Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ASCO 2021 Highlights

DAIICHI SANKYO CO., LTD.

Sunao Manabe

President and CEO

June 8, 2021

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Progress since ASCO 2020

Enhertu®

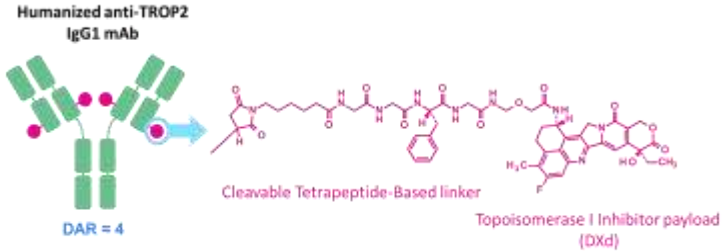
ENHERTU
trastuzumab deruxtecan

Strategic alliance with AZ delivering:

- **Strong market introduction/penetration**
  - **Addition of launched countries for HER2 positive breast cancer 3L**
- **New indications**
  - **HER2 positive gastric cancer**

  3L (Japan), 2L (US)
- **Steady progress for clinical development**
  - **Initiated nine studies for broad cancer types**

Dato-DXd

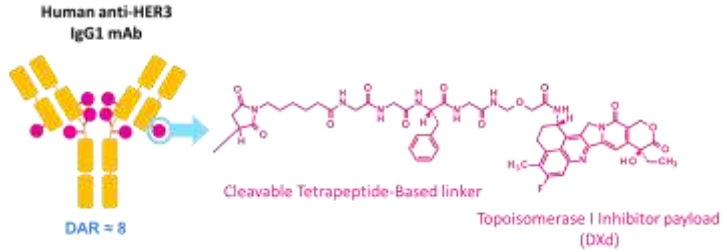


- **Formed strategic alliance with AZ**
- **Accelerating clinical development through the alliance**
  - **NSCLC 2/3L**

    Initiate pivotal trial
  - **Ph1 TNBC cohort**

    Acquired interim data
  - **Initiated three other NSCLC studies**

HER3-DXd



- **Initiated NSCLC 3L pivotal trial aiming for earliest launch through in-house development**
- **Initiated other NSCLC / CRC studies**

CRC: colorectal cancer, NSCLC:non-small cell lung cancer,TNBC: triple negative breast cancer

5-Year Business Plan (FY2021-FY2025) for Sustainable Growth

Under ESG management, we will realize our 2025 Vision, Global Pharma Innovator with Competitive Advantage in Oncology, and will shift to further growth toward our 2030 Vision

2030 Vision

Innovative Global Healthcare Company Contributing to the Sustainable Development of Society

- **Global top 10 in Oncology**
- **Additional growth pillars being source of revenue and profit**
- **New products being source of profit in each business unit**
- **Contributing to sustainable development of society through our business**

As of FY2020

- Oncology business launched
- Edoxaban growing
- Regional value being enhanced
- AZ strategic alliance
- Increased RD investment

Strategic Pillars for the 5-Year Business Plan (FY2021-FY2025)

Realize 2025 Vision and Shift to Further Growth

Maximize 3ADCs

- Maximize ENHERTU and Dato-DXd through strategic alliance with AstraZeneca
- Maximize HER3-DXd without a partner
- Expand work force and supply capacity flexibly depending on changes around product potential

Profit growth for current business and products

- Maximize Lixiana profit
- Grow Tarlige, Nilemdo, etc. quickly
- Transform to profit structure focused on patented drugs
- Profit growth for American Regent and Daiichi Sankyo Healthcare

Identify and build pillars for further growth

- Identify new growth drivers following 3ADCs
- Select and advance promising post DXd-ADC modalities

Create shared value with stakeholders

- Patients: Contributing to patients through “Patient Centric Mindset“
- Shareholders: Balanced investment for growth and shareholder returns
- Society: Environment load reduction across the value chain, and actions against pandemic risks
- Employees: Create one DS culture through fostering our core behaviors

- Data-driven management through DX, and company-wide transformation through advanced digital technology
- Agile decision making through new global management structure

*3ADCs:1) ENHERTU, Trastuzumab deruxtecan(T-DXd, DS-8201) , 2) Datopotamab deruxtecan(Dato-DXd、DS-1062) and 3) Patritumab deruxtecan(HER3-DXd、U3-1402)

Cash Allocation for the 5-Year Business Plan (FY2021-FY2025)

Prioritize R&D and capital investments for 3ADCs and pay dividends taking account of profit growth

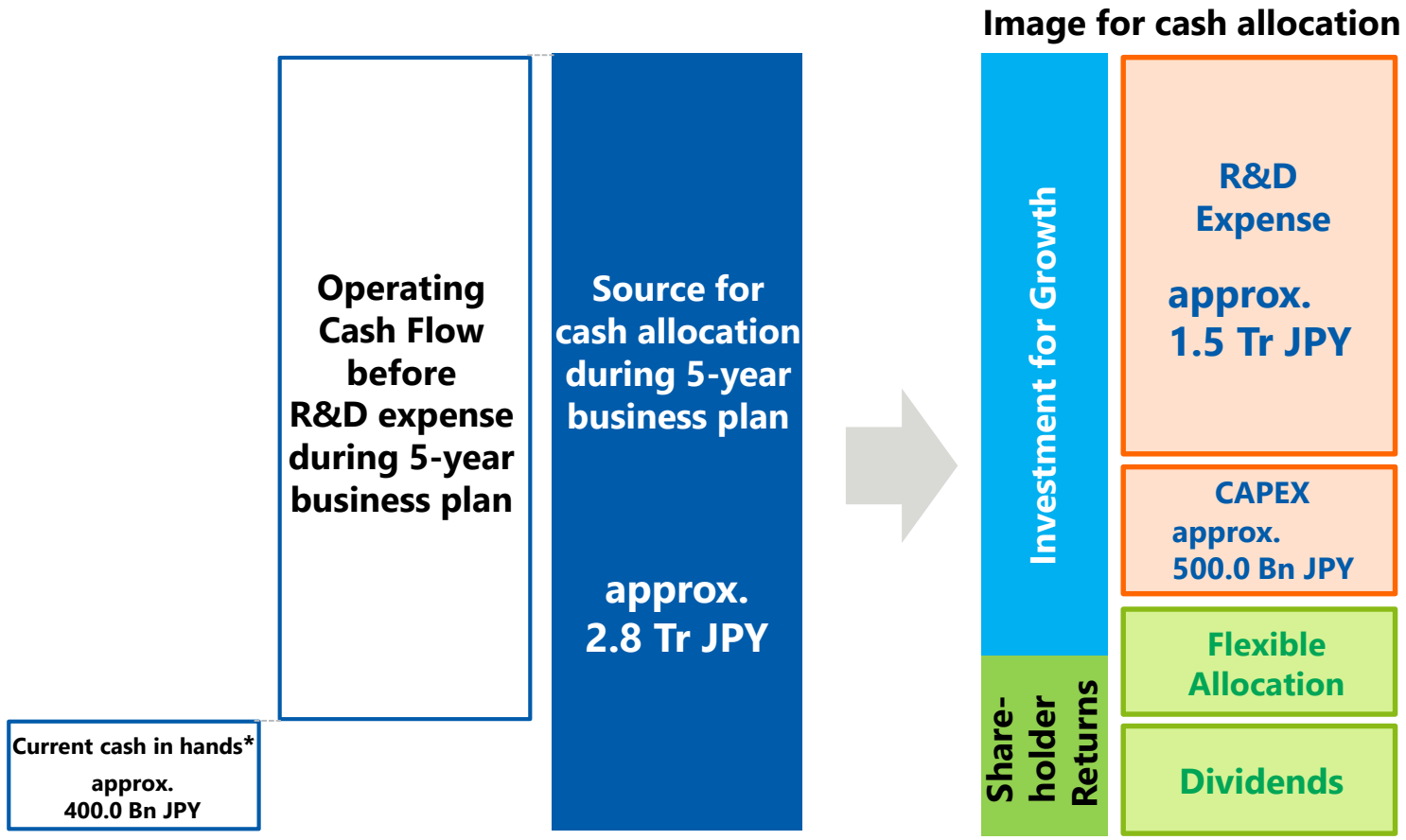


Image for cash allocation

Prioritized investment for 3ADCs

Investment focused on enhancing ADC supply capabilities

Flexible allocation depending on pipeline progress for 1) investment to build pillars for further growth (in-house/external); and 2) acquisition of own shares

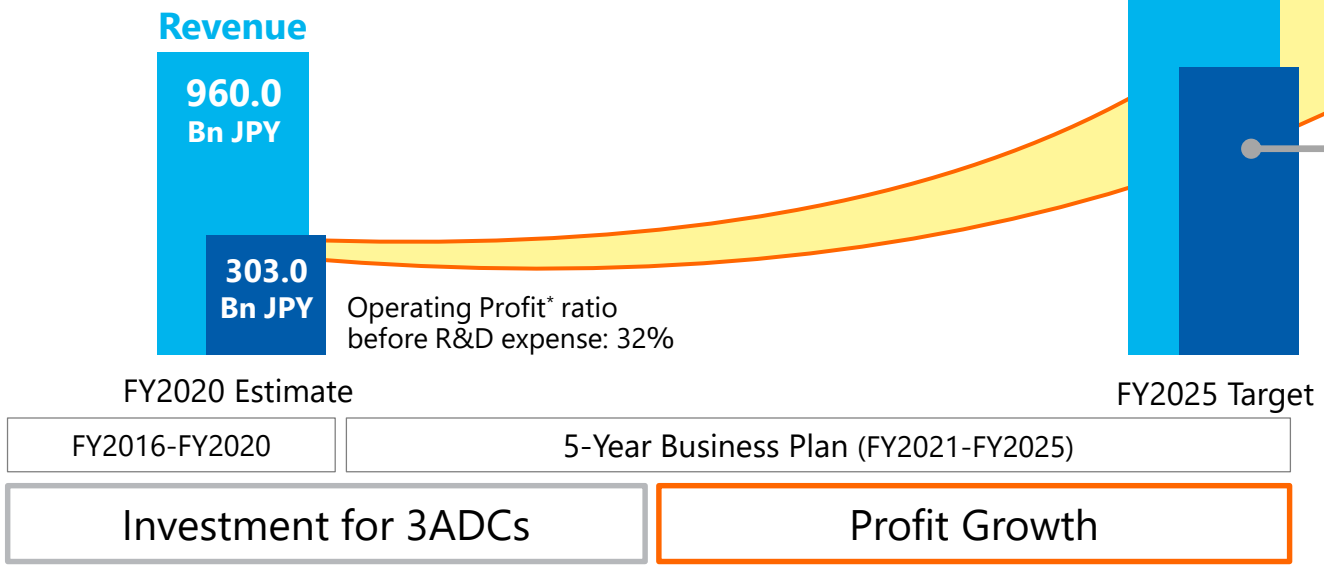
Stable dividends and dividend increase that take account of profit growth

*Cash in hands excluding working capital

Financial Targets for the 5-Year Business Plan (FY2021-FY2025)

◆**Revenue**
1.6 Tr JPY
➢ **Oncology > 600.0 Bn JPY**

Achieve significant revenue/profit growth after investment for 3ADCs, and shift to a new stage for realizing 2030 vision



◆ **Operating Profit* ratio before R&D expense: 40%**

◆ **ROE > 16%**

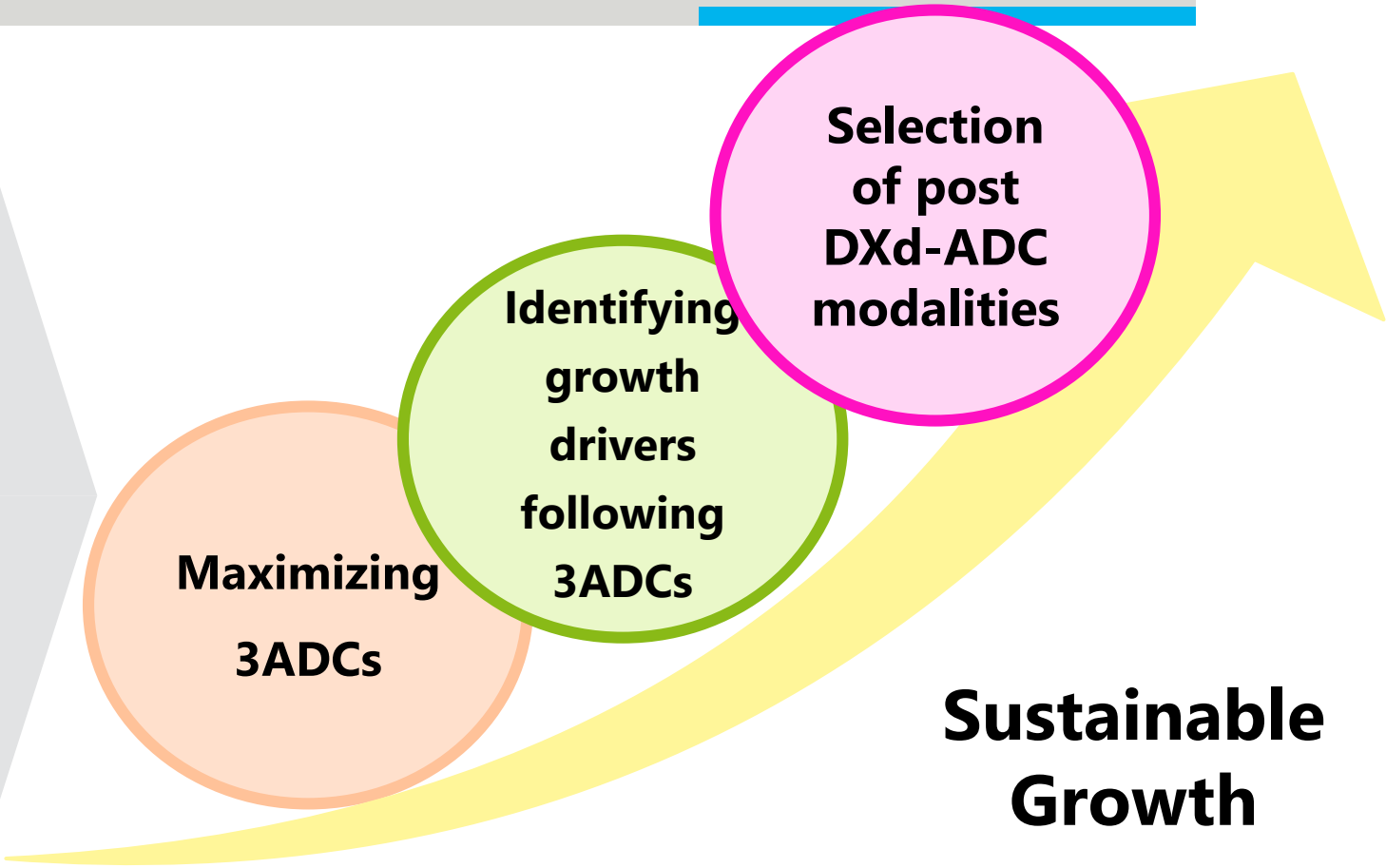
◆ **DOE > 8%**

*Excluding special items (gains and losses related to sale of fixed assets, restructuring, impairment, litigation, etc.)
FY2025 Currency rate assumptions: 1 USD=105 JPY, 1 EUR=120 JPY

Focusing on the 2030 Vision and beyond

Research activities taking advantage of our strength in cutting-edge science and technology

Steady global development bringing promising products



A strong leader that can effectively lead both “R” and “D”, and can assess/judge our next growth drivers is the key for sustainable growth

Leading Daiichi Sankyo to a New Phase

Daiichi-Sankyo

Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ASCO 2021 Highlights

DAIICHI SANKYO CO., LTD.

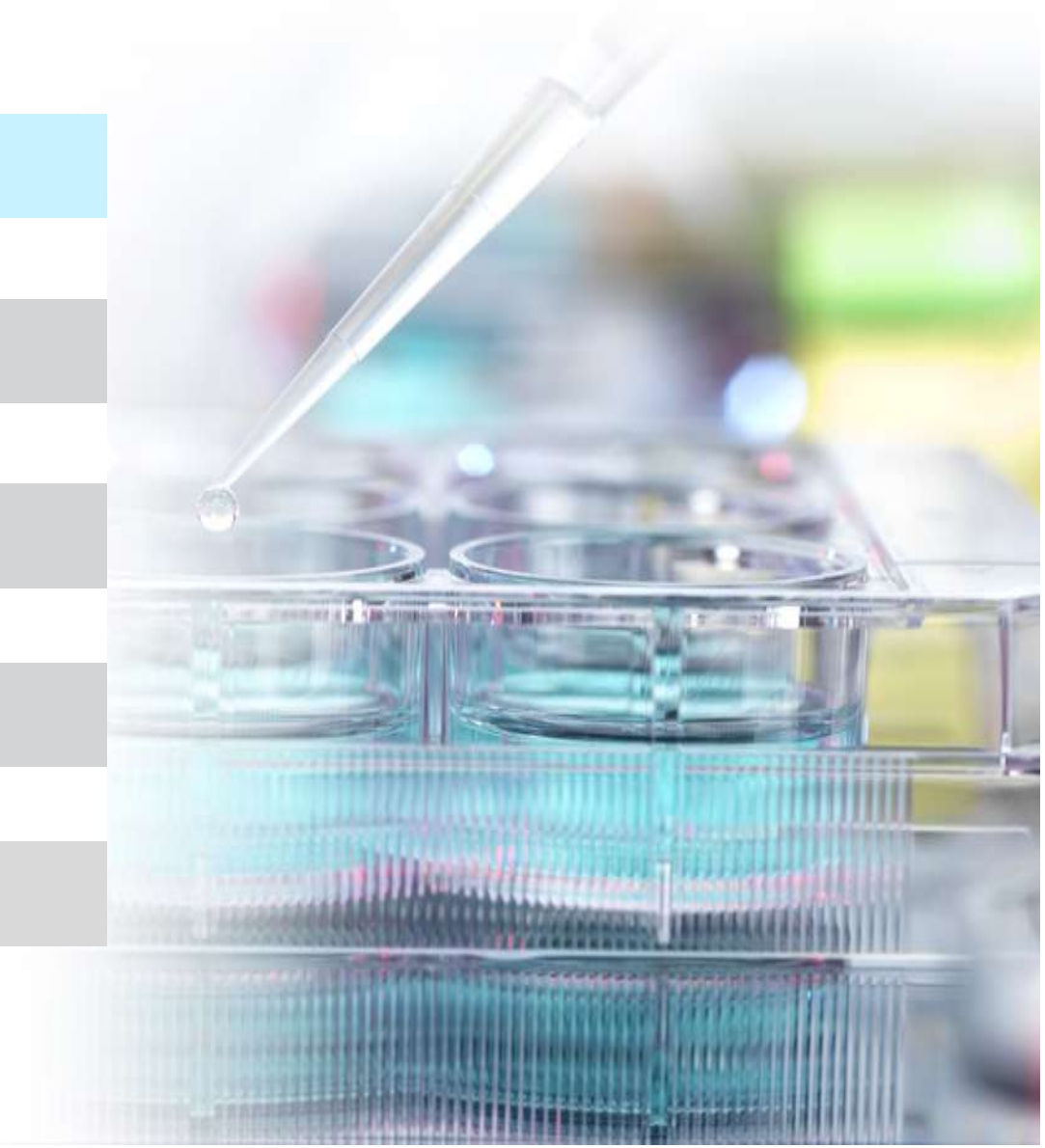
Ken Takeshita, MD

Global Head of R&D

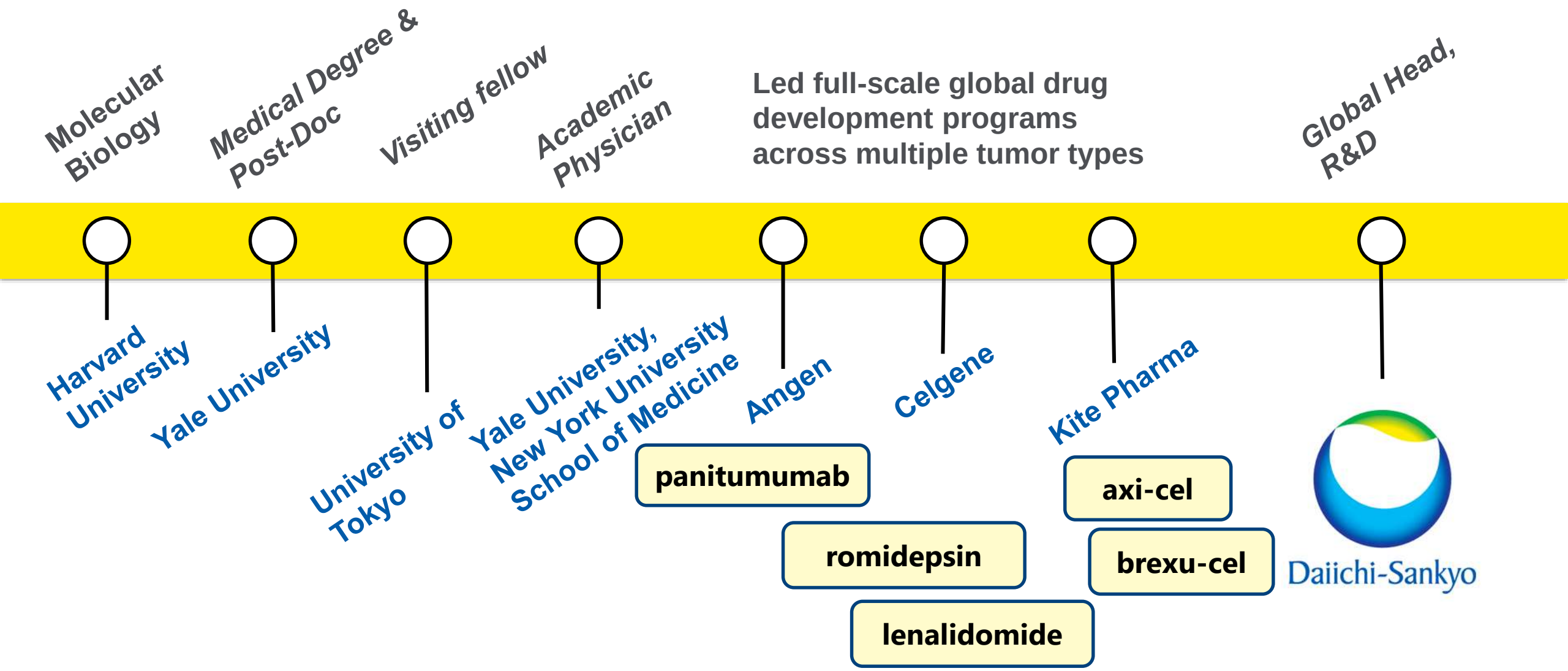
June 8, 2021

Agenda

1. **Introduction**
2. **ENHERTU®: New data & development plan**
3. **Dato-DXd: New data & development plan**
4. **HER3-DXd: New data & development plan**
5. **Future news flow**



My Educational & Professional History



Why Daiichi Sankyo Became My Destination

What I saw from the outside, looking in…

- **Very strong internal research**
- **Courage to change –**
  - **Cardiovascular to oncology**
  - **Japan focus to global focus**
- **Early successes in regulatory approvals**

My view and vision on our R&D

To be a true global pharmaceutical company…

Optimize the organization and cultivate human resources globally

- **Competitiveness**
  - Build upon our strengths to continually enhance our Science & Technology beyond 3ADCs
    - Cutting-edge science: next generation ADCs, mRNA, AAV, etc.
  - Implement unique modality strategies
- **R&D unity**
  - Research activities based on the right clinical questions, strong working relationship with development functions
  - Enhance smooth transition from research to development
- **Global development**
  - Strengthen clinical capabilities globally to accelerate the overall development speed
  - Grow and hire global talent

Daiichi Sankyo R&D Strategy

◆ 3 and Alpha strategy

- ➢ Prioritize investment and resource allocation to 3ADCs
- ➢ Alpha focuses on changing SOCs

3ADCs & **Alpha**

ENHERTU®	Dato-DXd	HER3-DXd	Oncology	Specialty Medicine	Vaccine

Swift expansion into broader cancer types & treatment lines

Identify competitive assets using reliable assessment capabilities and allocate appropriate resources

Our goals for ENHERTU®

Transform the treatment for HER2 targetable tumors

HER2 positive BC	**Establish ENHERTU® as the new SOC in metastatic & early BC** - Build on unprecedented data in HER2 positive -
HER2 low BC	**Redefine the BC treatment paradigm** - Disrupt the current BC treatment paradigm with new HER2 low characterization -
Other tumors	**Expand leadership across HER2 targeting tumors** - Transform treatment across HER2 tumors (GC, NSCLC, CRC, and others) -

ASCO 2021 data

BEGONIA study
Initial results of ENHERTU®+durvalumab
Exploration in HER2 low/HR- population

