March 2018.

In addition, phase 2 studies in patients with HER2-expressing colorectal cancer and a phase 2 study in those with HER2-overexpressing or HER2-mutated non-small-cell lung cancer were also started in March 2018 and May 2018, respectively.

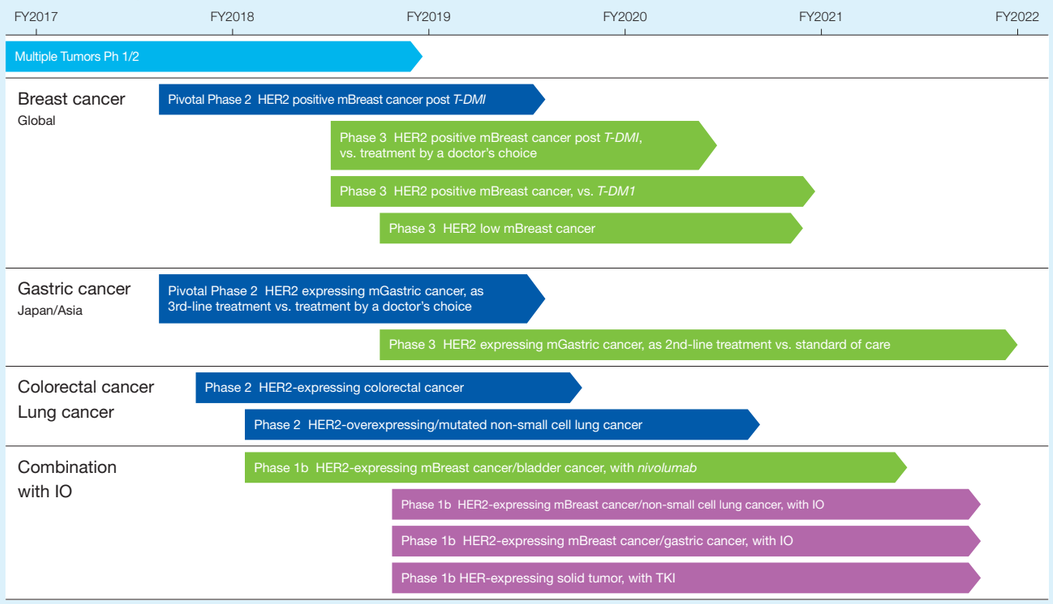
Various studies including the phase 3 study of previously mentioned HER2-low breast cancer are planned to be started sequentially after 2018.

Concerning breast cancer, we are aiming to submit the regulatory applications globally in fiscal 2020, while we are making every effort to submit them even earlier within fiscal 2019. For gastric cancer, we plan to file the application firstly in Japan in fiscal 2020.

▶ Development status

2015.9	2017.8	Fall 2017	2018.3	2020
Phase 1 started	Granted Breakthrough Therapy Designation by the FDA	Phase 2 started	Granted SAKIGAKE Designation by the Ministry of Health, Labour and Welfare	NDA application planned
Studies started for breast and gastric cancer. The breast cancer study was conducted in Japan and in the U.S., and the gastric cancer study was conducted in Japan.	Granted Breakthrough Therapy Designation by the U.S. FDA for the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have been treated with *trastuzumab* and *pertuzumab* and have disease progression after *ado-trastuzumab* (*T-DM1*).	The phase 2 studies started for breast and gastric cancer. The NDA application will be submitted after the results of these studies are obtained.	Granted SAKIGAKE Designation by the Ministry of Health, Labour and Welfare for unresectable advanced and relapsed gastric cancer with HER2 overexpression	

▶ *DS-8201*: Study schedule



Blue : studies initiated by July 2018
Green : studies planned to start in fiscal 2018
Pink : studies planned to start in future

d) Clinical results of *DS-8201*

As mentioned above, the phase 1 study of *DS-8201* was started in August 2015, and the interim data were presented at numerous medical conferences.

