Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Science & Technology Day 2024

DAIICHI SANKYO CO., LTD.

December 16th, 17th 2024

Forward-Looking Statements

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Science & Technology Day 2024 Presenters

Sunao Manabe
Executive Chairperson & CEO

Ken Takeshita
Head of Global R&D

Mark Rutstein
Head of Global Oncology Clinical Development

Dale Shuster
Head of Global Precision Medicine

Hiroto Kashiwase
Head of Global Technology

2024 Prix Galien USA Award

ENHERTU®
Daiichi Sankyo
& AstraZeneca

Daiichi Sankyo and AstraZeneca have been awarded The Galien Foundation 2024 Prix Galien USA Award for Best Biotechnology Product for ENHERTU®

World ADC Awards

Most Promising Clinical Candidates

2019 HER2 Directed ADC

2020 TROP2 Directed ADC

2021 HER3 Directed ADC

2024 B7-H3 Directed ADC

2024 CDH6 Directed ADC

All of the 5DXd ADCs have been awarded "Most Promising Clinical Candidate"

12 Breakthrough Therapy Designations

Agenda

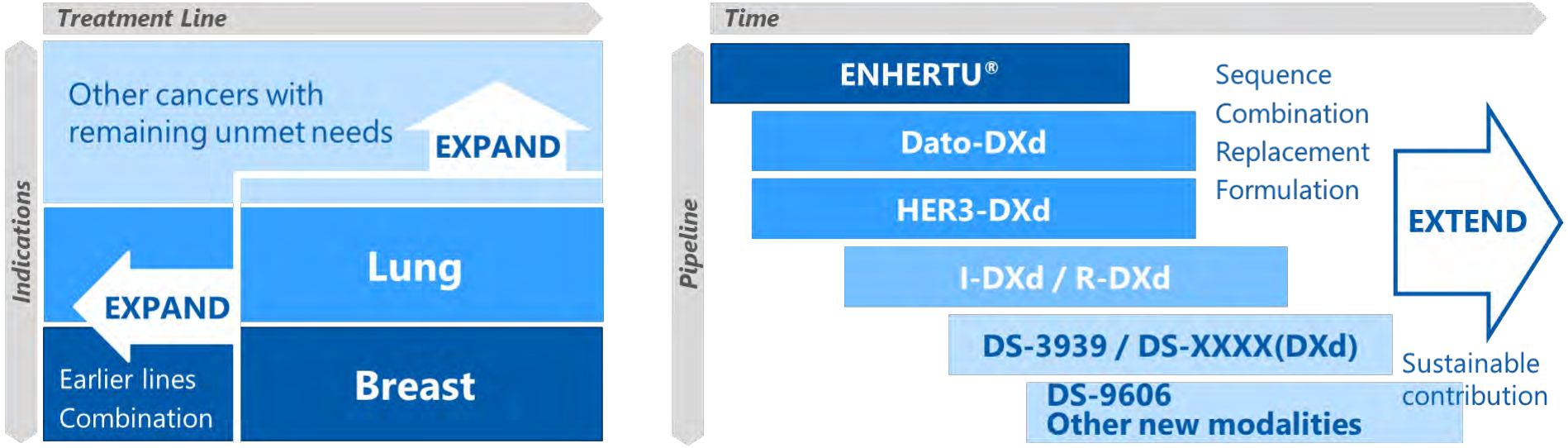
1. Opening
2. R&D Update
3. Clinical Progress
4. Translational Research
5. ADC Manufacturing & Supply
6. Q&A

Agenda

1. Opening
2. **R&D Update**
3. Clinical Progress
4. Translational Research
5. ADC Manufacturing & Supply
6. Q&A

EXPAND & EXTEND to deliver our technology to more patients

EXPAND and EXTEND



- Establish and expand DXd ADC therapies in **Breast** and **Lung** cancers
- **Go Earlier:** explore early lines of therapy/ stage of diseases; replace chemotherapy
- **Go Wider:** into new diseases beyond currently focusing areas to serve more patient needs

- Address unmet needs **after ENHERTU®** treatment
- Seek effective **treatment sequencing, novel combination, or formulation** to enhance efficacy and improve treatment
- **Grow early pipeline** following 5DXd ADCs to contribute to more patients in the future

Our Breast Cancer Strategy

To deliver transformative therapies that extend and improve the lives of all patients with Breast Cancer

- **Elevate Treatment Standards**
  - Leverage current DXd ADC portfolio to improve outcomes for patients treated with cytotoxic therapies.
  - Introduce the next generation of ADC platforms.

- **Expand the impact of our innovative pipeline**
  - Advance into patients segments currently not treated with cytotoxic therapies using combination strategies.
  - Develop new technologies to address patient segments not eligible for cytotoxic therapies.

- **Personalize Patient Care**
  - Leverage innovative technologies to tailor therapies for diverse patient subgroups to ensure personalized and effective treatment options

Breast Cancer

Major Progress since R&D day 2023

EXPAND & EXTEND

Daiichi-Sankyo

Pioneer & lead in HER2 low and ultralow BC

EXPAND

- DESTINY-Breast06 met its primary endpoint PFS in HR+/HER2 low BC (chemo naïve) in Apr 2024
- ENHERTU® demonstrated clinically meaningful PFS also in HER2 ultralow BC
- Under regulatory review in Japan, US and EU (US PDUFA date: February 1, 2025)

Go earlier

EXPAND

- TLR anticipated in FY2024 for TROPION-Breast02
- TLR anticipated in FY2025 H1 for DESTINY-Breast11
- TLR anticipated in FY2025 for DESTINY-Breast05 and DESTINY-Breast09

Proceed with Dato-DXd in HR+/HER2- BC 2L+ as primary indication

EXPAND

- Disclosed TROPION-Breast01 OS in Oct 2024
- Under regulatory review in Japan, US, EU and China
  (US PDUFA date: January 29, 2025)

Enhance pipeline value by combining with in-house assets

EXTEND

- DXd ADCs and valemetostat*
- ENHERTU® and DS-1103

*combination studies in other cancers are also ongoing

BC: breast cancer, HR: hormone receptor, OS: overall survival, PDUFA: prescription drug user fee act, PFS: progression-free survival, TLR: top line results

5DXd ADCs

Establish and Expand DXd ADCs to Address the Broader Spectrum of Breast Cancer

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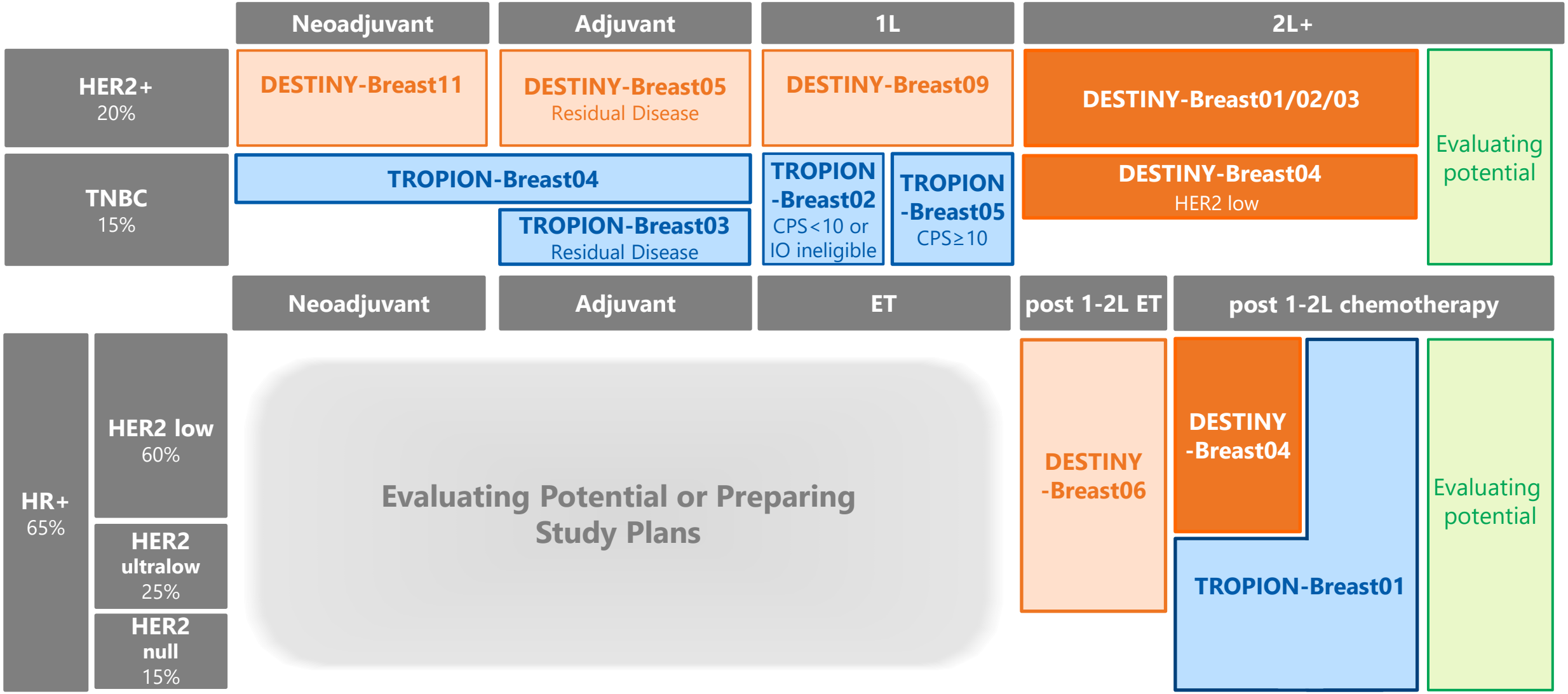


Launched | On-going | ENHERTU® | Dato-DXd | HER3-DXd, 1103, Valemetostat

- Pivotal studies only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

CPS: combined positive score; ET: endocrine therapy; HR: hormone receptor; IHC: immunohistochemistry, IO: immune oncology, TNBC: triple-negative breast cancer

Our Lung Cancer Strategy

Deliver practice-changing medicines to meet evolving unmet needs in lung cancer for a broad set of distinct patient types by harnessing the depth of the Daiichi Sankyo portfolio

- Provide superior 2L+ treatments and differentiated combinations in **metastatic NSCLC with DXd ADCs as the foundational treatment**
- Leverage the innovation in DXd ADCs **to move into biomarker-selected patients and early-stage NSCLC**
- Identify **novel therapeutic approaches for extensive-stage SCLC** to address significant unmet need

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer

Lung Cancer

Major Progress since R&D day 2023

EXPAND & EXTEND

Daiichi-Sankyo

Be the first TROP2 directed ADC in NSCLC

EXPAND

- Announced TROPION-Lung01 OS in May 2024
- Withdrawal of the application for NSQ NSCLC 2/3L based on TROPION-Lung01 in the US
- New submission for accelerated approval for EGFRm NSCLC based on pooled TROPION-Lung05, TROPION-Lung01 and TROPION-PanTumor01 in US in Nov 2024
- Granted Breakthrough Therapy Designation for EGFRm NSCLC in the US in Dec 2024

Add HER3-DXd as a potential new treatment option for EGFR mutated NSCLC

EXPAND

- Received CRL for HERTHENA-Lung01 from FDA in Jun 2024 and working closely with FDA and manufacturer to solve the issues
- HERTHENA-Lung02 met its primary endpoint in Sep 2024

Maximize value with new combination studies

EXTEND

- **NSCLC**: Combination with alliance partner's assets looking ahead to future SOCs (TROPION-Lung10, TROPION-Lung12, TROPION-Lung14 and TROPION-Lung15)
- **SCLC**: Collaboration with US Merck* for MK-6070 and started combination study with I-DXd

Initiated pivotal study for I-DXd

EXPAND

- IDeate-Lung02 (Ph3, ES-SCLC, FSD: Aug 2024)

Go earlier

EXPAND

- DESTINY-Lung04: TLR anticipated in FY2025
- AVANZAR: TLR anticipated in CY2025 H2

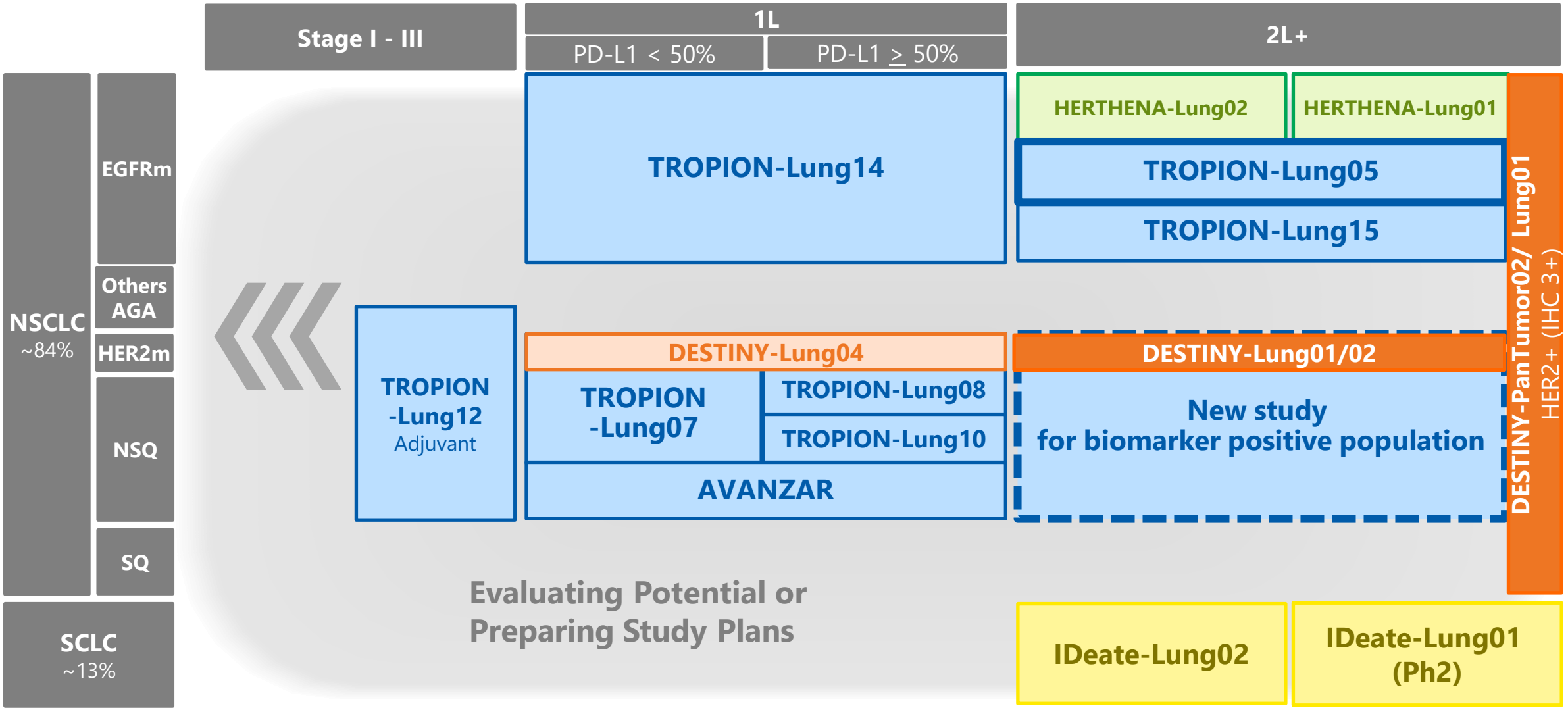
CRL: complete response letter, ES-SCLC: extensive-stage small cell lung cancer, FSD: first subject dosed, NSCLC: non-small cell lung cancer, NSQ: non-squamous, OS: overall survival, SOC: TLR: top line results

* Merck & Co., Inc., Rahway, NJ, USA

5DXd ADCs

Establish and Expand DXd ADCs to Address the Broad Spectrum of Lung Cancer

Daiichi-Sankyo



Launched | On-going | Planning | ENHERTU® | Dato-DXd | HER3-DXd | I-DXd

- Pivotal studies and major Ph2 only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

AGA: actionable genomic alteration, IHC: immunohistochemistry, NSQ: non- squamous, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, SQ: squamous

Others

Major Progress since R&D day 2023

Cancer other than BC and LC, cross-cancer initiatives

Daiichi-Sankyo

Expand indications of ENHERTU® beyond BC and LC

EXPAND

- ENHERTU® obtained indication for HER2+ (IHC3+) solid tumors 2L+ in the US in Apr 2024
- DESTINY-BTC01 in HER2 expressing BTC 1L started in Aug 2024

Explore potential of DXd ADCs in additional cancers

EXPAND

- HERTHENA-PanTumor01 (FSD: Mar 2024)
- IDeate-PanTumor02 (FSD: May 2024)
- REJOICE-PanTumor01 (Anticipated FSD: FY2024 H2)

Initiated pivotal study in OVC

EXPAND

- REJOICE-Ovarian01
  (Ph2/3, platinum-resistant OVC, FSD: Apr 2024)

Foster next-generation therapeutics

EXTEND

- First data presentation of DS-9606 (anti-CLDN6 ADC) at ESMO 2024
- Approval of valemetostat for r/r PTCL in Japan in Jun 2024

Develop a new formulation for patient convenience

EXTEND

- Planning to develop ENHERTU® subcutaneous injection in collaboration with Alteogen Inc., Korea

BC: breast cancer, BTC: biliary tract cancer, ESMO: European Society for Medical Oncology, CLDN6: claudin-6, IHC: immunohistochemistry, FSD: first subject dosed, LC: lung cancer, OVC: ovarian cancer, PTCL: peripheral T-cell lymphomas, r/r: relapse or refractory

Daiichi Sankyo Research Institutes for External Collaboration

DS Research Laboratories
Tokyo, Japan (Shinagawa, Kasai)

10+Research laboratories
(Wet/Dry)

new

DS Research Institute Munich
Located in Daiichi Sankyo Europe

DS Research Institute Boston
Located in CIC Cambridge @245 Main

new

Our Research Institute activities will accomplish the following objectives by deploying top scientists from Research function

- **Form networks** and approach technologies that drive scientific paradigm shifts
- Undertake **sponsored research**, foster startup incubation, and drive technology acquisition
- **Cultivate talent** to enhance global insights and perspectives

Agenda

1. Opening
2. R&D Update
3. **Clinical Progress**
4. Translational Research
5. ADC Manufacturing & Supply
6. Q&A

Clinical Progress

- Medical Congress Highlights
- DXd ADCs in brain metastases
- ENHERTU® early line studies in BC
- Analysis of drug-related ILD in Dato-DXd
- Early clinical stage development

Clinical Progress

Medical Congress Highlights

- DXd ADCs in brain metastases
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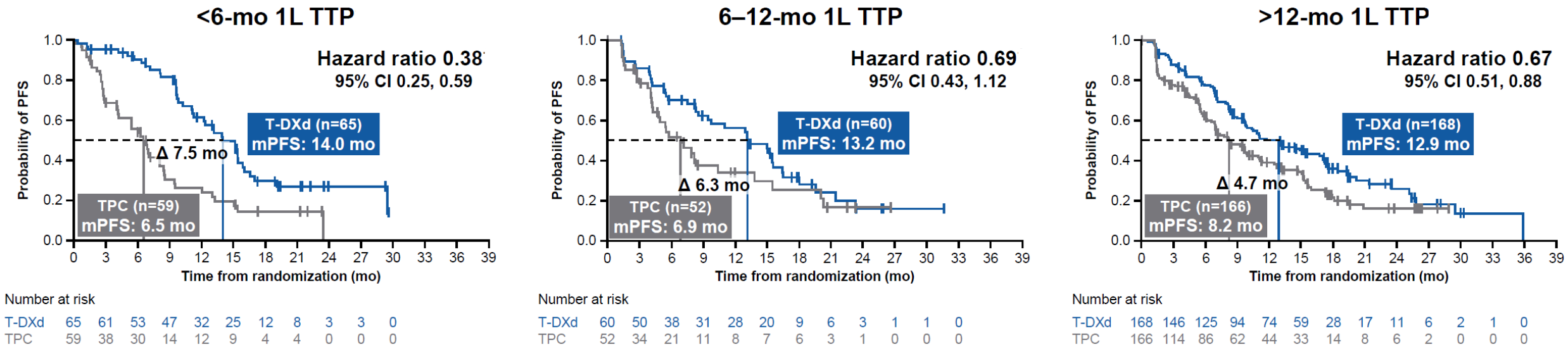
DESTINY-Breast06: PFS in Exploratory Subgroup Analysis

SABCS 2024

Daiichi-Sankyo

ENHERTU® improved PFS vs TPC regardless of time to progression on 1L endocrine therapy + CDK4/6i

<TTP subgroups>



- ENHERTU® demonstrated a clinically meaningful efficacy benefit vs TPC regardless of time to progression (TTP) on 1L ET + CDK4/6i (mPFS 12.9–14.0 mo with ENHERTU®)
  - ✓ This included patients with rapid (<6-mo) progression on 1L ET + CDK4/6i

CI: confidence interval, ET: endocrine therapy, mo: months, (m)PFS: (median) progression-free survival, PD: progressive disease, T-DXd: trastuzumab deruxtecan, TPC: treatment of physician's choice

DESTINY-Breast06: PFS in Exploratory Subgroup Analysis

SABCS 2024

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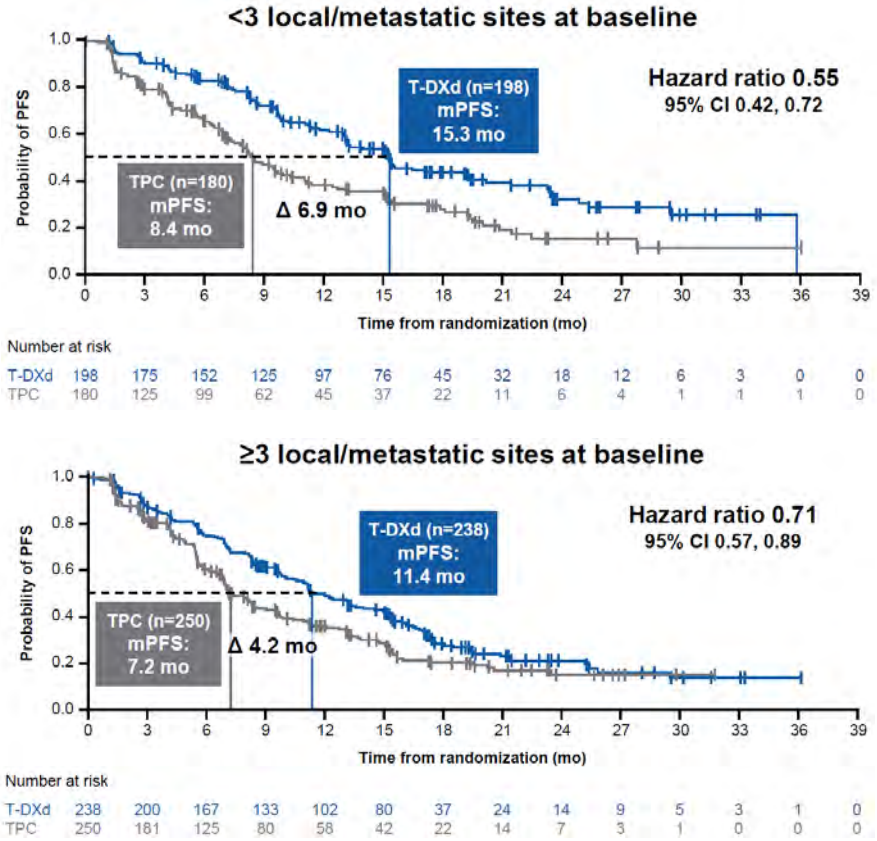
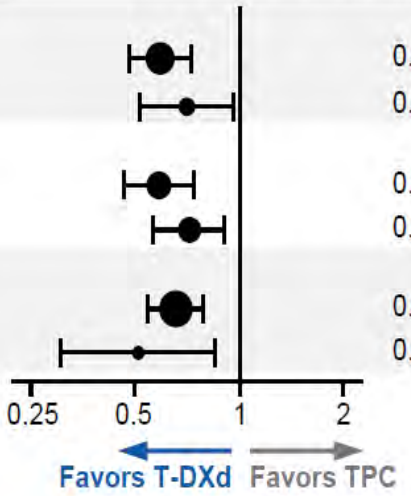
PFS benefit with ENHERTU® was observed regardless of disease burden, with notable efficacy in patients with lower disease burden

<Disease burden subgroups>



	Median PFS, mo (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	
Liver metastases			
Yes (n=579)	12.2 (10.4, 13.5)	7.0 (6.4, 8.1)	0.59 (0.48, 0.72)
No (n=287)	16.5 (13.2, 19.4)	11.3 (8.3, 15.2)	0.70 (0.51, 0.96)
Baseline tumor size			
>Median (n=432)	12.0 (9.9, 15.2)	7.1 (6.5, 8.3)	0.57 (0.45, 0.72)
≤Median (n=434)	15.0 (13.1, 16.1)	9.7 (7.5, 13.2)	0.71 (0.55, 0.90)
Visceral disease			
Yes (n=740)	13.1 (11.1, 15.1)	7.9 (6.9, 8.5)	0.65 (0.55, 0.78)
No (n=126)	23.3 (13.1, NE)	11.3 (6.9, 15.7)	0.51 (0.30, 0.85)



- ENHERTU® also demonstrated efficacy regardless of disease burden, with notable efficacy in patients with lower disease burden (mPFS 15.0–23.3 mo with ENHERTU®)