DESTINY-CRC01 study
Final results
Exploration of CRC indication

AACR 2021 data

Pooled analysis of drug-related ILD
Analysis of 8 single arm studies
Supporting benefit/risk profile of ENHERTU® across various tumors

BC: breast cancer, CRC: colorectal cancer, GC: gastric cancer, HR: hormone receptor, NSCLC: non small cell lung cancer, SOC: standard of care

Our goals for Dato-DXd

Establish the position of Best-in-Class TROP2-directed ADC

NSCLC	**Establish Dato-DXd as the First & Best-in-Class TROP2 ADC for NSCLC** - Introduce Dato-DXd as a key monotherapy for patients with R/R disease. Followed by combo with immunotherapy for 1L metastatic disease -
BC	**Establish Dato-DXd as ADC of choice for BC** - Take Dato-DXd therapy to an unprecedented level of efficacy in BC -

ASCO 2021 data

TROPION-PanTumor01 study
Dose analysis of NSCLC cohort
Supporting pivotal TROPION-Lung01 study

ESMO BC 2021 data

TROPION-PanTumor01 study
Initial results of TNBC cohort
Supporting further development

BC: breast cancer, NSCLC: non small cell lung cancer, R/R: relapsed/refractory, TNBC: triple negative breast cancer

Our goals for HER3-DXd

Establish the position of First-in-Class HER3-directed ADC

NSCLC	**Establish HER3-DXd as the First-in-Class ADC for EGFR-mutated NSCLC with diverse mechanisms of resistance to EGFR TKIs** - Aim for fast to market in monotherapy & expansion into combo w/ osimertinib -
Other tumors	**Expand indications across HER3 expressing tumors** -Transform treatment across HER3 tumors (CRC, BC, and others) -

ASCO 2021 data

Ph1 study
Updated data with a longer follow up of EGFR-mutated NSCLC cohort
Supporting pivotal HERTHENA-Lung01 study

BC: breast cancer, CRC: colorectal cancer, NSCLC: non small cell lung cancer, TKI: tyrosine kinase inhibitor

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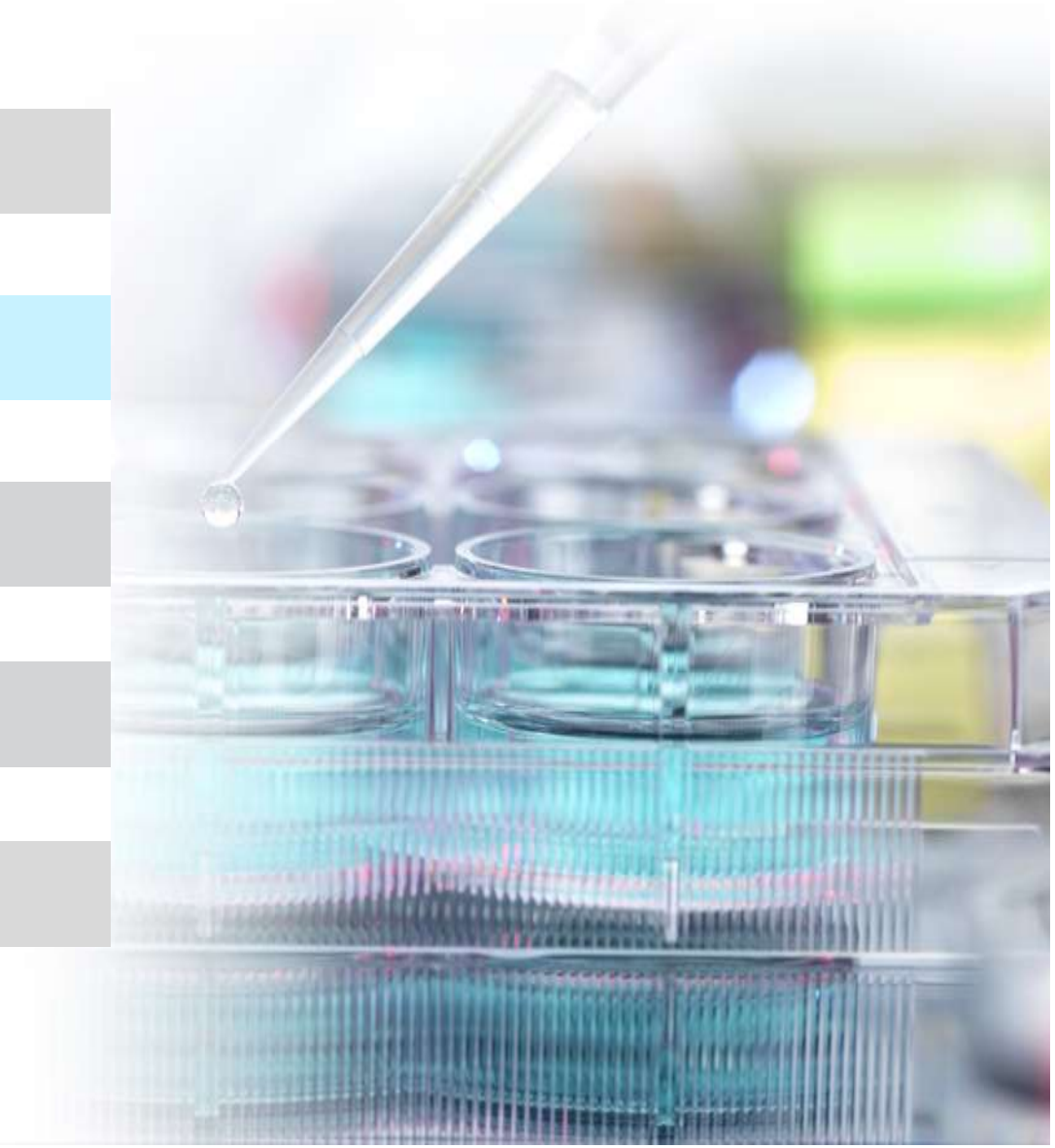
4. HER3-DXd: New data & development plan
5. Future news flow



Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-expressing Metastatic Colorectal Cancer: Final Results From a Phase 2, Multicenter, Open-label Study (DESTINY-CRC01)

Takayuki Yoshino; National Cancer Center Hospital East, Kashiwa, Japan

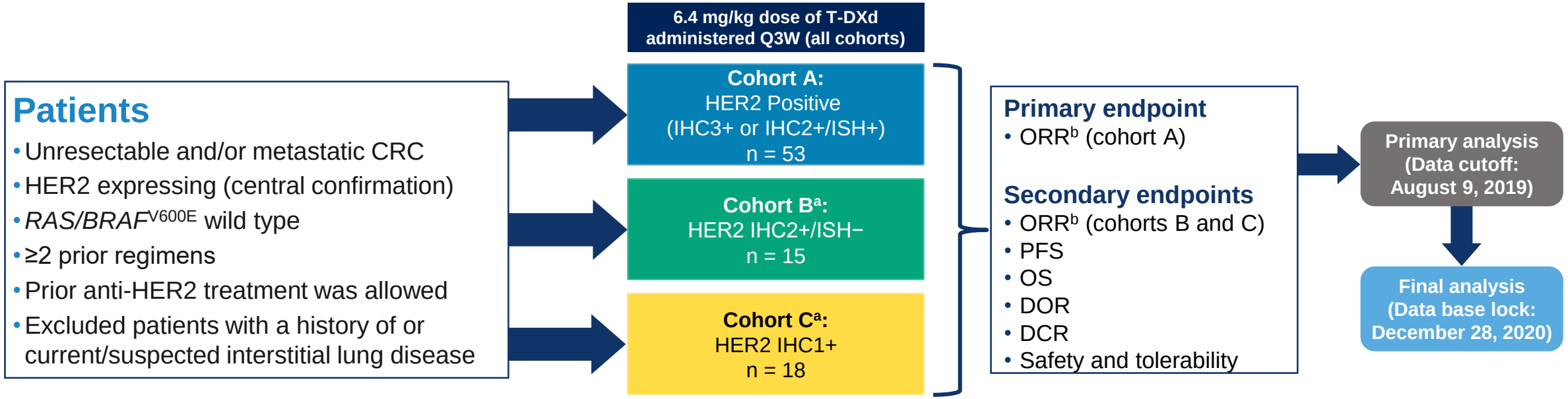
June 7, 2021

Additional authors: Maria Di Bartolomeo, Kanwal Raghav, Toshiki Masuishi, Fotios Loupakis, Hisato Kawakami, Kensei Yamaguchi, Tomohiro Nishina, Zev Wainberg, Elena Elez, Javier Rodriguez, Marwan Fakih, Fortunato Ciardiello, Kapil Saxena, Kojiro Kobayashi, Emarjola Bako, Yasuyuki Okuda, Gerold Meinhardt, Axel Grothey, Salvatore Siena

On behalf of the DESTINY-CRC01 investigators

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Efficacy Results

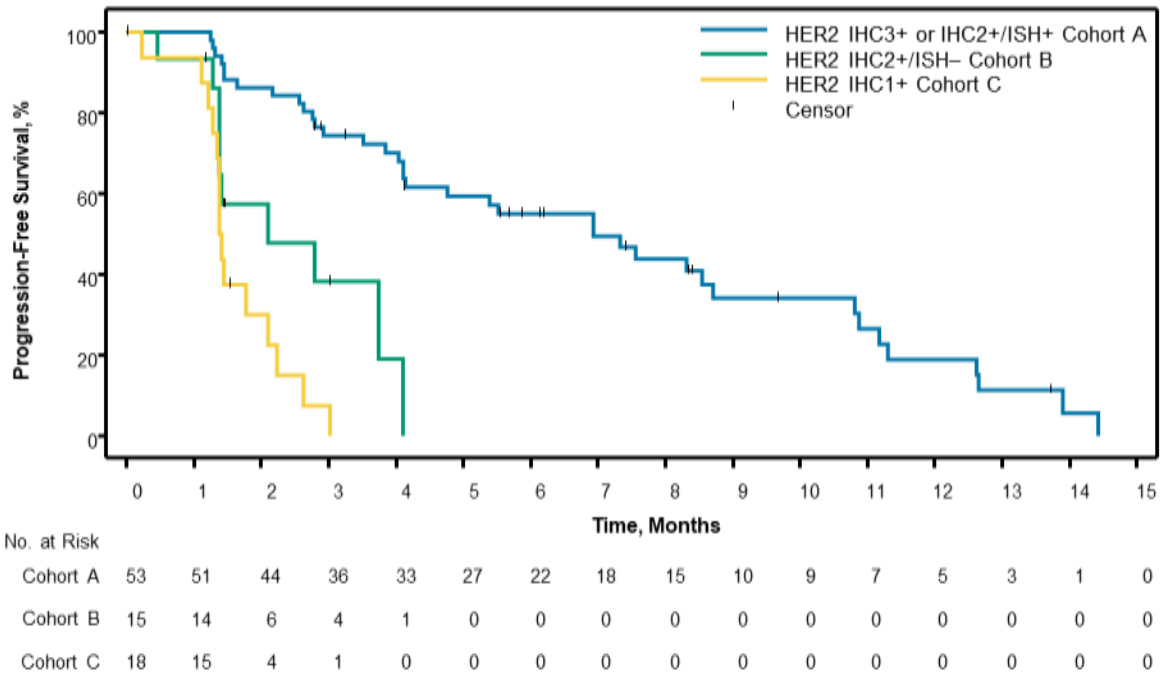
	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	**24 (45.3)** [31.6-59.6]	0 [0.0-21.8]	0 [0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median duration of response, (95% CI) months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)

CR, complete response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Patients were missing postbaseline scans.

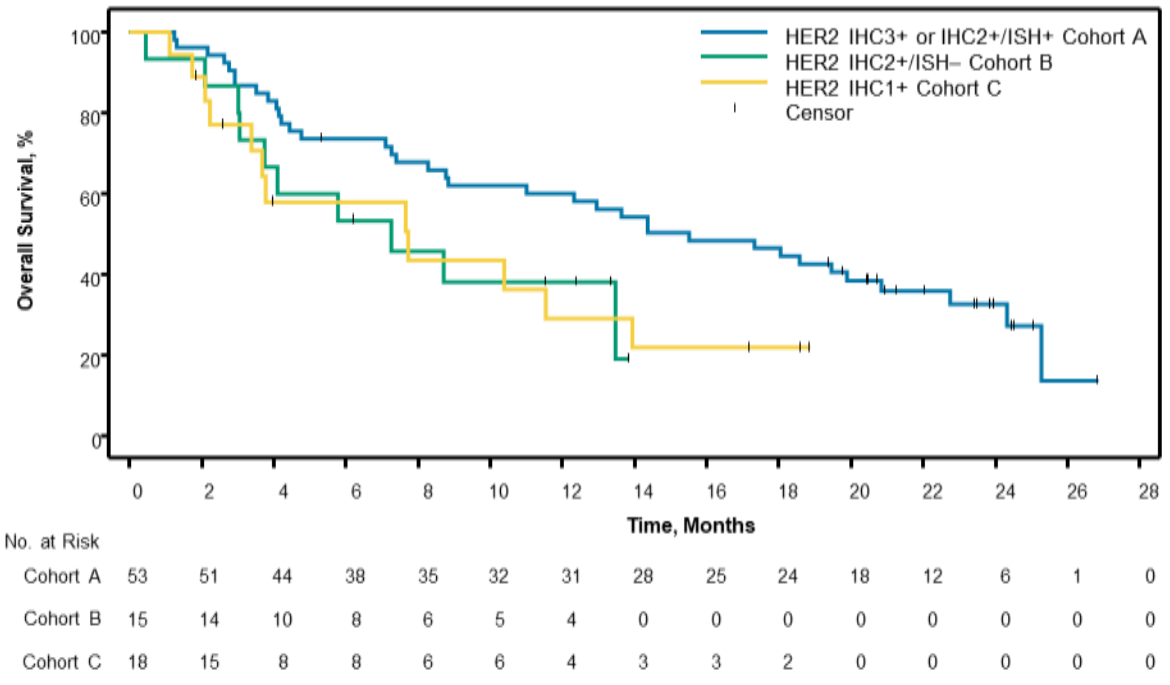
Progression-Free and Overall Survival

Progression-Free Survival



	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival



	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; NE, not-evaluable.

TEAEs in ≥20% of Patients

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)	
n (%)	Any Grade	Any Grade	Any Grade	Any Grade	Grade ≥3
Patients with any TEAE	**53 (100)**	**15 (100)**	**18 (100)**	**86 (100)**	**56 (65.1)**
Nausea	37 (69.8)	9 (60.0)	7 (38.9)	53 (61.6)	5 (5.8)
Anemia	21 (39.6)	4 (26.7)	6 (33.3)	31 (36.0)	12 (14.0)
Fatigue	21 (39.6)	7 (46.7)	3 (16.7)	31 (36.0)	1 (1.2)
Decreased appetite	18 (34.0)	5 (33.3)	7 (38.9)	30 (34.9)	0
Platelet count decreased	17 (32.1)	4 (26.7)	7 (38.9)	28 (32.6)	8 (9.3)
Vomiting	23 (43.4)	3 (20.0)	1 (5.6)	27 (31.4)	1 (1.2)
Neutrophil count decreased	20 (37.7)	2 (13.3)	4 (22.2)	26 (30.2)	19 (22.1)
Diarrhea	19 (35.8)	0	4 (22.2)	23 (26.7)	1 (1.2)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; TEAE, treatment-emergent adverse events.

AEs of Special Interest: Interstitial Lung Disease

All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

Adjudicated drug-related ILDs:

- Median time to adjudicated onset was 61.0 days (range, 9-165 days)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment in the 8 ILD cases was 3.5 days, (range 0-50)

Grade 5 ILDs:

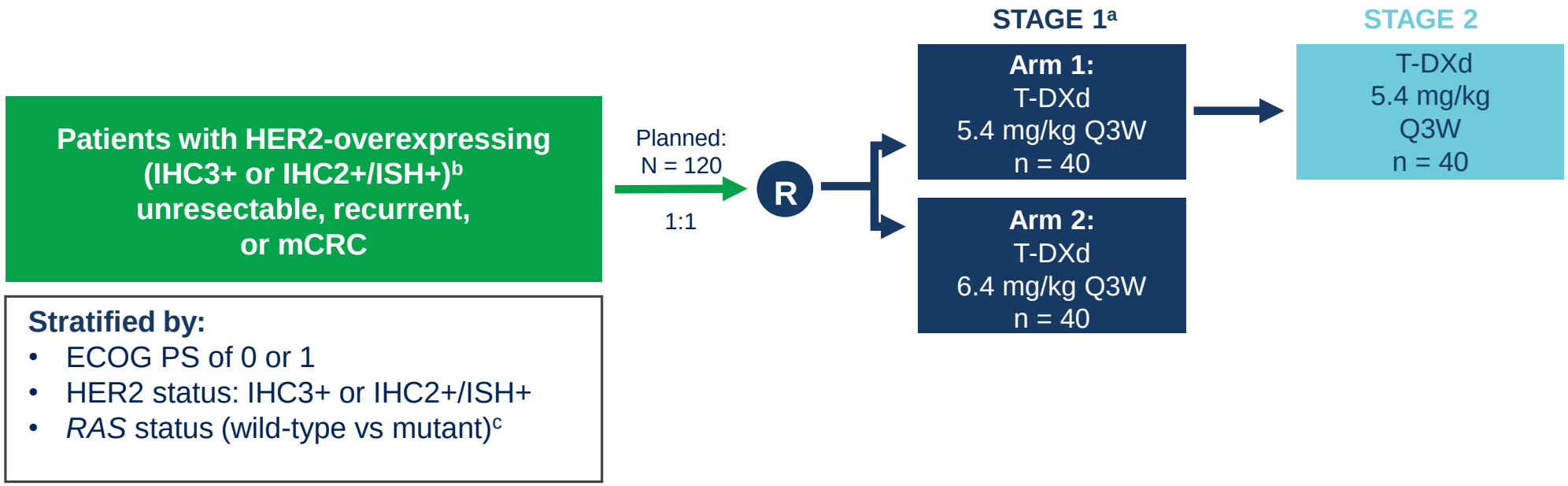
- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 9 days to 120 days (median: 22 days); and death occurred 6-19 days after diagnosis (median: 6 days)

Updated ILD/pneumonitis guidelines recommend to monitor for symptoms, interrupt or discontinue T-DXd, conduct imaging (as clinically indicated), and start steroids as soon as ILD is suspected.

AE, adverse events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
[a]2 patients were from cohort A, 1 from cohort B. [b]4 patients were from cohort A, 3 from cohort B and 1 from cohort C. [c]ILD grades are the highest/most severe grade recorded in a patient.

DESTINY-CRC02 Study Design

A randomized, 2-arm, 2-stage, phase 2, multicenter global study (NCT04744831)



DESTINY-CRC02 study has begun to enroll and the objective is to find the optimal dose (6.4 or 5.4 mg/kg) in patients with HER2 positive CRC.

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.

[a]Enrollment will not be interrupted between stages 1 and 2; it is not the intent to modify the study design based on the interim analysis results. Study will be blinded to investigators and patients.

[b]Maximum number of patients with HER2 IHC 2+/ISH+ will be n = 30.

[c]Maximum and minimum number of patients with *RAS* mutant status will be n = 30 and n = 20, respectively.

BEGONIA: PHASE 1B/2 STUDY OF DURVALUMAB (D) COMBINATIONS IN LOCALLY ADVANCED/METASTATIC TRIPLE-NEGATIVE BREAST CANCER: INITIAL RESULTS FROM ARM 6, D + TRASTUZUMAB DERUXTECAN (T-DXD)

Peter Schmid, Seock-Ah Im, Anne Armstrong, Yeon Hee Park, Wei-Pang Chung, Zbigniew Nowecki, Simon Lord,
Piotr Wysocki, Yen-Shen Lu, Hannah Dry, Vatsala Karwe,
Ross Stewart, Pia Herbolsheimer, Ana Nunes, Kyung Hae Jung

On behalf of the investigators

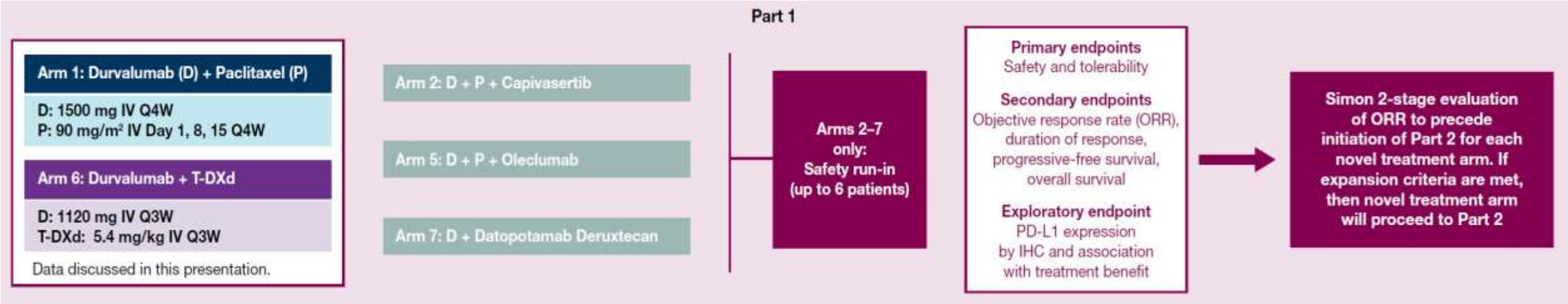
BEGONIA Study Design

Eligibility Criteria:

- Unresectable locally advanced or metastatic Stage IV TNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since taxane therapy for early-stage disease
- ECOG performance status of 0-1
- Measurable disease per RECIST 1.1
- No autoimmune, inflammatory illnesses

Additional Arm 6 Criteria:

- HER2-low-expressing (IHC 2+/ISH-, IHC 1+/ISH-, or IHC 1+/ISH untested, per local testing), estrogen receptor (ER)-negative, and progesterone receptor (PR)-negative tumors
- No ongoing pulmonary disorders



- **As of the data cutoff of March 2021, 21 patients received D+T-DXd with 19 still on treatment.**
- **Median (range) follow-up time: 3.6 (0–9) months.**

ASCO2021

Arm 6: Safety Summary (N=21)

- 2 cases of pneumonitis were observed (Grade 2 and Grade 3) and both were treated with steroids.
  - Grade 3 pneumonitis led to the patient discontinuing D+T-DXd.
  - Grade 2 pneumonitis led to the patient discontinuing T-DXd only.
- 1 additional discontinuation of D+T-DXd due to dyspnea (T-DXd discontinued) and disease progression (durvalumab discontinued).
- 1 additional discontinuation of T-DXd alone occurred and was due to thrombocytopenia.
- 1 case of troponin increase was nonserious, with no change in ejection fraction.

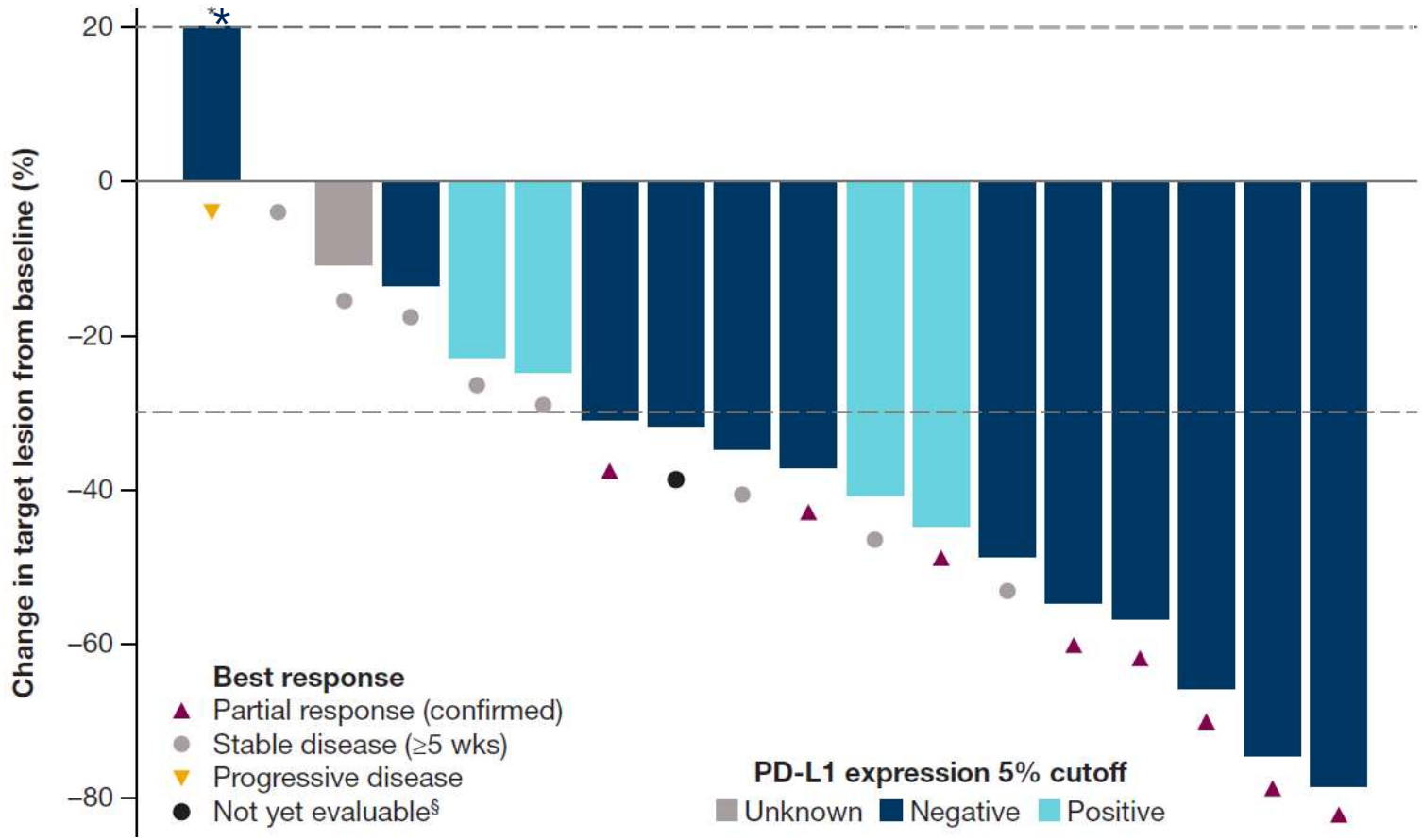
	n (%)
Any AE	21 (100)
Common AEs (≥20% patients, any grade)	
Nausea	16 (76.2)
Fatigue	11 (52.4)
Alopecia, neutropenia, anemia, constipation	6 (28.6) each
Decreased appetite, hypothyroidism, hypokalemia	5 (23.8) each
Any Grade 3/4 AE	8 (38.1)
Any SAE	5 (23.8)
Any treatment-related AE	20 (95.2)
Any AESI for durvalumab	11 (52.4)
Any AESI for T-DXd	2 (9.5)
AE leading to death	0
AE leading to dose interruption	7 (33.3)
Any durvalumab dose delay	9 (42.9)
Any T-DXd dose delay	9 (42.9)
T-DXd dose reduction	5 (23.8)

AESIs for T-DXd include pneumonitis/interstitial lung disease and left ventricular ejection fraction decrease.