▶ ADC Franchise

Period	Medical conference	Details of the presentation
October, 2016	European Society for Medical Oncology (ESMO)	Breast cancer, gastric cancer
June, 2017	American Society of Clinical Oncology (ASCO)	Breast cancer, gastric cancer
September, 2017	European Society for Medical Oncology (ESMO)	Colorectal cancer, lung cancer, and others
December, 2017	San Antonio Breast Cancer Symposium (SABCS)	Breast cancer
January, 2018	American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO G.I.)	Gastric cancer
June, 2018	American Society of Clinical Oncology (ASCO)	Breast cancer, gastric cancer, and others

The interim results from a phase 1 study conducted for multiple cancers including gastric cancer, colorectal cancer, and lung cancer as well as breast cancer were presented at ASCO in June 2018.

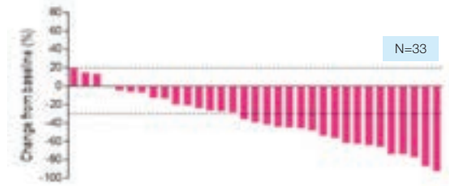
The graph below is waterfall chart presenting percent change of response from baseline, pre-treatment with *DS-8201*.

Each bar represents each individual patient's result in order of high to low tumor shrinkage rate from right to left.

Tumor shrinkage is observed in a high proportion of patients, both in HER2 positive breast cancer and HER2 low expressing breast cancer.

▶ HER2 positive breast cancer

▶ HER2 low breast cancer

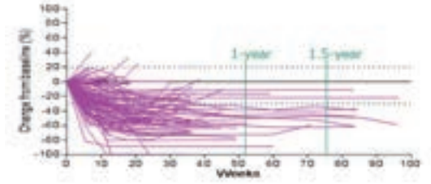


The graph in upper right (↗) is called spider plot, and shows the percentage change in tumor size after the treatment with *DS-8201* and the duration of treatment. Each line represents each individual patient's result. In the group of patients with high HER2 positive, tumor shrinkage was observed at an early stage after starting the treatment, and more patients had prolonged therapeutic effects. Of them, treatment effects maintained over 1.5 years in some patients.

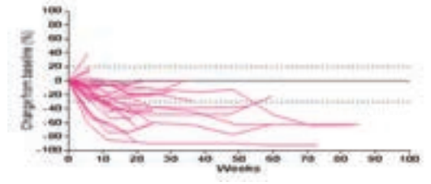
In the group of patients with HER2 low as well, although the onset of treatment effects was slower than those with high HER2 positive, tumor shrinkage was found as the treatment period extended.

This study result has opened up a possibility for providing the treatment option of *DS-8201* to patients with HER2-low breast cancer, whose number is twice as many as those with HER2-positive breast cancer.

▶ HER2 positive breast cancer



▶ HER2 low breast cancer



DS-8201 has so far shown a favorable efficacy in HER2-positive breast cancer, and in this study, the drug yielded the overall response rate*1 of 50.0% in HER2-low breast cancer, which is equivalent to 54.5% in HER2-positive breast cancer.

▶ Overall Response Rate (ORR)*1 and Disease Control Rate*2 (DCR) in confirmed patients (5.4 or 6.4 mg/kg)

	ORR N(%)	DCR N(%)
HER2 positive breast cancer	54/99 (54.5)	93/99 (93.9)
HER2 low breast cancer	17/34 (50.0)	29/34 (85.3)
HER2 positive gastric cancer	19/44 (43.2)	35/44 (79.5)
HER2-expressing colorectal cancer, lung cancer, and others	12/31 (38.4)	26/31 (83.9)

*1 Ratio of patients in which tumors had shrunken by more than 30% or completely disappeared.

*2 The percentage of patients with stable disease (a change of lesion size ranging from an increase of <20% to a decrease of <30%) plus those with ORR.

Regarding adverse events of special interest, laboratory abnormalities of liver and heart function were generally low grade, asymptomatic and, patients continued to receive *DS-8201* treatment.