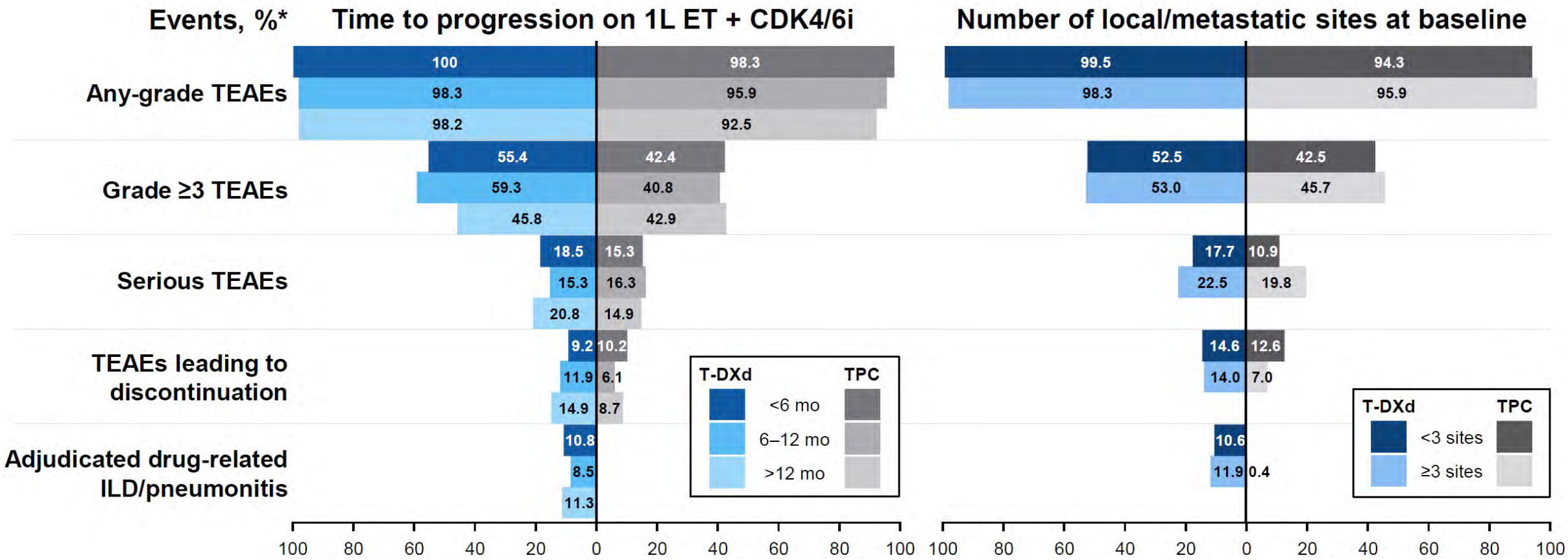
CI: confidence interval, ET: endocrine therapy, mo: months, NE, not evaluable, (m)PFS: (median) progression-free survival, T-DXd: trastuzumab deruxtecan, TPC: treatment of physician's choice

DESTINY-Breast06: Safety in Exploratory Subgroups

SABCS 2024

Daiichi-Sankyo

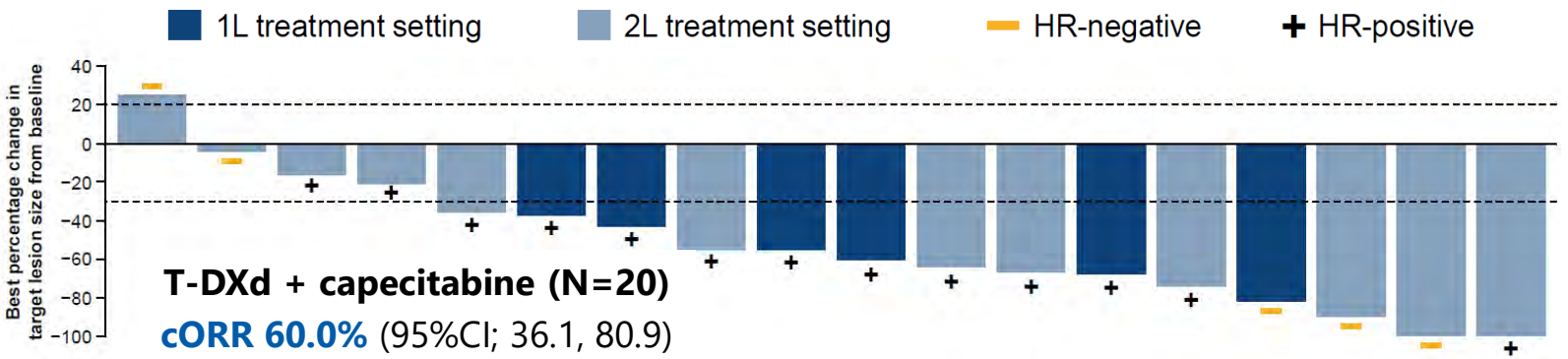
Safety profiles for ENHERTU® and TPC in TTP and disease burden subgroups in line with overall safety population†



*Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first); includes ILD/pneumonitis with an onset date or worsening on or after the date of first dose; †overall safety population (T-DXd vs TPC): any TEAEs, 98.8% vs 95.2%; Grade ≥3 TEAEs, 52.8% vs 44.4%; serious TEAEs, 20.3% vs 16.1%; TEAEs leading to discontinuation, 14.3% vs 9.4%; adjudicated drug-related ILD, 11.3% vs 0.2%
AE: adverse event, ET: endocrine therapy, ILD: interstitial lung disease, mo: months, T-DXd: trastuzumab deruxtecan, TEAE: treatment-emergent adverse event, TPC: treatment of physician's choice, TTP: time to progression

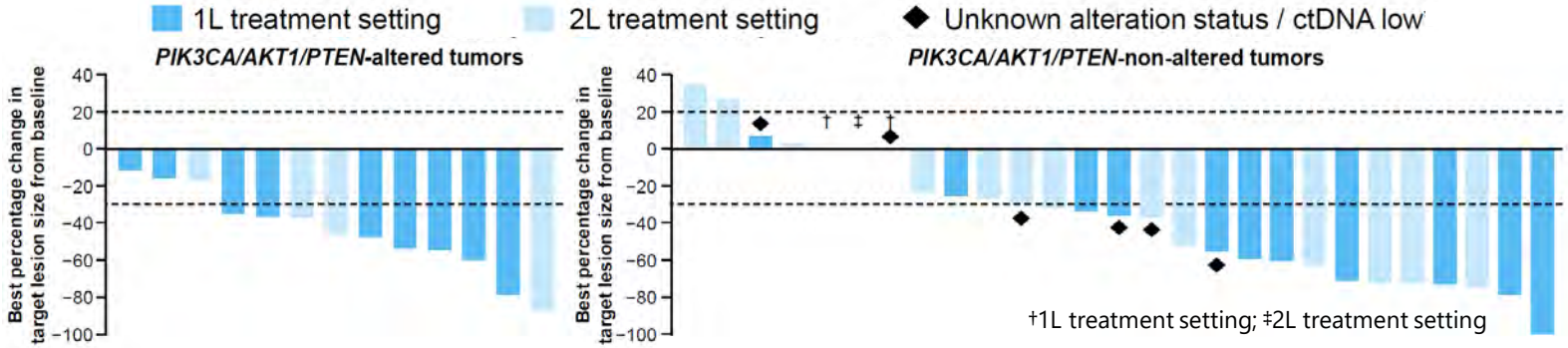
ENHERTU® + capecitabine or capivasertib are tolerable and active in patients with HER2 low mBC, potentially supporting further investigation

Efficacy



T-DXd + capecitabine (N=20)

cORR 60.0% (95%CI; 36.1, 80.9)



T-DXd + capivasertib (N=40)

cORR 60.0% (95%CI; 43.3, 75.1)

- **cORR** in patients with ***PIK3CA/AKT1/PTEN*-altered tumors** was **76.9%** (n=10/13; 95% CI 46.2, 95.0)
- **cORR** in patients with ***PIK3CA/AKT1/PTEN*-non-altered tumors** was **52.4%** (n=11/21; 95% CI 29.8, 74.3)
- **cORR** in patients with an **unknown** and **ctDNA low** status was **50.0%** (n=1/2) and **50.0%** (n=2/4), respectively

DESTINY-Breast08 Study :

A Ph1b study to investigate safety, tolerability, PK and preliminary anti-tumor activity of ENHERTU® in combination with other therapeutics in patients with HER2 low mBC

- ENHERTU® in combination with capecitabine or capivasertib demonstrated preliminary antitumor activity in patients with HER2-low mBC
- The safety profiles for ENHERTU® plus capecitabine and ENHERTU® plus capivasertib were generally consistent with the known safety profile of each agent

ctDNA: circulating tumor deoxyribonucleic acid, mBC: metastatic breast cancer, CI: confidence interval, HR: hormone receptor, PK: pharmacokinetics, cORR: confirmed objective response rate, SABCS: San Antonio Breast Cancer Symposium, T-DXd: trastuzumab deruxtecan

Pooled Analysis of TROPION-Lung01 and TROPION-Lung05

ESMO Asia 2024

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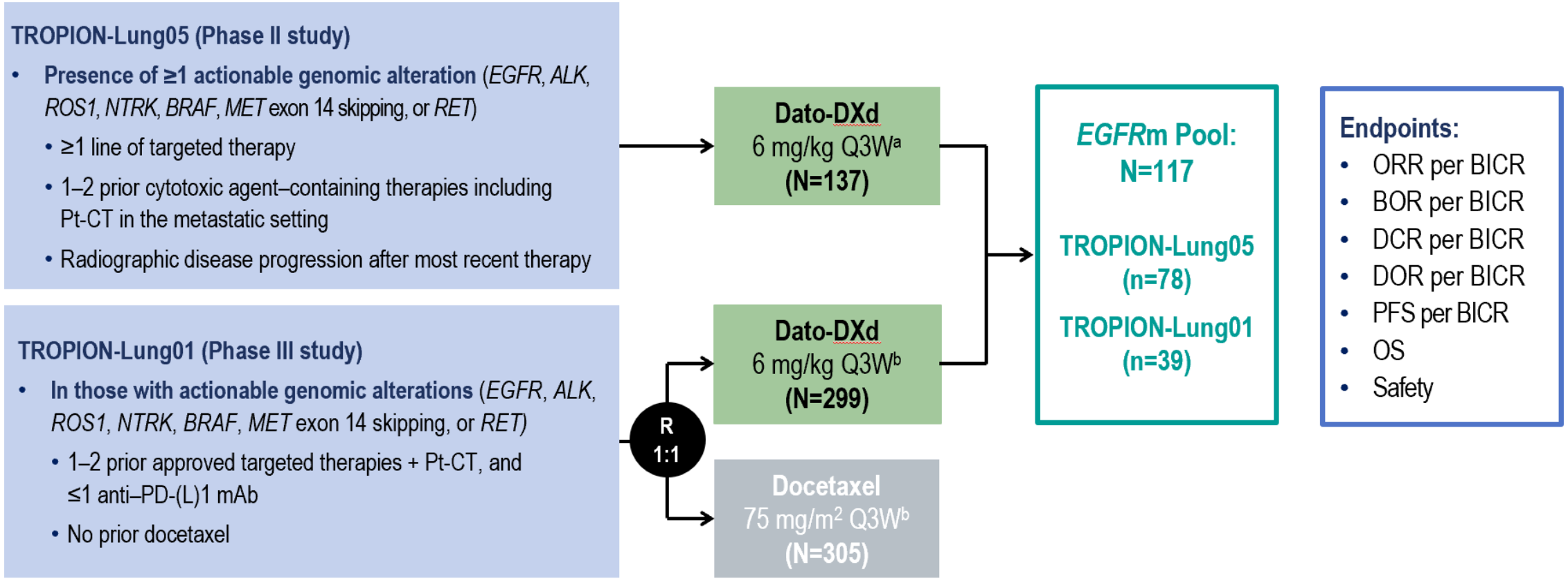
117 patients with EGFRm NSCLC who received Dato-DXd in TL01 and TL05 study were included in the pooled analysis



[a]Data cut off: December 14, 2022; [b]Data cut off: March 1, 2024 (OS and safety) or March 29, 2023 (all other efficacy endpoints).
BICR: blinded independent central review, BOR: best overall response, CT: chemotherapy, DCR: disease control rate, DOR: duration of response, ESMO: European Society for Medical Oncology, NSCLC: non-small cell lung cancer, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, Pt-CT: platinum-based chemotherapy, Q3W: once every 3 weeks

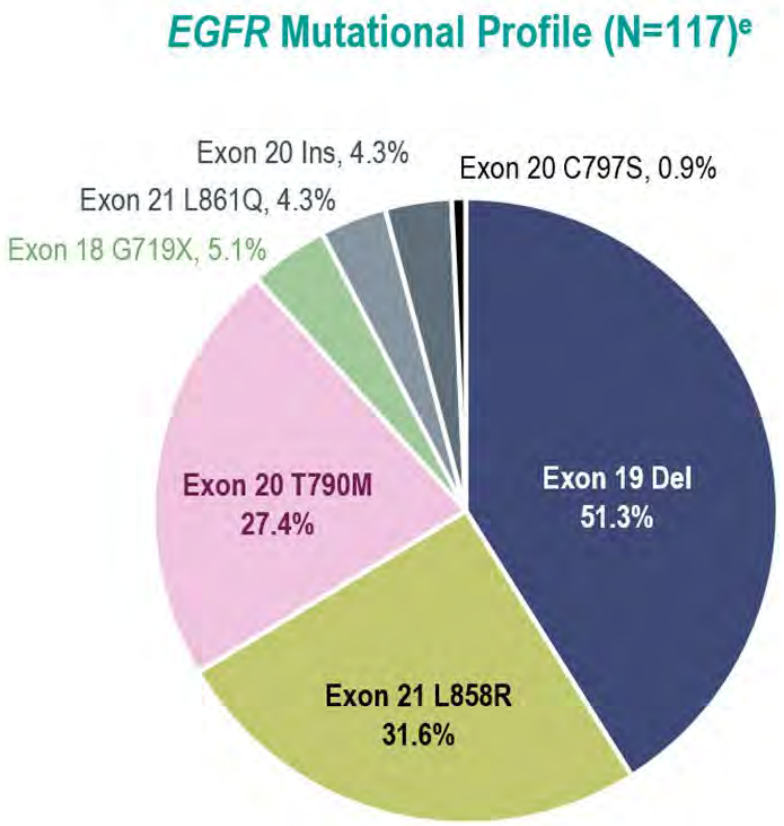
Pooled Analysis of TROPION-Lung01 and TROPION-Lung05

ESMO Asia 2024

Daiichi-Sankyo

Demographics and Baseline Characteristics

Characteristic	*EGFR*m Pool (N=117)	TROPION-Lung05 (N=78)	TROPION-Lung01 (N=39)
Median age (range), years	63 (36–81)	63 (36–77)	62 (39–81)
Sex, female, n (%)	73 (62.4)	52 (66.7)	21 (53.8)
Race, n (%)			
Asian	81 (69.2)	55 (70.5)	26 (66.7)
White	27 (23.1)	20 (25.6)	7 (17.9)
Black or African American	1 (0.9)	0	1 (2.6)
Other/missing	8 (6.8)	3 (3.8)	5 (12.8)
ECOG PS, n (%)			
0	39 (33.3)	24 (30.8)	15 (38.5)
1	78 (66.7)	54 (69.2)	24 (61.5)
Smoker[a], n (%)	55 (47.0)	34 (43.6)	21 (53.8)
Nonsquamous histology[b], n (%)	115 (98.3)	77 (98.7)	38 (97.4)
Brain metastasis at study entry, n (%)	36 (30.8)	21 (26.9)	15 (38.5)
Median lines systemic therapy (range)[c]	3 (1–5)	3 (1–5)	2 (1–5)
Prior osimertinib[d], n (%)	96 (82.1)	61 (78.2)	35 (89.7)
First line	47 (40.2)	27 (34.6)	20 (51.3)
Second line	34 (29.1)	20 (25.6)	14 (35.9)



[a]Current/former; [b]Adenocarcinoma and other nonsquamous types; [c]Prior lines in the locally advanced/metastatic setting; [d]Additional patients may have received osimertinib as third line or later therapy; [e]Analyses based on local testing reported by investigators in the electronic case report form. Patients may have ≥1 *EGFR* mutation with or without a non-*EGFR* mutation. Other mutation types identified alongside *EGFR* were *ALK* rearrangement, n=2; *ROS1* rearrangement, n=2; *NTRK* fusion, n=1; *MET* amplification, n=5; *MET* Exon 14 skipping, n=1.
Del: deletion, ECOG PS: Eastern Cooperative Oncology Group Performance Status, ESMO: European Society for Medical Oncology, Ins: insertion

Pooled Analysis of TROPION-Lung01 and TROPION-Lung05

ESMO Asia 2024

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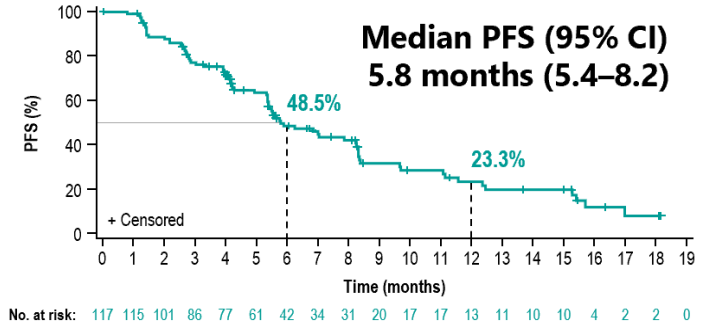
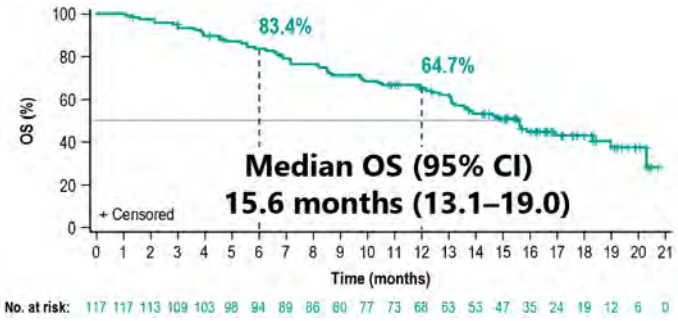
Dato-DXd is a potential treatment option for patients with EGFRm NSCLC in the second-line and later settings

Efficacy

Response	*EGFR*m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR,[a] n (%) [95% CI]	50 (**42.7**) [33.6–52.2]	43 (**44.8**) [34.6–55.3]
BOR, n (%)		
CR	5 (**4.3**)	4 (**4.2**)
PR	45 (**38.5**)	39 (**40.6**)
SD	48 (41.0)	37 (38.5)
Non-CR/Non-PD	3 (2.6)	2 (2.1)
PD	12 (10.3)	10 (10.4)
NE	4 (3.4)	4 (4.2)
Median DOR, months (95% CI)	**7.0** (4.2–9.8)	**6.9** (4.2–9.8)
DCR,[b] n (%) [95% CI]	101 (**86.3**) [78.7–92.0]	82 (**85.4**) [76.7–91.8]
Median PFS, months (95% CI)	**5.8** (5.4–8.2)	**5.7** (5.4–7.9)
Median OS, months (95% CI)	**15.6** (13.1–19.0)	**14.7** (13.0–18.3)

PFS and OS in the *EGFR*m Pool (N=117)





- **Robust clinical activity:**
  - ORR: 42.7% (95% CI: 33.6–52.2); median DOR: 7.0 mo (range: 4.2–9.8); median PFS: 5.8 mo; median OS: 15.6 mo
  - Outcomes for patients with prior osimertinib treatment were similar to the overall pooled population

[a]CR+PR; [b]CR+PR+SD or non-CR/non-PD.

BICR: blinded independent central review, BOR: best overall response, CI: confidence interval, CR: complete response, DCR: disease control rate, DOR: duration of response, ESMO: European Society for Medical Oncology, NE: not evaluable, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PD: progressive disease, PR: partial response, SD: stable disease.

Pooled Analysis of TROPION-Lung01 and TROPION-Lung05

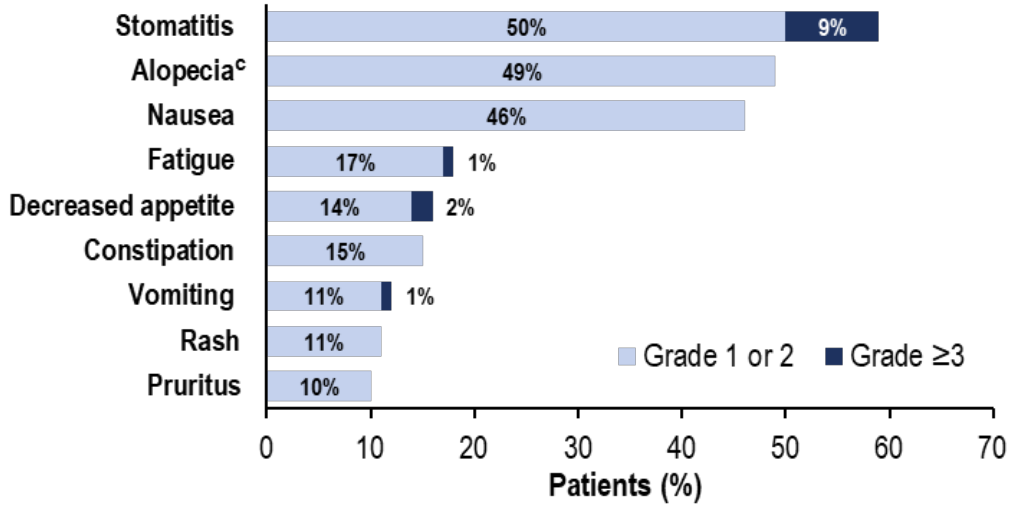
ESMO Asia 2024

Daiichi-Sankyo

Dato-DXd is a potential treatment option for patients with EGFRm NSCLC in the 2L and later settings

Safety

	*EGFR*m Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs[a], n (%)	
Stomatitis/oral mucositis	81 (69)
Grade 3[b]	11 (9)
Ocular surface events	38 (32)
Grade 3[b]	3 (3)
Adjudicated drug-related ILD	5 (4)
Grade 3[b]	1 (1)



■ **A manageable safety profile with no new safety signals**

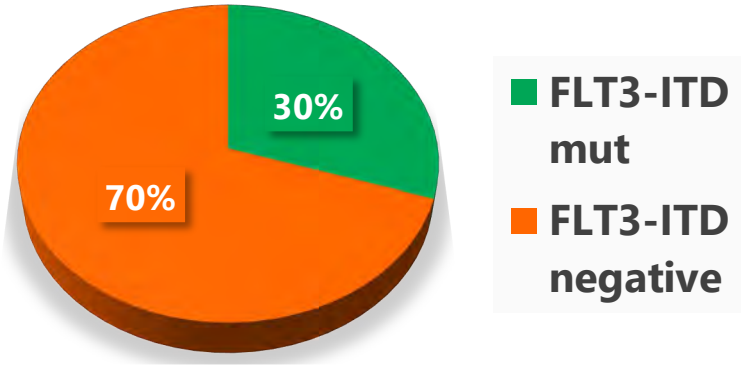
- Low rates of serious TRAEs or TRAEs leading to treatment discontinuations
- Grade ≥2 stomatitis/oral mucositis seen in ~1/3 patients was effectively managed with dose reductions/delays, and no treatment discontinuations due to stomatitis occurred
- No grade 4 or 5 ILD events

[a]AESIs listed are treatment emergent and include all preferred terms that define the medical concept. Some patients may have had >1 event. [b]No grade 4 or 5 events occurred. [c]Includes an event incorrectly reported as grade 3 per CTCAE grades.