Arm 6: Best change from baseline of target tumor size

- **Local testing of HER2 expression successfully identified patients with HER2 IHC1+ and HER2 IHC2+/ISH– tumors, who benefit from this treatment combination.**
- **In this small group of patients, responses were observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and PD-L1–negative (confirmed ORR 7/10 [70.0%]) groups**

Parameter	D+T-DXd
Patients who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n‡	12
Confirmed ORR, n (%)‡ 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	8
Progressive disease, n	1



* If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal or death, the value is imputed at +20%

‡ Number of subjects that had the opportunity to complete at least two on-treatment disease assessments or have PD or death

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Arm 6 Conclusions: Durvalumab + T-DXd

- Shows promising early efficacy signal in 1L metastatic HER2-low/ER-negative/ PR-negative breast cancer: confirmed ORR 8/12 (66.7%) patients in the response evaluable set.
  - Responses were observed regardless of PD-L1 expression (5% cutoff).
  - Local HER2 testing demonstrates benefit in both the HER2 1+ and HER2 2+/ISH− groups.
  - Responses were durable, with 87.5% remaining in response at time of data cutoff.
- Demonstrates a tolerable safety profile that is consistent with the known profile of the 2 agents individually.
  - Grade 3/4 AE rate was low at 8/21 (38.1%) and 2 cases of pneumonitis (Grade 2, Grade 3) were observed.
  - Overall safety assessment is limited by short follow-up and treatment duration to date.

The efficacy and durability of the combination will continue to be evaluated in BEGONIA study to determine the next steps.

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* Optimal scoring algorithms and cutoffs for PD-L1 expression that are relevant to durvalumab treatment for metastatic TNBC have not yet been established.

AACR 2021

Daiichi-Sankyo

Pooled Analysis of Drug-Related Interstitial Lung Disease in 8 Single-Arm Trastuzumab Deruxtecan Studies

Charles A. Powell,[1] Shanu Modi,[2] Hiroji Iwata,[3] Shunji Takahashi,[4] Egbert F. Smit,[5] Salvatore Siena,[6] Dwan-Ying Chang,[7] Kun Nie,[8] Amy Qin,[9]Jasmeet Singh,[9] Corina Taitt,[9] Sunil Verma,[8] D. Ross Camidge[10]

[1]Pulmonary Critical Care and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Aichi Cancer Center Hospital, Nagoya, Japan; [4]Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [5]Netherlands Cancer Institute, Amsterdam, the Netherlands; [6]Università degli Studi di Milano and Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy; [7]National Taiwan University Hospital (NTUH), Taipei, Taiwan; [8]AstraZeneca Pharmaceuticals, Gaithersburg, MD; [9]Daiichi Sankyo Inc., Basking Ridge, NJ; [10]University of Colorado Cancer Center, Aurora, CO

On behalf of the investigators

Incidence of ILD

Adjudicated study drug-related ILD by tumor type and grade

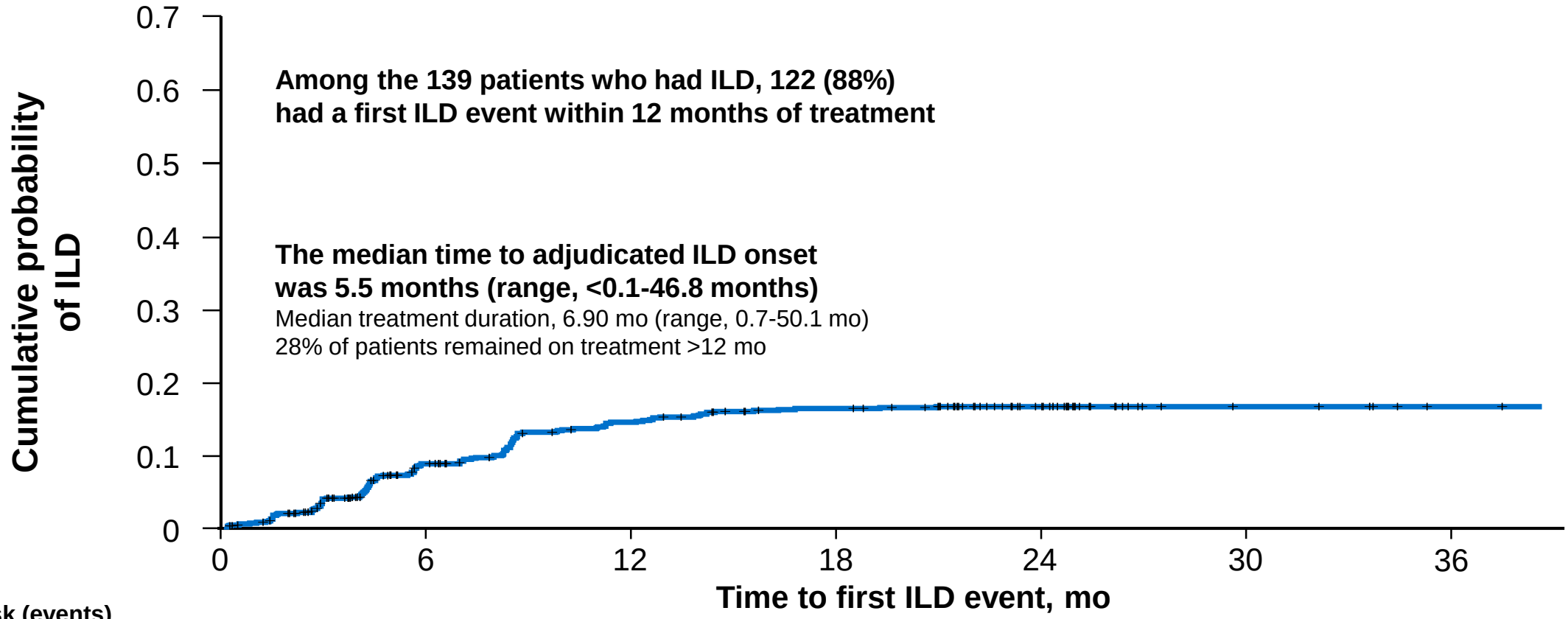
n (%)	All patients (N=879)	HER2+ Breast Cancer, 5.4 mg/kg (n=245)	Gastric cancer (n=78)	Lung cancer (n=148)	Colorectal cancer (n=107)
Grade 1	40 (4.6)	9 (3.7)	0	4 (2.7)	1 (0.9)
Grade 2	68 (7.7)	21 (8.6)	4 (5.1)	8 (5.4)	5 (4.7)
Grade 3	9 (1.0)	1 (0.4)	0	1 (0.7)	1 (0.9)
Grade 4	1 (0.1)	1 (0.4)[a]	0	0	0
Grade 5	21 (2.4)	6 (2.4)	0	4 (2.7)	3 (2.8)
Total	**139 (15.8)**	**38 (15.5)**	**4 (5.1)**	**17 (11.5)**	**10 (9.3)**

Of patients with ILD, most had grade 1 or 2 events (108/139 of patients with ILD - 78%)

[a] The severity was updated from Grade 4 to Grade 5 following ILD AC re-adjudication of the event after the database lock.

Kaplan-Meier analysis of time to first ILD event

The risk of all-grade ILD decreased after 12 months, as the cumulative probability of adjudicated drug-related ILD began to plateau at this point



No. at risk (events)							
All-Tumor	879 (0)	480 (75)	242 (122)	136 (136)	53 (138)	15 (138)	8 (138)
ILD rate	0	8.9%	14.8%	16.5%	16.8%	16.8%	16.8%

Treatment discontinuations due to reasons other than ILD were included as competing event.

Updated guidelines (2019) for ILD monitoring and management in clinical trials

Daiichi-Sankyo

STEP 1: Monitor

Suspected ILD

Interrupt drug

Rule out ILD if a patient develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever.

STEP 2: Confirm

Evaluations should include:

- High-resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD is suspected, if feasible

All events of ILD, regardless of severity or seriousness, should be followed until resolution including after drug discontinuation.

STEP 3: Manage

Drug must be interrupted for any ILD events regardless of grade

- **Grade 1**: **Interrupt until fully resolved**, then:
  - if resolved in 28 days or less from date of onset, maintain dose
  - if resolved in greater than 28 days from date of onset, reduce dose one level
  - however, if the event Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued
- **Grades 2-4**: **Permanently discontinue treatment.** Refer to toxicity management guidelines for trastuzumab deruxtecan

Modi S, et al. *N Engl J Med*. 2020;382(7):610-21.

Updated guidelines (2019) for ILD monitoring and management in clinical trials

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Guidelines were updated to be more specific regarding steroid dose and duration.

Toxicity management

Grade 1	Grade 2	Grade 3/4

• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
• Consider follow-up imaging in 1-2 weeks (or as clinically indicated)
• **Consider starting systemic steroids** (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by **gradual taper over at least 4 weeks**
• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines
  • **If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given**
	• Promptly start and **treat with systemic steroids** (e.g., at least 1mg/kg/day prednisone or equivalent) for at **least 14 days** or until complete resolution of clinical symptoms and chest CT findings, then followed by a **gradual taper over at least 4 weeks**
	• Monitor symptoms closely
	• Re-image as clinically indicated
	• If worsening or no improvement in clinical or diagnostic observations in 5 days,
	  • **Consider increasing dose of steroids** (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone)
	  • Re-consider additional work-up for alternative etiologies as described above
	  • Escalate care as clinically indicated
		• Hospitalization required
		• Promptly **initiate empiric high-dose methylprednisolone IV treatment** (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) **for at least 14 days** followed by a gradual taper over at least 4 weeks
		• Re-image as clinically indicated
		• If still no improvement within 3 to 5 days,
		  • Re-consider additional work-up for alternative etiologies as described above
		  • Consider other immuno-suppressants and/or treat per local practice

CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; IV, intravenous; PFT, pulmonary function test; PK, pharmacokinetic.

Modi S, et al. *N Engl J Med.* 2020;382(7):610-21.

Studies and patients included in the pooled analysis

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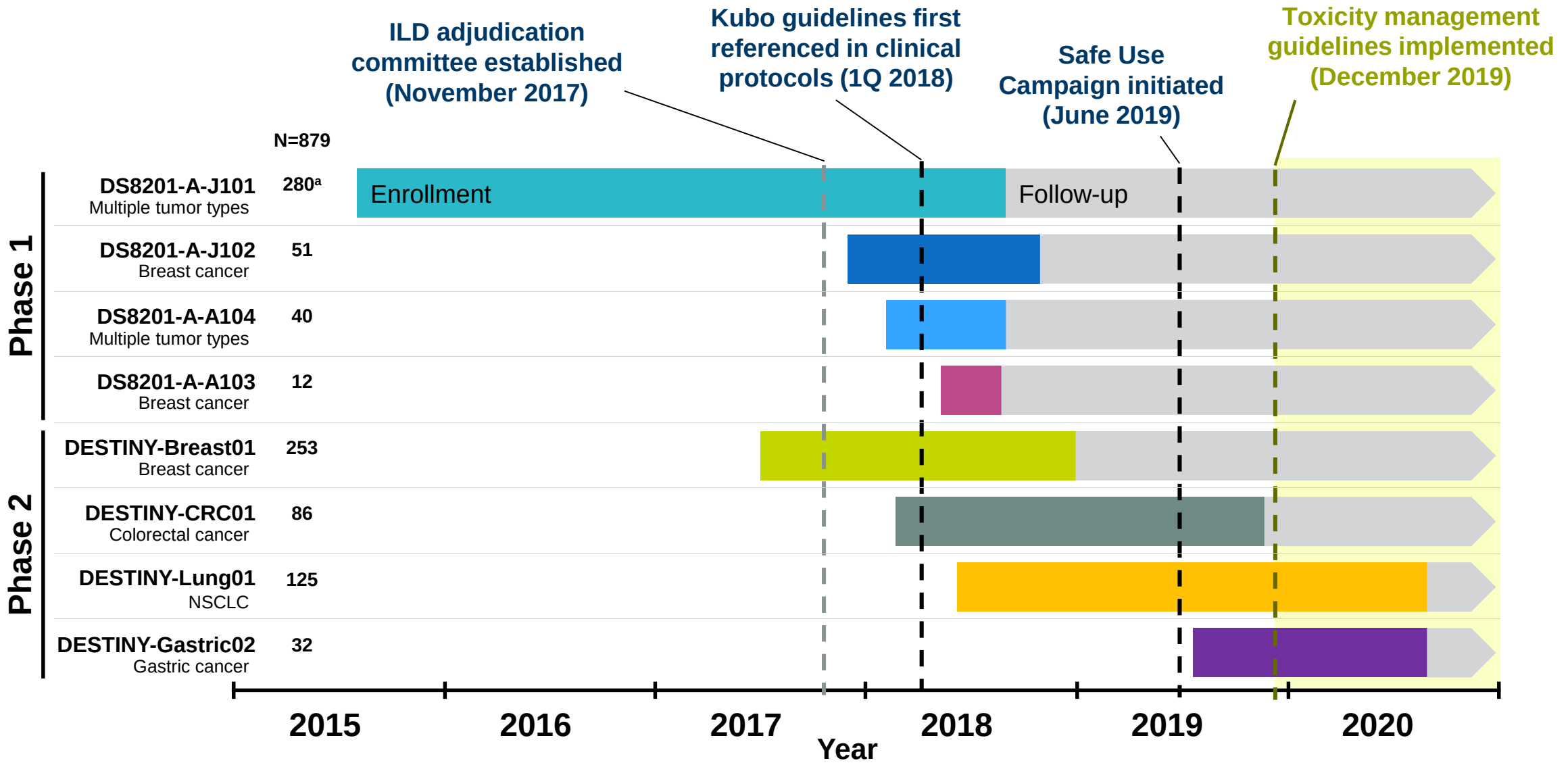

[a] Only patients who received T-DXd 5.4, 6.4, 7.4, or 8.0 mg/kg are included. All studies noted here are active but no longer recruiting, except for DESTINY-CRC01, which was completed in November 2020. Note that most patients were enrolled prior to the implementation of toxicity management guidelines. The color bar on each arrow indicates the time of patient enrollment and the gray is follow-up.

Incidence of ILD after implementation of toxicity management guidelines

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Updated toxicity management guidelines implemented (December 2019)

Incidence of ILD over time

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

- Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade ≥3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years based on a December 2020 snapshot; however, this may be partly due to the shorter treatment duration

ENHERTU®: Clinical Development Plan | Breast cancer

As of June 2021			FY2020	FY2021	FY2022	Planning
HER2 Positive		Metastatic 3L~	DESTINY-Breast01 completed			
			DESTINY-Breast02 monotherapy vs PC			
		Metastatic 2L	DESTINY-Breast03 monotherapy vs T-DM1			
			DESTINY-Breast07 combination (2L/1L) Ph1b/2			
		Metastatic 1L				
			DESTINY-Breast09 T-DXd ± pertuzumab vs THP			
		Post-neoadjuvant	DESTINY-Breast05 monotherapy vs T-DM1			
		Neoadjuvant				Phase 3
		Adjuvant				Phase 3
HER2 Low	HR+ HR-	Metastatic Post Chemo	DESTINY-Breast04 monotherapy vs PC			
			DESTINY-Breast08 combination			
		Post-neoadjuvant				Phase 3
	HR+	Metastatic Chemo Naive	DESTINY-Breast06 monotherapy vs PC			
		Metastatic Endocrine Therapy				Phase 3
	HR-	Metastatic 1L	BEGONIA durvalumab combination Ph1b/2 (Arm 6)			
		Neoadjuvant				Phase 3

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

PC: physician's choice

ENHERTU®: Clinical Development Plan | Gastric cancer & NSCLC

As of June 2021			FY2020	FY2021	FY2022	Planning
Gastric	HER2 Positive	Advanced/ Metastatic 3L~	DESTINY-Gastric01			
		Advanced/ Metastatic 2L	DESTINY-Gastric02 monotherapy - West			
				DESTINY-Gastric04 mono vs ramucirumab+paclitaxel		
			DESTINY-Gastric03 combination (2L/1L) Ph1b/2			
		Advanced/ Metastatic 1L				Phase 3
NSCLC	HER2 Expressing	Advanced/ Metastatic 2L~	DESTINY-Lung01 monotherapy			
			HUDSON durvalumab combination			
		Advanced/ Metastatic 2L				Phase 3
		Advanced/ Metastatic 1L		DESTINY-Lung03 combination		
						Phase 3
	HER2 Mutated	Advanced/ Metastatic 2L~	DESTINY-Lung01 monotherapy			
				DESTINY-Lung02 monotherapy		
		Advanced/ Metastatic 1L				Phase 3
	Expressing /Mutated	Early disease				Phase 3

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

NSCLC: non small cell lung cancer

ENHERTU®: Clinical Development Plan | CRC & other tumors

As of June 2021			FY2020	FY2021	FY2022	Planning
CRC	HER2 Expressing	Metastatic 3L	DESTINY-CRC01 monotherapy	DESTINY-CRC02 monotherapy		
		Metastatic 2L				Phase 3
		Metastatic 1L				Phase 3
Other Tumors/ multiple tumors	HER2 Expressing	Metastatic 2L	Nivolumab combination (breast, bladder)			
			Pembrolizumab combination (breast, NSCLC)			
			DESTINY-PanTumor02			
		Ovarian				Phase 2
	HER2 Mutated	Metastatic 2L	DESTINY-PanTumor01			

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

CRC: colorectal cancer, NSCLC: non small cell lung cancer

ENHERTU®: Key data readout

DESTINY-Breast02 | HER2 positive mBC vs standard of care	• Event-driven primary analysis, projected FY2022 Q2
DESTINY-Breast03 | HER2 positive mBC vs T-DM1	• Event-driven interim analysis, projected FY2021 Q2
DESTINY-Breast04 | HER2 low mBC vs standard of care	• Event-driven primary analysis, projected FY2021 Q4
DESTINY-Lung01 | HER2 overexpressing/mutated NSCLC	• Primary analysis, projected FY2021 Q2

BC: breast cancer, NSCLC: non small cell lung cancer

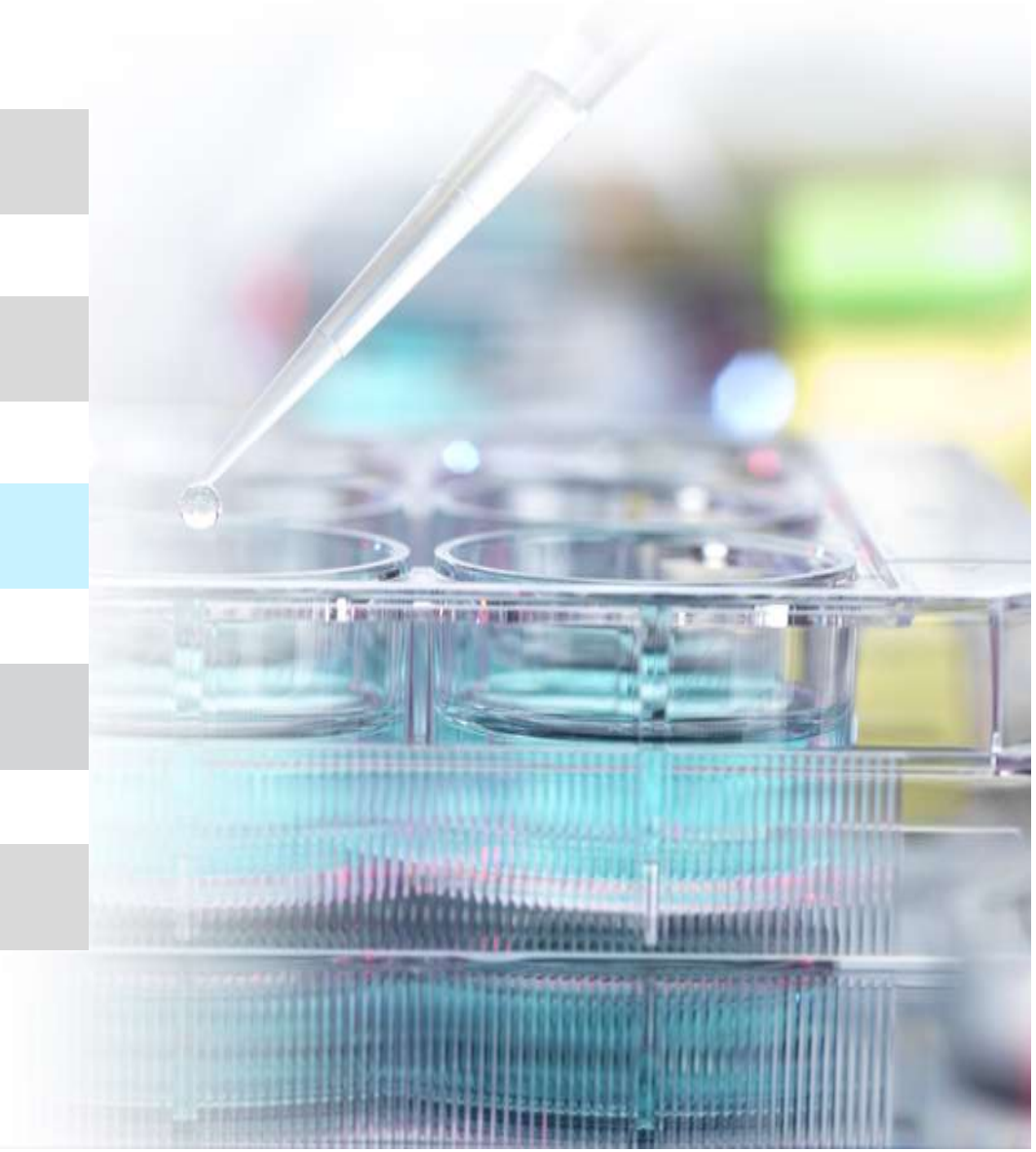
ENHERTU®: Recently started & upcoming pivotal studies

DESTINY-Breast09 | HER2 positive mBC vs THP	• Ph3 study in 1st line advanced/metastatic HER2 positive breast cancer	Initiated in Jun 2021
DESTINY-Gastric04 | HER2 positive mGC vs ramucirumab+paclitaxel	• Ph3 study in 2nd line advanced/metastatic HER2 positive gastric cancer	Planned initiation in FY2021 1H

BC: breast cancer, GC: gastric cancer, THP: taxane, herceptin, pertuzumab

Agenda

1. Introduction
2. ENHERTU®: New data & development plan
3. **Dato-DXd: New data & development plan**
4. HER3-DXd: New data & development plan
5. Future news flow