Concerning interstitial lung disease and pneumonitis, five fatal cases were observed. An external committee responsible for evaluating interstitial lung disease is now in the process of conducting evaluation in each case.

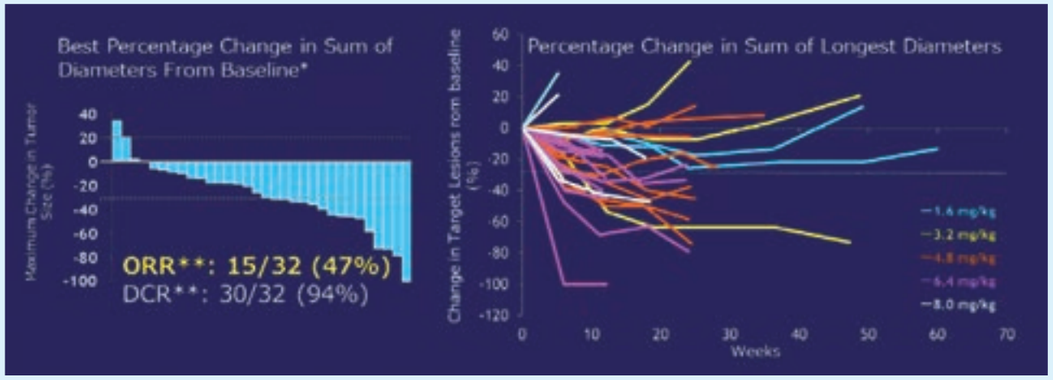
(2) *U3-1402* (anti-HER3-ADC)

U3-1402 is an anti-HER3-ADC, in which *patritumab* (an anti-HER3 antibody) is loaded with our proprietary linker and payload. HER3, present on the cell surface, is a receptor tyrosine kinase classified into the HER family as with HER2 (see P37). It is overexpressed on the surface of breast cancer cells, lung cancer cells and other tumor types. HER3-positive breast cancer patients are suggested to have poor prognosis.

In HER3-positive refractory/metastatic breast cancer patients, the phase 1/2 study was started in December 2016, for which we presented the interim efficacy and safety data at the American Society of Clinical Oncology (ASCO) in June 2018. As for preliminary efficacy, the overall response rate and disease control rate were 47% (15/32) and 94% (30/32), respectively.

Concerning safety, although bone marrow or liver function test abnormalities were found in 34 patients receiving 1.6 to 8.0 mg/kg body weight every three weeks, the maximum tolerated dose had not yet been reached. The efficacy data of *U3-1402* obtained from this study is similar to the initial data of *DS-8201* which was presented at the meeting of the European Society for Medical Oncology (ESMO) in 2016. Accordingly, we believe that Daiichi Sankyo's ADC technologies are applicable even after changing antibodies.

Furthermore, the phase 1 study in patients with advanced EGFR-mutated non-small cell lung cancer has been ongoing since January 2018.



(3) *DS-1062* (anti-TROP2-ADC)

DS-1062 is an anti-TROP2-ADC, in which an anti-TROP2 antibody is loaded with our proprietary linker and payload. TROP2 is overexpressed on the membrane of various cancer cells including those of lung cancer, and is known to be associated, in particular, with the promotion of cancer cell proliferation, metastasis, and the acquisition of drug resistance. The phase 1 study in patients with recurrent/progressive non-small cell lung cancer was started in February 2018, Once safety and efficacy are confirmed with non-small cell lung cancer, additional evaluation is planned on other TROP2 over-expressing solid tumor patients.

(4) Other ADCs

DS-7300 is an anti-B7-H3-ADC, in which an anti-B7-H3 antibody is loaded with our proprietary linker and payload. B7-H3 is known to be expressed in esophageal cancer, lung cancer, endometrial cancer and prostate cancer. A pre-clinical study is currently underway with a view to entering the clinical phase in fiscal 2019.The pre-clinical research is underway for *DS-6157* targeting gastrointestinal stromal tumor (GIST), and *DS-6000* targeting kidney cancer and ovarian cancer (target antigens of both ADCs are not disclosed).