AESI: adverse event of special interest, CTCAE: Common Terminology Criteria for Adverse Events, ILD: interstitial lung disease, NSCLC: non-small cell lung cancer, TRAE: treatment-related adverse event

VANFLYTA®

Beyond *FLT3*-ITD Mutation



R/R AML
***FLT3*-ITD mut**

QuANTUM-R, Ph3
VANFLYTA® Mono
2014-18

Newly Diagnosed AML
***FLT3*-ITD mut**

QuANTUM-First, Ph3
SOC + VANFLYTA®
2016-21

Newly Diagnosed AML
***FLT3*-ITD negative**

QuANTUM-Wild, Ph3
SOC + VANFLYTA®
2024-ongoing

IIS QUIWI, Ph2
SOC + VANFLYTA®
2019-24

AML: acute myeloid leukemia

Background

- **Potential contribution of ITD-negative FLT3 to the survival and proliferation of leukemic cells**
  - ✓ Elevated expression of the FLT3 receptor is observed in nearly all cases of AML
  - ✓ High levels of FLT3 gene expression are detected in 70–100% of AML blasts, independent of the presence of *FLT3* mutations
- **VANFLYTA® has potent binding affinity for the FLT3 receptor regardless of mutation**
- **The clinical utility of VANFLYTA® in patients with *FLT3*-ITD negative AML is supported by evidence from preclinical models and clinical trials**
  - ✓ **Preclinical**: *ex vivo* plasma inhibitory assays showed robust suppression of FLT3 phosphorylation with VANFLYTA® in cells expressing wild-type FLT3
  - ✓ **Clinical**: The effectiveness of the VANFLYTA® for *FLT3*-ITD negative AML has been demonstrated (Ph1 and Ph2 (**QUIWI**))

AML: acute myeloid leukemia

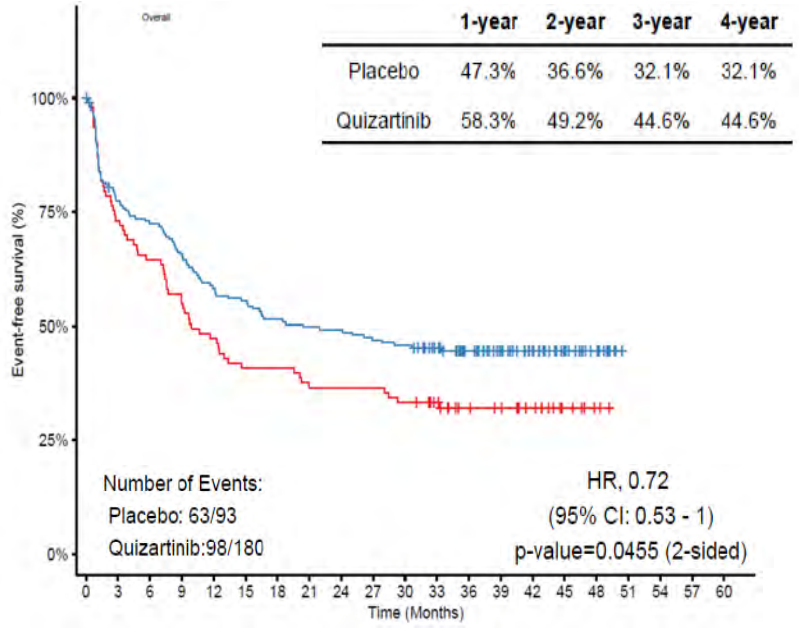
Final Results of Ph2 PETHEMA-QUIWI study

ASH 2024

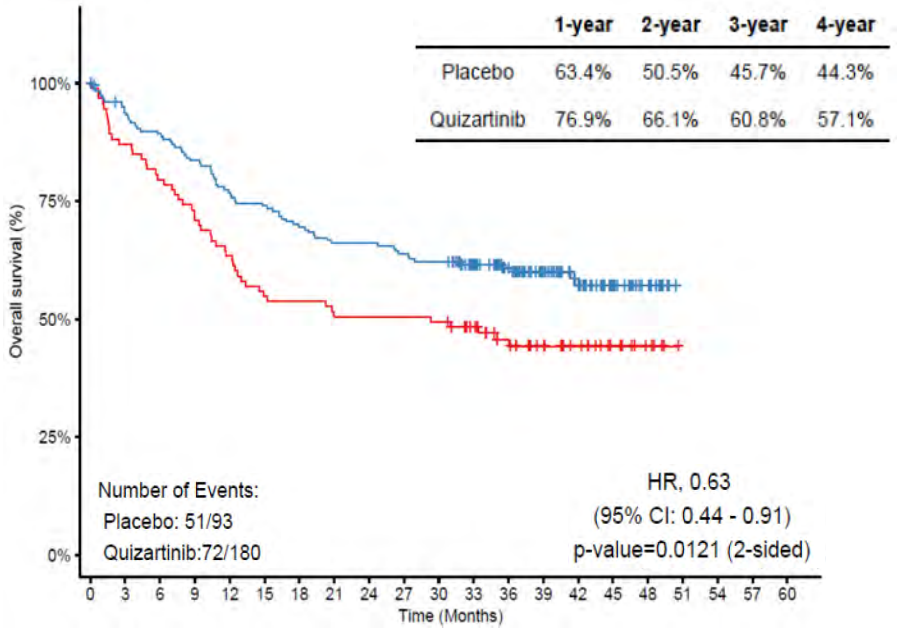
Daiichi-Sankyo

Data supports indication expansion potential of VANFLYTA® to newly diagnosed *FLT3*-ITD negative AML

■ Primary Endpoint: EFS



■ Secondary Endpoint: OS



■ Secondary Endpoint: CR/CRi

CR/CRi rate after 2 cycles was 77.2% in the VANFLYTA® arm and 76.3% in the placebo arm

■ Secondary Endpoint: Safety

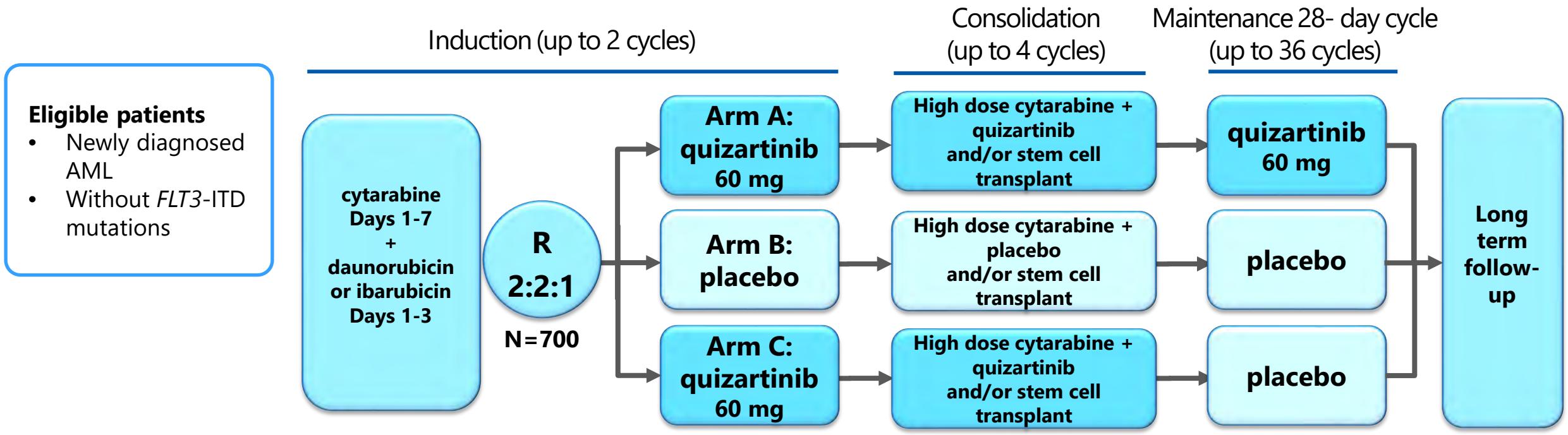
No new safety signals were observed among VANFLYTA® and placebo arms

AML: acute myeloid leukemia, ASH: American Society of Hematology, CR: complete remissions, CRi: complete remissions with incomplete recovery, EFS: event-free survival, HR: hazard ratio, OS: overall survival

QuANTUM-Wild Study Design

Started QuANTUM-Wild Ph3 study for *FLT3*-ITD negative AML based on data from QUIWI study

QuANTUM-Wild study design



- VANFLYTA® + chemotherapy demonstrated preliminary efficacy in patients with newly diagnosed *FLT3*-ITD negative AML compared to placebo+ chemotherapy in the interim analysis of QUIWI study (EHA 2023)
- Started the study in Dec 2024 to expand indication for *FLT3*-ITD negative AML based on QUIWI study results

Primary endpoint
- OS

Secondary endpoint
- EFS, DCR, RFS, CR rate etc.

AML: acute myeloid leukemia, CR: complete response, DCR: disease control rate:, EFS: event-free survival, EHA: European Hematology Association, OS: overall survival, RFS: relapse-free survival

Clinical Progress

Medical Congress Highlights

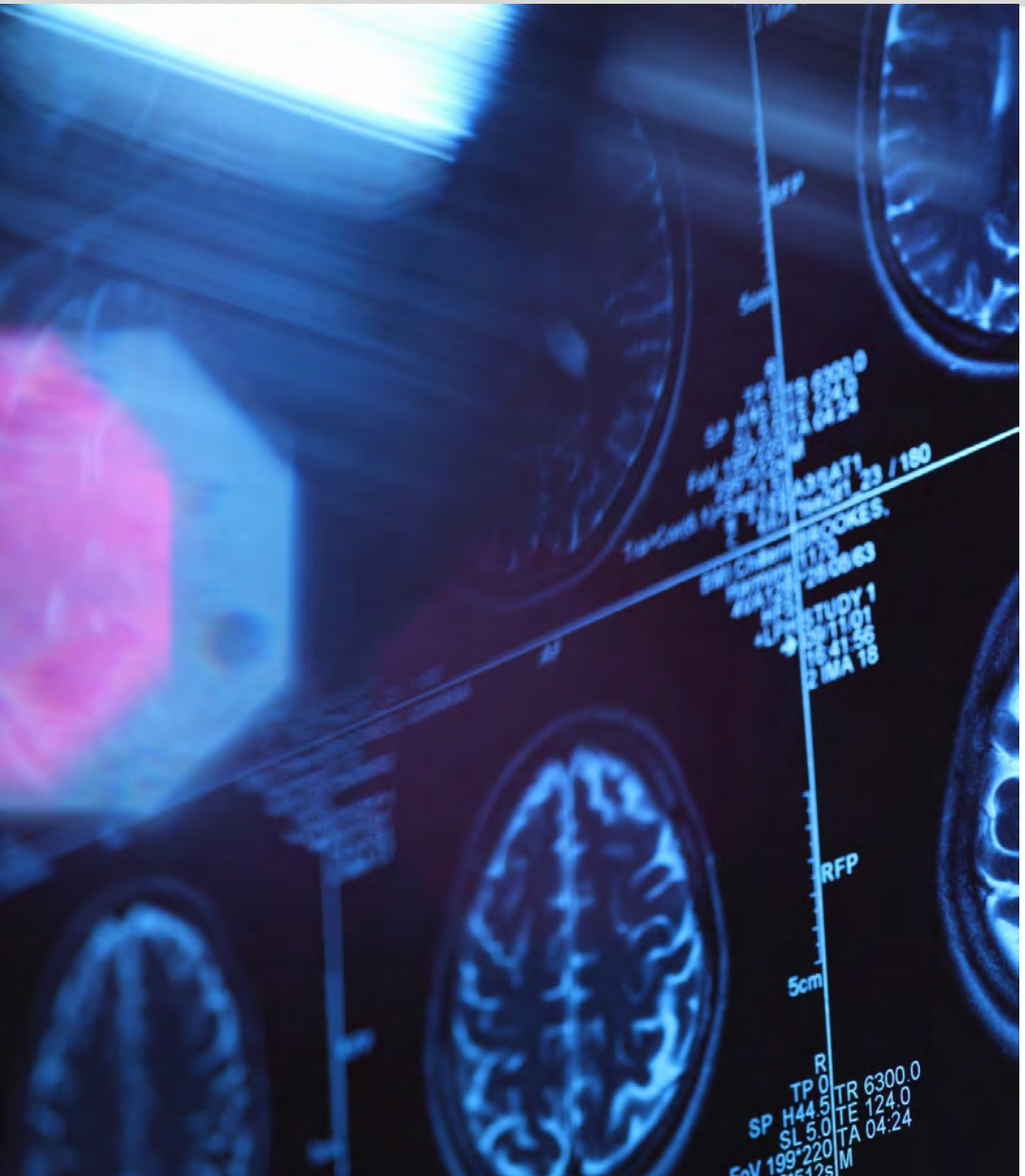
DXd ADCs in brain metastases

ENHERTU® early line studies in BC

Analysis of drug-related ILD in Dato-DXd

Early clinical stage development

Brain Metastases in Breast and Lung Cancers



- Brain metastases (BMs) occur in nearly one-third patients with HER2+ BC or TNBC[1]
- 10-20% NSCLC patients have BMs at the time of diagnosis, and the rate increases as the disease progresses[2]
- Patients with SCLC are twice as likely to develop BMs as those with NSCLC[3]
- BM impacts significantly on disease prognosis and patient's QOL[4]

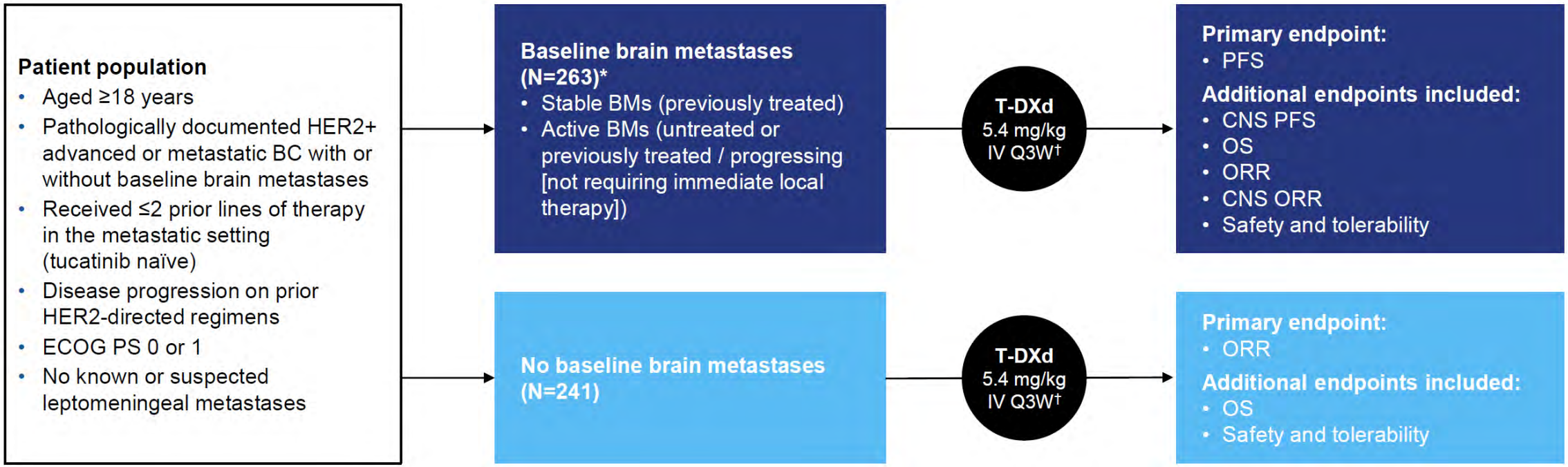
1: Neuro Oncol. 2020 23(6):894; 2: Clin Lung Cancer. 2018 19(4):e373 etc.; 3: ASCO Daily News Jan 12, 2023 etc.; 4: Curr Oncol Rep 2012 14(1):48 etc.
NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, QOL: quality of life

DESTINY-Breast12 Study Design

ESMO 2024

Daiichi-Sankyo

Phase 3b/4 study of ENHERTU® in patients with or without baseline brain metastases (BMs) with previously treated advanced/metastatic HER2-positive BC



- The largest prospective study of ENHERTU® in patients with stable or active BMs

Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and US

***Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only)**; †until RECIST 1.1-defined disease progression outside the CNS

BC: breast cancer, CNS: central nervous system, ECOG PS: Eastern Cooperative Oncology Group Performance Status, ICR: independent central review, IV: intravenous, OS: overall survival, ORR: objective response rate, PFS: progression-free survival, Q3W: every 3 weeks, RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1, T-DXd: trastuzumab deruxtecan

DESTINY-Breast12: Key Endpoints with Baseline BMs

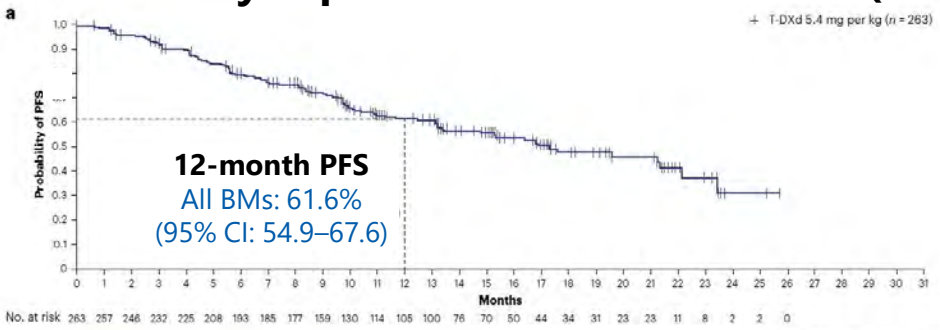
ESMO 2024

Daiichi-Sankyo

Data support use of ENHERTU® in previously treated patients with HER2+ mBC, irrespective of stable/active baseline brain metastases (BMs)

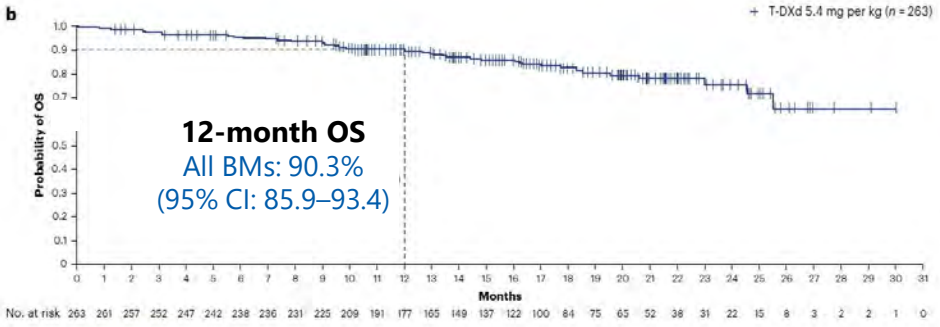
Efficacy in patients with baseline BMs (N=263)

- Stable BMs (n=157)
- Active BMs (n=106)



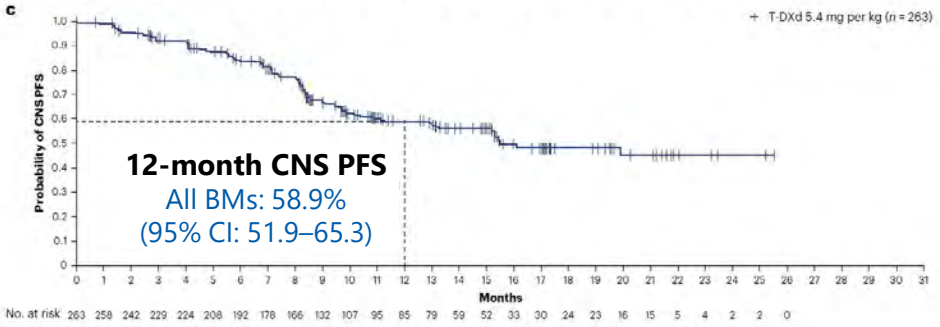
12-month PFS
All BMs: 61.6%
(95% CI: 54.9–67.6)

Stable BMs: 62.9% (54.0-70.5)
Active BMs: 59.6% (49.0-68.7)



12-month OS
All BMs: 90.3%
(95% CI: 85.9–93.4)

Stable BMs: 93.2% (87.7-96.3)
Active BMs: 86.1% (77.6-91.5)



12-month CNS PFS
All BMs: 58.9%
(95% CI: 51.9–65.3)

Stable BMs: 57.8% (48.2-66.1)
Active BMs: 60.1% (49.2-69.4)

ENHERTU® showed:

- **Consistent 12-month PFS in patients with stable and active BMs**
- **Consistent 12-month CNS PFS in patients with stable and active BMs**
- **Consistent 12-month OS in patients with BMs (90.3%) and without BMs (90.6%, graph not shown)**

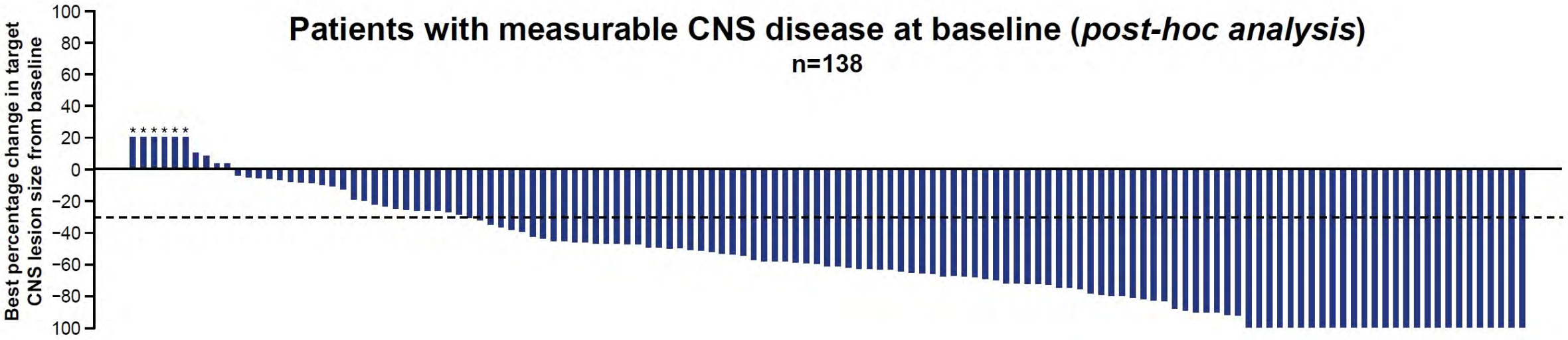
CI: confidence interval, CNS: central nervous system, mBC: metastatic breast cancer, OS: overall survival, PFS: progression-free survival, T-DXd: trastuzumab deruxtecan

ENHERTU®

CNS ORR in Baseline BMs Patients

DESTINY-Breast12

Daiichi-Sankyo



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

- ENHERTU® showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Dashed line indicates a 30% decrease in target tumor size (PR)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD

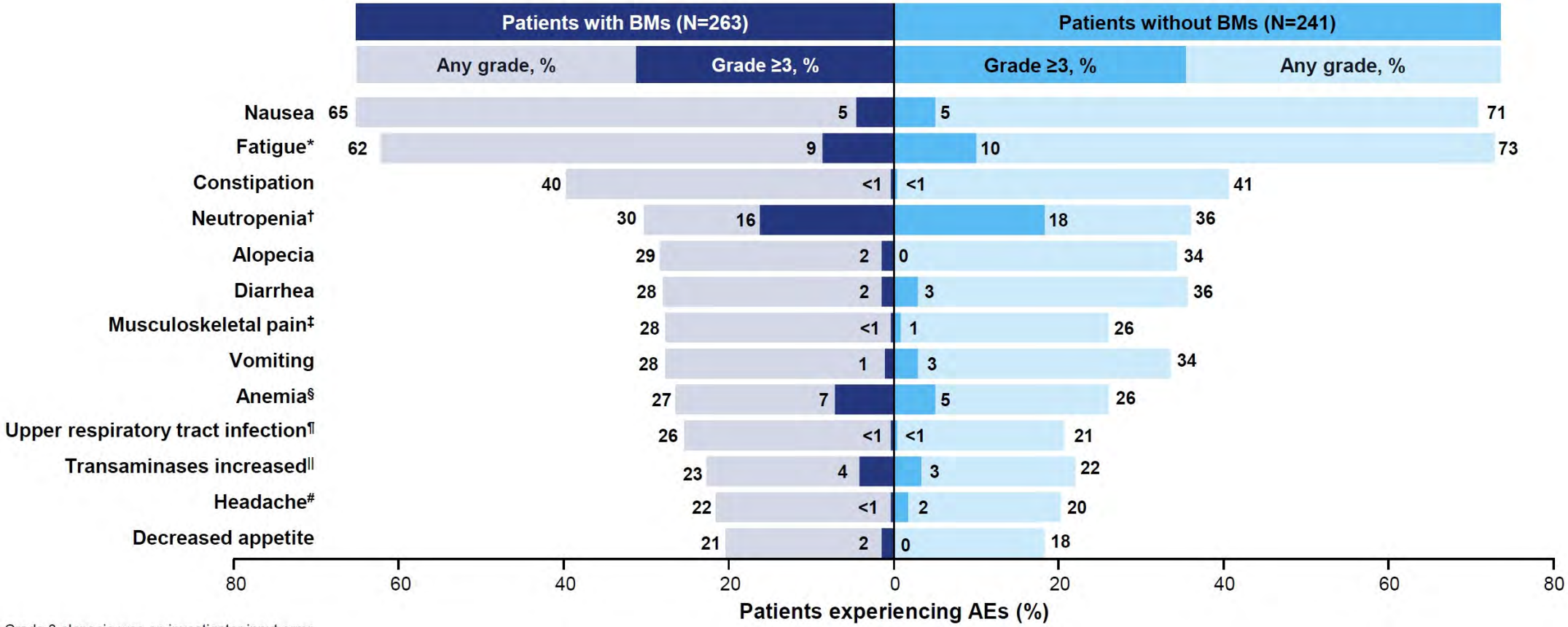
BMs: brain metastases, CI: confidence interval, CNS: central nervous system, ORR: objective response rate, PD: progressive disease, PR: partial response

ENHERTU®

AEs in ≥20% of Patients in Either Cohort

DESTINY-Breast12

Daiichi-Sankyo



Grade 3 alopecia was an investigator input error

*Includes the preferred terms 'asthenia', 'fatigue', 'lethargy', and 'malaise'; †includes the preferred terms 'neutropenia' and 'neutrophil count decreased'; ‡includes the preferred terms 'back pain', 'bone pain', 'limb discomfort', 'muscle spasms', 'musculoskeletal chest pain', 'musculoskeletal pain', 'myalgia', 'neck pain', and 'pain in extremity'; §includes the preferred term 'anemia', 'hemoglobin decreased', and 'red blood cell count decreased'; ¶includes the preferred terms 'influenza', 'influenza-like illness', 'laryngitis', 'nasopharyngitis', 'pharyngitis', 'rhinitis', 'sinusitis', and 'upper respiratory tract infection'; ‖includes the preferred terms 'alanine aminotransferase increased', 'aspartate aminotransferase increased', 'gamma-glutamyltransferase increased', 'hypertransaminasemia', 'liver function test abnormal', and 'transaminases increased'; #includes the preferred terms 'headache', 'migraine', and 'sinus headache'

- The safety profile of ENHERTU® was consistent with previous reports; no new safety signals were identified

AE: adverse event, BMs: brain metastases

DXd-ADC Efficacy in NSCLC Patients with BMs

Recent publications

ENHERTU®

- ENHERTU® monotherapy demonstrated intracranial activity in patients with or without prior BMs treatment in exploratory pooled analyses from **DESTINY-Lung01/02** (ESMO 2023)

Dato-DXd

- Dato-DXd showed intracranial activity in heavily pretreated NSCLC patients with AGA in a post hoc analysis of **TROPION-Lung05** (ASCO 2024)
- In patients receiving Dato-DXd, trends towards improved systemic efficacy were observed vs docetaxel in patients with and without baseline BMs in results from **TROPION-Lung01** (ESMO 2024)

HER3-DXd

- HER3-DXd showed durable intracranial responses in patients with EGFR-mutated NSCLC with BMs at baseline that had not been treated with radiotherapy in results from **HERTHENA-Lung01** (ESMO 2023, J Clin Oncol 2024)

Additional clinical trials are ongoing investigating DXd-ADCs' efficacy in BMs (e.g., TUXEDO-2, TUXEDO-3, DATO-BASE)

AGA: actionable genomic alteration, ASCO: American Society of Clinical Oncology, BMs: brain metastases, ESMO: European Society for Medical Oncology, NSCLC: non-small cell lung cancer

I-DXd Efficacy in SCLC Patients with BMs

IDeate-Lung01 subset analysis

Daiichi-Sankyo

Intracranial response

	Patients with brain metastases at baseline			Subset of patients with brain target lesions		
	8 mg/kg (n=19)	12 mg/kg (n=18)	Total (N=37)	8 mg/kg (n=6)	12 mg/kg (n=10)	Total (N=16)
CNS confirmed ORR, % (95% CI)	36.8 (16.3–61.6)	38.9 (17.3–64.3)	37.8 (22.5–55.2)	66.7 (22.3–95.7)	50.0 (18.7–81.3)	56.3 (29.9–80.2)
CNS confirmed BOR, n (%)						
CR	5 (26.3)	4 (22.2)	9 (24.3)	2 (33.3)	2 (20.0)	4 (25.0)
PR	2 (10.5)[a]	3 (16.7)[a]	5 (13.5)[a]	2 (33.3)	3 (30.0)	5 (31.3)
SD or non-CR/non-PD[b]	8 (42.1)	10 (55.6)	18 (48.6)	2 (33.3)	5 (50.0)	7 (43.8)
PD	1 (5.3)	0	1 (2.7)	0	0	0
Not evaluable	3 (15.8)	1 (5.6)	4 (10.8)	0	0	0
CNS confirmed DCR,[c] % (95% CI)	78.9 (54.4–93.9)	94.4 (72.7–99.9)	86.5 (71.2–95.5)	100 (54.1–100.0)	100 (69.2–100.0)	100 (79.4–100.0)
CNS DOR, median (95% CI), months	4.3 (3.3–NE)	7.4 (3.0–NE)	6.2 (3.3–NE)	3.9 (3.3–NE)	6.5 (3.0–NE)	4.4 (3.0–6.7)
CNS TTR, median (range), months	1.4 (1.2–1.5)	1.2 (0.9–2.8)	1.3 (0.9–2.8)	1.3 (1.2–1.4)	1.2 (0.9–2.8)	1.3 (0.9–2.8)

[a]All patients with PR had target lesions at baseline. [b]Only patients without baseline brain target lesions could have response classified as "non-CR/non-PD". [c]CR + PR + SD + non-CR/non-PD.