TROPION-PanTumor01: Dose Analysis of the TROP2-Directed Antibody-Drug Conjugate Datopotamab Deruxtecan (Dato-DXd; DS-1062) for the Treatment of Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Funda Meric-Bernstam,[1] Alexander Spira,[2] Aaron E. Lisberg,[3] Jacob M. Sands,[4] Noboru Yamamoto,[5] Melissa L. Johnson,[6] Kiyotaka Yoh,[7] Edward B. Garon,[8] Rebecca S. Heist,[9] Adam Petrich,[10] Jonathan Greenberg,[10] Naoyuki Tajima,[10] Yui Kawasaki, [11] Wen Gu,[10] Fumiaki Kobayashi,[11] Yasong Lu,[10] Ferdinand Guevara,[10] Toshio Shimizu[5]

[1]University of Texas, MD Anderson Cancer Center, Houston, TX; [2]Virginia Cancer Specialists, Fairfax, VA; [3]UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [6]Sarah Cannon Research Institute, Nashville, TN; [7]National Cancer Center Hospital East, Chiba, Japan; [8]University of California, Los Angeles, Los Angeles, CA; [9]Massachusetts General Hospital, Boston, MA; [10]Daiichi Sankyo, Basking Ridge, NJ; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

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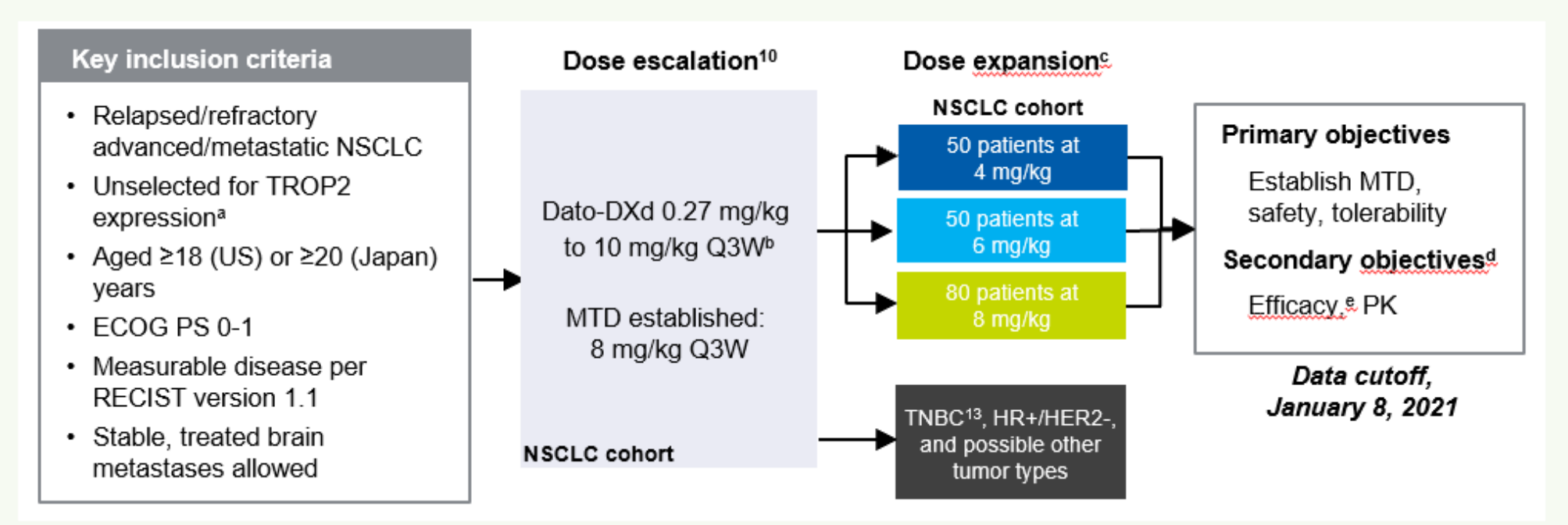
On behalf of the investigators

TROPION-PanTumor01 study design



- Updated clinical efficacy and safety results for the NSCLC cohort (data cutoff, January 8, 2021) as well as pharmacometric analyses are presented herein
- Pharmacometric analyses, including population pharmacokinetics (PopPK) and exposure-response modeling, were conducted by pooling data from all doses to inform dose selection for further development

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell-surface antigen 2.
[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] The 4-, 6-, and 8-mg/kg dose levels are being further evaluated for safety and efficacy. [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Additional exploratory endpoints include analyses of biomarkers associated with response. [e] Response assessments are based on RECIST v1.1.

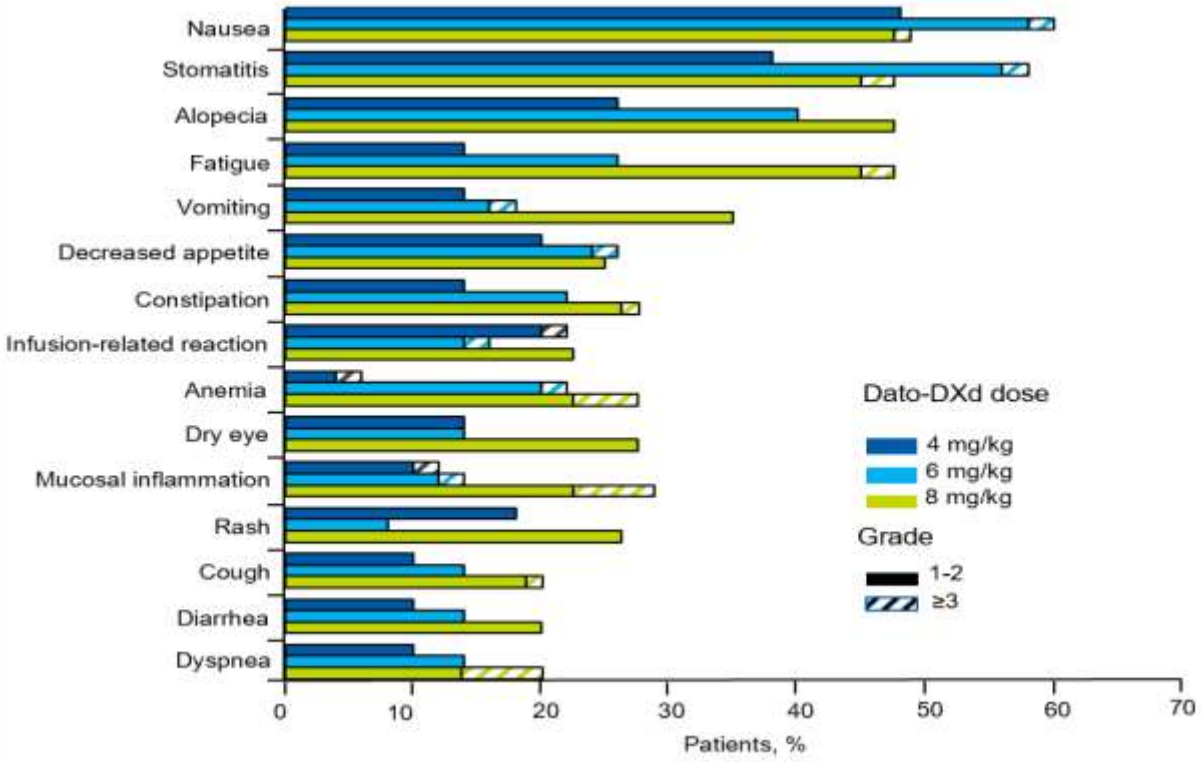
Safety results

Overall Safety Summary

Patients, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	48 (96)	80 (100)
Grade ≥3	15 (30)	24 (48)	46 (58)
Drug-related TEAE	46 (92)	41 (82)	77 (96)
Grade ≥3	7 (14)	8 (16)	28 (35)
Serious TEAE	11 (22)	24 (48)	39 (49)
Grade ≥3	10 (20)	18 (36)	36 (45)
Dose adjustments			
TEAEs associated with discontinuation	7 (14)	5 (10)	15 (19)
TEAEs associated with dose interruption	7 (14)	9 (18)	17 (21)
TEAEs associated with dose reduction	1 (2)	4 (8)	24 (30)
Interstitial lung disease	5 (10)	2 (4)	12 (15)
Grade ≤2	4 (8)	2 (4)	8 (10)
Grade 3	1 (2)	0	1 (1)
Grade 4	0	0	0
Grade 5	0	0	3 (4)
Deaths			
Drug-related fatal ILD/pneumonitis[a]	0	0	3 (4)

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] All fatal TEAEs reported as drug-related were pulmonary events and therefore were adjudicated for ILD/pneumonitis by an independent, external committee.

Treatment-Emergent Adverse Events in ≥15% of Patients



[a] Of 180 patients (4 mg/kg [n=50]; 6 mg/kg [n=50]; 8 mg/kg [n=80]).
[b] Grade ≥3 neutropenia occurred in 1 patient at the 8-mg/kg dose; no cases of febrile neutropenia were reported.

- Overall, Dato-DXd demonstrated a manageable safety profile and no new safety signals were observed
- Preliminary results suggest that some adverse events (AEs; gastrointestinal (GI) toxicity and anemia) are reversible, and the clinical course of AEs will be further analyzed with more mature study results

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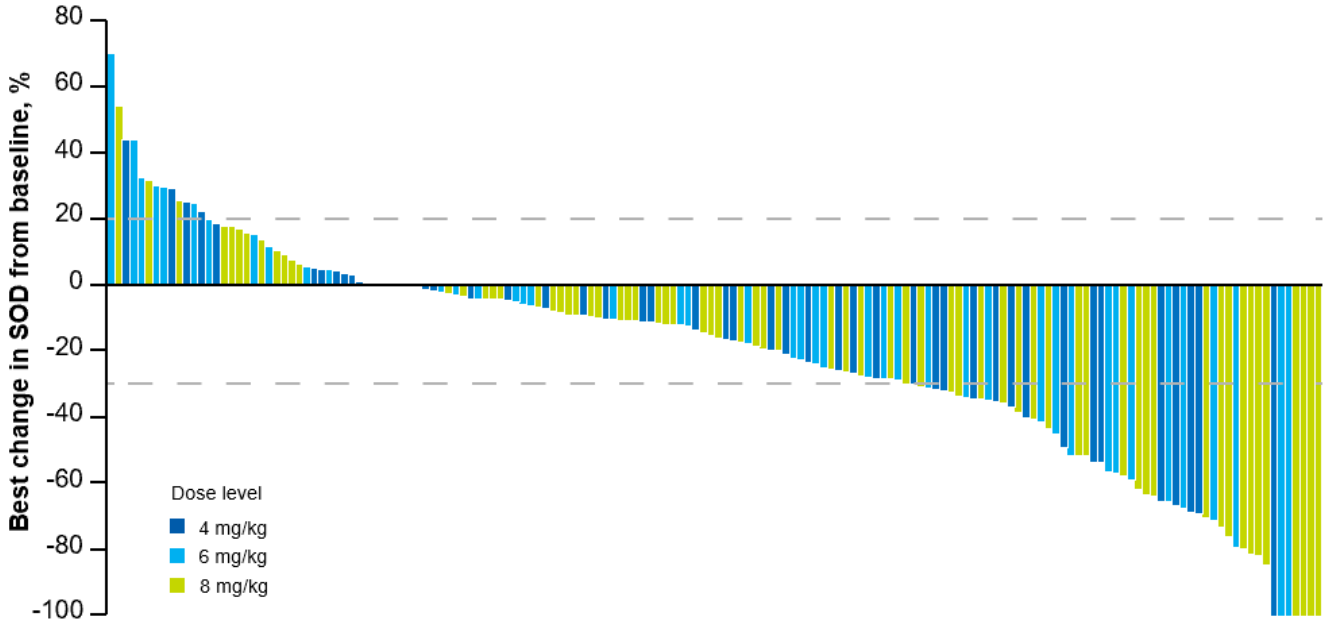
Efficacy results

Best Overall Response (BICR)

Patients[a]	Dato-DXd Dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)	12 (24)	13 (26)	19 (24)
CR/PR	10 (20)	11 (22)	19 (24)
CR/PR (too early to be confirmed)	2 (4)	2 (4)	0
DCR, n (%)	38 (76)	35 (70)	64 (80)
PD, n (%)	7 (14)	10 (20)	7 (9)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (4.1-NE)	9.0 (5.8-NE)
PFS, median (95% CI), mo[b]	4.3 (3.5-8.4)	6.9 (2.7-8.8)	5.2 (4.1-7.1)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] Median PFS was limited by immature duration of follow-up in the 4- and 6-mg/kg dosing cohorts.

Best Change in Sum of Diameters (BICR)



BICR, blinded independent central review; SOD, sum of diameters.

Antitumor activity was observed at 4-, 6-, and 8-mg/kg of Dato-DXd

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Pharmacometric Analysis: Projected Probabilities in a Virtual Population

Endpoint for model projection	Dato-DXd dose		
	4 mg/kg	6 mg/kg	8 mg/kg
Probability of response, mean (90% CI)	18.7 (14.4-23.6)	23.4 (18.4-29.1)	26.3 (19.9-33.6)
Probability of dose reductions, mean (90% CI)	4.9 (2.6-8.1)	15.6 (11.9-19.7)	27.4 (21.7-33.1)
Probability of grade ≥2 stomatitis/mucosal inflammation, mean (90% CI)	17.3 (12.1-23.9)	35.0 (29.4-40.7)	47.7 (41-53.9)

A virtual population of N=200 patients per dose was created by random sampling of the patients in the TROPION-PanTumor01 study. The factors that affect pharmacokinetics (weight, baseline albumin, sex) were well balanced across doses. No dose reductions were considered for the simulation.

- Model simulations suggest that the probabilities of dose reductions and grade ≥2 stomatitis/mucosal inflammation will be higher at the 8-mg/kg dose than at the 4- or 6-mg/kg dose
- Model simulations also suggest a higher probability of response at the 6-mg/kg dose than at the 4-mg/kg dose

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Summary/Conclusions

- Dato-DXd shows highly encouraging antitumor activity with a manageable safety profile in patients with advanced or metastatic NSCLC, although results are limited by immature and unequal duration of follow-up across doses
- Tumor responses were durable across doses, with a trend toward a longer PFS at the 6-mg/kg dose
- Pharmacometric analyses preliminarily suggest that:
  - Increased exposure was associated with improved efficacy
  - Increased exposure was associated with higher rates of dose reductions and TEAEs
- These analyses support Dato-DXd 6 mg/kg as the selected dose for the randomized phase 3 TROPION-Lung01 trial (NCT04656652)
- Although the frequency and severity of AEs such as interstitial lung disease and GI toxicities appeared similar to those observed with T-DXd, higher rates of stomatitis and lower rates of bone marrow suppression were observed with Dato-DXd, suggesting DAR, ADC target, or other factors likely impact toxicity profiles

Pivotal TROPION-Lung01 study is ongoing based on the result of this study.

Datopotamab Deruxtecan (Dato-DXd), a TROP2-Directed Antibody Drug Conjugate, for Triple-Negative Breast Cancer: Preliminary Results from an Ongoing Phase 1 Trial

Aditya Bardia,[1] Dejan Juric,[1] Toshio Shimizu,[2] Anthony Tolcher,[3] Raghad Karim,[3] Alexander Spira,[4] Toru Mukohara,[5] Aaron E. Lisberg,[6] Takahiro Kogawa,[7] Ian Krop,[8] Kyriakos P Papadopoulos,[9] Erika Hamilton,[10] Senthil Damodaran,[11] Jonathan Greenberg,[12] Wen Gu,[12] Fumiaki Kobayashi,[13] Ferdinand Guevara,[12] Takahiro Jikoh,[13] Yui Kawasaki,[13] Funda Meric-Bernstam[11]

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On behalf of the investigators

TROPION-PanTumor01 (NCT03401385) – TNBC Cohort

Phase 1, First-in-human, Dose Escalation and Expansion Study

- Advanced/metastatic HR-/HER2-negative breast cancer (TNBC)[a]
- Relapsed/progressed on standard treatment
- Unselected for TROP2 expression[b]
- Measurable disease (per RECIST version 1.1)

→

Dato-DXd 6mg/kg IV Q3W

N≈40

2 patients received 8 mg/kg prior to selection of the 6-mg/kg dose for dose expansion

→

Primary objectives include:

- Safety, Tolerability

Secondary objectives include:

- Efficacy, Pharmacokinetics

Data cutoff January 8, 2021

- Current analysis includes 24 patients treated at the 6-mg/kg dose (n=22) and 8-mg/kg dose (n=2)[c]
- Treatment ongoing in 18 patients (75%); 6 patients (25%) discontinued treatment, all due to disease progression[d]

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Estrogen receptor positivity <1%; [b] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression; [c] An HR+ cohort is currently open for enrollment at 6 mg/kg; [d] Progression includes progressive disease per RECIST 1.1 and clinical progression.

Majority of Patients Were Heavily Pretreated

Patient characteristics	N=24
Age, median (range), y	57.0 (32-82)
Country, n (%)	
US	18 (75)
Japan	6 (25)
ECOG PS, n (%)	
0	8 (33)
1	16 (67)
De-novo metastatic disease, n (%)	
Yes	9 (38)
No	15 (63)

Patient characteristics	N=24
Brain metastases, n (%)	2 (8)
Prior therapies, median (range), n[a]	4 (1-9)
≥2 prior lines of therapy, n (%)[a]	21 (88)
Previous systemic treatment, n (%)[a]	
Taxanes	20 (83)
Platinum-based chemotherapy	12 (50)
Immunotherapy	8 (33)
Sacituzumab govitecan	2 (8)
PARPi	1 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status; PARPi, Poly (ADP-ribose) polymerase inhibitor; US, United States.
[a] Includes prior lines of therapy in the (neo)adjuvant and/or metastatic setting.

Data cutoff: January 8, 2021

Dato-DXd Demonstrated a Manageable Safety Profile

Patients, n (%)	N=24	
	Any grade	Grade ≥3
TEAEs	24 (100)	8 (33)
Treatment related	24 (100)	4 (17)
Serious TEAEs[a]	3 (13)	3 (13)
Treatment related	0	0
Fatal TEAEs	0	–
Treatment related	0	–

- Dose reductions due to AEs occurred in 6 patients (25%) and were most commonly due to stomatitis (3 patients [13%]) and mucosal inflammation (2 patients [8%])
- No patients discontinued treatment due to AEs

TEAE, treatment-emergent adverse event.
[a] A serious TEAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect or is an important medical event.

Data cutoff: January 8, 2021

Manageable, Predominantly Nonhematologic AEs

- Predominantly grade 1 or 2 (67%) and nonhematologic
- No cases of grade ≥3 diarrhea or neutropenia
- No cases adjudicated as drug-related ILD were observed

Preferred Term, n (%)[a]	N=24	
	Any grade	Grade ≥3
TEAEs	**24 (100)**	**8 (33)**
Stomatitis	15 (63)	3 (13)
Nausea	15 (63)	0
Fatigue	10 (42)	1 (4)
Vomiting	10 (42)	0
Alopecia	6 (25)	–
Cough	5 (21)	0
Pruritus	5 (21)	0
Anemia	4 (17)	1 (4)
Headache	4 (17)	0
Constipation	4 (17)	0

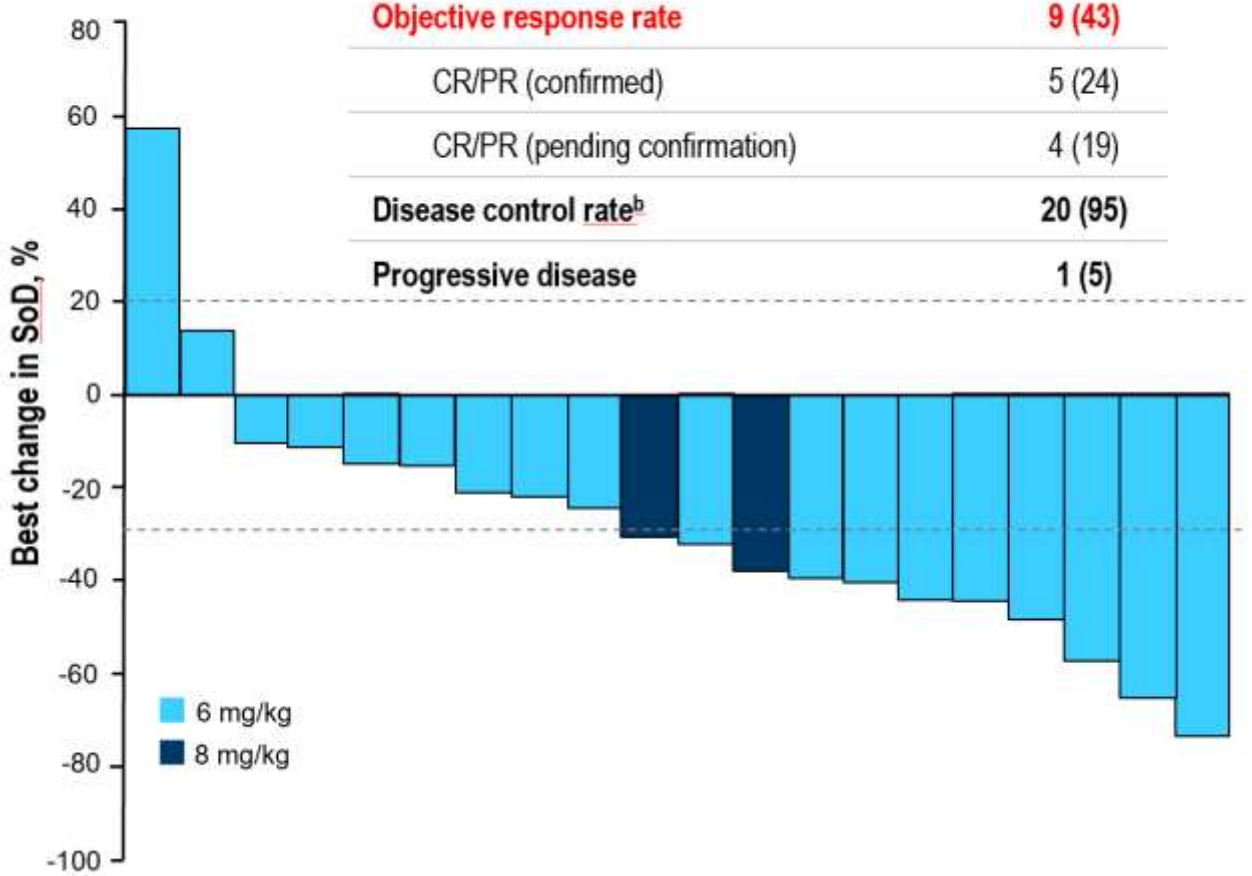
ILD, interstitial lung disease.
[a] TEAEs observed in ≥15% of patients.

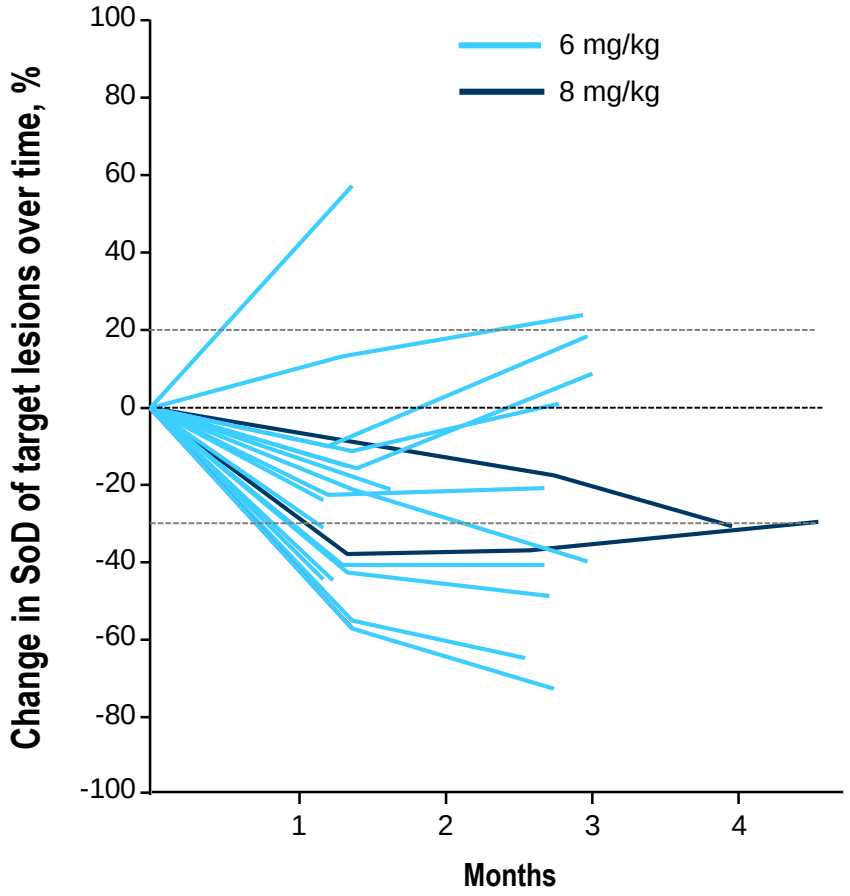
ESMO2021

Data cutoff: January 8, 2021

Antitumor Activity (by BICR)

Patients, n (%)[a]	N=21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)





BICR, blinded independent central review; CR, complete response; PD, progressive disease; PR, partial response; SoD, sum of diameters.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 3 patients at the data cutoff. One patient was not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD; [b] Includes patients with a best overall response of CR, PR, stable disease, or non-CR/non-PD.