In any of these compounds, the same linker and payload as *DS-8201*, *U3-1402*, and *DS-1062* are used.

(5) Creation of new ADCs by partnership

As part of a strategy to maximize the business value of our ADC technologies, we have entered into a licensing agreement with Glycotope for the research, development and commercialization of *Gatipotuzumab* (anti TA-MUC1 antibody) using the ADC technologies.

Gatipotuzumab is a humanized monoclonal antibody, which specifically binds to TA-MUC1 that is highly expressed in many types of cancers including ovarian cancer, lung cancer, and breast cancer.

In this way, we will also create further partnerships in the future.

COLUMN

Breast Cancer

The current status for breast cancer and the existing standard of care

Breast cancer is the most common cancer in women, and the numbers of new and recurrent breast cancer cases in Japan, U.S. and Europe in 2017 are provided in the figure to the right.

Data published by the Ministry of Health, Labour and Welfare shows that the number of patients who died of breast cancer in Japan continues to rise and reached approximately 14,000 in 2016, more than three times higher than 35 years ago, with breast cancer ranked first as the cause of death in women aged 30 to 64 years.

▶ Breast cancer patients by stage (new, recurrence) 2017 (N)

	Japan		U.S.		Europe	
	New	Recurrence	New	Recurrence	New	Recurrence
Stage 0	12,018	53	62,802	336	—	—
Stage I	40,456	386	132,652	1,879	120,442	551
Stage II	32,912	714	83,711	2,035	87,211	1,963
Stage III	7,340	1,047	26,195	3,464	35,134	4,241
Stage IV	2,153	8,811	15,636	26,677	15,717	30,683
Total	94,879	11,011	320,996	34,391	258,504	37,438

Breast cancer is generally classified into the stages below, and surgery is the standard of care. Pre-operative or post-operative drug therapy is given to some patients to prevent cancer recurrence. In addition, in patients in whom surgical procedures are inappropriate because of metastases and other conditions, drug therapy is principally used.

Stage 0	Non-invasive cancer (including Paget's disease)
Stage I	The lump (tumor) in the breast is 20 mm or smaller and has not spread to the lymph nodes
Stage II	The lump is between 20 mm-50 mm and has not spread to the lymph nodes or the lump is 20 mm or smaller and has spread to the lymph nodes
Stage III	The lump has spread to several lymph nodes The lump is larger than 50 mm and has spread to the lymph nodes The lump has spread to skin and chest wall, inflammatory breast cancer
Stage IV	The lump has spread to other organs (lung, bone, liver, brain, etc.)

In drug therapy for breast cancer, tests are performed to look at receptors on cancer cells first, and select anticancer drugs appropriate for the receptor status.

Subtype	Treatment option (example)
HER2 positive	HER2 targeted drugs
HR* positive / HER2 negative	Hormone therapy
HR negative / HER2 negative (triple negative)	Chemotherapy

* hormone receptor

Breast cancer treatment has significantly improved compared to previous treatments with the emergence of *trastuzumab*, *pertuzumab*, and *T-DM1*, which are HER2 targeted drugs. Notwithstanding, as shown in the table above, not a few patients still experience recurrence. Furthermore, we believe that there still remain many challenges to be dealt with (unmet medical needs) such as patients refractory to treatment with existing drugs and attenuation of drug efficacy due to acquired drug resistance.

DS-8201 is an ADC that acts on the HER2 like *trastuzumab* and other drugs, and it has become apparent that it has the potential to produce a certain effect as well on breast cancer cells not overexpressing HER2. We are continuing our development in order to respond to unmet medical needs that cannot be resolved with existing approved drugs, and we are working to deliver the drug to patients as soon as possible.