- In the 37 patients with brain metastases at baseline, CNS confirmed ORR was 37.8% (95% CI, 22.5–55.2) and median CNS DOR was 6.2 months (95% CI, 3.3–NE)
- In the subset of 16 patients with brain target lesions at baseline, CNS confirmed ORR was 56.3% (95% CI, 29.9–80.2) and median CNS DOR was 4.4 months (95% CI, 3.0–6.7)
- The safety profile of I-DXd was similar between patients with and without BMs at baseline

BMs: brain metastases, BOR: best overall response, CI, confidence interval, CNS: central nervous system, CR: complete response, DCR: disease control rate, DOR, duration of response, NE, not estimable, ORR: objective response rate, PD: progressive disease, PR: partial response, SCLC: small cell lung cancer, SD: stable disease, TTR: time to response

Source: Johnson, M et al. ESMO 2024 #1787P

DXd ADCs Become Promising Treatment Options for BMs

- **Accumulating evidence is establishing the fact that DXd ADCs are effective against BMs in Breast and Lung cancers**

BMs: brain metastases,

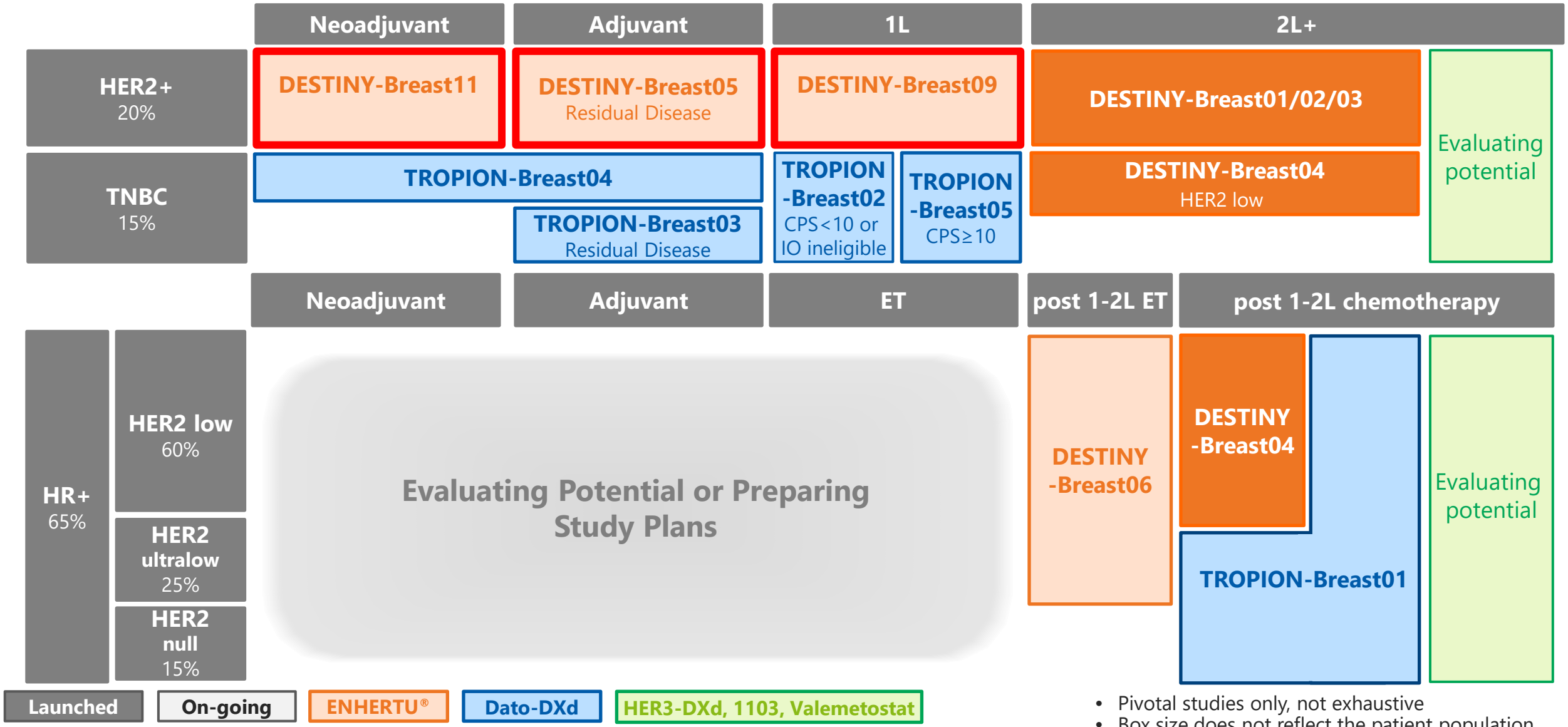
Clinical Progress

- Medical Congress Highlights
- DXd ADCs in brain metastases
- **ENHERTU® early line studies in BC**
- Analysis of drug-related ILD in Dato-DXd
- Early clinical stage development

5DXd ADCs

Establish and Expand DXd ADCs to Address the Broader Spectrum of Breast Cancer

Daiichi-Sankyo



- Pivotal studies only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

CPS: combined positive score; ET: endocrine therapy; HR: hormone receptor; IO: immune oncology, TNBC: triple-negative breast cancer

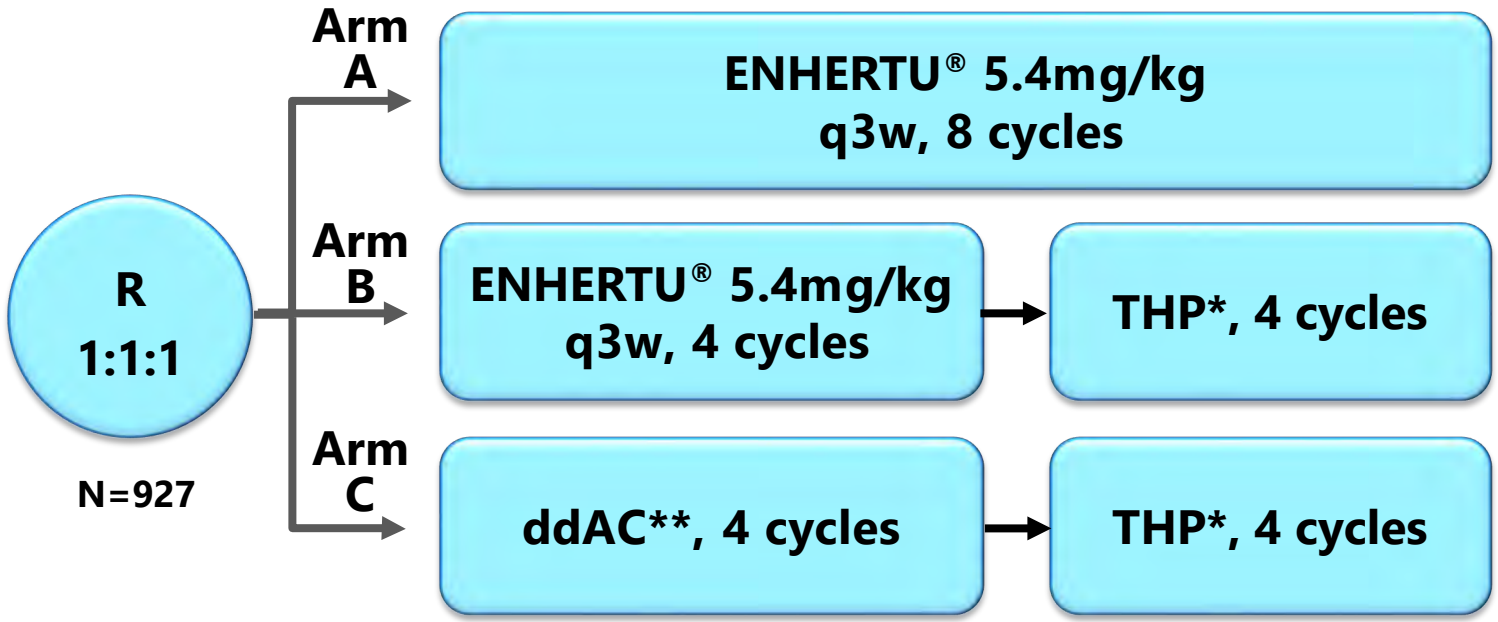
ENHERTU®

DESTINY-Breast11 Study

Ph3 study of ENHERTU® monotherapy or ENHERTU® followed by THP vs. ddAC-THP in neoadjuvant setting for high-risk HER2-positive early-stage BC

Key Eligibility Criteria

- HER2-positive locally advanced BC
- HR positive or negative
- Histologically documented HER2 positive early BC participants, including clinical stage at presentation (based on mammogram or breast MRI assessment): T0-4 (inclusive of inflammatory breast cancer), N1-3, M0 or ≥ T3, N0, M0 as determined by the AJCC staging system, 8th edition



* THP: paclitaxel qw + trastuzumab q3w + pertuzumab q3w

** ddAC: doxorubicin + cyclophosphamide q2w

Primary endpoint: pCR

Secondary endpoint: EFS, OS

TLR anticipated in FY2025 H1

AJCC: American Joint Committee on Cancer, BC: breast cancer, EFS: event-free survival, HR: hormone receptor, MRI: Magnetic Resonance Imaging, OS: overall survival, pCR: pathological complete response, qw: once weekly, q2w: every 2 weeks, q3w: every 3 weeks, TLR: top line results

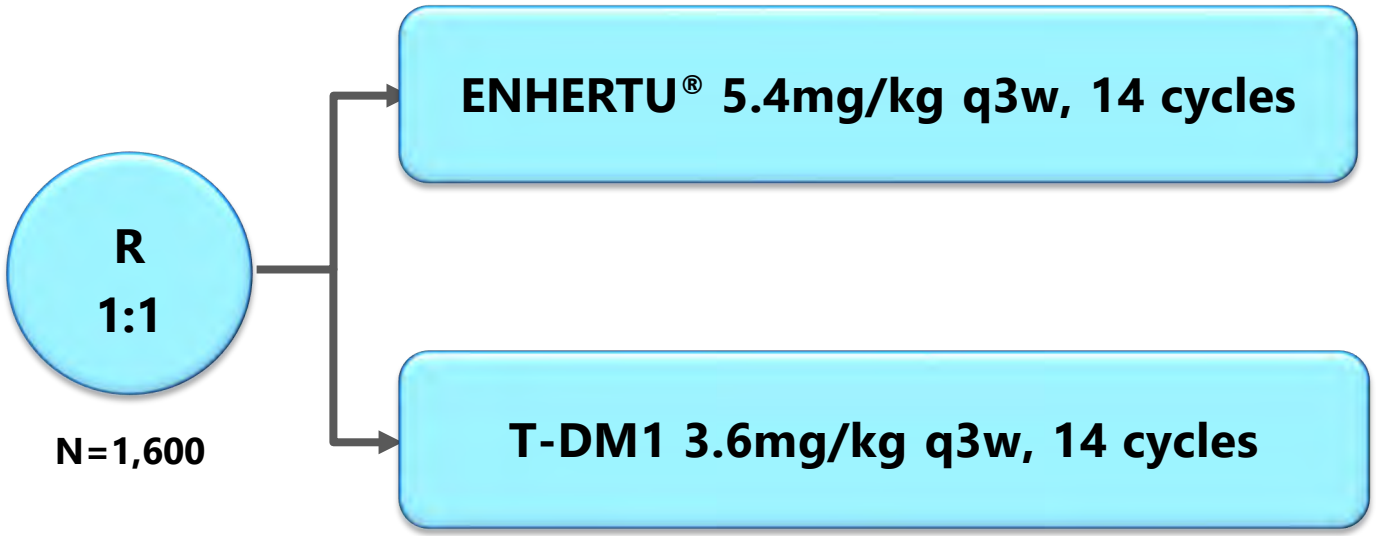
ENHERTU®

DESTINY-Breast05 Study

Ph3 study of ENHERTU® vs. T-DM1 in high-risk HER2 positive participants with residual invasive BC following neoadjuvant therapy

Key Eligibility Criteria

- HER2 positive BC (IHC3+ or ISH+ as confirmed by a central laboratory) histologically
- Completion of neoadjuvant systemic chemotherapy and HER2-directed treatment
- Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes
- Pathologic evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of neoadjuvant therapy meeting high-risk criteria



Primary endpoint: IDFS,

Secondary endpoint: DFS, OS, DRFI, BMFI, safety and tolerability, PK, ADA

TLR anticipated in FY2025

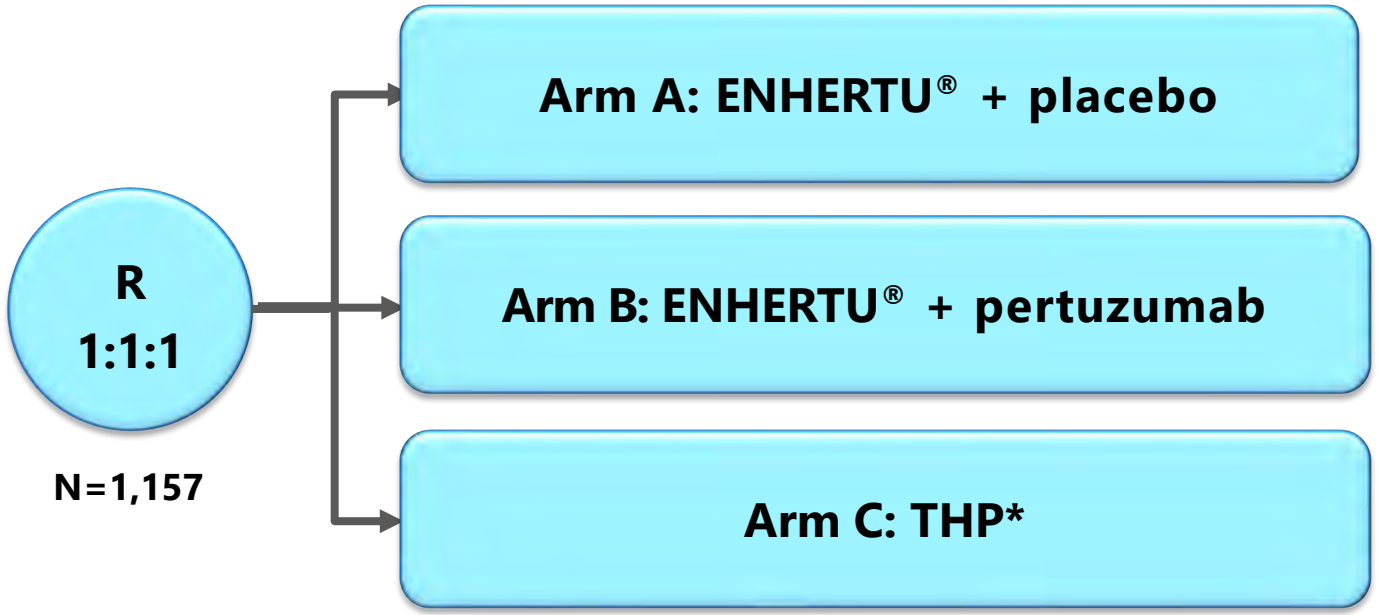
ADA: anti-drug antibody, BC: breast cancer, BMFI: brain metastases-free interval, DFS: disease-free survival, DRFI: distant recurrence-free interval, IDFS: invasive disease-free survival, IHC: immunohistochemistry, ISH: in situ hybridization, OS: overall survival, pCR: pathological complete response, PK: pharmacokinetics, q3W: every 3 weeks, TLR: top line results

DESTINY-Breast09 Study

Ph3 study of ENHERTU® monotherapy or in combination with pertuzumab vs. SOC in 1L setting for HER2 positive BC

Key Eligibility Criteria

- Advanced and/or metastatic BC
- HER2 positive (IHC3+ or ISH+) by central confirmation
- No previous chemotherapy or HER2-targeted therapy for advanced or metastatic BC except for 1 previous line of endocrine therapy in the metastatic setting



*THP: paclitaxel qw + trastuzumab q3w + pertuzumab q3w

Primary endpoint: PFS by BICR
Secondary endpoint: PFS by investigator, OS, ORR, DOR, PK, safety and tolerability etc.

TLR anticipated in FY2025

BC: breast cancer, BICR: blinded independent central review, DOR: duration of response, EFS: event-free survival, IHC: immunohistochemistry, ISH: in situ hybridization, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, PK: pharmacokinetics, qw: once weekly, q3W: every 3 weeks, SOC: standard of care, TLR: top line results

Clinical Progress

Medical Congress Highlights

DXd ADCs in brain metastases

ENHERTU® early line studies in BC

Analysis of drug-related ILD in Dato-DXd

Early clinical stage development

Pooled Analysis of Drug-related ILD

ASCO 2024

Incidence and severity of adjudicated drug-related ILD across 5 studies of Dato-DXd in patients with advanced solid tumors

Adjudicated drug-related ILD, n (%)	NSCLC+BC (N=927)	NSCLC[a] (N=484)	BC[b] (N=443)	Other tumors[c] (N=272)
Grade 1	9 (1.0)	4 (0.8)	5 (1.1)	1 (0.4)
Grade 2	21 (2.3)	17 (3.5)	4 (0.9)	3 (1.1)
Grade 3	5 (0.5)	2 (0.4)	3 (0.7)	3 (1.1)
Grade 4	2 (0.2)	2 (0.4)	0	1 (0.4)
Grade 5	9 (1.0)	8 (1.7)	1 (0.2)	1 (0.4)[d]
Total	**46 (5.0)**	**33 (6.8)[e]**	**13 (2.9)**	**9 (3.3)**
Associated with dose reduction	3 (0.3)	2 (0.4)	1 (0.2)	0 (0)
Associated with drug interruption	14 (1.5)	11 (2.3)	3 (0.7)	4 (1.5)
Associated with drug withdrawal	26 (2.8)	20 (4.1)	6 (1.4)	3 (1.1)

Across all tumor types, overall incidence of adjudicated drug-related ILD cases seen with Dato-DXd was low

- The majority of cases were low grade (grade 1 or 2)
- Grade ≥3 events have been reported, highlighting the need for careful monitoring and adherence to management guidelines
- In the NSCLC+BC pool, the median time to onset of first adjudicated drug-related ILD event was 48 days and the median duration was 39 days
- Dato-DXd–related ILD was more commonly observed in patients with NSCLC, and risk factors are currently under investigation
- This pooled analysis further supports a favorable benefit/risk profile of Dato-DXd for patients with advanced solid tumors

a: TROPION-Lung01 (n=297); TROPION-Lung05 (n=137); TROPION-PanTumor01 (n=50). b: TROPION-Breast01 (n=360); TROPION-PanTumor01 (n=83). c: TROPION-PanTumor01 (n=137); TROPION-PanTumor03 (n=135). d: One patient with prostate cancer from the TROPION-PanTumor01 trial experienced a grade 5 event. e: In TROPION-Lung01, 1 additional patient had a drug-related grade 2 ILD event according to the Adjudication Committee. The event was removed from the clinical database by the investigator as the investigator attributed the ILD event to disease progression and is not included in the above analyses.
BC: Breast cancer, NSCLC: non-small cell lung cancer, ILD: interstitial lung disease

Clinical Progress

Medical Congress Highlights

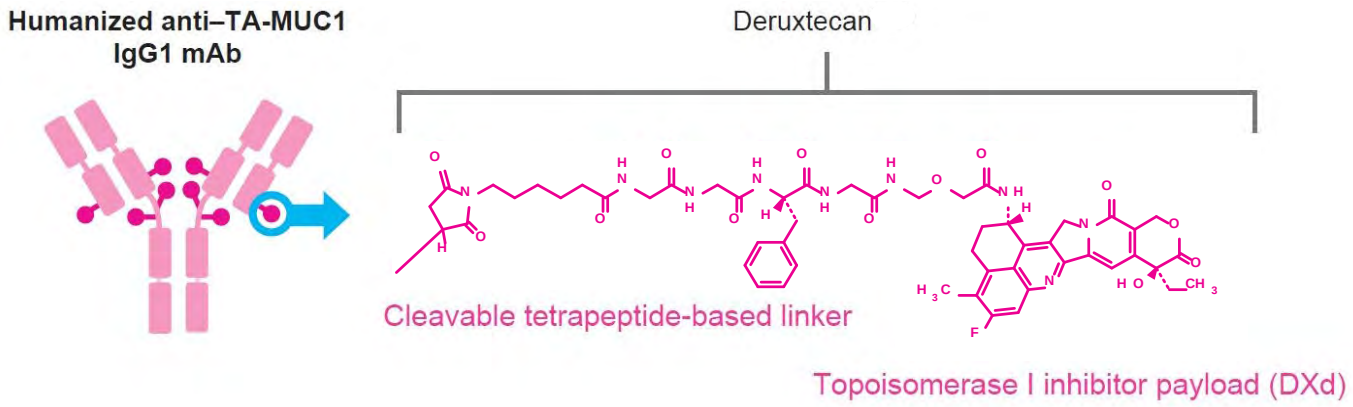
DXd ADCs in brain metastases

ENHERTU® early line studies in BC

Analysis of drug-related ILD in Dato-DXd

Early clinical stage development

DS-3939 is the 6th DXd ADC and Directed Against TA-MUC1



What is TA-MUC1?

- MUC1 is a transmembrane glycoprotein that is highly glycosylated in normal tissues and is localized to the apical membrane of epithelial surfaces.
- In cancers, MUC1 loses cell polarity and is redistributed over the cell surface and within the cytoplasm. Glycosylation of MUC1 is dysregulated in cancers and predominantly modified with shorter glycans, leading to the emergence of aberrantly glycosylated MUC1, known as tumor-associated MUC1 (TA-MUC1).
- TA-MUC1 is overexpressed in **broad range of tumors** including NSCLC, BC, UC, OVC, BTC and PDAC

DS-3939 features

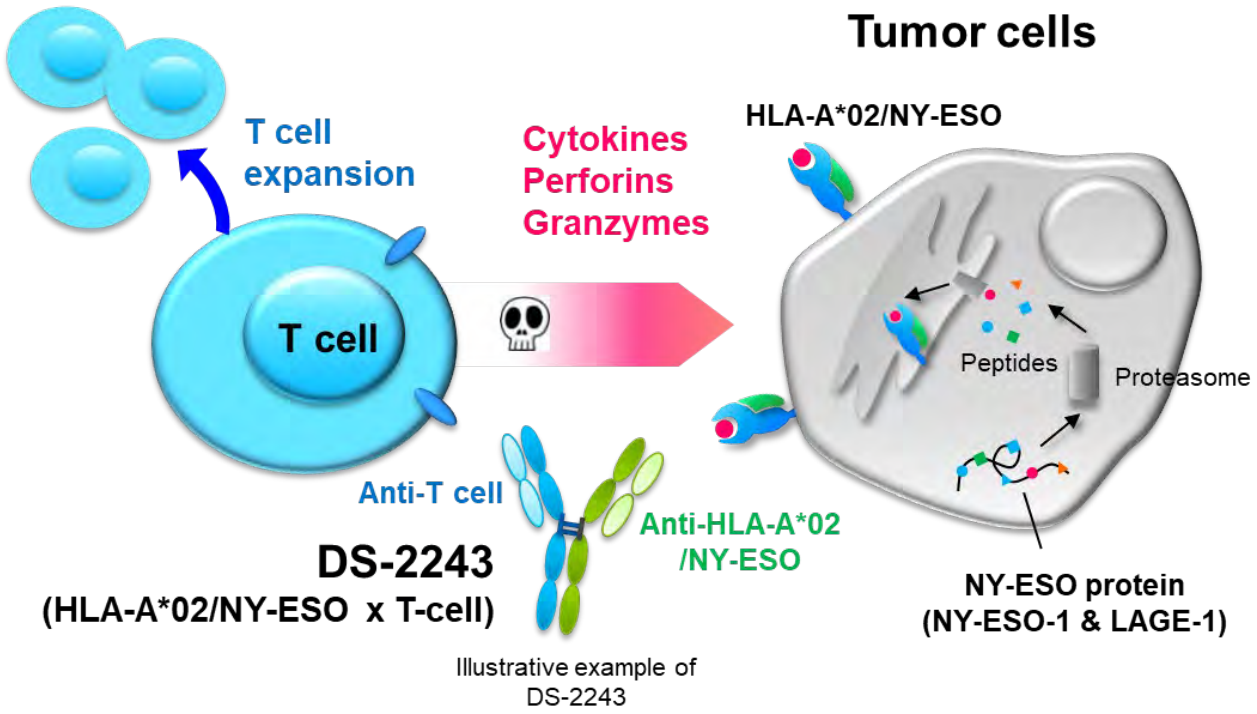
- High drug-to-antibody ratio ≈8
- DS-3939 specifically binds to TA-MUC1 by recognizing both the tumor specific glycan and backbone peptide moieties
- DS-3939 exhibited tumor regression against various preclinical in vivo models and also induced tumor regression after treatment of other FDA approved ADCs in xenograft model

BC; breast cancer, BTC: biliary tract cancer, FDA: Food and Drug Association, NSCLC: non-small cell lung cancer, OVC: ovarian cancer, PDAC: Pancreatic invasive ducatal adenocarcinoma, UC: urothelial cancer

DS-2243 Overview

A Potential First-in-Class Bispecific T-cell Engager (Bi-TCE) Targeting HLA-A*02/NY-ESO Tumors

Mode of Action



Illustrative example of DS-2243

- **Cutting-Edge Bi-TCE:** Engineered to selectively engage both tumor antigens and T-cells, driving a targeted and potent immune response.
- **Tumor-Specific Targeting**: Precise targeting through the HLA-A*02/NY-ESO complex mediated by NY-ESO, a highly tumor-specific antigen. NY-ESO is only expressed in the testis in normal tissue, where it is present without HLA-A molecules.
- **Broad Applicability**: High/moderate frequency of NY-ESO expression observed in Synovial Sarcoma, Myxoid/Round Cell Liposarcoma, NSCLC, UC etc.
- **Promising Efficacy**: Exhibits robust anti-tumor activity and significant combination therapy potential in preclinical studies.