Data cutoff: January 8, 2021

Conclusions

- Dato-DXd demonstrated a manageable safety profile and no patients discontinued treatment due to adverse events
- Emerging efficacy results showed antitumor activity in heavily pretreated patients with metastatic TNBC
  - ORR by BICR was 43% and disease control rate was 95%
- Further study in breast cancer is warranted
  - HR+ cohort is now enrolling

Pivotal study for TNBC is currently being planned based on this data.

ESMO2021

Dato-DXd: Clinical Development Plan | NSCLC & breast cancer

As of June 2021			FY2020	FY2021	FY2022	Planning
NSCLC	All comers	Advanced/ Metastatic 2L~	TROPION-PanTumor01			
	Without actionable mutations	Advanced/ Metastatic 2L~		TROPION-Lung01 monotherapy vs Docetaxel		
		Advanced/ Metastatic 2L		TROPION-Lung02 & 04 ICI combination		
		Advanced/ Metastatic 1L				Phase 3
	With actionable mutations	Advanced/ Metastatic 2L~		TROPION-Lung05 monotherapy		
		Advanced/ Metastatic 1L				
Breast	TNBC	Metastatic 2L~	TROPION-PanTumor01			Phase 3
		Metastatic 1L		BEGONIA durvalumab combination Ph1b/2 (Arm 7)		
	HR+/ HER2-	Metastatic 2L~		TROPION-PanTumor01		Phase 3
		Metastatic 1L				

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

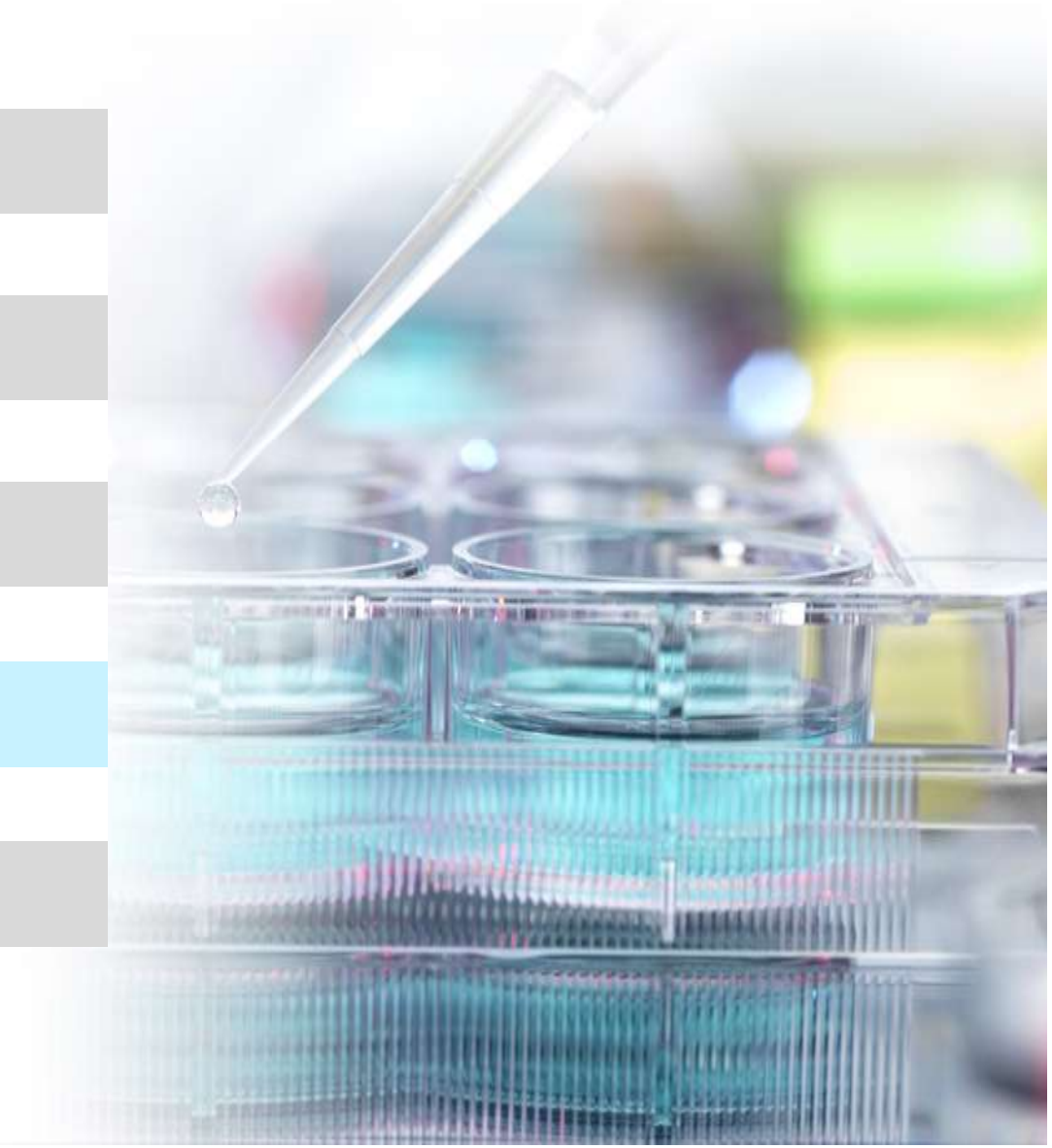
ICI: immuno-checkpoint inhibitor, NSCLC: non small cell lung cancer, TNBC: triple negative breast cancer

Dato-DXd: Recent update

TROPION-PanTumor01 | HR+ BC cohort	• Opened HR+ BC cohort in Ph1 • First subject dosed in Mar 2021
BEGONIA | TNBC Combination with durvalumab	• AstraZeneca-led Ph1b/2 study for 1L TNBC • Arm 7 (Dato-DXd+durvalumab) newly added • First subject dosed in May 2021

Agenda

1. Introduction
2. Enhertu: New data & development plan
3. Dato-DXd: New data & development plan
4. **HER3-DXd: New data & development plan**
5. Future news flow



EFFICACY AND SAFETY OF PATRITUMAB DERUXTECAN (HER3-DXd) IN EGFR INHIBITOR–RESISTANT, *EGFR*-MUTATED (*EGFR*m) NON-SMALL CELL LUNG CANCER (NSCLC)

Pasi A. Jänne,[1] Christina Baik,[2] Wu-Chou Su,[3] Melissa L. Johnson,[4] Hidetoshi Hayashi,[5] Makoto Nishio,[6] Dong-Wan Kim,[7] Marianna Koczywas,[8] Kathryn Gold,[9] Conor Steuer,[10] Haruyasu Murakami,[11] James C. H. Yang,[12] Sang-We Kim,[13] Michele Vigliotti,[14] Zhenhao Qi,[14] Yang Qiu,[14] Lihui Zhao,[14] David Sternberg,[14] Channing Yu,[14] Helena A. Yu[15]

04 June 2021

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Seattle Cancer Care Alliance, Seattle, WA; [3]National Cheng Kung University Hospital, Tainan, Taiwan; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLCC, Nashville, TN; [5]Kindai University Hospital, Osaka-Sayama City, Japan; [6]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan; [7]Seoul National University Hospital, Seoul, South Korea; [8]City of Hope Medical Center, Duarte, CA; [9]University of California, San Diego, San Diego, CA; [10]Emory University Hospital, Atlanta, GA; [11]Shizuoka Cancer Center, Sunto-gun, Japan; [12]National Taiwan University Cancer Center, Taipei, Taiwan; [13]University of Ulsan College of Medicine, Seoul, South Korea; [14]Daiichi Sankyo, Inc., Basking Ridge, NJ; [15]Memorial Sloan Kettering Cancer Center, New York, NY

On behalf of the investigators

HER3-DXd: Ph1 study in advanced EGFR-mutated NSCLC

Dose escalation[a]

HER3-DXd IV Q3W (21-day cycles)

Locally advanced/metastatic NSCLC with *EGFR* mutations

Progression on prior EGFR TKI treatment

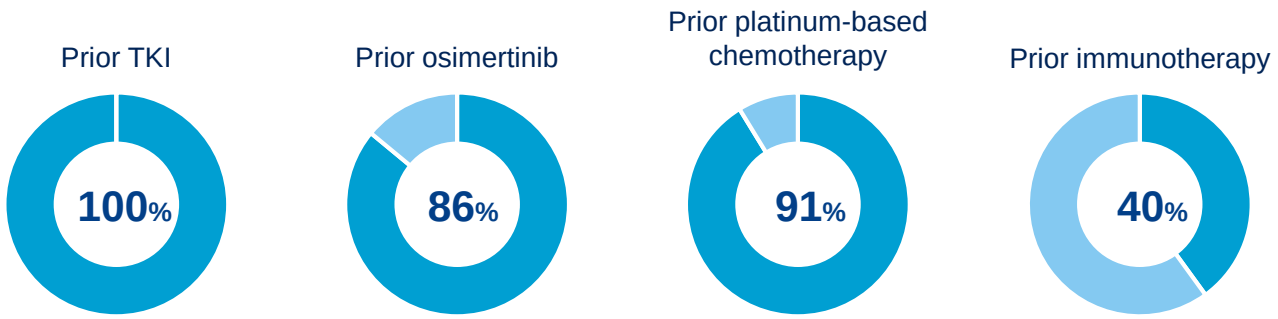
- **6.4 mg/kg (N=5)**
- **5.6 mg/kg (N=12)**
- **4.8 mg/kg (N=15)**
- **3.2 mg/kg (N=4)**

Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

Dose expansion[a]

1	Adenocarcinoma NSCLC with *EGFR* mutations; prior EGFR TKI and platinum-based chemotherapy	**5.6 mg/kg (N=45)**
2	Squamous or nonsquamous NSCLC without *EGFR*-activating mutations	
3	NSCLC with *EGFR* mutations including any histology other than combined small and nonsmall cell	

Baseline Patient Characteristics



Patients in U102 were **heavily pre-treated**, with a median of 4 lines of prior systemic therapy

Data cutoff: September 24, 2020

Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.

[a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

HER3-DXd Demonstrated Durable Antitumor Activity After Failure of EGFR TKI and Platinum-based Chemotherapy (PBC)

Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	HER3-DXd 5.6 mg/kg Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD	9 (16)	8 (18)
Not evaluable	7 (12)	6 (14)
Disease control rate, % (95% CI)	72 (59-83)	68 (52-81)
Time to response, median (range), mo	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), mo	6.9 (3.1-NE)	7.0 (3.1-NE)
PFS, median (95% CI), mo	8.2 (4.4-8.3)	8.2 (4.0-NE)

The subgroup of patients treated with prior **osimertinib (OSI)** and **platinum-based chemotherapy** demonstrated similar efficacy to the overall efficacy population

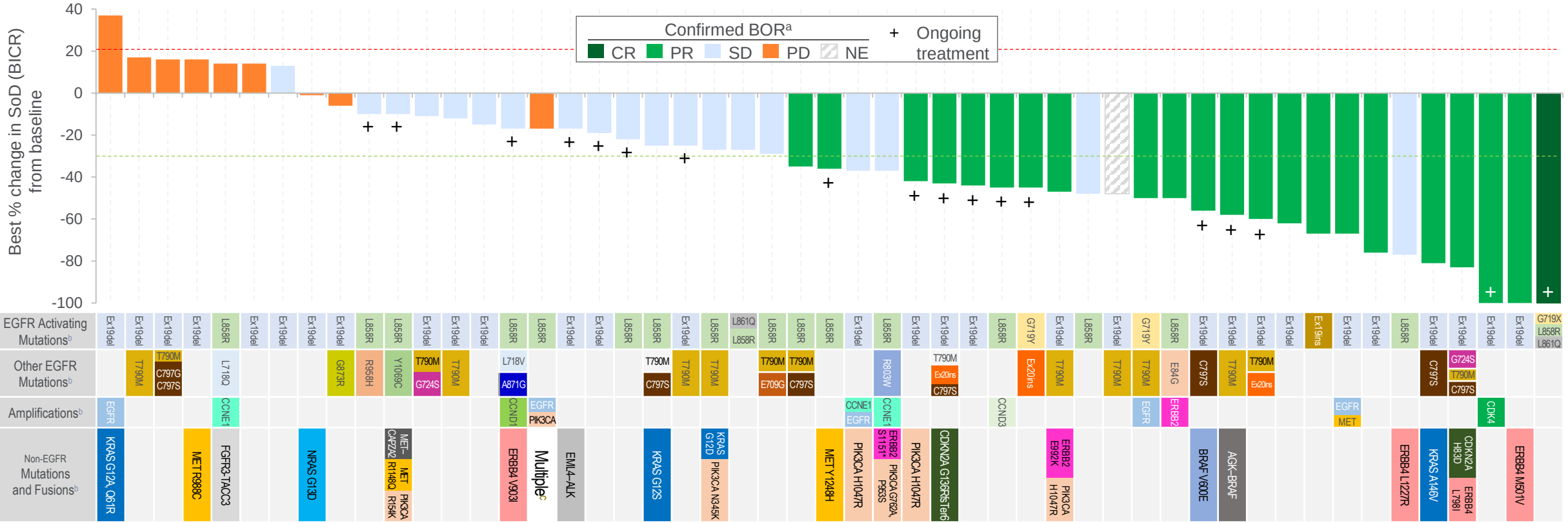
BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.
[a] For patients treated with the recommended dose for expansion of HER3-DXd (N=57)

HER3-DXd Demonstrated Activity in Patients With Diverse Mechanisms of EGFR TKI Resistance

Confirmed ORR 39%

Median Duration of Response 6.9 months

Median PFS 8.2 months

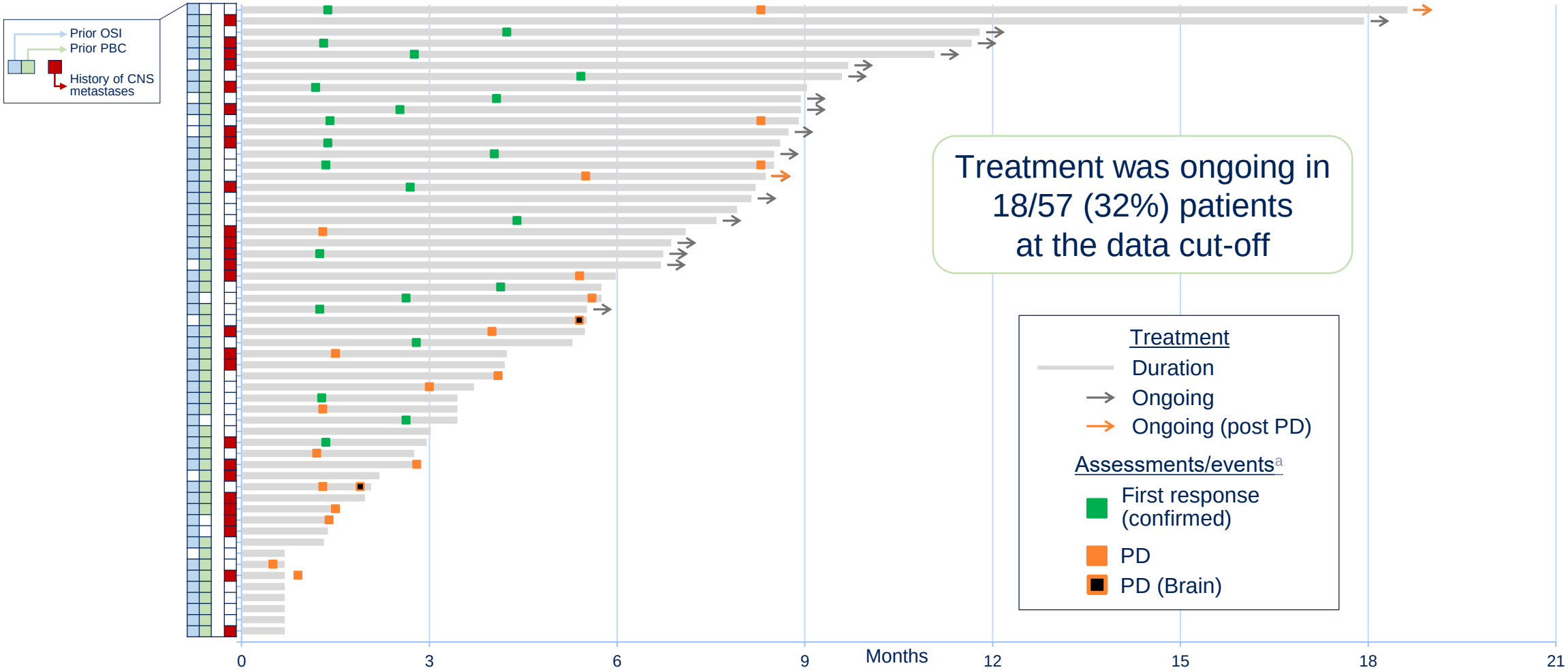


BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD stable disease; SoD, sum of diameters.

Data cutoff: September 24, 2020.

[a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood, collected prior to treatment with HER3-DXd. [c] CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; ERBB3 Q847*, Q849*.

Durable Responses Observed Regardless of Prior Treatments or History of Brain Metastases

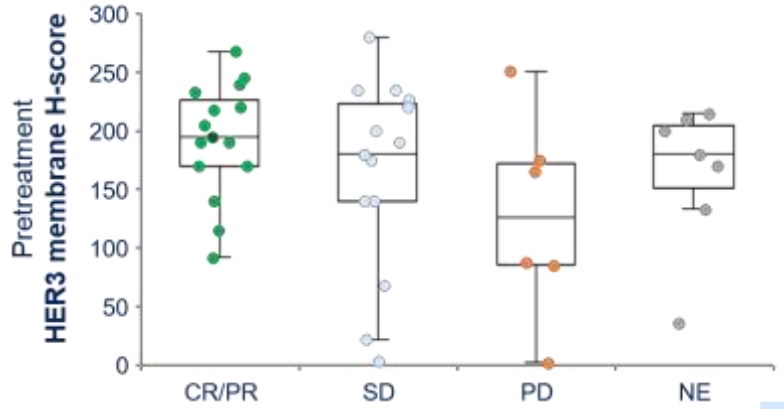


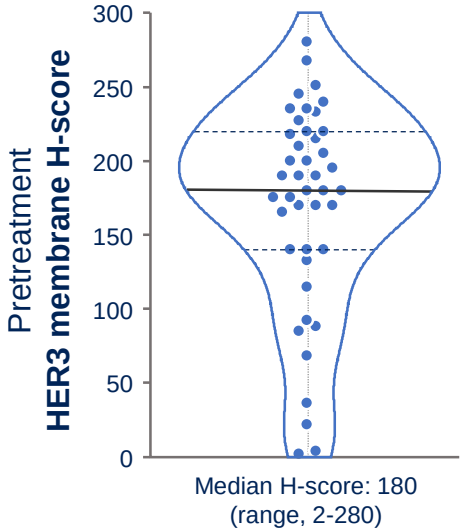
CR/PR, complete response/partial response; NE, not evaluable; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; SD stable disease
Data cutoff: September 24, 2020; By blinded independent central review.
[a] First sign of confirmed response or PD.

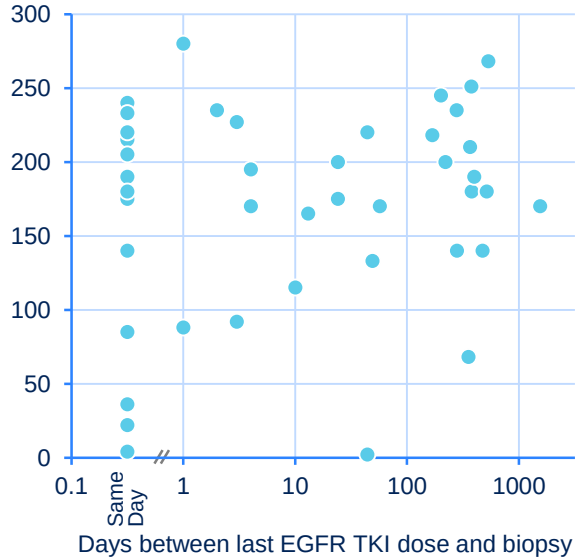
Clinical Responses Were Observed Across the Spectrum of Baseline HER3 Expression

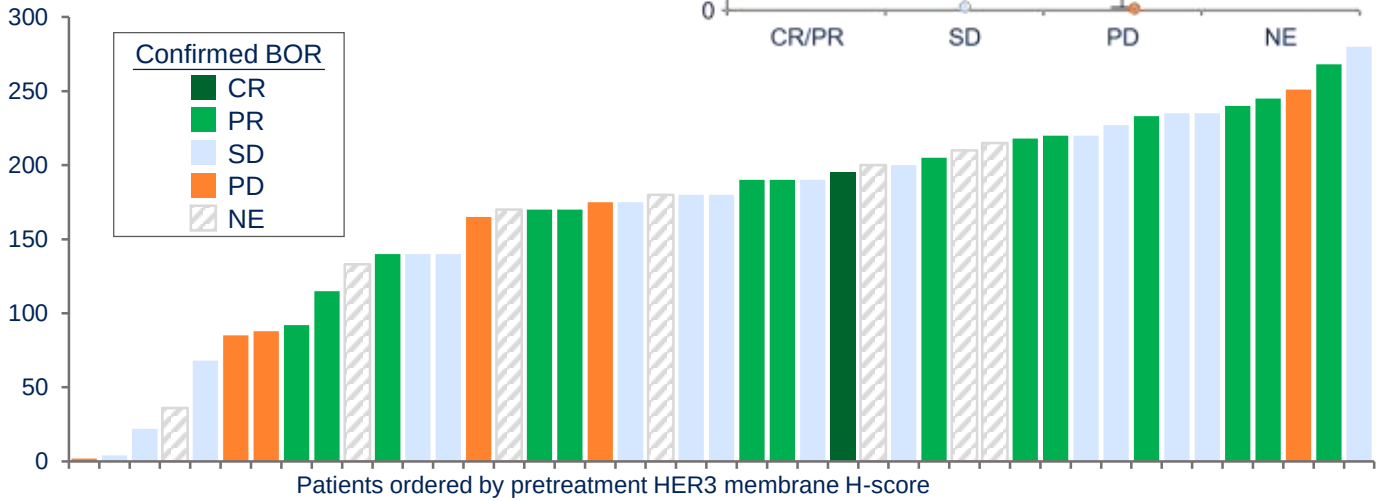
- HER3 was expressed in all evaluable patients' (43/57) tumors[a]
- HER3 expression was not correlated with time since last EGFR TKI dose

Responses were observed in patients with a wide range of baseline HER3 membrane H-scores





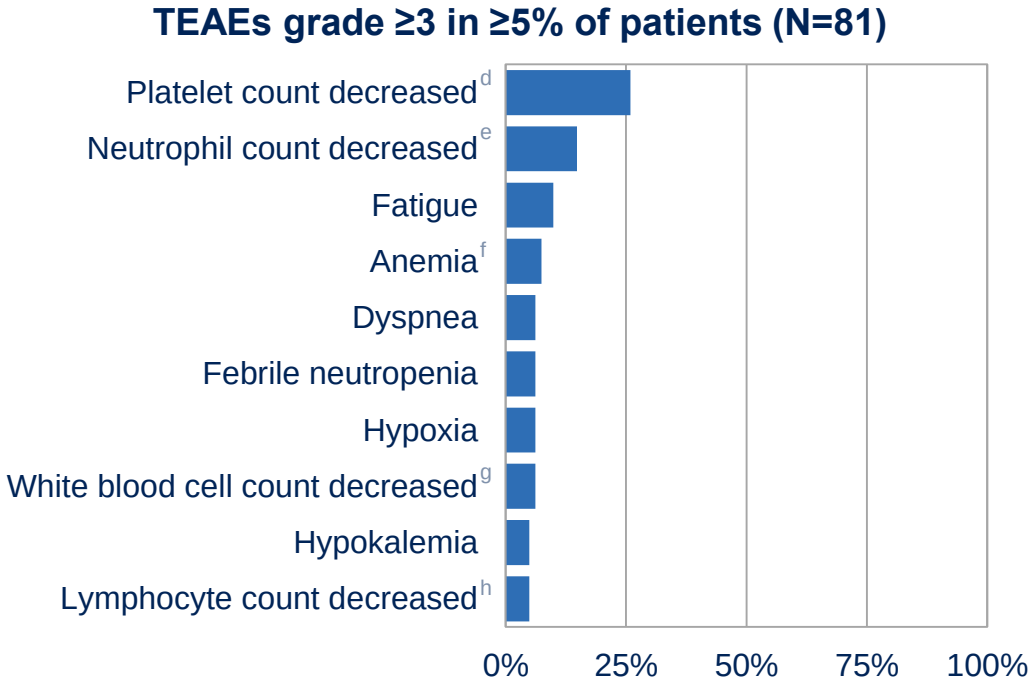




BOR, best overall response; CR/PR, complete response/partial response; NE, not evaluable; PD, progressive disease; SD stable disease.
Data cutoff: September 24, 2020; BOR by blinded independent central review.
[a] Immunohistochemistry analysis of membrane HER3 in pre-treatment biopsy tissue from patients subsequently receiving HER3-DXd 5.6 mg/kg (N=43; taken since progression on last treatment and within the 6 months prior to enrollment).