NSCLC: non-small cell lung cancer, UC: urothelial cancer

Agenda

1. Opening
2. R&D Update
3. Clinical Progress
4. **Translational Research**
5. ADC Manufacturing & Supply
6. Q&A

Dale Shuster, PhD Career Highlights

Daiichi Sankyo

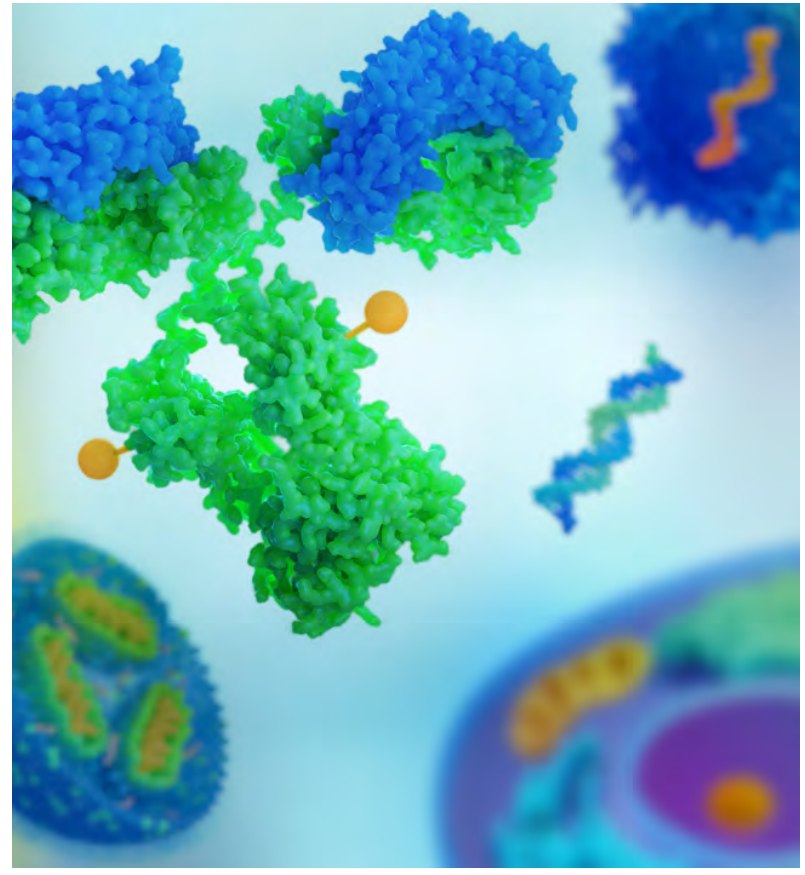
2022 SVP, Head of Global Precision Medicine
2019 VP, Global Team Leader of Dato-DXd
2013 Ex Dir, Global Team Leader of Pexidartinib and other oncology assets
2010 Sr Dir, Integrated Strategy Team Leader and Global Team Leader of multiple oncology assets

Eisai Medical Research

2007 Director, Global Project Team Leader of Eribulin
2005 Assoc Dir, Global Project Manager of Eribulin

Other Pharma Experience

Total of 32 years of experience in the pharmaceutical industry, including drug discovery, preclinical research and assay development, and drug development across a range of therapeutic areas.



Dato-DXd Exploration in NSCLC

TROPION-Lung01 study design

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

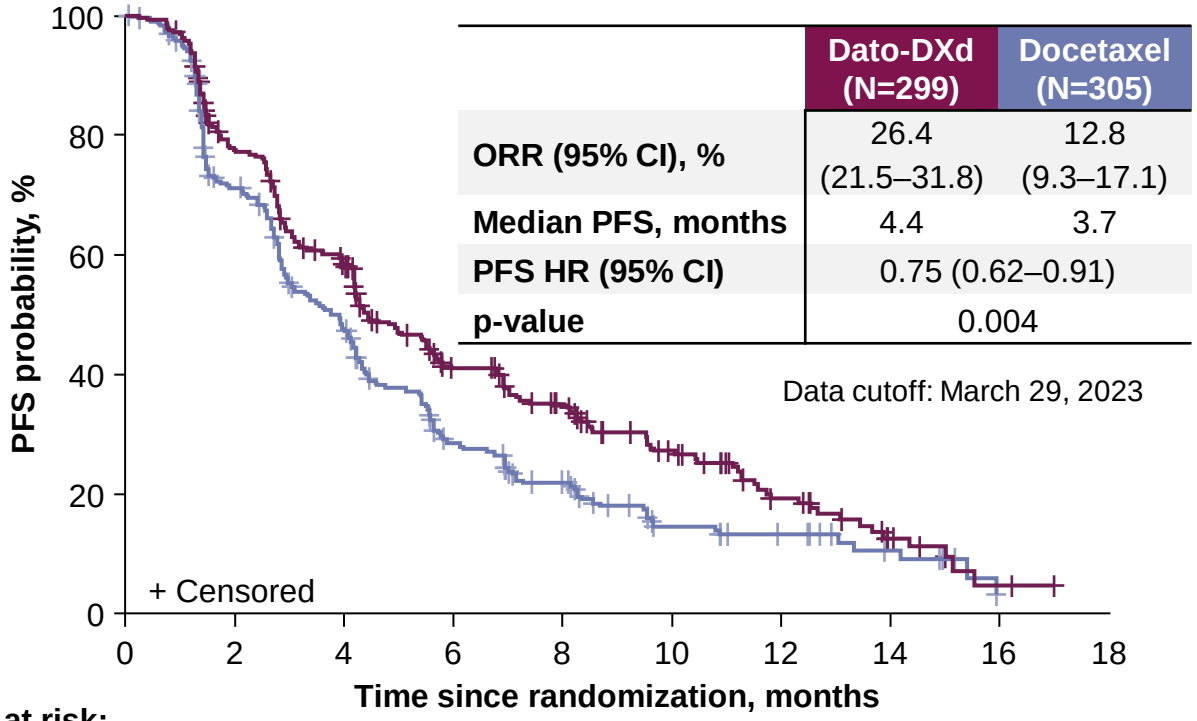
Dato-DXd
6 mg/kg q3w
N=299

Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

PFS by BICR and ORR in ITT



	Dato-DXd (N=299)	Docetaxel (N=305)
ORR (95% CI), %	26.4 (21.5–31.8)	12.8 (9.3–17.1)
Median PFS, months	4.4	3.7
PFS HR (95% CI)	0.75 (0.62–0.91)	
p-value	0.004	

Data cutoff: March 29, 2023

No. at risk:

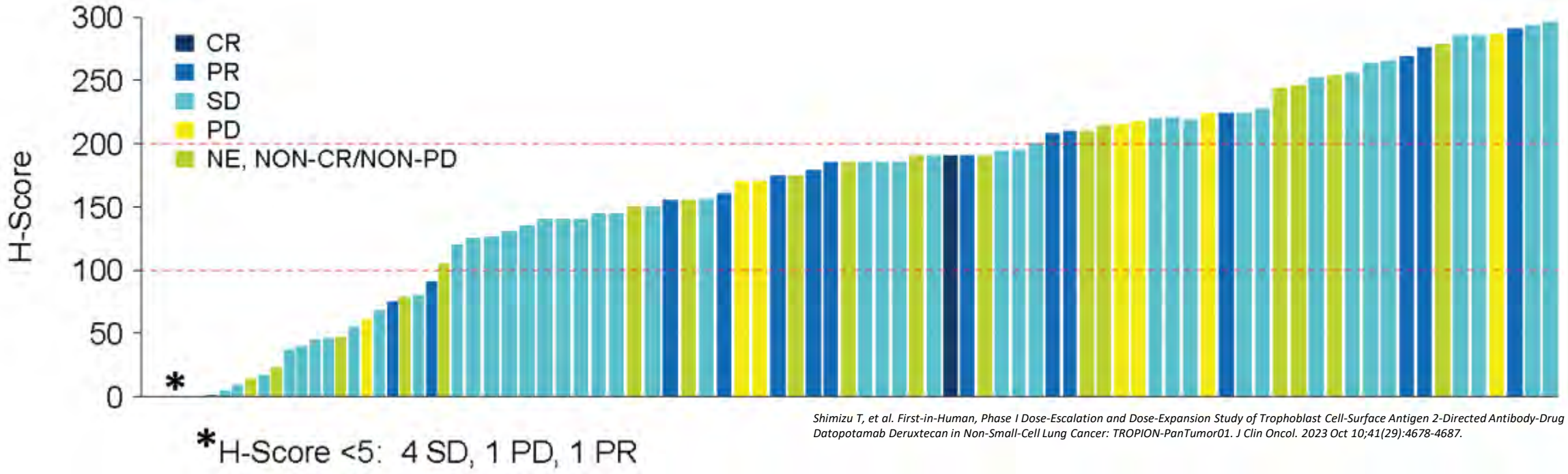
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

- Although the study met its one of primary endpoints; PFS, a predictive biomarker is needed to segregate the subpopulation who benefits the most from Dato-DXd

AGA; actionable genomic alteration, BICR; blinded independent central review, CI; confidence interval, CT; chemotherapy, DOR; duration of response, ECOG PS; Eastern Cooperative Oncology Group Performance Status, HR; hazard ratio, ITT; intension to treat, NSCLC; non-small cell lung cancer, ORR; objective response rate, OS; overall survival, PFS; progression free survival

TROPION-PanTumor01: Dato-DXd Anti-tumor Activity by TROP2 IHC

Response by TROP2 Membrane Expression



Shimizu T, et al. First-in-Human, Phase I Dose-Escalation and Dose-Expansion Study of Trophoblast Cell-Surface Antigen 2-Directed Antibody-Drug Conjugate Datopotamab Deruxtecan in Non-Small-Cell Lung Cancer: TROPION-PanTumor01. J Clin Oncol. 2023 Oct 10;41(29):4678-4687.

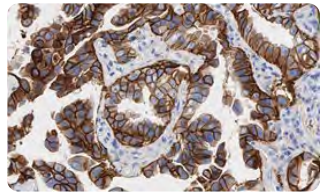
- TROP2 expression by immunohistochemistry using manual pathologist scoring failed to segregate the subpopulation with high efficacy

CR; complete response, IHC: immunohistochemistry, NE; not evaluable, PD; progressive disease, PR; partial response, SD; stable disease,

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

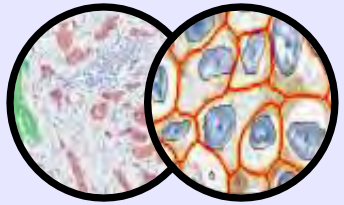
QCS is a novel computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

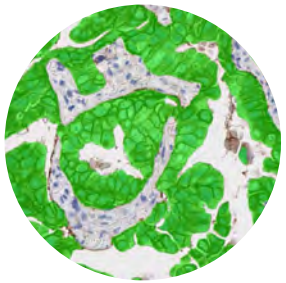


4 Patient Biomarker Status Determination

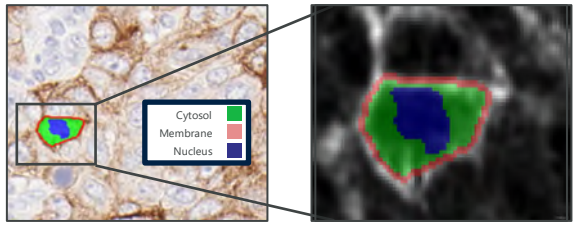
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <75% of tumor cells with TROP2 NMR ≤0.56*

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

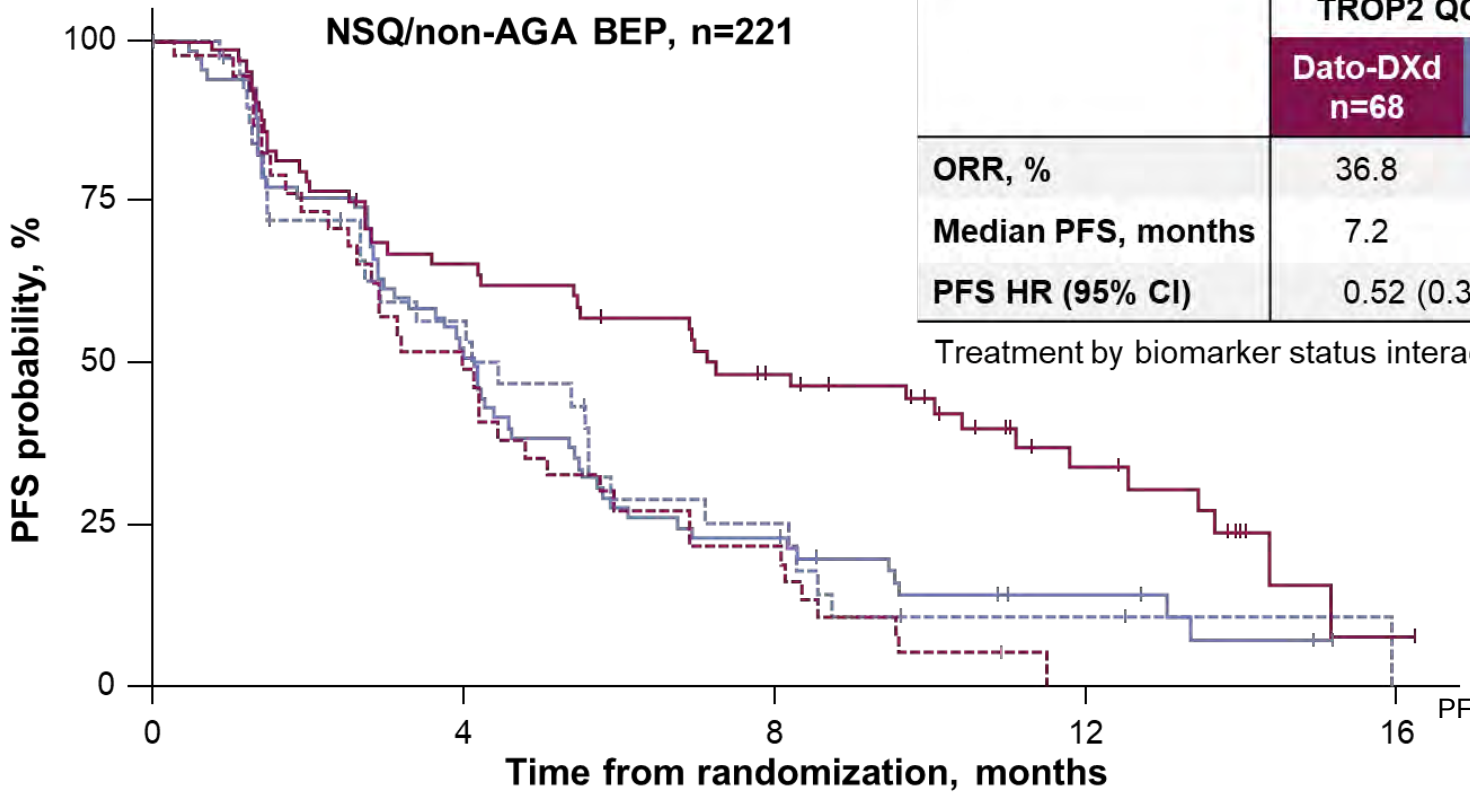
Lower NMR → higher cytoplasm proportion

Dr Marina Chiara Garassino | Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

IHC; immunohistochemistry

NSQ/non-AGA BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the NSQ/non-AGA biomarker-evaluable population



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Treatment by biomarker status interaction: p=0.0098

Dato-DXd, QCS-NMR+
Dato-DXd, QCS-NMR–
Docetaxel, QCS-NMR+
Docetaxel, QCS-NMR–

Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment:
- ✓ Dato-DXd: 0.40 [0.25-0.64]
- ✓ Docetaxel:0.94 [0.60-1.49]

- AVANZAR and TROPION-Lung10 have the potential to clinically validate the TROP2 QCS biomarker for Dato-DXd
- An additional trial in patients with biomarker-positive tumors in the 2L NSQ NSCLC setting is planned

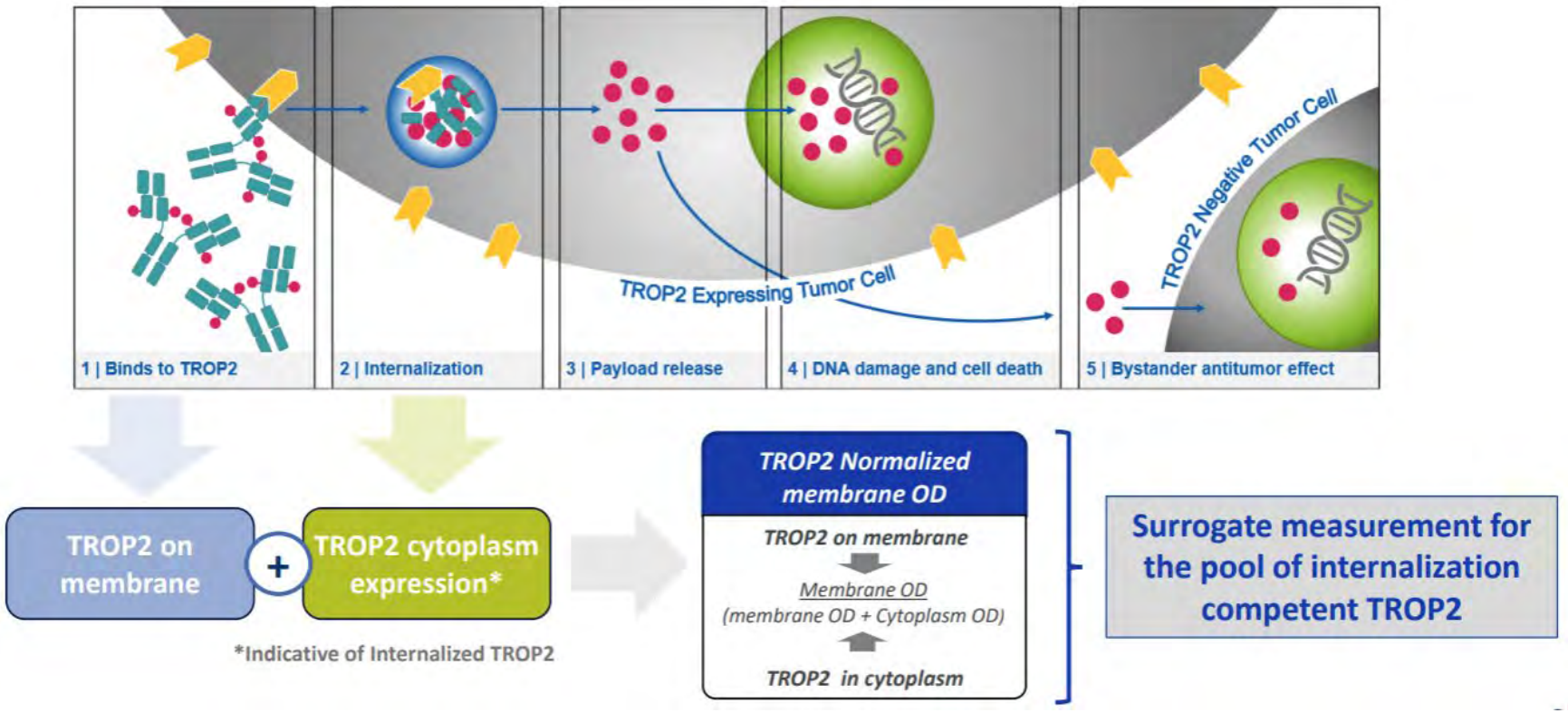
AGA; actionable genomic alteration, BEP; biomarker evaluable population, CI: confidence interval, HR; hazard ratio, NMR; Normalized Membrane Ratio, NSCLC; non-small cell lung cancer, NSQ; non-squamous, ORR; objective response rate, PFS; progression free survival, QCS; Quantitative Continuous Scoring,

QCS in Dato-DXd

A success case of hypothesis-driven predictive biomarker discovery

Hypotheses

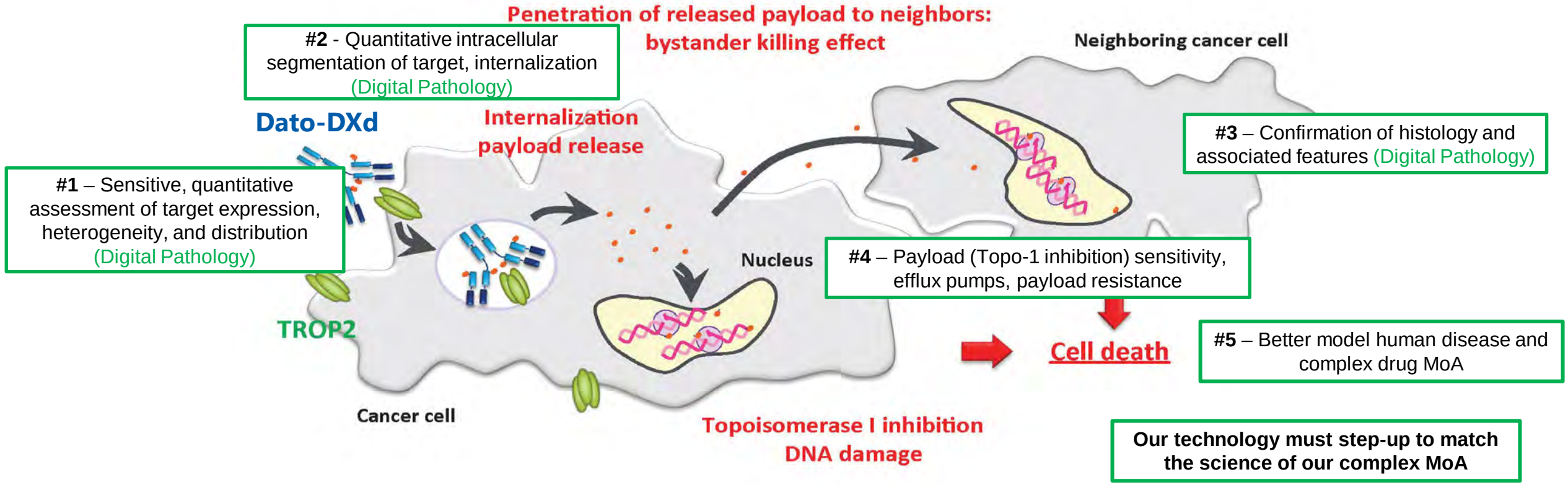
1. Precise, quantitative measurement of TROP2 in the membrane and cytoplasm, and their relationship, predict efficacy of Dato-DXd in NSCLC
2. Increased cytoplasmic expression of TROP2 identify a greater pool of cytoplasmic TROP2 capable of internalizing Dato-DXd bound to TROP2 and predict efficacy of Dato-DXd in NSCLC



NSCLC; non-small cell lung cancer, OD; optical density, QCS; quantitative continuous scoring,

Predictive Biomarkers from Focus on ADC Mechanism of Action

The mechanism of action (MoA) is more complex for DXd ADCs than conventional targeted therapies



- For conventional targeted therapies, a predictive biomarker often derives from target expression
- Target expression along with attention to key steps in the MoA may bring more success predicting efficacy
- Access to large datasets with clinical results will be critical

Daiichi Sankyo Precision Medicine

Bridge molecular science from preclinical to clinic and back

Research → **Preclinical & Early Development** → **Late Development**

Compiled Data & Biospecimens
- Preclinical research
- Patient biomarker profiles
  - genomics, proteomics, imaging
- Clinical study biomarkers
- Clinical study data
- External data

Disease pathophysiology
Target biology and drug MoA in disease
Drug-target interaction

Pharmacodynamic biomarkers
Predictive biomarkers
Profile biomarkers in disease
PK assays
Quantitative systems pharmacology

Precise development
Proof of mechanism
Dose ranging
Evaluate predictive BMs

Confirm dose
Confirm predictive BM
CDx Development
Adv analytics/integrating data

BLA/NDA
- ClinPharm modules
- Dose justification
- Efficacy in biomarker subgroups

CDx PMA
Scientifically guide additional indications & drug combos

Key issues > specific hypotheses

Tools to interrogate hypotheses

Cross-project learnings

Marketing applications

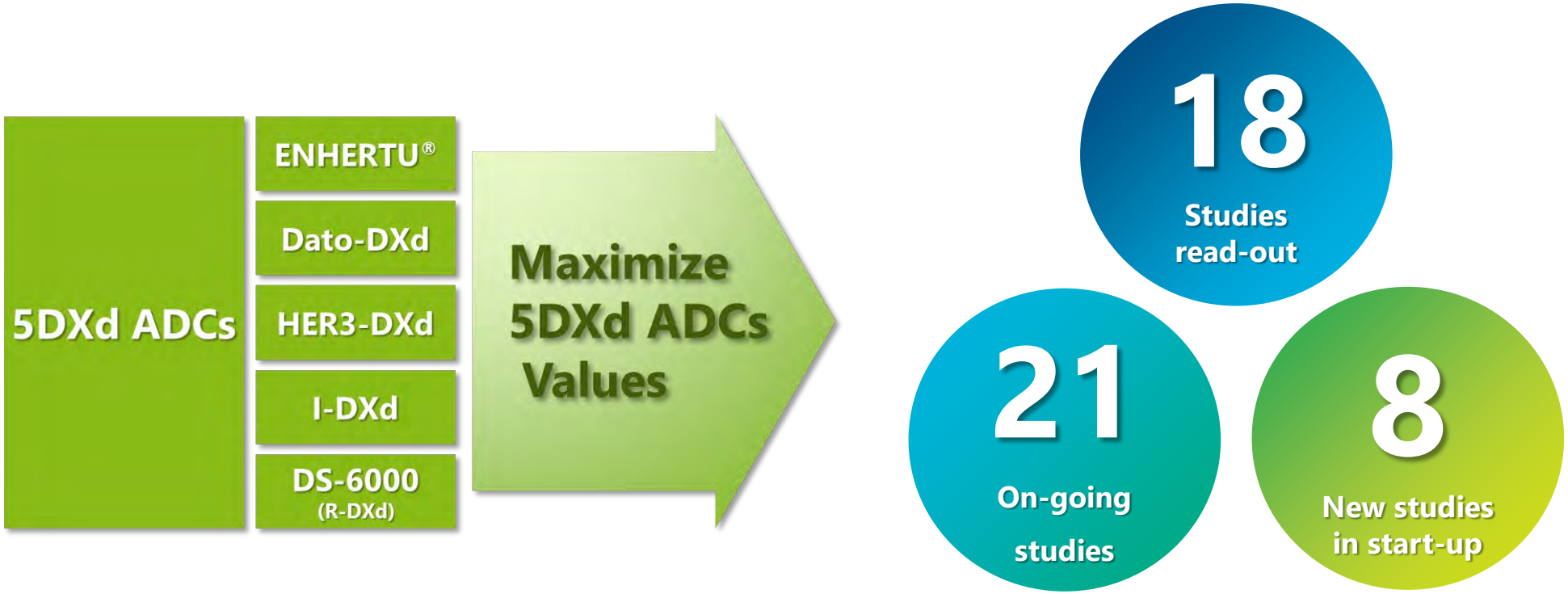
Reverse Translation:
- Rational combinations
- Drug discovery
- Disease pathophysiology
- Development strategy

Precision Medicine
Integration of molecular science for precise early development, enable and learn from late development, provide key parts of approval dossiers

BLA; biologic license application, BM; biomarker, CDx; companion diagnostics, NDA; new drug application, PK; pharmacokinetics, PMA; premarket approval

Deep Experience, Large Datasets, and Much Potential

Registrational studies across 5 DXd ADCs in numerous tumor types

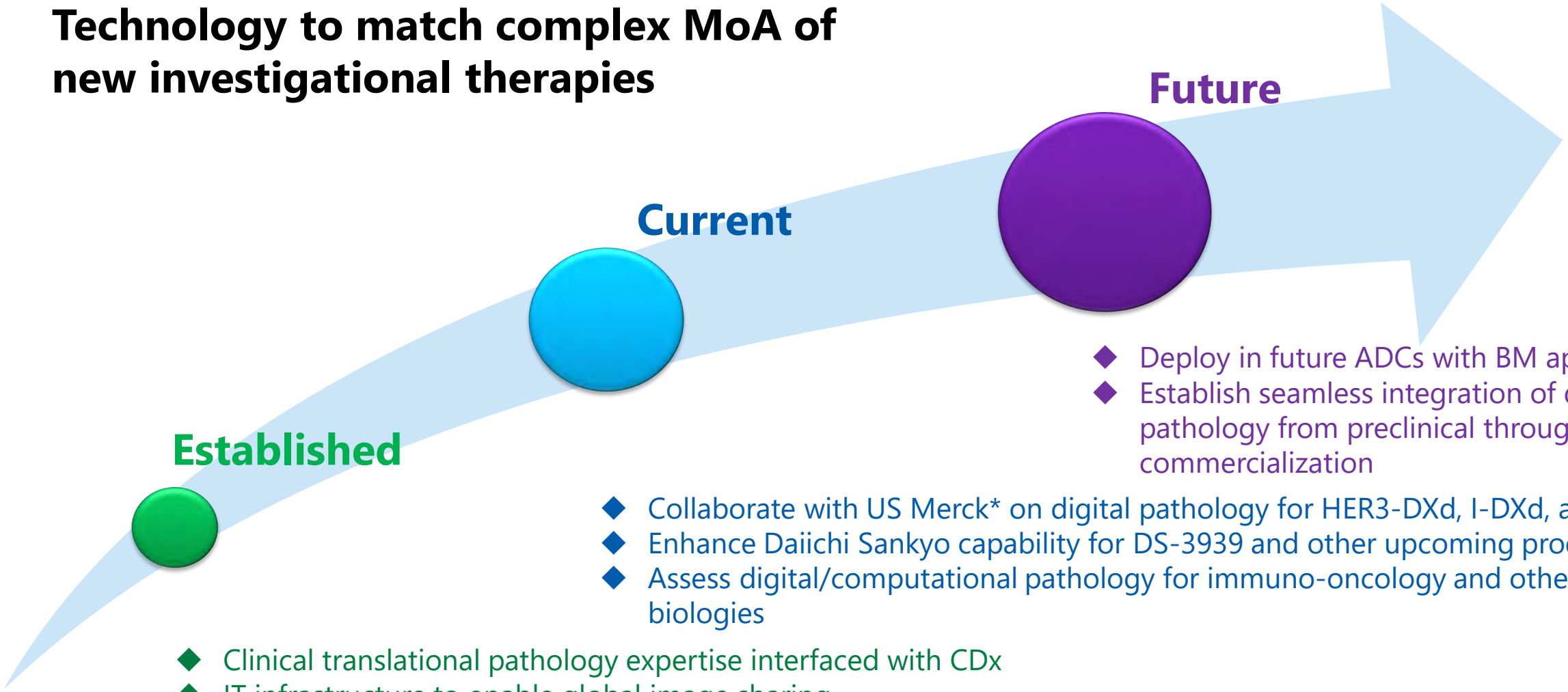


■ Learnings from 5DXd ADCs will be utilized for early asset programs

ENHERTU® : trastuzumab deruxtecan (International Nonproprietary Name: INN), T-DXd, DS-8201 (HER2-directed ADC), **Dato-DXd**: datopotamab deruxtecan (INN), DS-1062 (TROP2-directed ADC), **HER3-DXd**: patritumab deruxtecan (INN), U3-1402 (HER3-directed ADC), **I-DXd**: ifinatamab deruxtecan (INN), DS-7300 (B7-H3-directed ADC), **DS-6000**: raludotatug deruxtecan, R-DXd（CDH6-directed ADC）

Steps to Build Digital Pathology in Daiichi Sankyo

Technology to match complex MoA of new investigational therapies



- Deploy in future ADCs with BM approach
- Establish seamless integration of digital pathology from preclinical through CDx commercialization

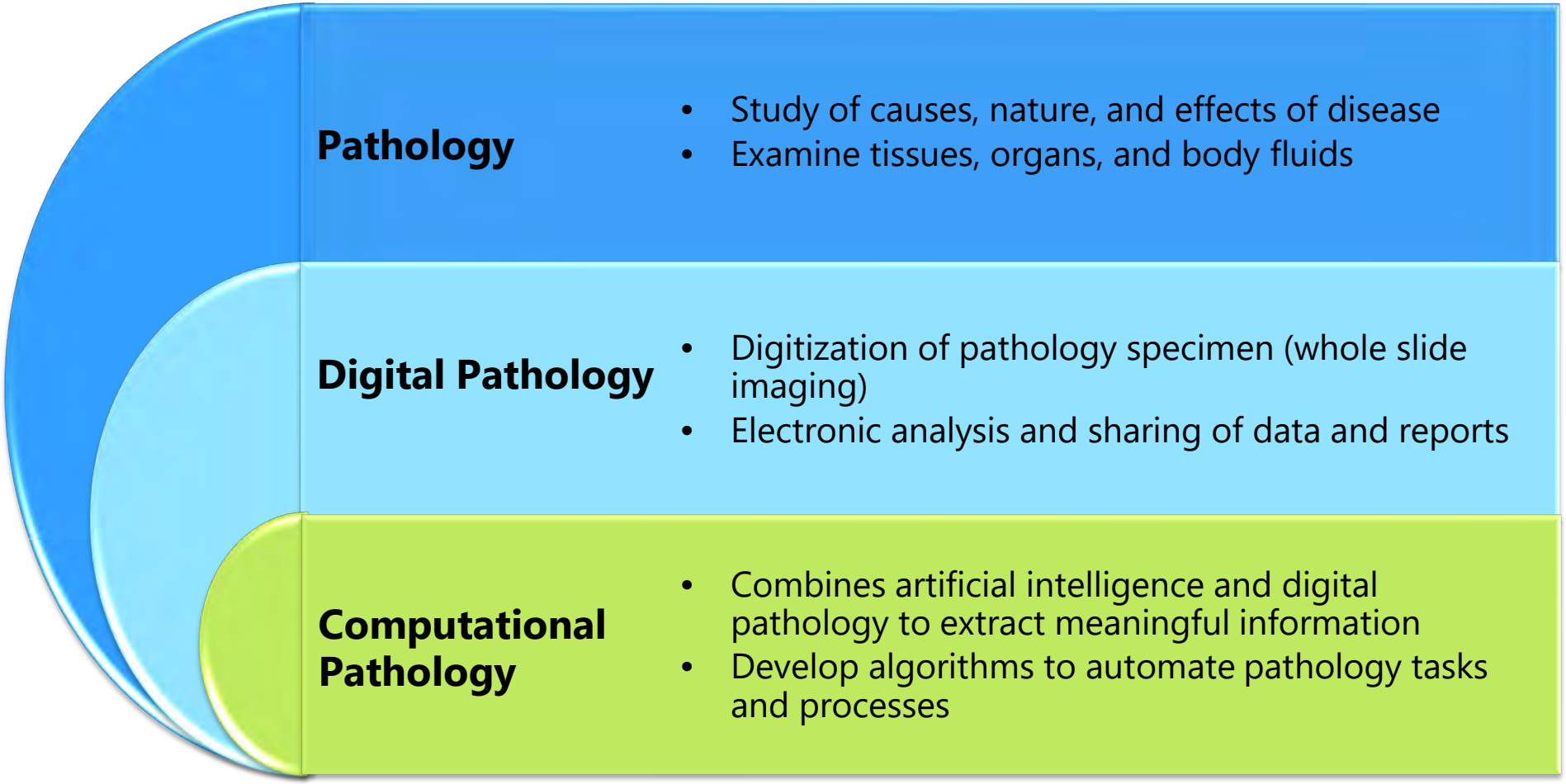
- Collaborate with US Merck* on digital pathology for HER3-DXd, I-DXd, and R-DXd
- Enhance Daiichi Sankyo capability for DS-3939 and other upcoming products
- Assess digital/computational pathology for immuno-oncology and other complex biologies

- Clinical translational pathology expertise interfaced with CDx
- IT infrastructure to enable global image sharing
- Collaborate with AstraZeneca to foster computational pathology for T-DXd and Dato-DXd

BM; biomarker, CDx; companion diagnostics, MoA; mechanism of action

* Merck & Co., Inc., Rahway, NJ, USA

Overview of Pathology Expertise and Its Build

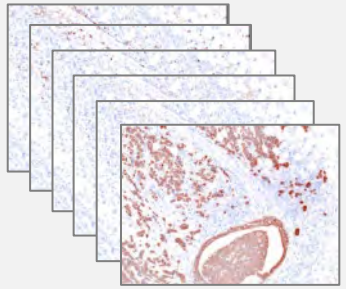


- **Achieved**
- **Established vendors**
- **Alliance partners and internal build**

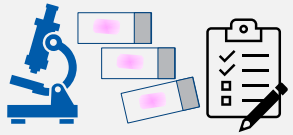
High-quality AI Model for Fluorescent Multiplex IHC

Daiichi-Sankyo

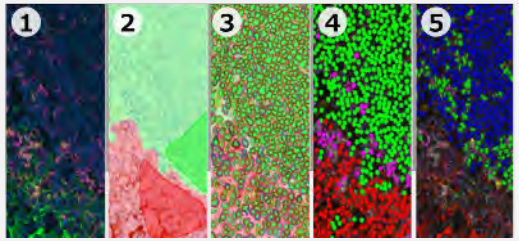
Single IHC



Manual scoring

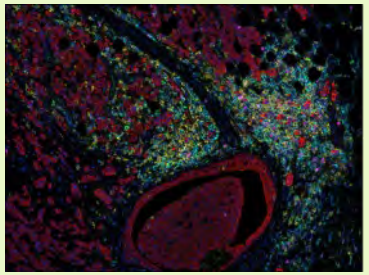


Conventional analysis flow



① Stained with 7 targets IHC
② Tissue segmentation
③ Cell segmentation
④ Phenotyping
⑤ Count cells

Multiplex IHC



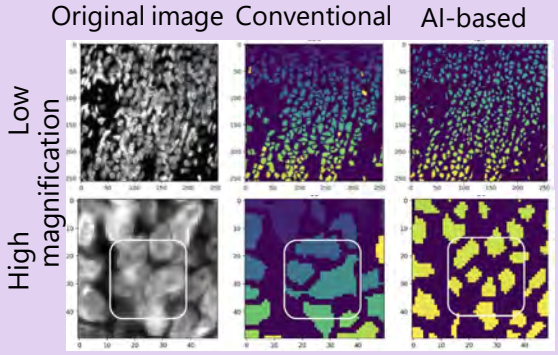
An immunostaining method, which allows the simultaneous detection of multiple markers on a single tissue section

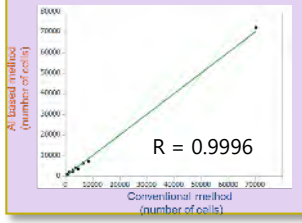
Digitalization

- Established pilot model with over 20 cell phenotyping to apply for breast, colorectal and pancreas cancers, by combining the expertise of Daiichi Sankyo and LPIXEL Inc., which is one of the leading companies of image analysis AI technologies

Improvement of the algorithm for AI-based automated analysis

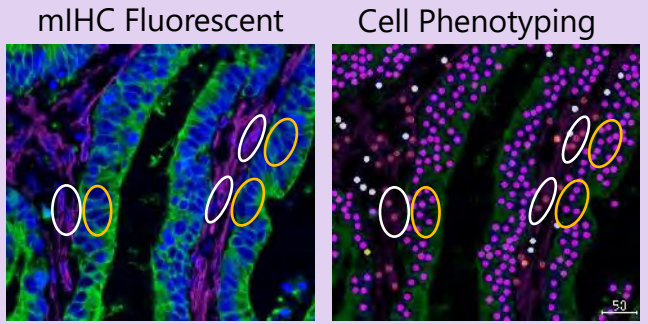
Recognition of nucleus





High correlation with conventional method in the quantitative value of the number of cells for each phenotype.

Recognition of cell type



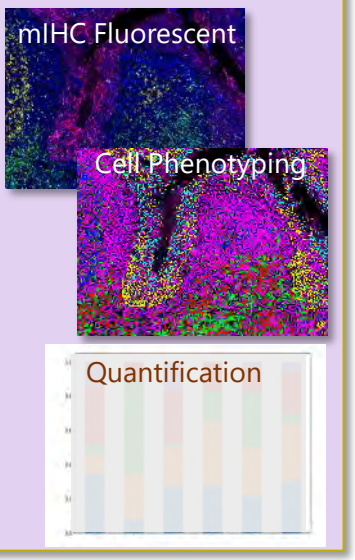
White circle: myofibroblast annotated by αSMA+ and morphology.

Yellow circle: tumor cells annotated by CK+.

Brown dot: myofibroblast

Pink dot: tumor cells recognized by the algorism

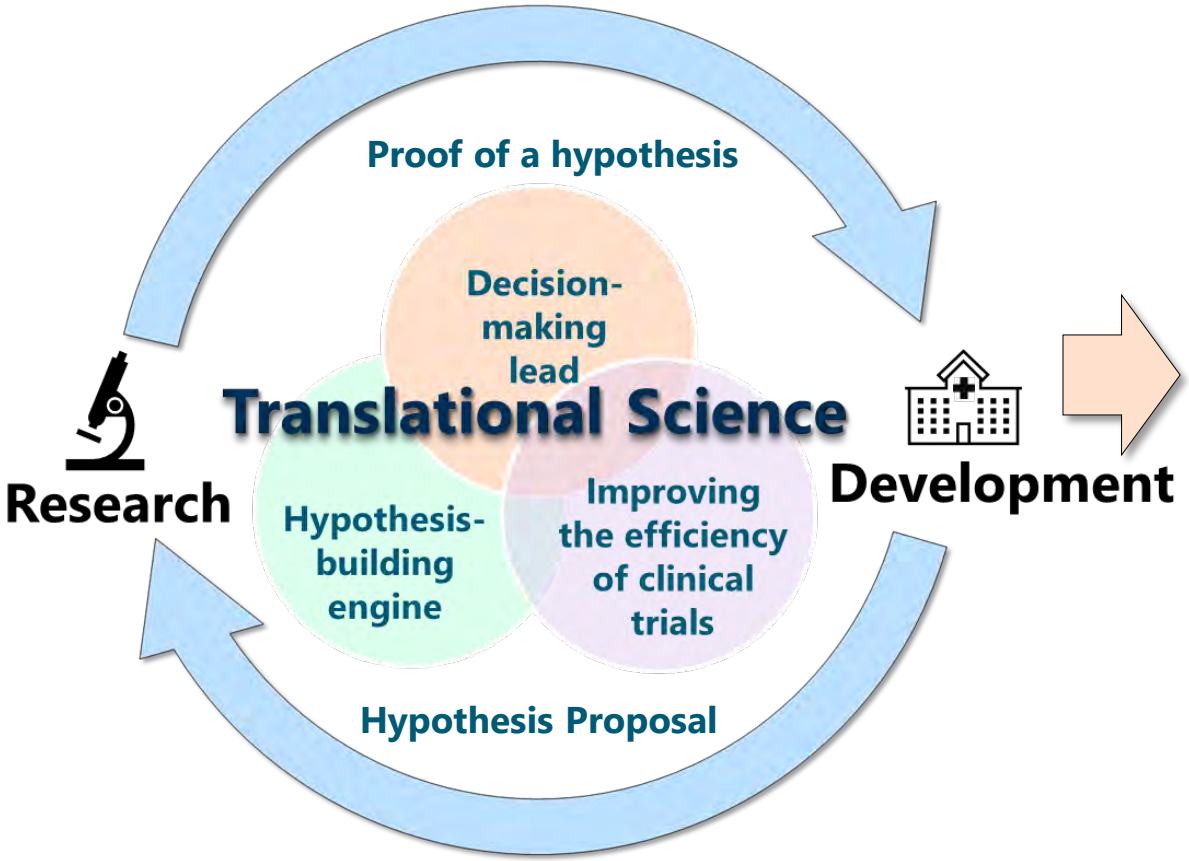
Cell phenotyping with quantification

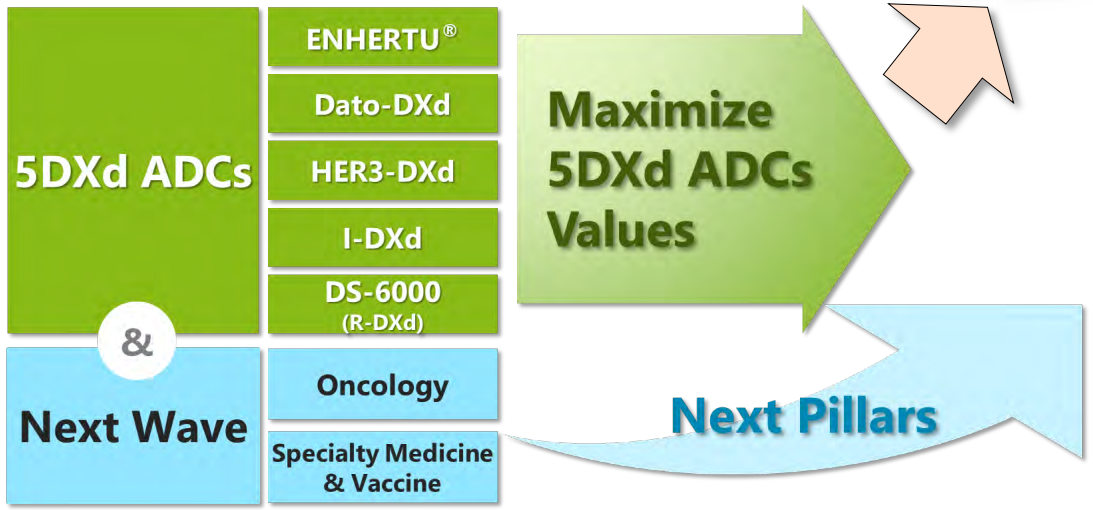


AI; artificial intelligence, IHC; immunohistochemistry

Vision of Precision Medicine at Daiichi Sankyo

- **A ROLE** that is responsible for efficient clinical trials that make optimal use of biomarkers
- **A FUNCTION** that leads decision-making based on scientific data
- **An ENGINE** that continuously generates innovation by forming a loop of hypothesis proposal and hypothesis verification in clinical trials and non-clinical trials





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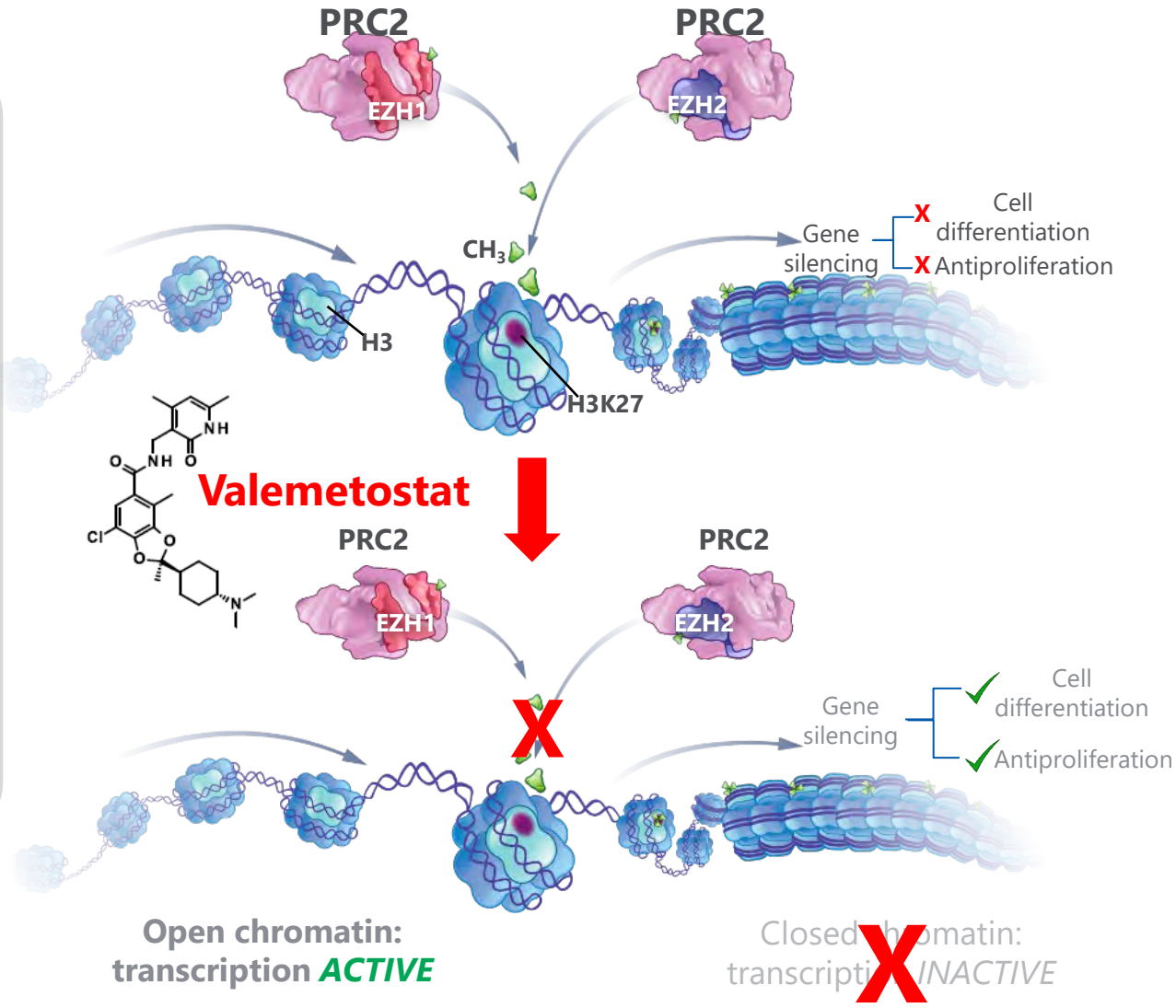
Another Example of Deep Focus on MoA: Valemetostat

Inhibition of both EZH2 and EZH1 are likely needed to fully induce pharmacological effect