HER3-DXd Was Associated With a Manageable Safety Profile and a Low Rate of Discontinuations Due to Adverse Events

TEAEs, n (%) Median treatment duration: 5.7 (range, 0.7-28.3) mo	5.6 mg/kg (N=57)	All Doses (N=81)
Any TEAE	57(100)	81 (100)
Associated with treatment discontinuation[a]	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death[b]	4 (7)	5 (6)
Grade ≥3 TEAE	42 (74)	52 (64)
Treatment-related TEAE:	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
Interstitial lung disease[c]	4 (7)	4 (5)
Grade 1	2 (4)	2 (2)
Grade 2	1 (2)	1 (1)
Grade 3	1 (2)	1 (1)
Grade 4/5	0	0



- The rate of adjudicated treatment-related interstitial lung disease was 5%; none were grade 4/5
- Median time to adjudicated onset of treatment-related interstitial lung disease was 53 (range, 13-130) days

Data cutoff: September 24, 2020.

[a] TEAEs associated with treatment discontinuation were fatigue (2); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection; none were for thrombocytopenia (1 each). [b] TEAEs associated with death were: disease progression (2), respiratory failure (2), and shock (1). [c] One additional occurrence of Grade 5 ILD was determined by adjudication to be unrelated to study treatment. [d] Includes thrombocytopenia. [e] Includes neutropenia. [f] Includes hemoglobin decreased. [g] Includes leukopenia. [h] Includes lymphopenia.

HER3-DXd: Targeting the unmet medical need in EGFR-TKI resistant *EGFR*m NSCLC

Antitumor activity	**Clinically meaningful, durable efficacy** (ORR, 39%; median PFS, 8.2 months) • Efficacy shown across EGFR TKI resistance mechanisms in a difficult to treat patient population • Antitumor activity observed across a wide range of baseline HER3 expression
Safety	**Tolerable and manageable safety profile** • Low rate of discontinuation due to AEs (7/81; none due to thrombocytopenia) • Low rate of treatment-related interstitial lung disease (4/81; none were grade 4/5)

Pivotal HERTHENA-Lung01 study is ongoing based on the result of this study.

ASCO2021

HER3-DXd: Clinical Development Plan | NSCLC & other tumors

As of June 2021			FY2020	FY2021	FY2022	Planning
NSCLC	EGFR mutated	Advanced/ Metastatic 3L~	Ph1 dose expansion			
			HERTHENA-Lung01 monotherapy			
		Advanced/ Metastatic 2L		Osimertinib combination Ph1b		
		Advanced/ Metastatic 1L				
CRC	All comers	Metastatic 3L~	Monotherapy			
Breast	All comers	Metastatic 3L~	Monotherapy Ph1/2			

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

CRC: colorectal cancer, NSCLC: non small cell lung cancer

Agenda

1. Introduction
2. Enhertu: New data & development plan
3. Dato-DXd: New data & development plan
4. HER3-DXd: New data & development plan
5. **Future news flow**

FY2021 News Flow

As of Jun 2021

Planned publications

European Hematology Association (Jun 9-17)	
DS-3201	NHL Ph1 • ATL, PTCL data (oral)
WCLC (Sep 8-14)	
Dato-DXd	TROPION-PanTumor01: Ph1 NSCLC cohort • Updated data
ESMO (Sep 16-21)	
ENHERTU®	DESTINY-Lung01: HER2+/mutated NSCLC, 2L, Ph2 • HER2 mutated cohort data
DS-7300	Solid tumor Ph1 • Ph1 dose escalation data
DS-6000	Non-clinical pharmacology data

Not yet determined whether the abstracts are accepted for ESMO

Regulatory decision

DS-1647/G47Δ	Malignant glioma • JP: FY2021 Q1
Lixiana®	Atrial fibrillation in the very elderly • JP: FY2021 Q2
Efient®	Ischemic stroke • JP: FY2021 Q3

Key data readout

ENHERTU®	DESTINY-Breast03: HER2 positive BC, 2L, Ph3 • FY2021 Q2 DESTINY-Lung01: HER2 positive/mutated NSCLC, 2L, Ph2 • FY2021 Q2 DESTINY-Breast04： HER2 low BC, post chemo, Ph3 • FY2021 Q4
Quizartinib	QuANTUM-First: AML, 1L, Ph3 • FY2021 Q3

Pivotal study initiation

ENHERTU®	DESTINY-Breast09: HER2 positive BC, 1L, Ph3 • Jun 2021 (already initiated) DESTINY-Gastric04: HER2 positive GC, 2L, Ph3 • FY2021 1H
DS-3201	PTCL, Ph2 pivotal • FY2021 Q1

Underlined: New or updated from FY2020 Q4

ATL: adult T-cell leukemia, BC: breast cancer, DMD: Duchenne muscular dystrophy, NHL: non-Hodgkin's lymphoma, NSCLC: non-small cell lung cancer, PTCL: peripheral T-cell lymphoma

Daiichi Sankyo will contribute to the enrichment of quality of life around the world

Appendix

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with human epidermal growth factor receptor 2–positive advanced gastric cancer or gastroesophageal junction adenocarcinoma: final overall survival results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01)

Kensei Yamaguchi

The Cancer Institute Hospital of JFCR, Tokyo, Japan June 2021

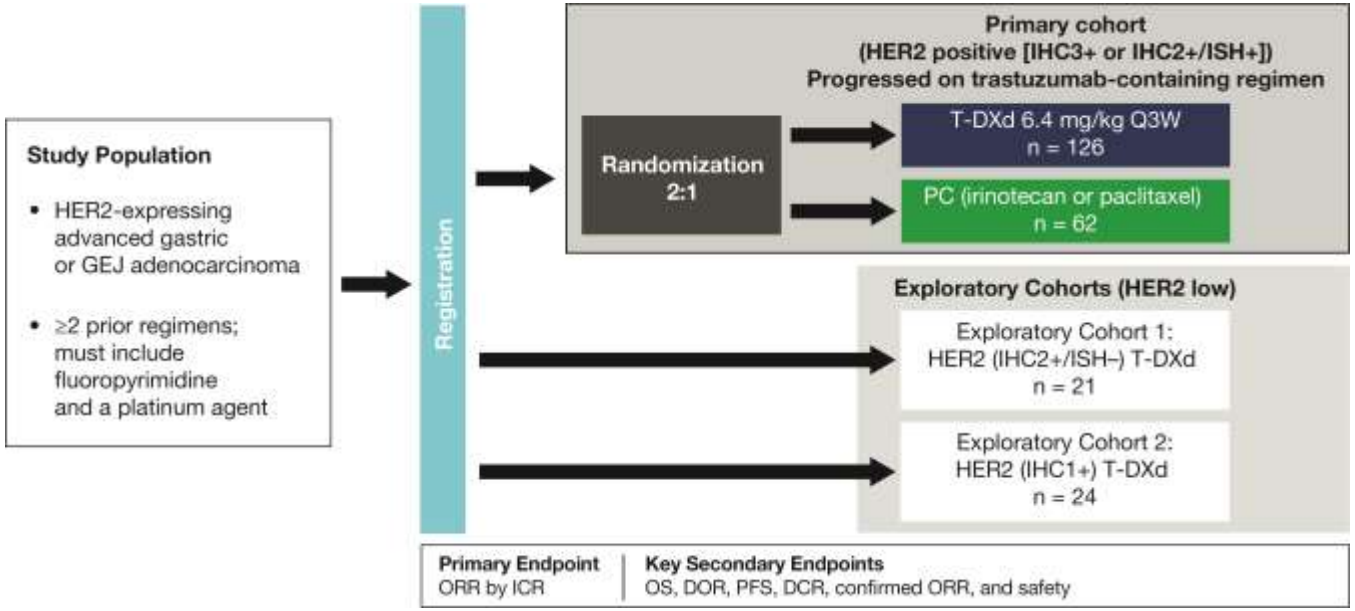
ON BEHALF OF THE DESTINY-Gastric01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

Background and Study Design

- T-DXd is an antibody–drug conjugate comprising an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload (DXd)[1] approved in the United States and Japan for adult patients with advanced HER2+ gastric or GEJ adenocarcinoma[2,3]
- In the primary DESTINY-Gastric01 analysis, T-DXd exhibited statistically significant ORR and OS benefit vs standard chemotherapy
- Here, we present final OS results as well as updated efficacy and safety data
- Patients had a median of 2 prior lines of therapy (range, 2-9); 44.4% of patients had ≥3 previous lines
- As of June 3, 2020, 10 patients (8%) receiving T-DXd and no patients receiving PC remained on treatment

DESTINY-Gastric01 Study Design



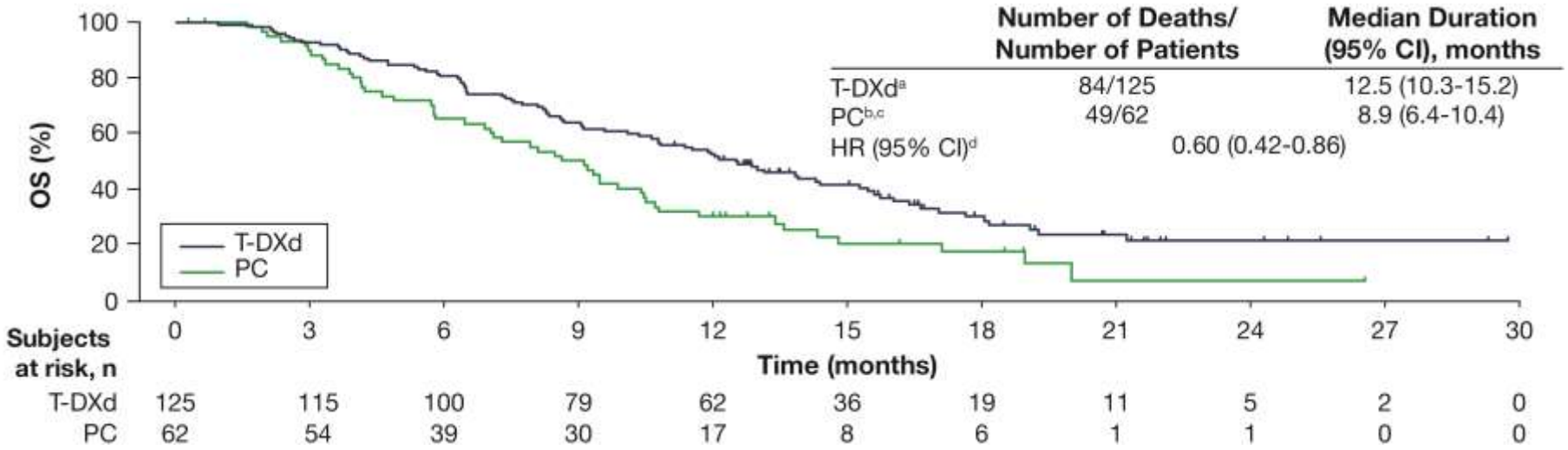
Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant

DCR, disease control rate; DOR, duration of response; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PC, physician's choice; PFS, progression-free survival; Q3W, every three weeks; T-DXd, trastuzumab deruxtecan.

1. Shitara K et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382:2419-2430. 2. Enhertu. Prescribing information. Daiichi Sankyo Inc.; 01/2021. 3. Enhertu. Summary of product characteristics. Daiichi Sankyo Co. LTD.; 2020.

Results: Overall Survival

Kaplan-Meier Analysis of Overall Survival



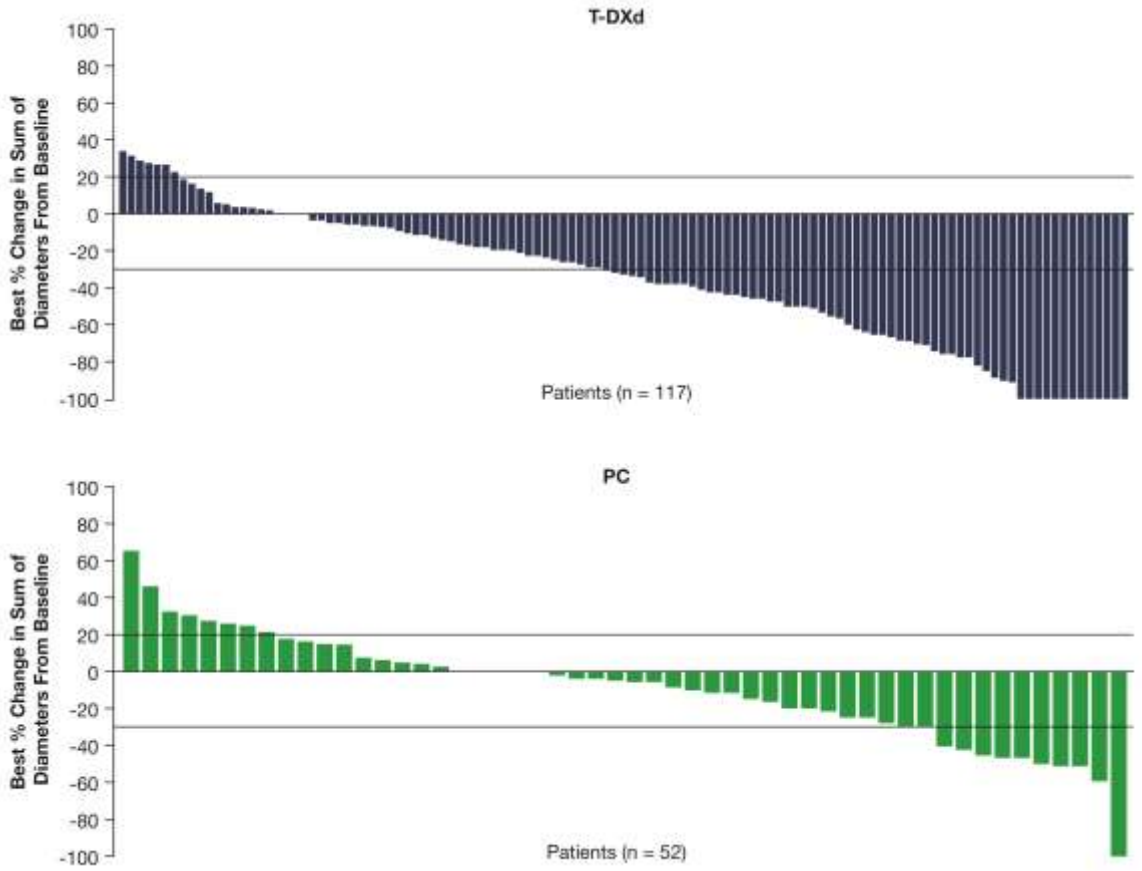
As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

Results: ORR and Other Efficacy Endpoints

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	61 (51.3) 95% CI, 41.9-60.5	8 (14.3) 95% CI, 6.4-26.2
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40 (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
PFS, median, months	5.6 95% CI, 4.3-6.9	3.5 95% CI, 2.0-4.3
	P = 0.0003[c]	
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

Best Percentage Change from Baseline in Tumor Size for Individual



CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; PC, physician's choice; PD, progressive disease; PFS, progression-free response; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response. [a]Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline. [b]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region. [c]Comparison between T-DXd and PC overall using stratified Log-rank test stratified by region.

Safety

- Grade ≥3 AEs occurred in 85.6% of T-DXd patients vs 56.5% with PC
  - The most common were decreased neutrophil count (51.2%, 24.2%), anemia (38.4%, 22.6%), and decreased white blood cell count (20.8%, 11.3%)
- 16 patients (12.8%) had T-DXd–related ILD, as determined by an independent adjudication committee
  - There were 13 grade 1 or 2, two grade 3, one grade 4, and no grade 5 events
  - There were four ILD events since the primary analysis; one grade 1 and three grade 2
  - Among the 16 total ILD events, the median time to first onset was 102.5 days (range, 36-638 days)
  - There were no ILD events in the PC arm
- There was one T-DXd-related death from pneumonia (non-ILD), as reported in the primary analysis
- There were no AE-related deaths in the PC arm

TEAEs in ≥20% of Patients Treated with T-DXd

	T-DXd n = 125			PC Overall n = 62		
	Grade			Grade		
Preferred Term, %	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0

AE, adverse event; ILD, interstitial lung disease; PC, physician's choice; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent AE.
No additional TEAEs were observed in ≥20% of patients receiving PC. [a]There were no grade 5 events. [b]Includes preferred terms "neutrophil count decreased" and "neutropenia." [c]Includes preferred terms "hemoglobin decreased," "red blood cell count decreased," "anemia," and "hematocrit decreased." [d]Includes preferred terms "platelet count decreased" and "thrombocytopenia." [e]Includes preferred terms "leukopenia" and "white blood cell count decreased." [f]Includes preferred terms "lymphocyte count decreased" and "lymphopenia."

Conclusions

- With continued follow-up after the primary analysis, T-DXd demonstrated clinically meaningful OS benefit (~40% reduced risk of death) and clinically relevant improvement in ORR compared with PC standard chemotherapy in HER2+ advanced gastric or GEJ cancer
- The overall safety profile of T-DXd was manageable and consistent with that of the primary analysis
  - The most common AEs were gastrointestinal or hematologic in nature
  - 16 patients (12.8%) had T-DXd-related ILD as determined by an independent adjudication committee. Most were grade 1 or 2
- Additional follow-up provides continued evidence that T-DXd is an effective treatment option for patients with HER2+ advanced gastric or GEJ adenocarcinoma who have progressed after ≥2 previous lines of therapy, including trastuzumab, fluoropyrimidine, and a platinum agent

AE, adverse event; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

Unmet Clinical Need for Approved Targeted Therapies in HER2-Positive Metastatic CRC

- **HER2 overexpression in mCRC**
  - CRC is the 3rd most common type of cancer and ≈25% of patients have metastatic CRC, of which around 2-3% of patients have HER2-amplified tumors
  - Current treatment options are fluoropyrimidine with oxaliplatin and/or irinotecan with an anti-VEGF compound or anti-EGFR monoclonal antibody (depending on the *RAS* mutational status)
  - Other therapies including regorafenib and trifluridine/tipiracil are recommended in the third-line or subsequent settings
    - Median OS was 6.4 months for regorafenib compared to 5.0 months for placebo and 7.1 months for trifluridine/tipiracil compared to 5.3 months for placebo
  - There are currently no approved HER2-targeted therapies for CRC

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metatstatic colorectal cancer; OS, overall survival; VEGF, vascular endothelial growth factor.

ASCO2021 | DESTINY-CRC01

Baseline Characteristics

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Age, median (range), years	57.0 (27-79)	62.0 (37-78)	58.5 (43-79)	58.5 (27-79)
Female, %	52.8	33.3	38.9	46.5
Region, %				
Europe	52.8	60.0	50.0	53.5
Asia	28.3	20.0	44.4	30.2
North America	18.9	20.0	5.6	16.3
ECOG performance status, %				
0	69.8	53.3	50.0	62.8
1	30.2	46.7	44.4	36.0
2	0	0	5.6	1.2
Sum of target lesions, median, cm	8.1	8.1	10.2	9.0
Primary tumor site, %[a]				
Left	88.6	93.3	94.4	90.7
Right	11.4	6.7	5.6	9.3

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
[a]Left: rectum, sigmoidal, descending; Right: cecum, ascending, transverse.

Baseline Characteristics (cont)

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Microsatellite status, %[a]				
MSI-H	0	0	0	0
Microsatellite stable	81.1	93.3	66.7	80.2
Unknown	18.9	6.7	33.3	19.8
***RAS* wild type, %[a,b]**	98.1	93.3	100	97.7
***BRAF*^{V600E} wild type, %[a,c]**	100	100	94.4	98.8
HER2 status, %[d]				
IHC 3+	75.5	0	0	46.5
IHC 2+	24.5	100	0	32.6
IHC 1+	0	0	100	20.9
ISH+	98.1[e]	0	22.2	65.1
ISH–	0	100	77.8	33.7

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MSI-H, microsatellite instability status-high.
[a]By local assessment. [b]1 patient cohort A had an *NRAS* mutation; 1 patient in cohort B was not examined. [c]1 patient in cohort C was not examined. [d]By central assessment. Sums may not total 100% due to rounding. [e]1 patient was non-evaluable for ISH testing.

Prior Treatments

Prior Treatment, %	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Irinotecan	100	100	100	100
Fluorouracil / capecitabine	100 / 54.7	93.3 / 46.7	100 / 55.6	98.8 / 53.5
Oxaliplatin	100	93.3	100	98.8
Cetuximab or panitumumab	100	100	94.4	98.8
Bevacizumab	75.5	73.3	83.3	76.7
Prior anti-HER2 agents	30.2	0	0	18.6

- Median prior regimens for metastatic disease was 4 (range, 2–11)

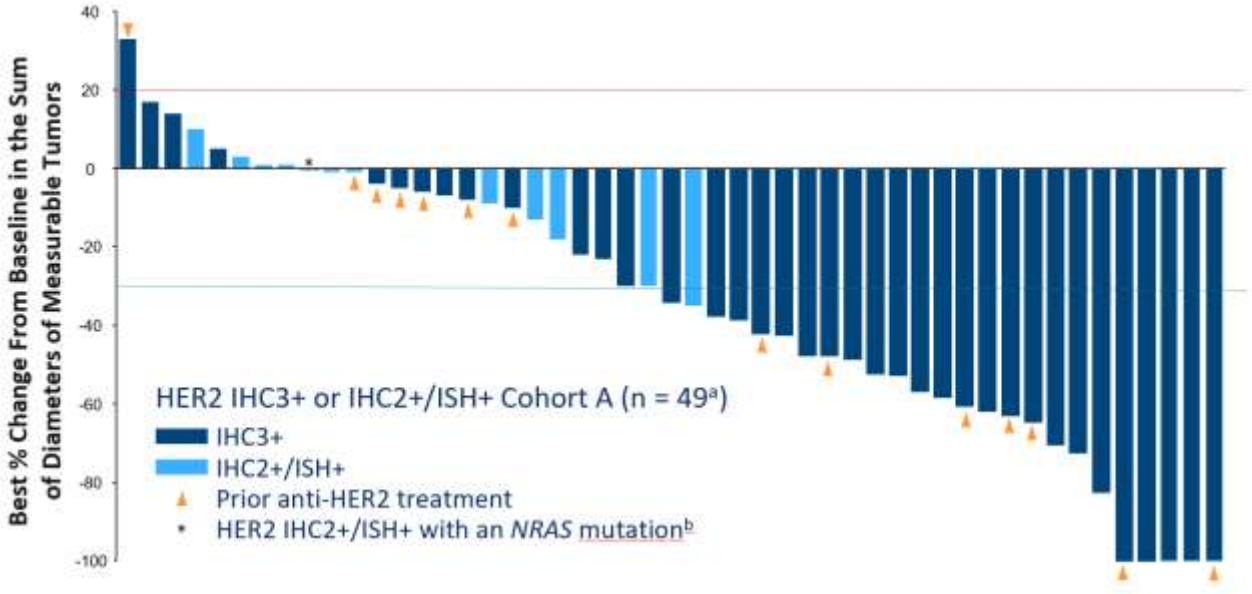
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

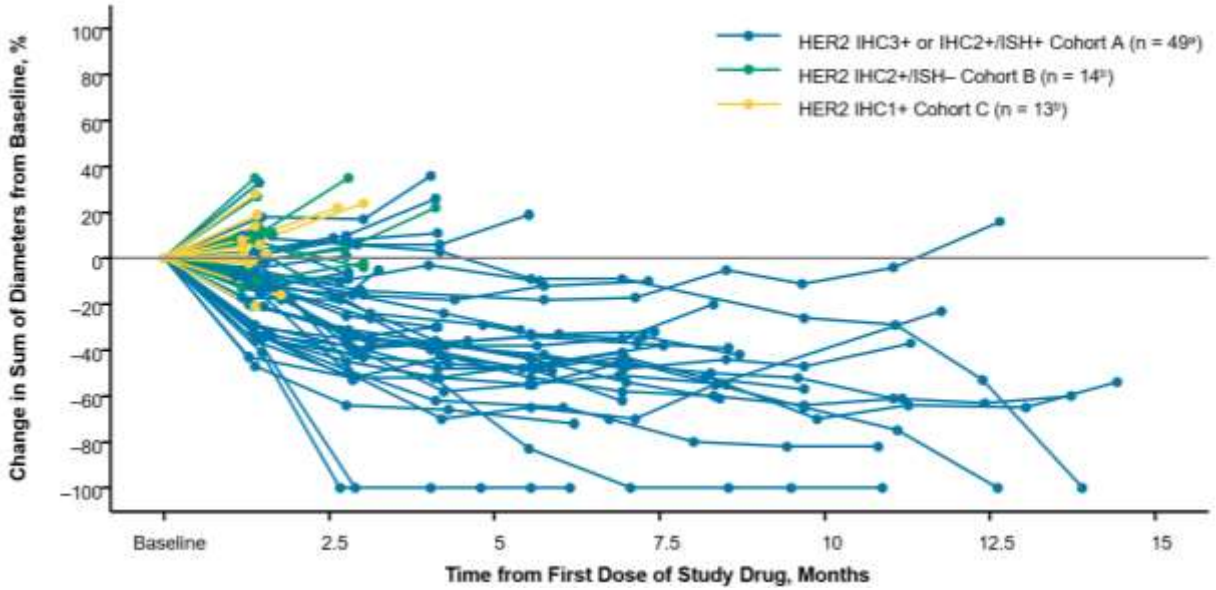
Overall Safety Summary

n (%)	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
TEAEs	53 (100)	15 (100)	18 (100)	86 (100)
Grade 3 or above	35 (66.0)	7 (46.7)	14 (77.8)	56 (65.1)
Drug-related TEAEs	51 (96.2)	15 (100)	15 (83.3)	81 (94.2)
Grade 3 or above	29 (54.7)	4 (26.7)	9 (50.0)	42 (48.8)
Serious TEAEs	20 (37.7)	6 (40.0)	9 (50.0)	35 (40.7)
Drug-related serious TEAEs	12 (22.6)	2 (13.3)	2 (11.1)	16 (18.6)
TEAEs leading to drug discontinuations	8 (15.1)	2 (13.3)	3 (16.7)	13 (15.1)
Drug-related TEAEs leading to drug discontinuations	4 (7.5)	2 (13.3)	1 (5.6)	7 (8.1)
TEAEs leading to dose reduction	11 (20.8)	0	4 (22.2)	15 (17.4)
Drug-related TEAEs leading to dose reduction	10 (18.9)	0	4 (22.2)	14 (16.3)
TEAEs leading to drug interruption	26 (49.1)	3 (20.0)	5 (27.8)	34 (39.5)
Drug-related TEAEs leading to drug interruption	19 (35.8)	1 (6.7)	3 (16.7)	23 (26.7)
TEAEs associated with death	5 (9.4)	2 (13.3)	2 (11.1)	9 (10.5)
Drug-related TEAEs associated with death[a]	2 (3.8)	1 (6.7)	0	3 (3.5)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; TEAE, treatment-emergent adverse events.
[a]3 drug-related TEAEs associated with death were 3 fatal ILDs adjudicated as drug-related.