Valemetostat

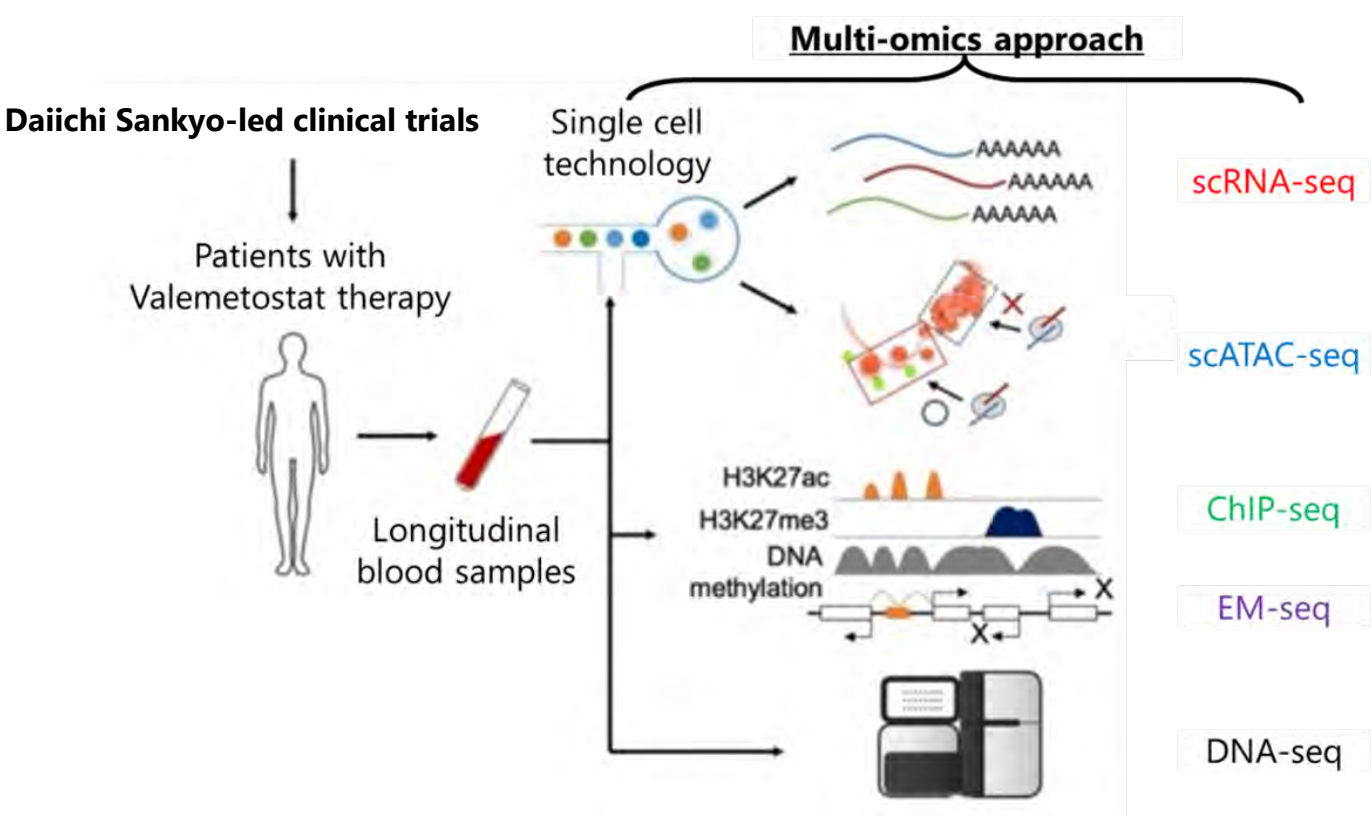
- A potent and selective dual inhibitor of EZH1 and EZH2, preventing the trimethylation of H3K27
- Alters gene expression patterns and attenuates the proliferation of EZH1/2-dependent cancer cells
- EZH1 has been shown to compensate for loss of EZH2 in some lymphoma models highlighting the importance of dual inhibition

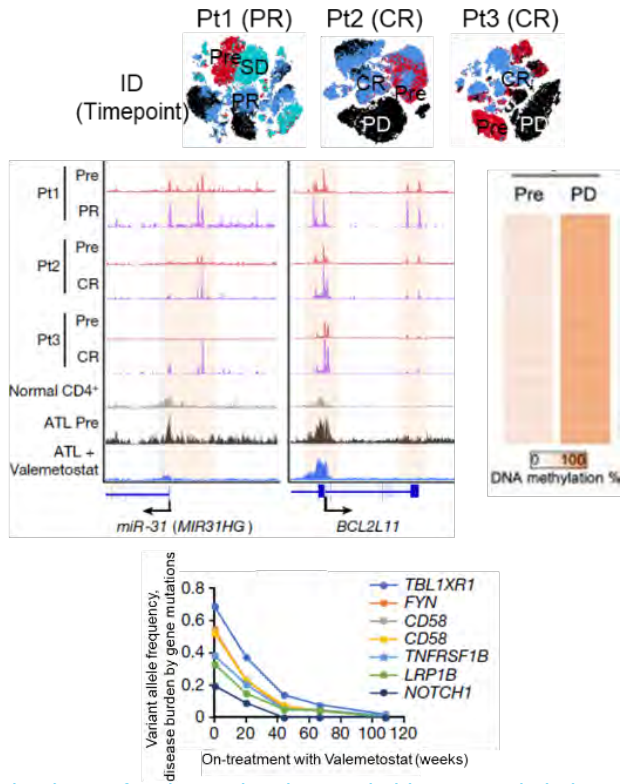


Nakagawa M, et al. AACR 2017 [abstract 4670], Nakagawa M, et al. ASH 2017 [abstract 590], Honma D, et al. Cancer Sci. 2017;108(10):2069-2078, Yamagishi M, et al. Cell Rep. 2019;29:2321-2337

MoA; mechanism of action

Mechanistic Discovery Lays the Breakthrough of Epigenetics Therapy in Refractory Hematologic Cancer





Mechanisms of action and resistance in histone methylation-targeted therapy | Nature
Yamagishi M et a. *Nature*. 2024;627:221-228

- Integration of the multilayered omics analyses and clinical resources revealed that eliminating H3K27me3 leads to the reprogramming of the cancer epigenome, including upregulation of IO and ADC targets
- The resistant mutations appeared on the docking interface of EZH2 itself or on very pivotal epigenome factors with cooperative roles in gene silencing
- These deep insights will expand program value by rationalizing various combination studies including with ICI and/or DXd ADCs

ATAC; Assay for Transposase-Accessible Chromatin, ATL; adult t-cell leukemia, ChIP; chromatin immunoprecipitation, CR: complete response, DNA; deoxyribonucleic acid, EM; Enzymatic Methyl, ICI; immune checkpoint inhibitor, IO; immuno oncology, PD; progressive disease, PR; partial response, Pt: patient, RNA; ribonucleic acid,

Agenda

1. Opening
2. R&D Update
3. Clinical Progress
4. Translational Research
5. **ADC Manufacturing & Supply**
6. Q&A

Career Highlights：Hiroto Kashiwase

2023 Executive officer, Head of Global Technology
2022 Executive officer, Head of Supply Chain Unit
2020 Corporate officer,
Head of Pharmaceutical Technology Unit
2019 Head of Pharmaceutical Technology Unit
2017 Vice President, CMC planning Department
2013 Board Member of Luitpold Pharmaceuticals Inc.*1
2011 Daiichi Sankyo Inc.
2008 CMC Planning Department
2005 Daiichi Sankyo Co., Ltd. Corporate Integration Promotion Department
2004 Corporate Management Department
2001 Planning Department
1993 Biological Research Laboratories Ⅱ
1989 Bioscience Research Laboratories, Sankyo Co., Ltd.

*1 Currently American Regent Inc.

Agenda

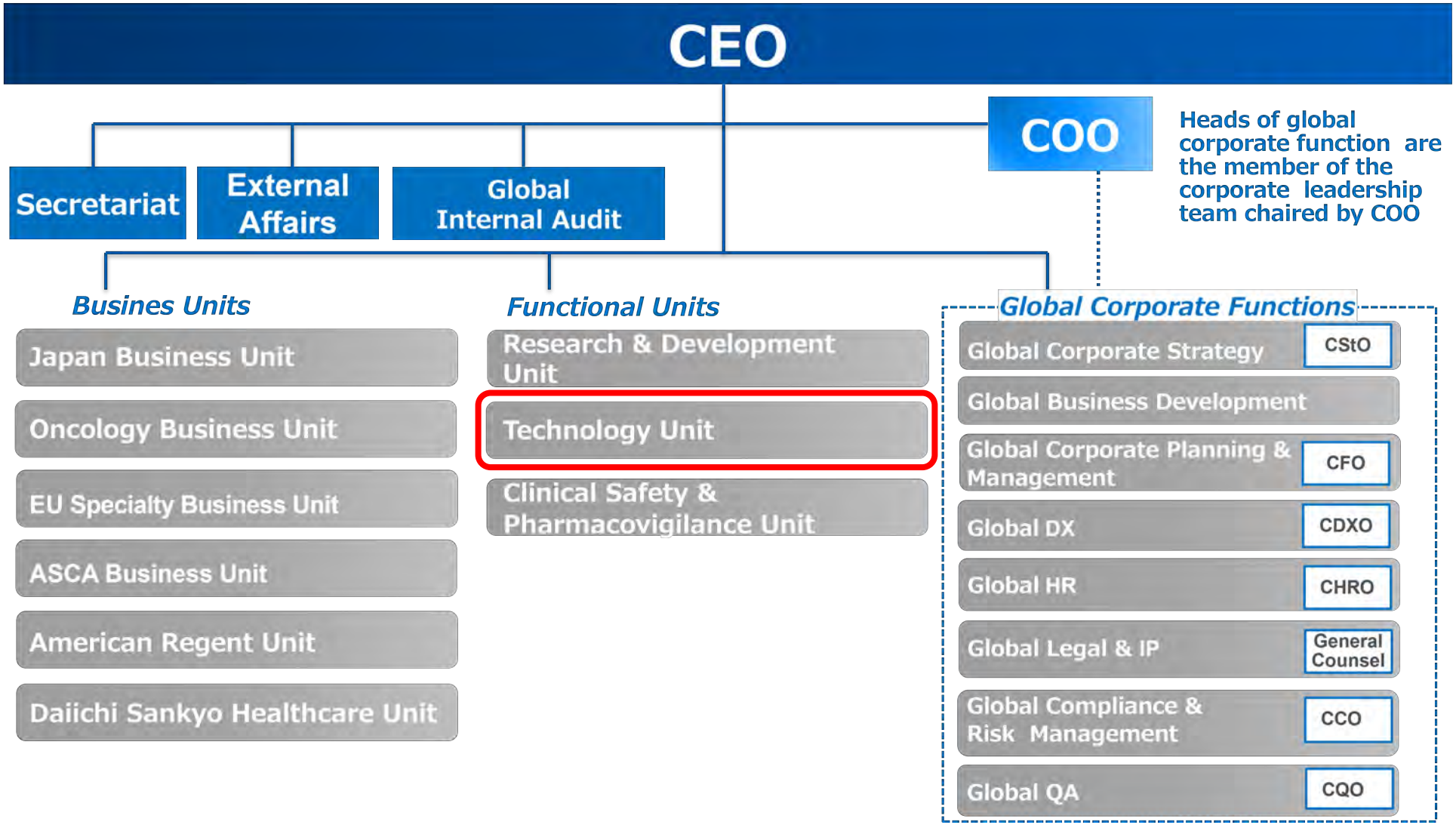
1. Introduction of Technology Unit
2. ADC manufacturing process
3. Supply strategy for 5DXd ADCs

Agenda

1. **Introduction of Technology Unit**
2. ADC manufacturing process
3. Supply strategy for 5DXd ADCs

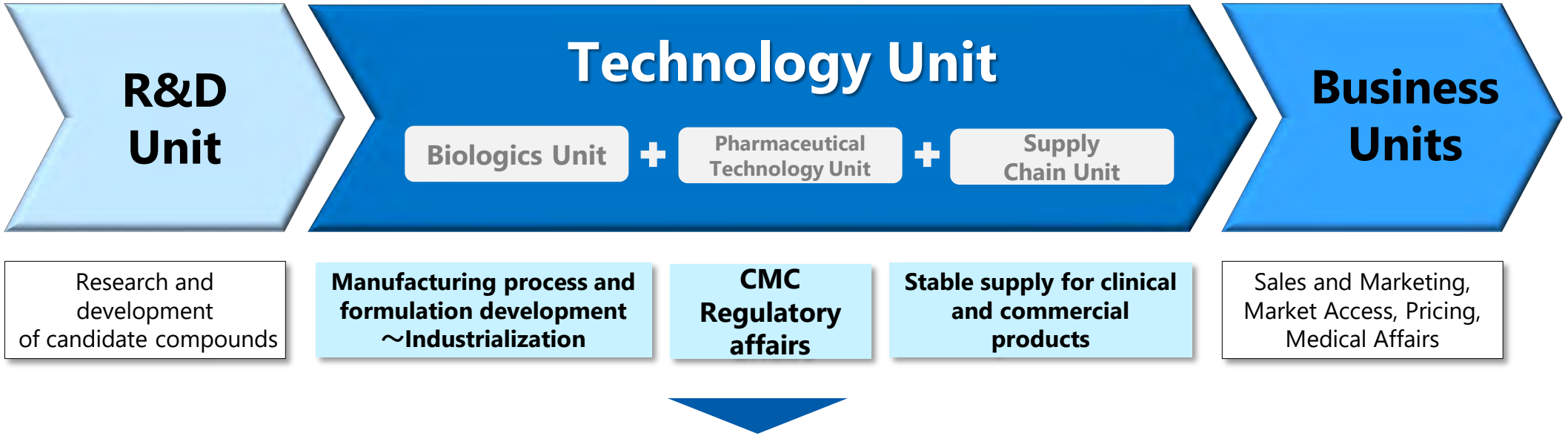
Global Management Structure

As of April 1st, 2024



Role of Technology Unit

Launched in 2023 by integrating three units, Biologics unit, Pharmaceutical Technology unit, and Supply Chain unit



Responsible for the entire manufacturing and supply processes from early development to commercial production, Contributing to Daiichi Sankyo's "Science & Technology"

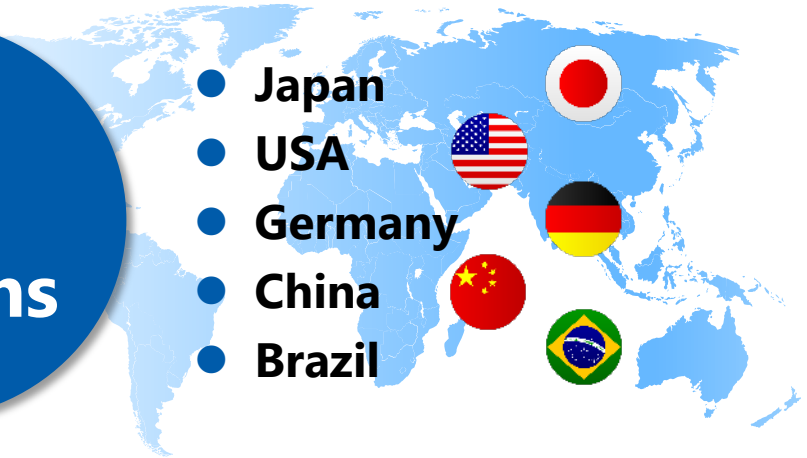
Characteristics of Technology Unit

6 Functions

- Strategy・Planning・General affairs・L&D[*1]
- CMC management
- CMC research development
- Supply chain management
- Regulatory affairs CMC
- Plant management

[*1] Learning & Development

5 Regions



- Japan
- USA
- Germany
- China
- Brazil

>4000 People

- More than 4,000 people are working in the Tech. Unit
- Equivalent to approx. 1/5 of the total number of Daiichi Sankyo employees

Agenda

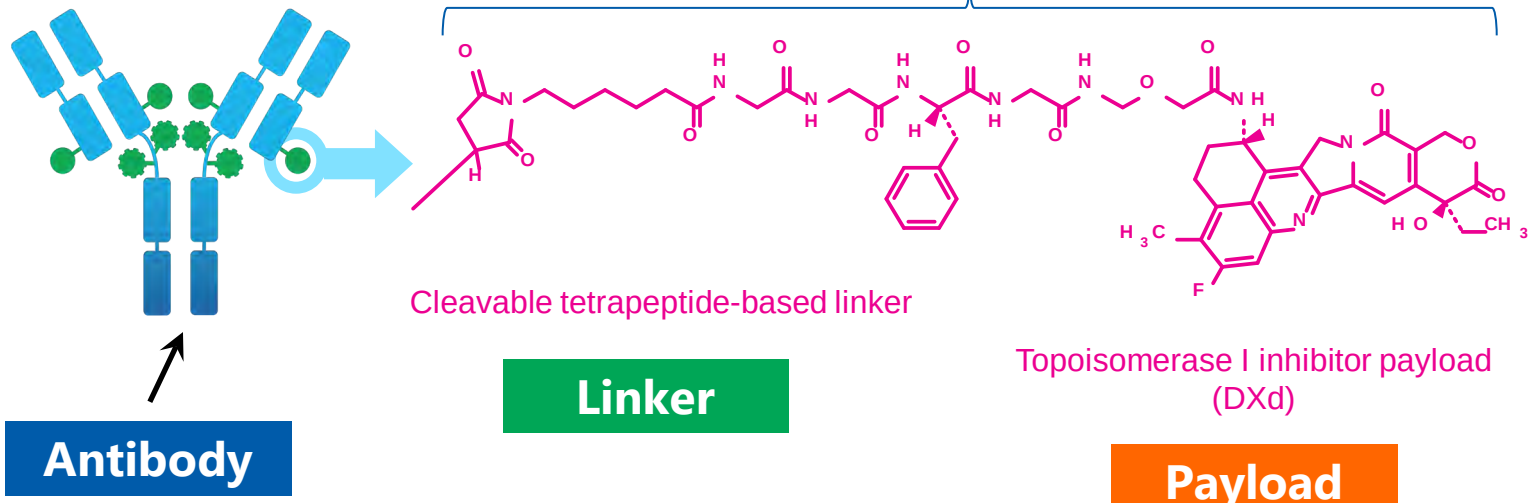
1. Introduction of Technology Unit
2. **ADC manufacturing process**
3. Supply strategy for 5DXd ADCs

Attributes of DXd ADC Technology

DXd ADCs has 3 components

- Antibody：A tumor-selective antibody
- Linker：A tetrapeptide-based cleavable linker that covalently bonds the antibody and payload
- Payload：A topoisomerase I inhibitor (an exatecan derivative, DXd)

DXd ADC Technology



7 Key Attributes of DXd ADC

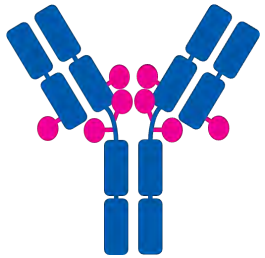
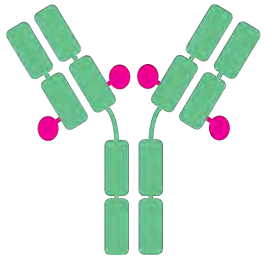
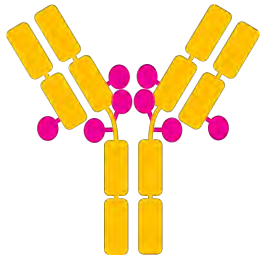
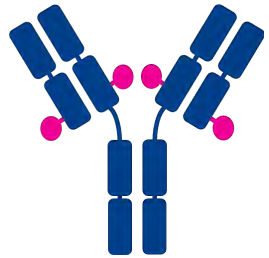
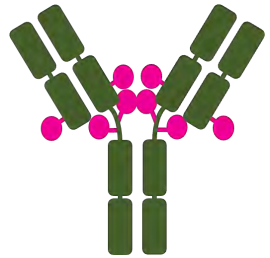
- **Payload MoA: Topoisomerase I inhibitor**
- **High potency of payload**
- **High drug to antibody ratio (DAR)**
- **Stable linker-payload**
- **Payload with short systemic half-life**
- **Tumor-selective cleavable linker**
- **Bystander antitumor effect**[*1]

[*1] The effect of the payload released within cancer cells acting on surrounding cancer cells

MoA; mechanism of action

5DXd ADCs

- Utilizing our unique ADC technology (DXd ADC Technology), high product value is anticipated
- Although the payload is the same, the target antigens and the average number of drug bindings (DAR) differ

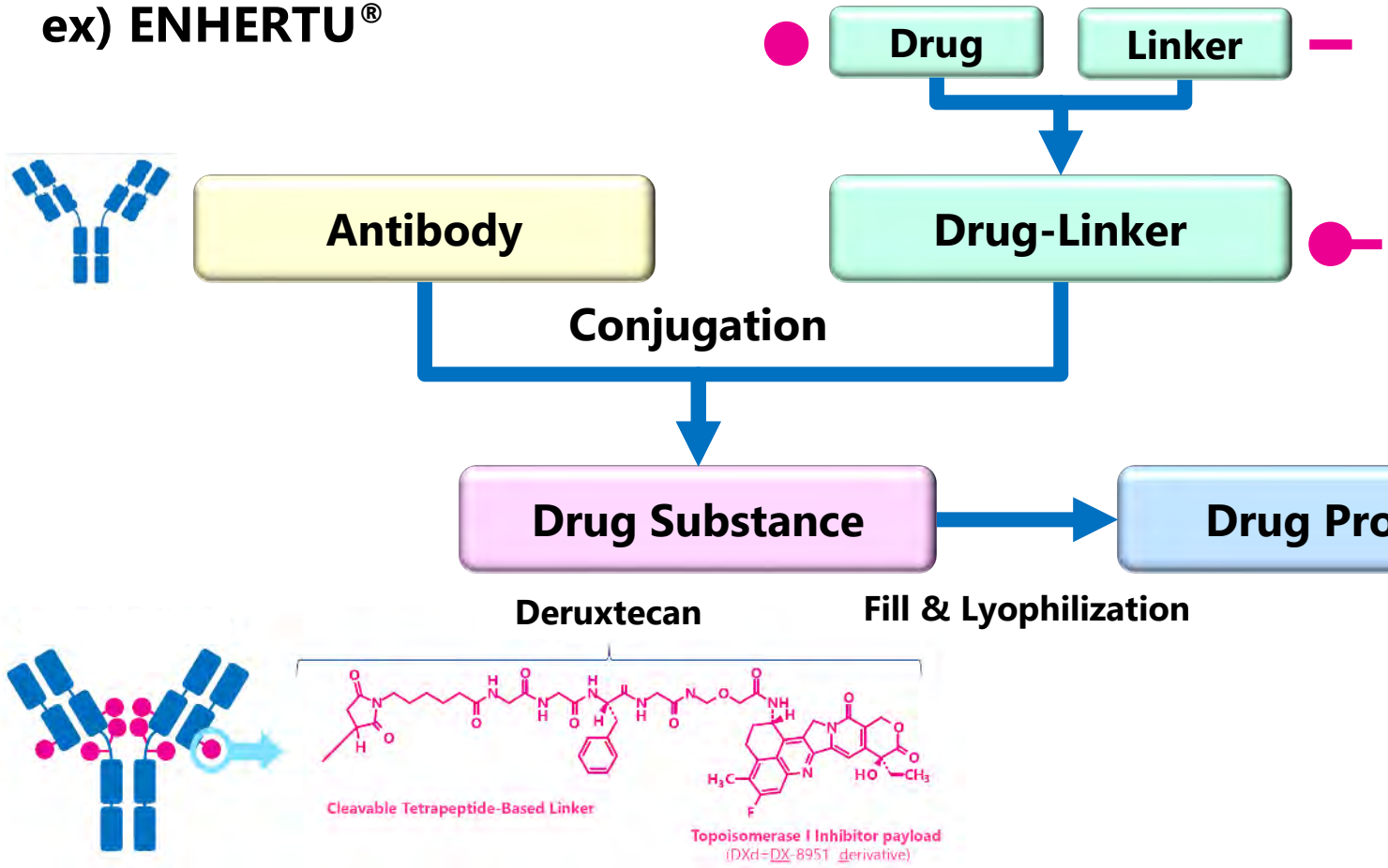
	ENHERTU®	Dato-DXd	HER3-DXd	I-DXd	DS-6000 (R-DXd)
ADC image					
Generic name	Trastuzumab deruxtecan	Datopotamab deruxtecan	Patritumab deruxtecan	Ifinatamab deruxtecan	Raludotatug deruxtecan*
Target antigens	HER2	TROP2	HER3	B7-H3	CDH6

*Japanese Accepted Names for Pharmaceuticals, JAN undecided

ADC Manufacturing Process

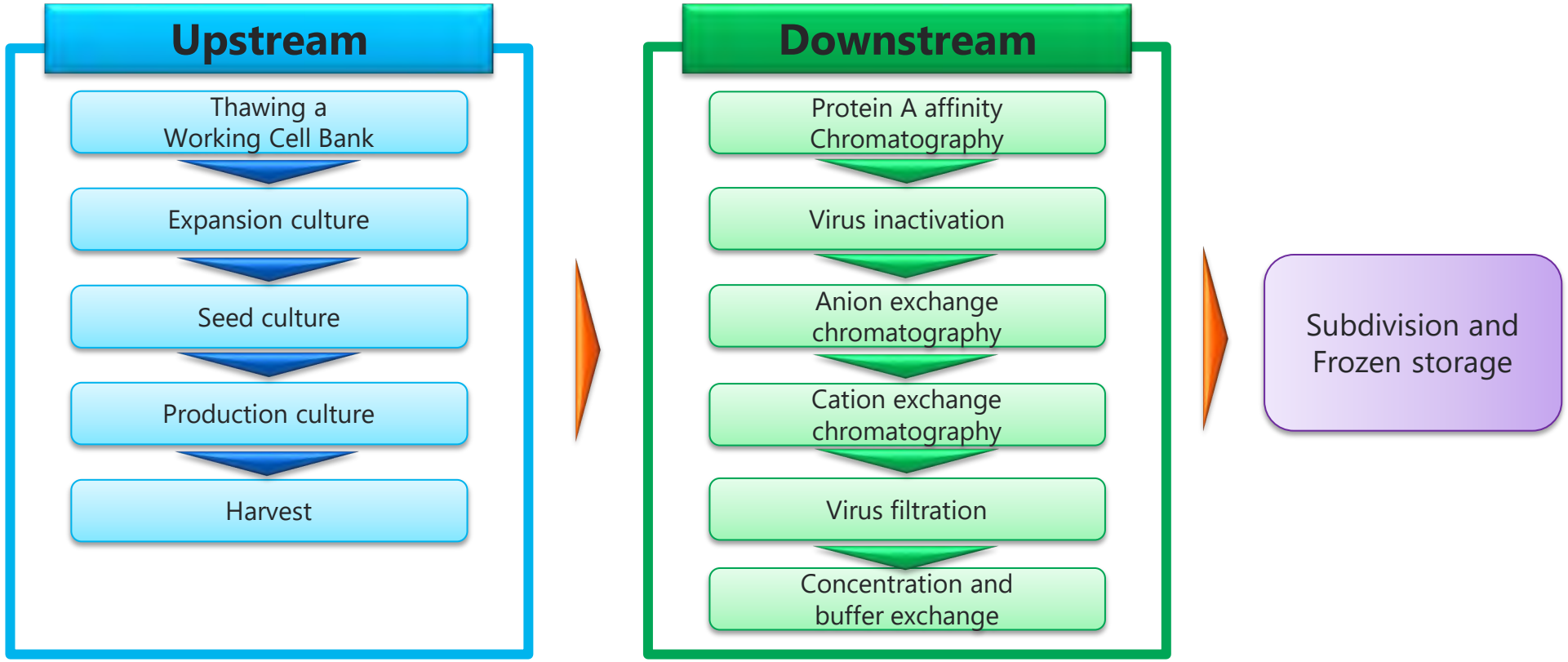
ADCs are composed of multiple components, which are manufactured and managed separately

ex) ENHERTU®



Manufacturing Process of Antibody

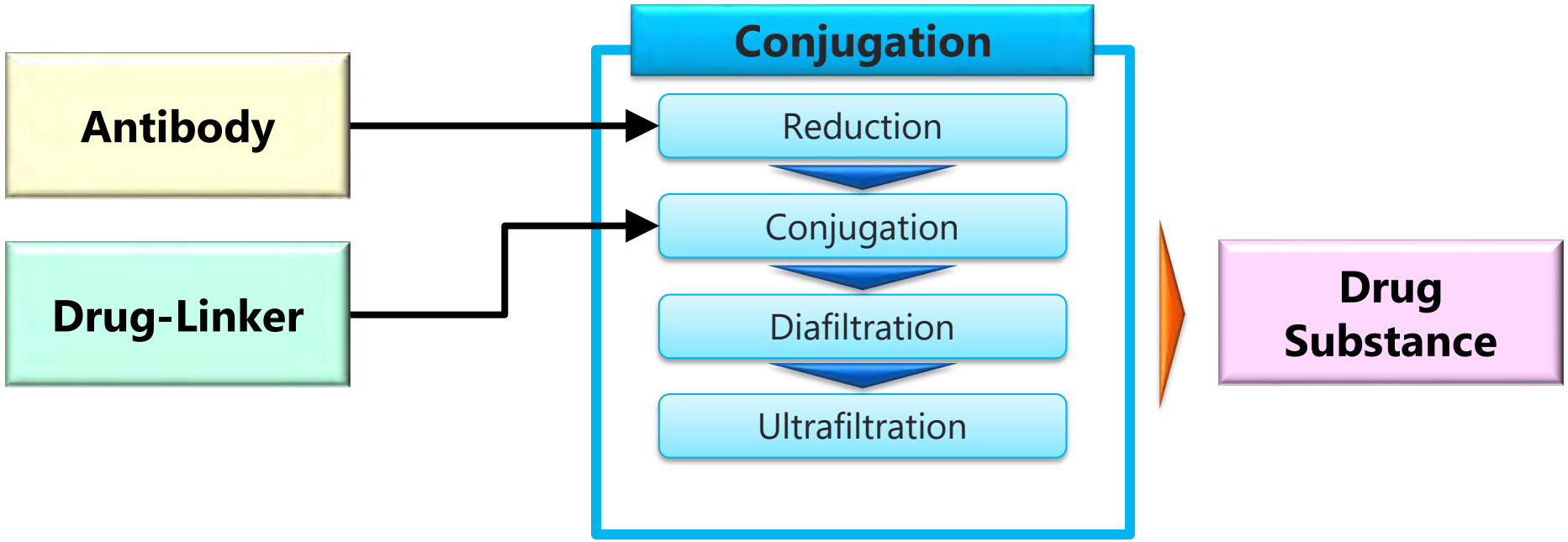
Antibody mfg. process



- Upstream process : Gradually scale up the culture to proliferate cells to a certain density and produce antibodies
- Downstream process : Remove impurities and viruses efficiently to obtain high purity target antibodies

Manufacturing Process of Drug Substance

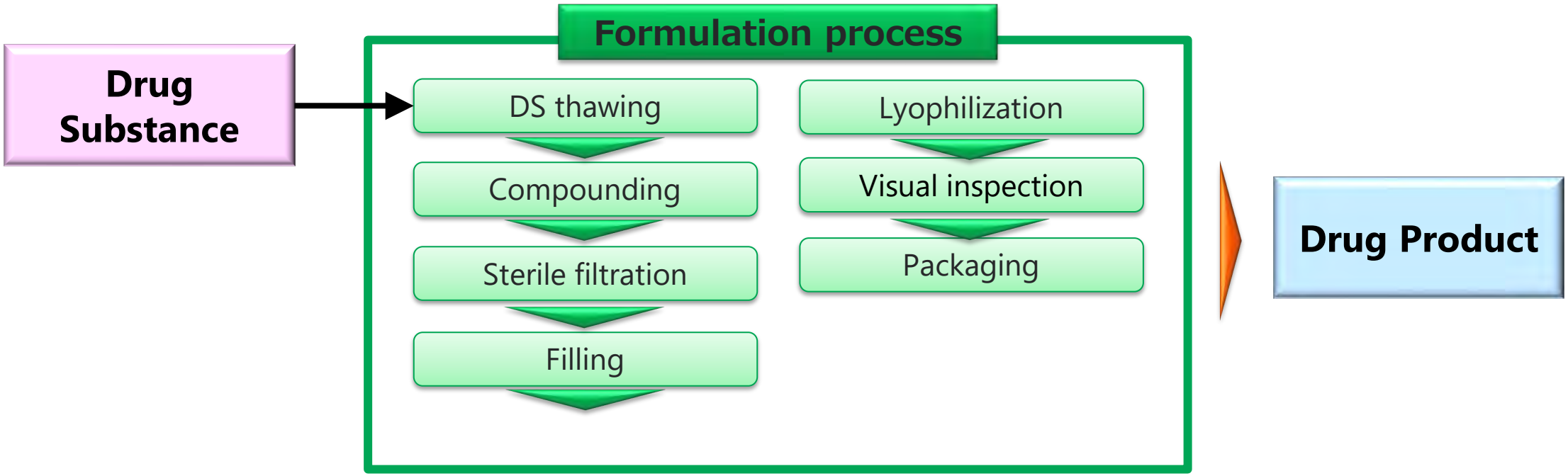
Drug Substance mfg. process



- The synthesis is achieved by reducing the disulfide bonds of the antibody and conjugating it with drug-linkers
- The drug to antibody ratio can be highly controlled through elaborate design and management of the manufacturing process. It enables high-quality drug substance production with good reproducibility

Manufacturing Process of Drug Product

Drug Product mfg. process



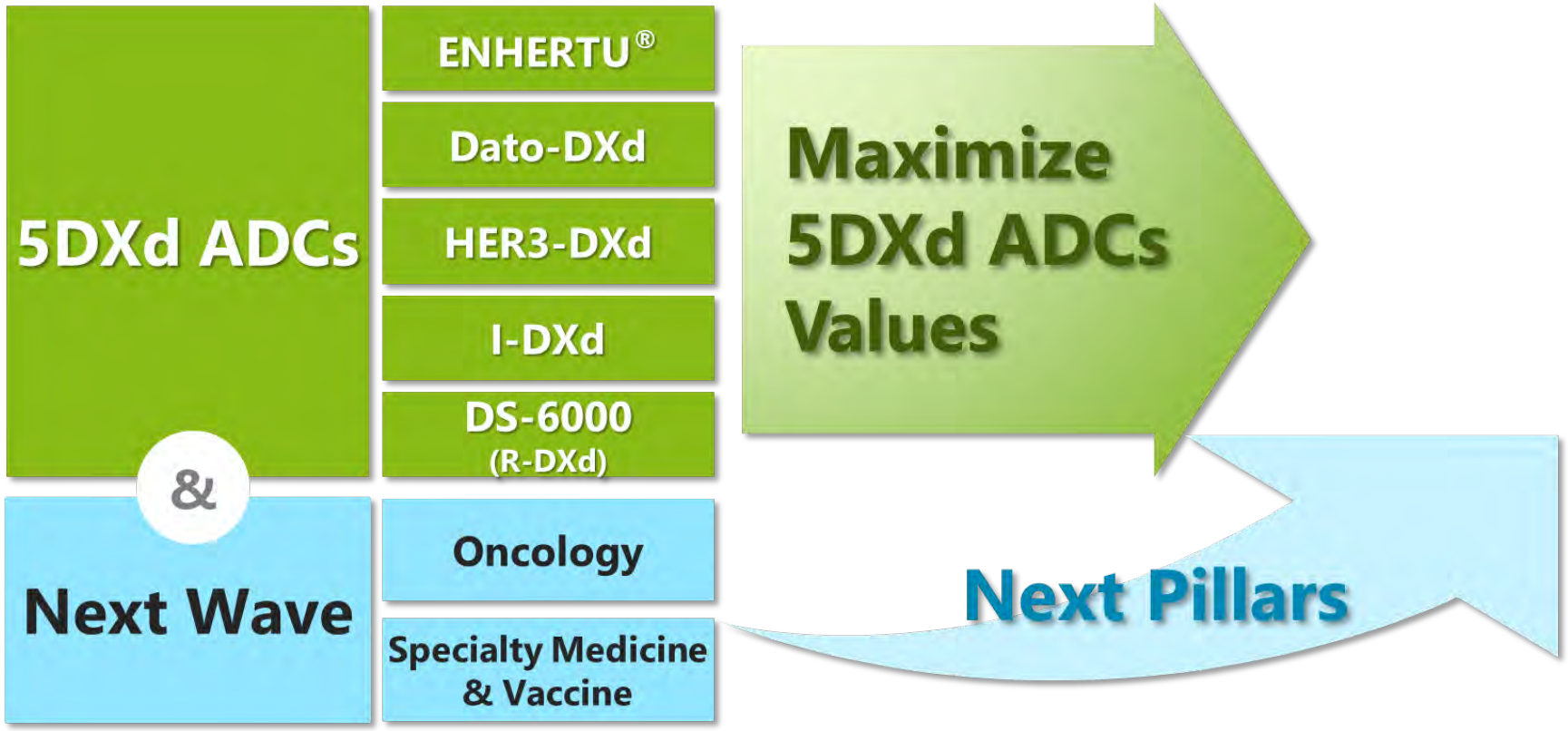
- Lyophilization technology allows long shelf-life while retaining the properties of the drug substance

Agenda

1. Introduction of Technology Unit
2. ADC manufacturing process
3. **Supply strategy for 5DXd ADCs**

5DXd ADCs and Next Wave

The most important challenge for Technology Unit
Stable deliver of our promising 5DXd ADCs to patients



ENHERTU® : trastuzumab deruxtecan (International Nonproprietary Name: INN), T-DXd, DS-8201 (HER2-directed ADC), **Dato-DXd**: datopotamab deruxtecan (INN), DS-1062 (TROP2-directed ADC),
HER3-DXd: patritumab deruxtecan (INN), U3-1402 (HER3-directed ADC), **I-DXd**: ifinatamab deruxtecan (INN), DS-7300 (B7-H3-directed ADC), **DS-6000**: raludotatug deruxtecan, R-DXd（CDH6-directed ADC）

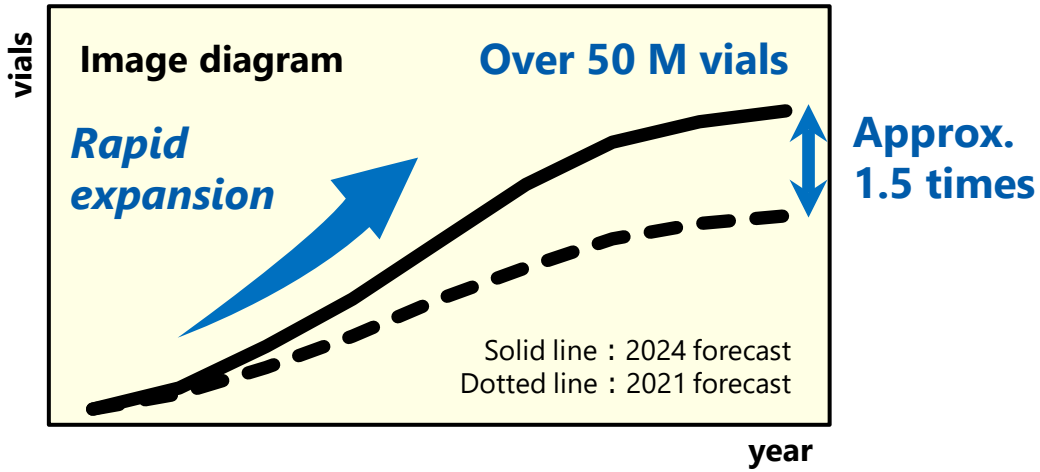
Rapid Expansion of Demand for 5DXd ADCs

With strong progress of clinical development, the overall demand forecast for 5DXd ADCs has significantly increased.

- **Strong progress of Enhertu®, Product sales forecast for FY2024 : 508.4 Bn yen**
- **The emergence of a new growth driver following 3ADC (3ADCs ➡ 5DXd ADCs)**
- **Strategic partnership with AstraZeneca (Enhertu®, Dato-DXd) and US Merck* (HER3-DXd, I-DXd, DS-6000)**

* Merck & Co., Inc., Rahway, NJ, USA

- **A demand of over 50 M vials*1 is expected for 5DXd ADCs in total.（Approx. 1.5 times*2 increased compared to the original demand forecast in the 5-Year Business Plan (FY2021-FY2025)）**



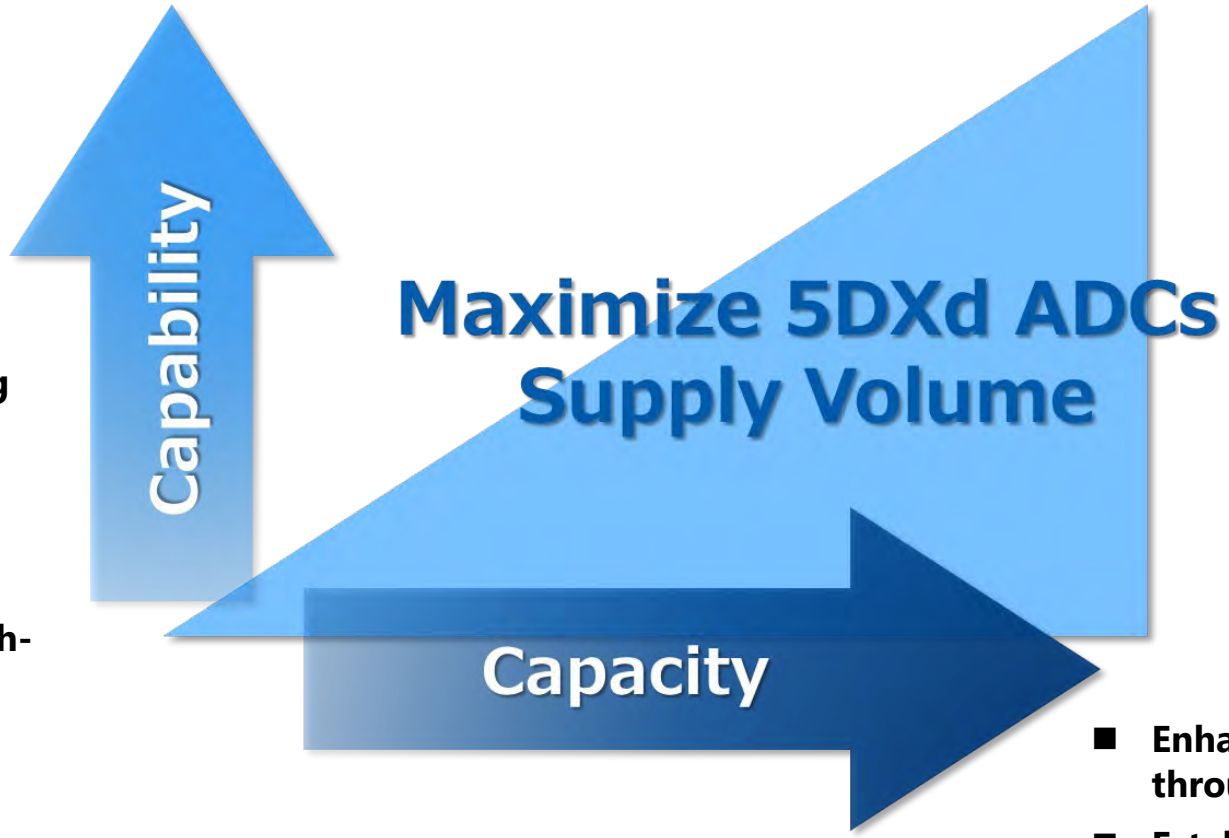
*1 Number of vials required per year at peak time (Total of 5DXd ADCs)
*2 Comparison with number of vials required per year at peak time calculated in the 5-Year Business Plan

It is essential to establish a supply system that can meet peak demand for 5DXd ADCs in total (Over 50 M vials)

Supply Strategy for 5DXd ADCs

Capacity (Expansion of production capacity) × **Capability** (Improvement of productivity) = **Maximization of supply volume**

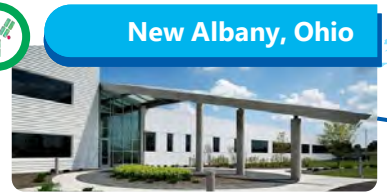
- Further improvement of productivity by leveraging technology.
- Development and strengthening of biotechnology specialist
- Transformation into a high-productivity organization

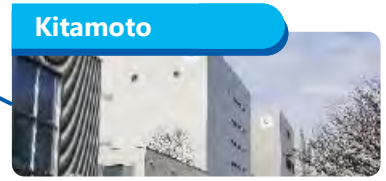


- Enhancement of production capacity through capital investment
- Establishment and expansion of a global supply system

Enhancement of Supply Capacity through Capital Investment in in-house and CMOs

Daiichi-Sankyo





Promoted capital investment of approx. 600 Bn yen*1 globally, including in-house and CMOs

Supply capacity expected to meet peak demand for the 5 DXd ADCs in total

Sites executing or considering capital investment for ADCs

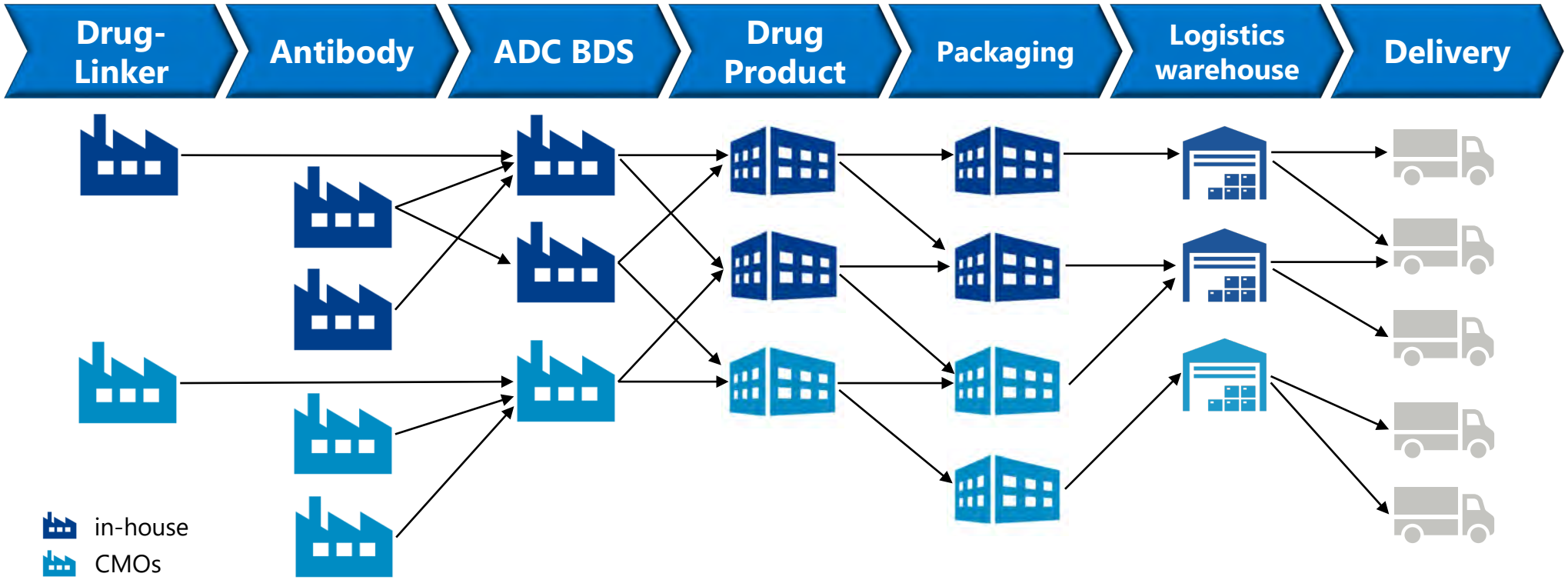
*1 The total amount of capital investment related to ADCs planned in the 5-Year Business Plan

CMO; contract manufacturing organization

Establishment and Expansion of a Global Supply System

Multiple manufacturing and supply routes have been established by effectively utilizing both in-house and CMOs

- By effectively utilizing both in-house and CMOs, we have secured supply capacity to adjust to the rapid increase in demand
- By establishing multiple manufacturing and supply routes globally, we are reducing product supply risks



※The above supply routes are an image and differs from the actual supply system

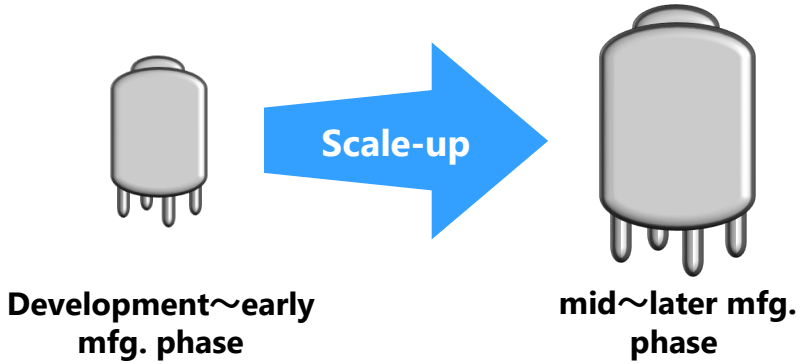
BDS; bio drug substance, CMO; contract manufacturing organization

Improvement of Productivity through Technological Enhancements

By continuously strengthening our technology,
we will achieve further improvements in productivity and stable production.

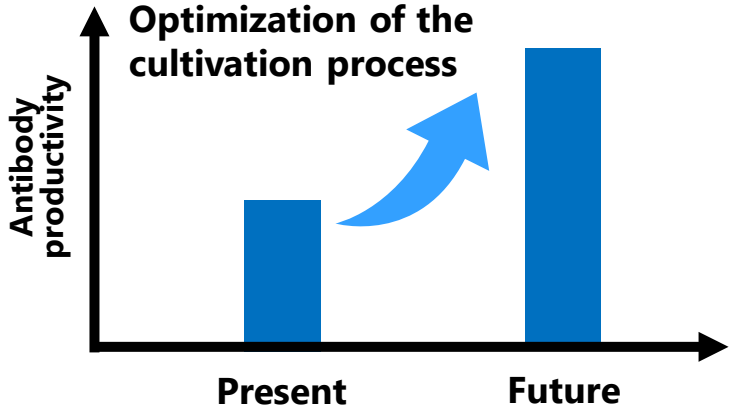
■ Scale-up of manufacturing processes

✓ Improvement of productivity through the scale-up of manufacturing processes for antibodies, Drug Substance, and Drug Products



■ Optimization of the antibody manufacturing process

✓ Enhancing the productivity of antibodies by utilizing highly productive cell lines and optimizing the cultivation process (such as medium improvement and culture conditions)



Development and Strengthening of Biotechnology Specialist

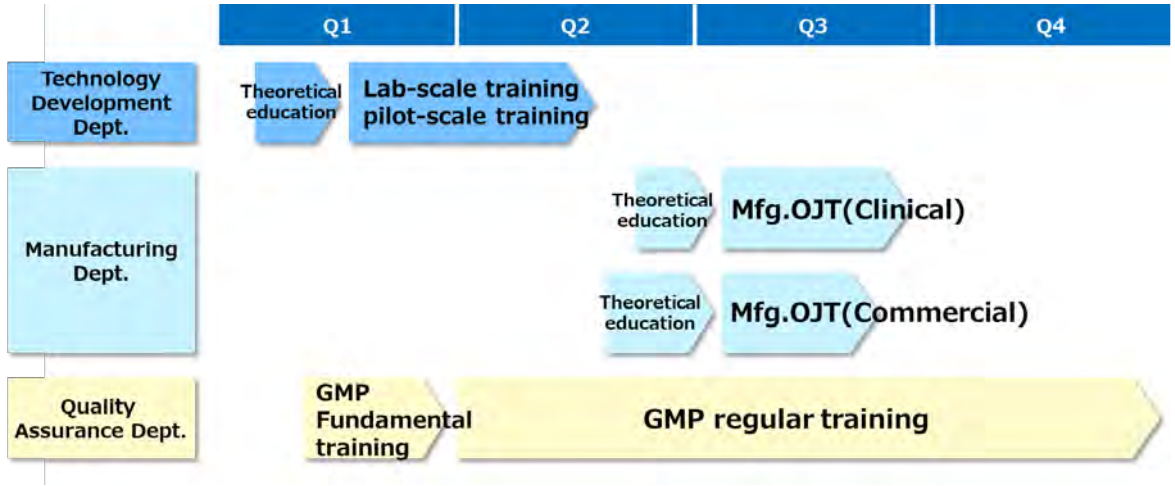
Developing and strengthening biotechnology specialist is essential for the development and stable supply of ADC products

Priority area	Target profile
Development of antibody manufacturing processes	A person who has a deep understanding of the manufacturing processes involved in biopharmaceuticals and can carry out process development research that contributes to drug discovery research for biopharmaceuticals and cost reduction for 5DXd ADCs.
QC, QA, RA, manufacturing	A person who understands the manufacturing processes of biopharmaceuticals and can utilize their expertise to promote biopharmaceutical-related activities within the technology unit and throughout the entire value chain.

- **Proactive recruitment activities and effective utilization of internal talent through reskilling**
- **Implementation of training programs to accelerate people development of biotechnology specialist**
- **Seamless personnel exchange through the integration of organizations and functions**

■ Training program for antibody manufacturing operators

Related departments collaborate to promote the training of operators throughout the year.



GMP; good manufacturing practice, OJT; on-the-job training, QA; quality assurance, QC; quality check, RA; regulatory affairs

Agenda

1. Opening
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Contact address regarding this material

Daiichi Sankyo Co., Ltd.
Corporate Communications Department

TEL: +81-3-6225-1125
Email: DaiichiSankyoIR_jp@daiichisankyo.com