Change in Tumor Size in Cohort A





HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
The line at 20% indicates progressive disease. The line at -30% indicates partial response. [a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment.

[a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]1 patient from cohort B and 5 patients from cohort C had missing postbaseline data.
Adapted from *The Lancet Oncology*, Siena S et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. 2021, with permission from Elsevier.

Conclusions

- **T-DXd monotherapy at the 6.4 mg/kg Q3W dose showed promising activity and durability with longer-term follow-up (additional 35.3 weeks from the primary analysis) in patients with HER2+ mCRC**
  - For cohort A, confirmed ORR was 45.3% (95% CI, 31.6–59.6), mDOR was 7.0 months (95% CI, 5.8–9.5), mPFS was 6.9 months (95% CI, 4.1-8.7), and mOS was 15.5 months (95% CI, 8.8–20.8)
- **No responses for ORR were observed in cohorts B and C**
- **The safety profile is consistent with the known safety profile of T-DXd**
  - Low grade gastrointestinal and hematologic AEs were most common[1]
  - ILD/pneumonitis (9.3% of patients; 3.5% grade 5) is an important risk and requires careful monitoring and prompt intervention
- **These promising results support continued exploration of T-DXd in patients with HER2+ mCRC**

AE, adverse events; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mCRC, metastatic colorectal cancer; mDOR, median duration of response; mOS, median overall survival; ORR, objective response rate; q3w, every three weeks; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Introduction

- BEGONIA (NCT03742102) is an ongoing 2 part, multicenter, multiarm, open-label platform study evaluating safety and efficacy of durvalumab + paclitaxel (D+P) and durvalumab with or without paclitaxel (P) combined with novel therapies as first-line (1L) treatment for metastatic TNBC.

Objectives

- Determine initial safety, tolerability, and efficacy of the combination of durvalumab with other therapies of known or potential efficacy in patients with metastatic TNBC enrolled in Part 1 of the BEGONIA study
- Here we present preliminary results from Arm 6 (durvalumab + trastuzumab deruxtecan)

Methods

- The first 6 patients treated with D+T-DXd were evaluated for dose-limiting toxicities (DLTs), with additional patients enrolled if D+T-DXd was tolerated.
- Tumors were assessed every 8 weeks for D+P or every 6 weeks for D+T-DXd per RECIST 1.1.
- HER2-low expression was determined by local testing and defined as immunohistochemistry (IHC) score 1+ or 2+ and in situ hybridization (ISH) negative or untested.
- PD-L1 expression was assessed retrospectively by IHC using an SP263-based assay.
- An exploratory analysis using an area-based scoring algorithm was employed. PD-L1 expression was defined as the proportion of the tumor area populated by tumor cells or immune cells with membranous PD-L1 staining.*
- A sample was considered positive if it demonstrated ≥5% PD-L1 expression.
- **Study arms were noncomparable due to differing eligibility criteria, treatment periods, and data maturity.**

* Optimal scoring algorithms and cutoffs for PD-L1 expression that are relevant to durvalumab treatment for metastatic TNBC have not yet been established.

ARM 1: Durvalumab + Paclitaxel

Arm 1: Patient Disposition and Characteristics (N=23)

- As of the data cutoff of September 2020, 23 patients received D+P with 7 still on treatment.
  - 2 patients discontinued D+P due to an AE.
  - 16 discontinued due to disease progression.
  - 2 of these patients discontinued for >1 reason.
- Median (range) follow-up time: 16.6 (8.5–19.8) months.

Characteristic	
Age, median (range), years	52 (30–63)
Race	
Asian	18 (78.3)
White	4 (17.4)
Other	1 (4.3)
No prior treatment	6 (26.1)
Prior treatments for early-stage disease	
Radiotherapy	15 (65.2)
Cytotoxic chemotherapy	17 (73.9)
Taxane	14 (60.9)
Anthracycline	15 (65.2)
Platinum compound	4 (17.4)
Hormonal therapy	1 (4.3)
Targeted therapy	1 (4.3)
Visceral metastases[a]	17 (73.9)
Lymph node metastases	16 (69.6)
PD-L1 expression ≥5%	
TIP ≥5% (positive)	7 (30.4)
TIP <5% (negative)	14 (60.9)
Missing	2 (8.7)

Data cutoff September 2020. n (%) unless otherwise stated.
[a]Visceral metastases is defined as liver/hepatic and/or respiratory metastases.
PD-L1, programmed death ligand-1.

Arm 1: Safety Summary (N=23)

- **Grade 3/4 AEs were mainly hematologic; the most frequent was decreased neutrophil count (n=4, 17.4%)**

	n (%)
Any AE	22 (95.7)
Common AEs (≥20% patients, any grade)	
Alopecia	14 (60.9)
Peripheral sensory neuropathy	13 (56.5)
Nausea	10 (43.5)
Rash	9 (39.1)
Fatigue, neutrophil count decreased	8 (34.8) each
Peripheral edema	7 (30.4)
Hypothyroidism, myalgia	6 (26.1) each
ALT increased, nail discoloration, pruritus	5 (21.7) each
Any Grade 3/4 AE	10 (43.5)
Any SAE	1 (4.3)
Any treatment-related AE	22 (95.7)
Any AESI for durvalumab	11 (47.8)
AE leading to death	0
AE leading to dose interruption	13 (56.5)
Any durvalumab dose delay	7 (30.4)

Arm 1: Safety Summary (N=23), cont'd

Grade 3/4 AEs

Preferred term	n (%)
Hematological	
Neutrophil count decreased	4 (17.4)
WBC count decreased	1 (4.3)
Febrile neutropenia	1 (4.3)
Neutropenia	1 (4.3)
Gastrointestinal	
Diarrhea	1 (4.3)
Stomatitis	1 (4.3)
Others	
Rash	1 (4.3)
ALT increased	1 (4.3)
AST increased	1 (4.3)
Neuropathy peripheral	1 (4.3)
Peripheral sensory neuropathy	1 (4.3)
Hypokalemia	1 (4.3)
Pneumonitis	1 (4.3)

Data cutoff September 2020.

Additional AE Details

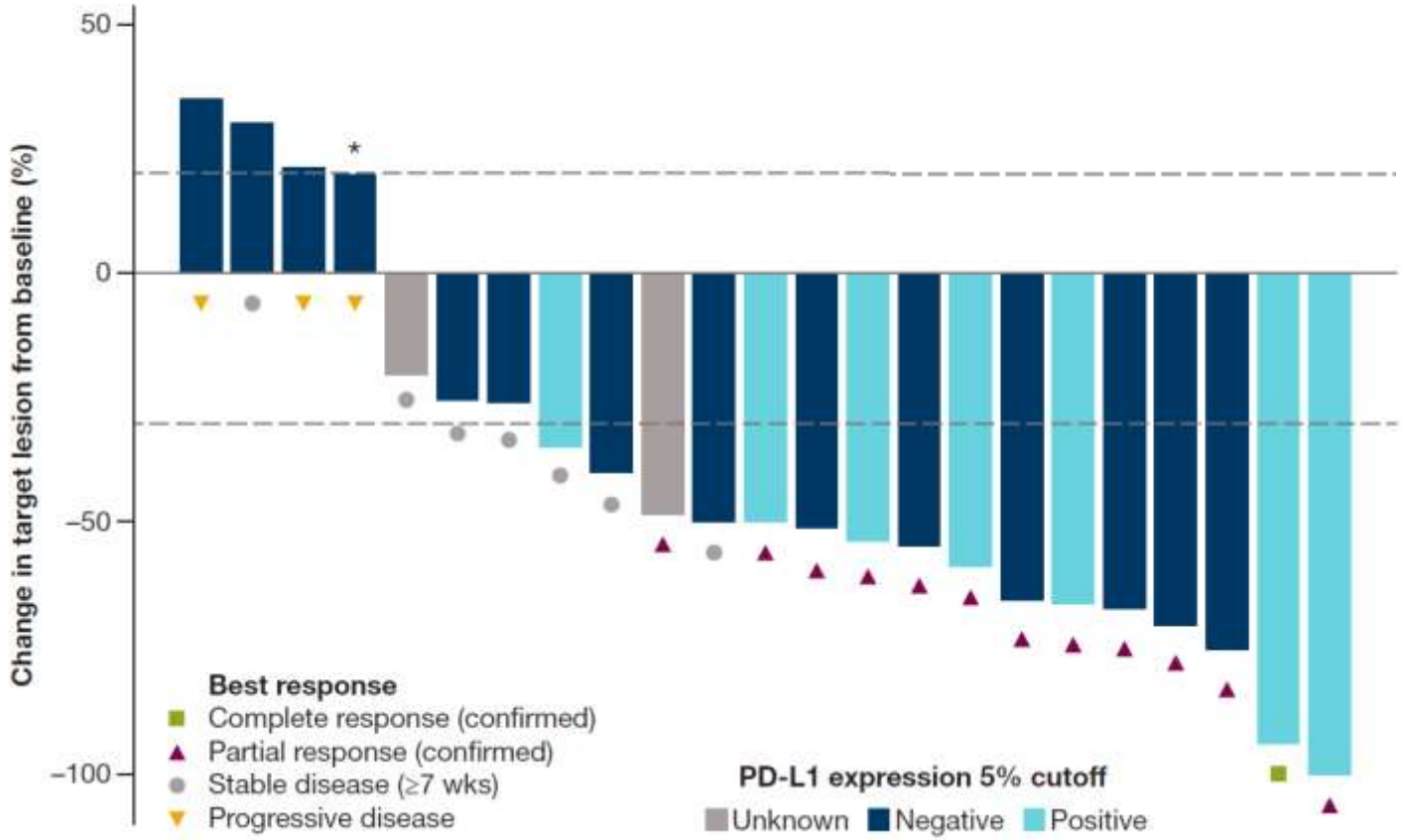
Any Grade 3/4 AE	10 (43.5)
Any SAE	1 (4.3)
Any treatment-related AE	22 (95.7)
Related to durvalumab only	11 (47.8)
Related to paclitaxel only	21 (91.3)
Any AESI for durvalumab	11 (47.8)
Rash	9 (39.1)
Hypothyroidism	6 (26.1)
Diarrhea	3 (13.0)
Hyperthyroidism	1 (4.3)
Pneumonitis	1 (4.3)
AE leading to death	0
AE leading to dose interruption	13 (56.5)
Any durvalumab dose delay	7 (30.4)

Data cutoff September 2020.

Arm 1: Best change from baseline of target tumor size

- **In this small population, responses occurred for both PD-L1–positive (confirmed ORR 6/7 [85.7%]) and PD-L1–negative (confirmed ORR 6/14 [42.9%]) groups**

Parameter	D+P
Response evaluable analysis set, N‡	23
Confirmed ORR,‡ n (%) 95% CI Complete response, n (%) Partial response, n (%)	13 (56.5) 34.5, 76.8 1 (4.3) 12 (52.2)
Unconfirmed ORR, n (%) 95% CI	16 (69.6) 47.1, 86.8
Stable disease, n (%)	7 (30.4)
Progressive disease, n (%)	3 (13.0)

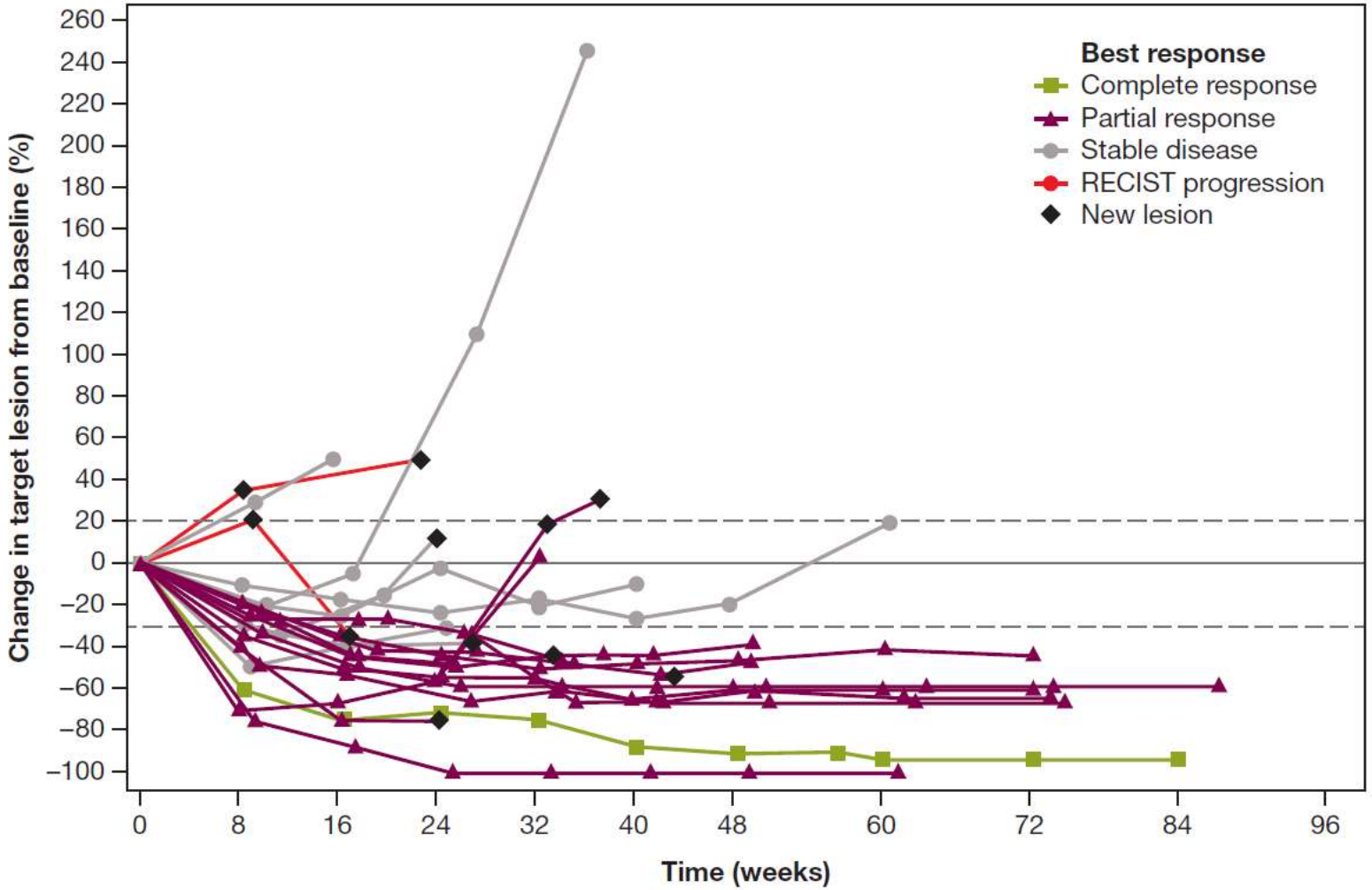


* If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal or death, the value is imputed at +20%

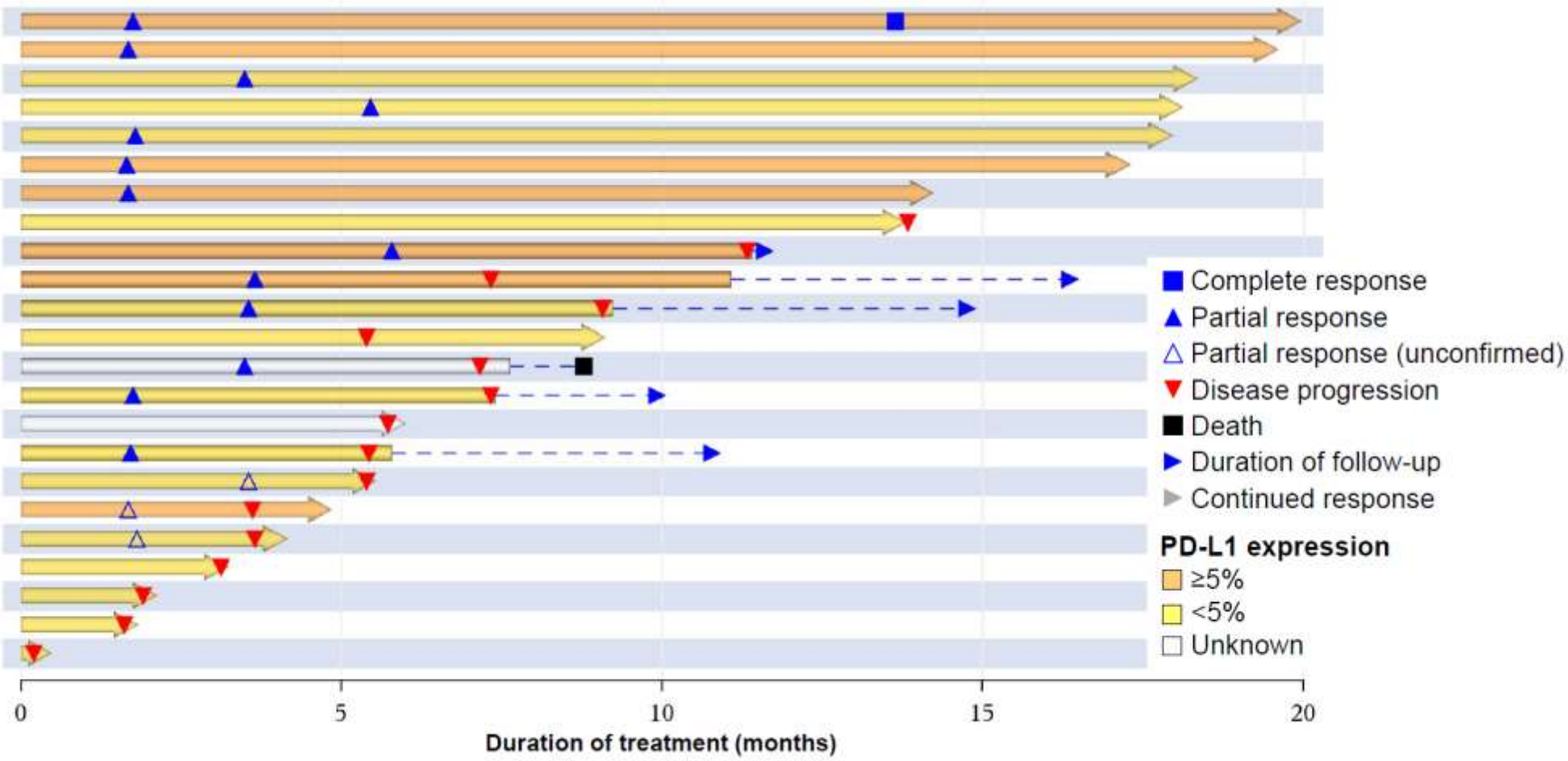
‡ Number of subjects that had the opportunity to complete at least two on-treatment disease assessments or have PD or death

Arm 1: Change from baseline in target tumor size over time

- **A total of 7/13 (53.8%) patients remained in response at the time of data cutoff**



Arm 1: Treatment Exposure & Duration of Response (N=23)

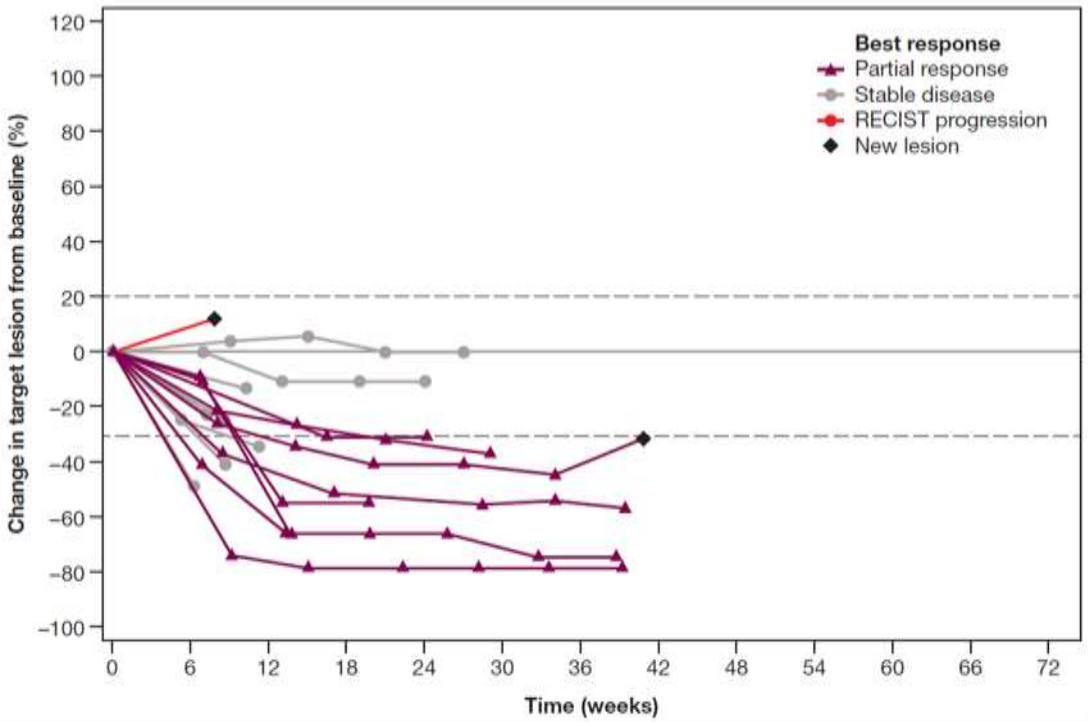


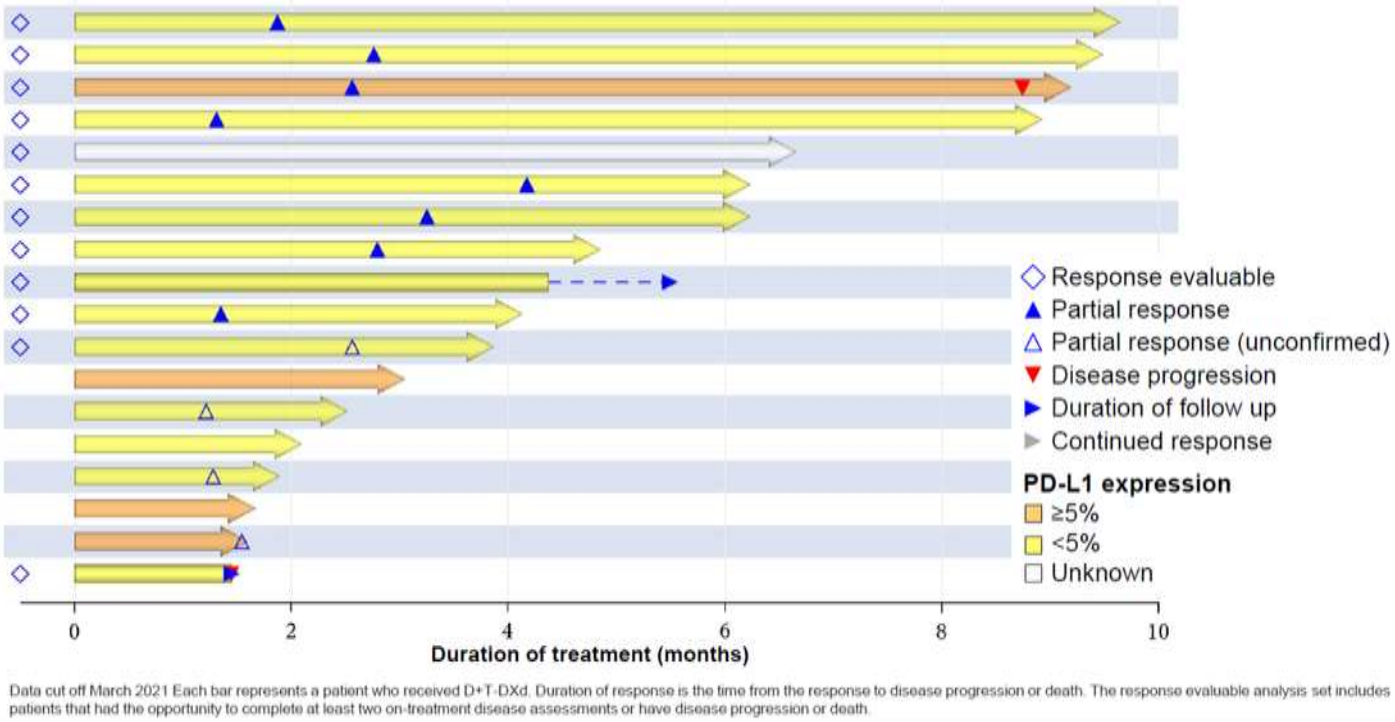
Data cutoff September 2020. Each bar represents a patient who received D+P. Duration of response is the time from the response to disease progression or death.

Arm 1 Conclusions: Durvalumab + Paclitaxel

- Acceptable safety/tolerability profile and demonstrates a response rate (confirmed ORR 56.5%) consistent with published data for 1L TNBC IO/taxane combination studies.
  - This was also consistent for patients with positive PD-L1 expression.
- Responses were observed regardless of PD-L1 expression (5% cutoff).
- Responses were durable with 53.8% of patients remaining in response for 12 months.

Arm 6: Change in target lesion & duration of treatment





Data cut off March 2021 Each bar represents a patient who received D+T-DXd. Duration of response is the time from the response to disease progression or death. The response evaluable analysis set includes patients that had the opportunity to complete at least two on-treatment disease assessments or have disease progression or death.

- **A total of 7/8 (87.5%) patients remained in response at the time of data cutoff**

Arm 6: Patient Disposition and Characteristics (N=21)

- As of the data cutoff of March 2021, 21 patients received D+T-DXd with 19 still on treatment.
- Median (range) follow-up time: 3.6 (0–9) months.

Characteristic	
Age, median (range), years	58 (35–81)
Race	
Asian	6 (28.6)
White	13 (61.9)
Black/African American	2 (9.5)
No prior treatment	4 (19.0)
Prior treatments for early-stage disease	
Radiotherapy	13 (61.9)
Cytotoxic chemotherapy	15 (71.4)
Taxane	11 (52.4)
Anthracycline	15 (71.4)
Platinum compound	7 (33.3)
Hormonal therapy	5 (23.8)
Visceral metastases[a]	17 (80.9)
Lymph node metastases	12 (57.1)
PD-L1 expression	
TIP ≥5% (positive)	6 (28.6)
TIP <5% (negative)	13 (61.9)
Missing	2 (9.5)
HER2 status per local testing	
IHC 2+/ISH–	6 (28.6)
IHC 1+/ISH–	2 (9.5)
IHC 1+/ISH untested	13 (61.9)

Data cutoff March 2021. n (%) unless otherwise stated.
[a]Visceral metastases is defined as liver/hepatic and/or respiratory metastases.

Arm 6: Safety Summary (N=21), cont'd

Grade 3/4 AEs

Preferred term	n (%)
Hematological	
Neutropenia	4 (19.0)
Anemia	3 (14.3)
Thrombocytopenia	2 (9.5)
Platelet count decreased	1 (4.8)
Hemolysis	1 (4.8)
Gastrointestinal	
Ascites	1 (4.8)
Diarrhea	1 (4.8)
Other	
Hypophosphatemia	2 (9.5)
Hyponatremia	2 (9.5)
CMV viremia	1 (4.8)
COVID-19	1 (4.8)
Decreased appetite	1 (4.8)
Fatigue	1 (4.8)
Lipase increased	1 (4.8)
Pneumonitis	1 (4.8)
Transaminases increased	1 (4.8)

Data cutoff March 2021.

Additional AE Details

Any Grade 3/4 AE	8 (38.1)
Any SAE	5 (23.8)
Any treatment-related AE	20 (95.2)
Related to durvalumab only	7 (33.3)
Related to T-DXd only	16 (76.2)
Related to both	13 (61.9)
Any AESI for durvalumab	11 (52.4)
Hypothyroidism	5 (23.8)
Diarrhea	4 (19.0)
Hyperthyroidism	3 (14.3)
Rash	3 (14.3)
Pneumonitis	2 (9.5)
Ulcerative Colitis	1 (4.8)
Thyroiditis	1 (4.8)
Urticaria	1 (4.8)
Any AESI for T-DXd	2 (9.5)
Pneumonitis	2 (9.5)
Troponin increased	1 (4.8)
AE leading to death	0
AE leading to dose interruption	7 (33.3)
Any durvalumab dose delay	9 (42.9)
Any T-DXd dose delay	9 (42.9)
T-DXd dose reduction	5 (23.8)

Data cutoff March 2021.

TRASTUZUMAB DERUXTECAN (T-DXD) IN PATIENTS WITH HER2+ METASTATIC BREAST CANCER WITH BRAIN METASTASES: A SUBGROUP ANALYSIS OF THE DESTINY-BREAST01 TRIAL

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On behalf of the investigators

Background

- Here we describe a subgroup analysis from the ongoing DESTINY- Breast01 study, analyzing the efficacy of T-DXd in patients with a history of brain metastases

Methods

- Patients with brain metastases who were treated, asymptomatic, and did not require therapy to control symptoms were eligible for enrollment
  - All treatment to control symptoms of brain metastases, including radiation, surgery, or other therapy (including steroids or anticonvulsants), had to be completed more than 60 days before randomization
- For patients with brain metastases at baseline, brain lesions were monitored by CT or MRI
  - A CT or MRI scan of the brain was required every 6 weeks in these patients
  - All measurements for brain lesions were retrospectively reported by the investigators
- The CNS subgroup included patients with a history of brain metastases who received T-DXd at the approved dose of 5.4 mg/kg every 3 weeks; CNS responses were analyzed among patients in the CNS subgroup who had brain lesions at baseline1

Baseline Characteristics & Clinical Activity Outcomes

Baseline Characteristics[9]

	CNS subgroup (n=24)	All patients (N=184)
Age, median (range), years	58.0 (33-85)	55.0 (28-96)
Female, %	100	100
Region, %		
Asia	37.5	34.2
Europe	37.5	37.0
North America	25.0	28.8
ECOG performance status, %		
0	62.5	55.4
1	37.5	44.0
2	0	0.5
HR status, %		
Positive	37.5	52.7
Negative	58.3	45.1
Unknown	4.2	2.2
HER2 expression, %[a]		
IHC 3+	79.2	83.7
IHC 2+; ISH+	20.8	15.2
IHC 1+; ISH+	0	1.1
Presence of visceral disease, %	100	91.8
Prior CNS treatment, %[b]		
Radiotherapy only	54.2	
Surgery only	4.2	
Radiotherapy + surgery	20.8	
None reported	20.8	

Clinical Activity Outcomes of T-DXd[1]

Intent-to-treat analysis	CNS subgroup (n=24)	All patients (N=184)
Confirmed ORR by ICR, n (%)	**14 (58.3)** (95% CI, 36.6-77.9)	**112 (60.9)** (95% CI, 53.4-68.0)
CR	1 (4.2)	11 (6.0)
PR	13 (54.2)	101 (54.9)
SD	8 (33.3)	67 (36.4)
PD	1 (4.2)	3 (1.6)
Not evaluable	1 (4.2)	2 (1.1)
Duration of response (CR or PR), median	16.9 months (95% CI, 5.7-16.9)	14.8 months (95% CI, 13.8-16.9)

- Efficacy of T-DXd in the CNS subgroup was comparable to that of the overall population
- In the overall population, 4 of 184 (2.2%) patients had CNS progression events
  - In the CNS subgroup, 2 of 24 (8.3%) patients had CNS progression events occur at 78 and 85 days
  - In the non-CNS subgroup, 2 of 160 (1.3%) patients without a history of CNS metastases had CNS progression events occur at 323 and 498 days

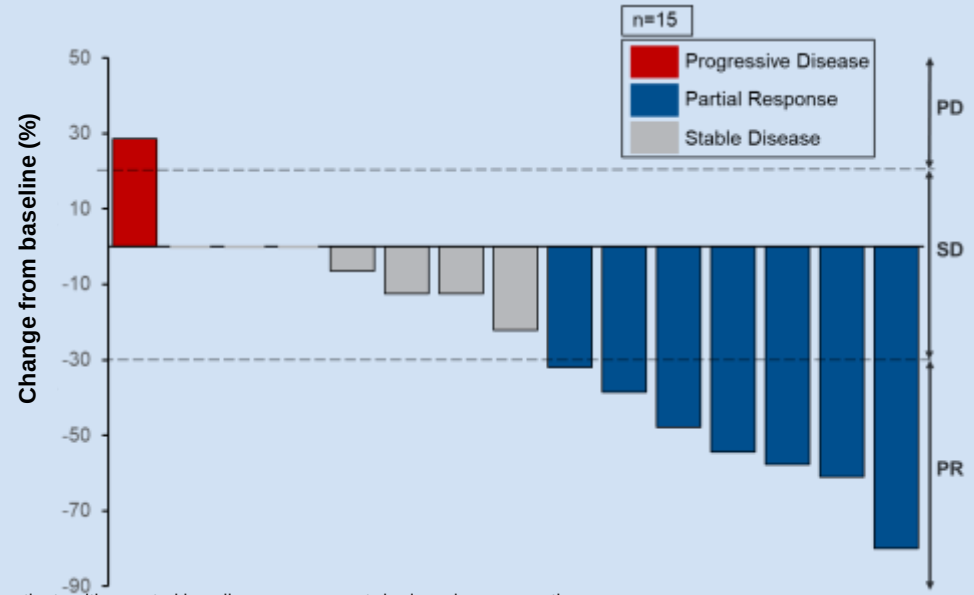
CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease
Data cutoff: August 1, 2019.

1. Jerusalem G, et al. Presented at: European Society for Medical Oncology Breast Cancer 2020 Virtual Meeting. Abstract 138O.

CNS Response

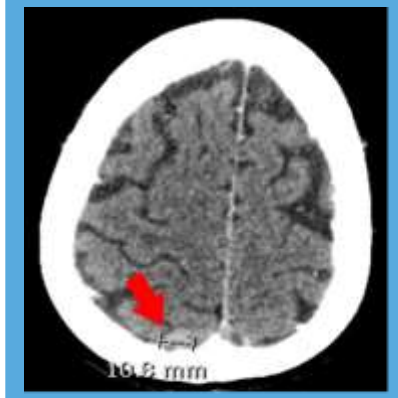
Best Response in Brain Lesions in Patients in the CNS Subgroup

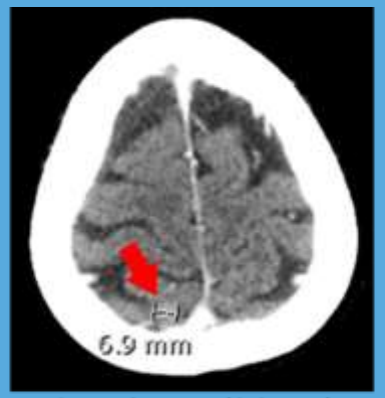
- Of 24 patients in the CNS subgroup, 17 had brain lesions at baseline; data were available to evaluate responses in the brain for 15 of these 17 patients
  - Of the 15 patients, 13 completed radiotherapy at least 60 days prior to randomization, which could have contributed to continued shrinkage in brain metastases during the study
- Per investigator assessment, 7of 17 patients (41.2%) had a reduction in brain lesion diameters consistent with a best response of PR in the brain



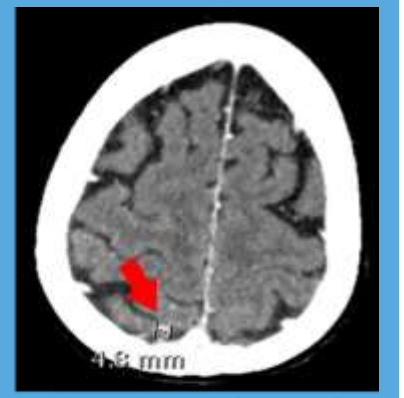
3 patients with reported baseline measurements had no change over time.
2 patients with brain metastases at baseline did not have sufficient data to evaluate response in the brain and are not shown.

Example Brain Scans


Baseline scan (10.6 mm)



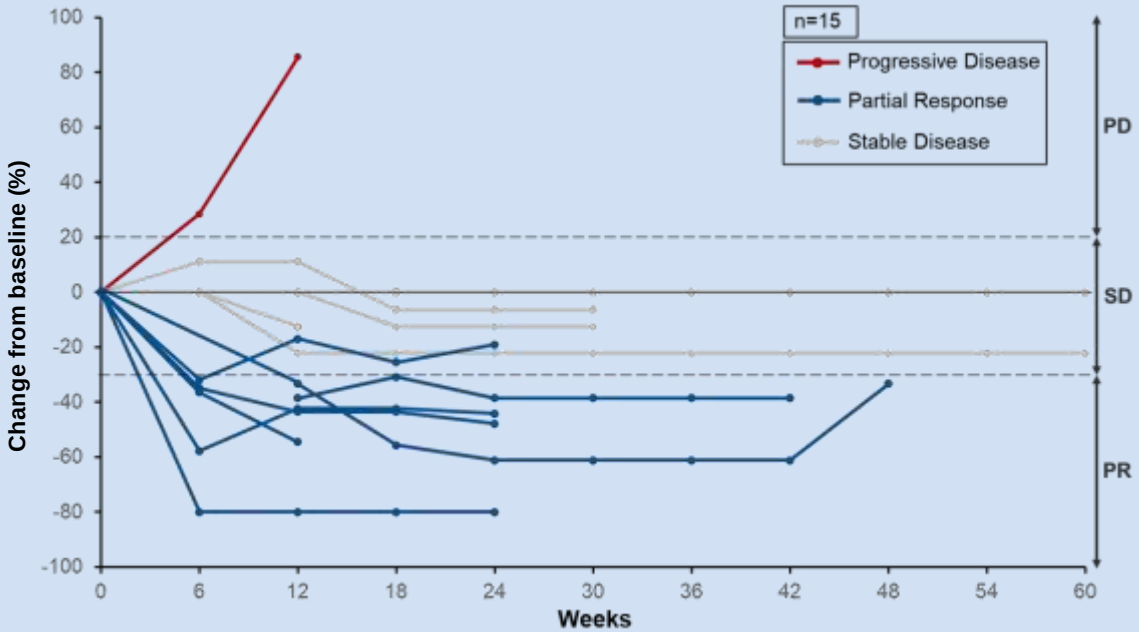
6-week scan (6.9 mm)
35% reduction


12-week scan (4.6 mm)
57% reduction

- Patient with HER2+ (IHC3+)/HR-negative mBC
- Prior brain lesion treatment included:
  - Whole-brain radiotherapy 5 years prior to enrollment
  - Stereotactic radiosurgery 3 years prior to enrollment
- This patient experienced tumor shrinkage consistent with a PR in the brain

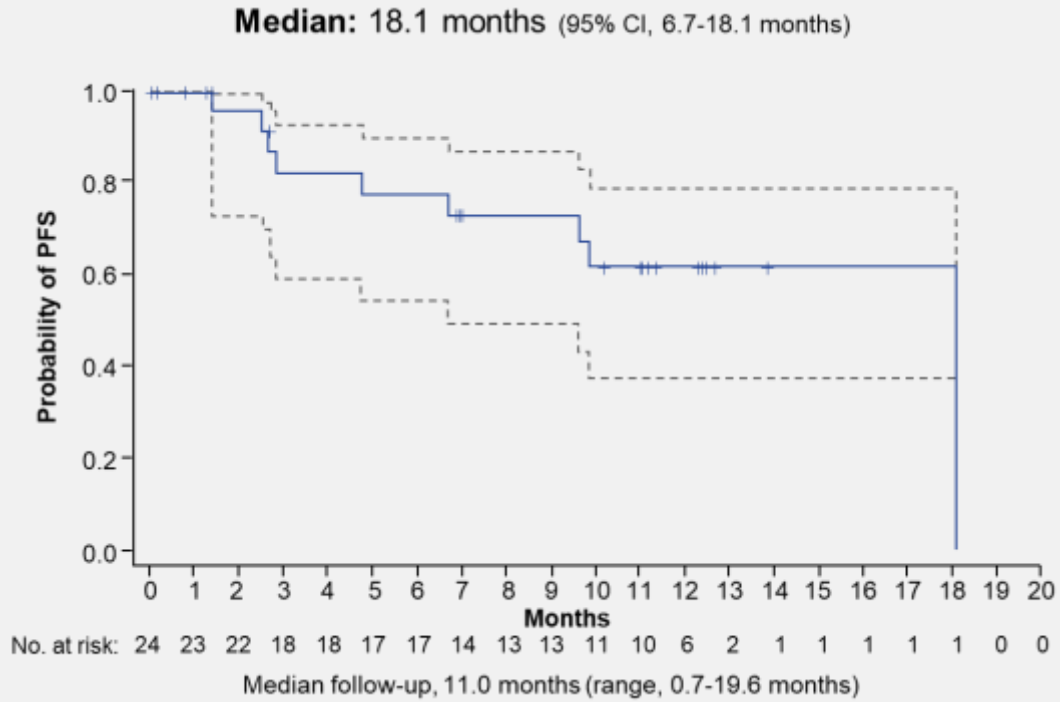
CNS Response

Brain Lesion Measurements Over Time in Patients in the CNS Subgroup



3 patients with reported baseline measurements had no change over time.
2 patients with brain metastases at baseline did not have sufficient data to evaluate response in the brain and are not shown.

Progression-Free Survival in the CNS Subgroup (n=24)



PFS, progression-free survival.
Data cutoff: August 1, 2019.

Conclusions

- T-DXd showed durable systemic disease control in patients with stable, treated brain metastases at baseline, with clinical outcomes similar to those of the overall population (as of the August 1, 2019, data cutoff)
- Of 17 patients with brain lesions at baseline, 41.2% (n=7) experienced tumor shrinkage consistent with a PR in the brain and 41.2% (n=7) were consistent with SD
- Interpretation of these results is limited by the small patient number and post hoc analysis of CNS response
- Ongoing trials will continue to assess the activity of T-DXd in patients with breast cancer and active brain metastases, for which treatment options remain limited
  - DESTINY-Breast07 (NCT04538742)
  - TUXEDO-1 (NCT04752059)
  - DESTINY-Breast12 (NCT04739761)
  - DEBBRAH (NCT04420598)

Trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing salivary duct carcinoma: Subgroup analysis of two phase 1 studies

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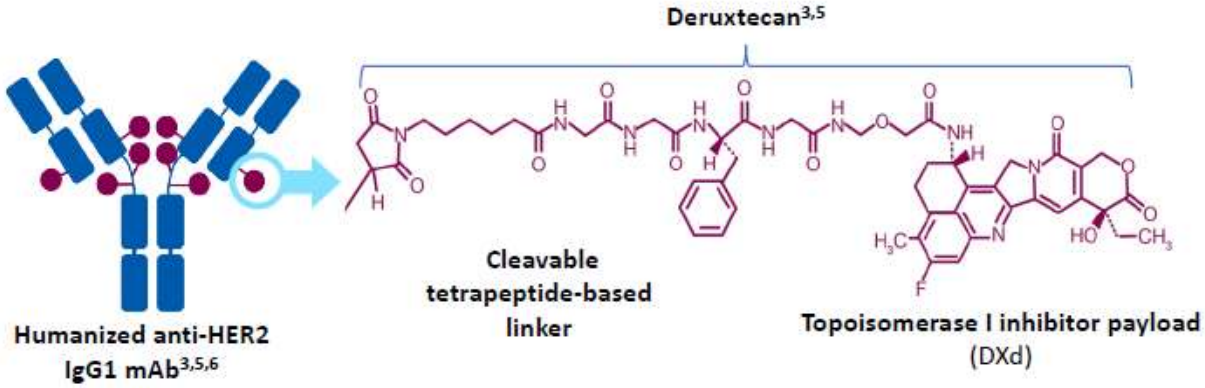
Background

- In salivary duct carcinoma (SDC), 16%–83% of patients are reported to show human epidermal growth factor receptor 2 (HER2) expression by immunohistochemistry (IHC) or HER2 amplification by in situ hybridization (ISH)/next-generation sequencing (NGS)[1]
- There are no established HER2-targeted therapies for SDC
- The National Comprehensive Cancer Network (NCCN) guidelines include HER2-targeted therapy (trastuzumab, ado-trastuzumab emtansine [T-DM1], or pertuzumab combined with trastuzumab) as a therapeutic option for the treatment of HER2-positive SDC[2]
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 monoclonal antibody having the same amino acid sequence as trastuzumab, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor payload[3] (Figure 1)
- T-DXd was approved for treatment of patients with HER2-positive metastatic breast cancer in US, EU, UK and Japan. And it was also approved for treatment of patients with HER2-positive unresectable advanced or recurrent gastric cancer in US[4] and Japan
- Here we present the pooled analysis of HER2-expressing SDC who received T-DXd from 2 phase1 studies: DS8201-A-J101 (NCT02564900) and DS8201-A-A104 (NCT03383692)

Figure 1. Structure of trastuzumab deruxtecan



Methods

- DS8201-A-J101: first-in-human phase 1 study of T-DXd including patients with HER2-expressing SDC
  - –Dose-escalation phase: T-DXd 5.4 and 6.4 mg/kg (every 3 weeks) was recommended for the dose-expansion phase of the study[7]
  - –Dose-expansion phase: T-DXd demonstrated promising activity and an acceptable safety profile in a heterogeneous population, including in HER2-expressing or mutated solid tumors[8]
- DS8201-A-A104: a phase 1 crossover study evaluating the drug-drug interaction potential of T-DXd + ritonavir or T-DXd + itraconazole in patients with HER2-expressing advanced solid tumors[9]
  - –No clinically meaningful pharmacokinetic drug-drug interactions were observed with manageable safety profile
- 17 patients with SDC were pooled in this analysis: out of 289 and 40 patients (total 329) in DS8201-A-J101 and DS8201-A-A104, respectively
- HER2 expression was defined by IHC and/or amplification, by ISH or NGS via local testing at enrollment
  - –A retrospective IHC and ISH analysis of archived HER2 samples was conducted after enrollment by a central laboratory per the American Society of Clinical Oncology/College of American Pathologists guidelines for gastric cancer
- Patients received intravenous T-DXd every 3 weeks at 6.4 mg/kg and 5.4 mg/kg in DS8201-A-J101 (8 patients) and DS8201-A-A104 (9 patients), respectively
- Tumor response was evaluated by investigator per evaluation criteria In Solid Tumors (RECIST) version 1.1

Results

- Of the 17 patients with HER2-expressing SDC, 8 and 9 patients were enrolled from DS8201-A-J101 and DS8201-A-A104, respectively (Table 1)
- The cutoff date for the data analysis is 1 Aug 2019 for DS8201-A-J101 and 26 Sep 2018 for DS8201-A-A104
- At data cutoff, 41.2% of patients continued T-DXd treatment; the median duration of follow-up was 5.6 months (Table 2)

Results (cont'd)

Table 1. Demographics and baseline clinical characteristics

Characteristic	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Age, years, median (range)	51.5 (44–69)	58.0 (34–71)	57.0 (34–71)
Sex, n (%)			
Male	6 (75.0)	9 (100.0)	15 (88.2)
Female	2 (25.0)	0 (0.0)	2 (11.8)
Race,[a] n (%)			
Asian	7 (87.5)	9 (100.0)	16 (94.1)
Other	1 (12.5)	0 (0.0)	1 (5.9)
ECOG performance status, n (%)			
0	6 (75.0)	4 (44.4)	10 (58.8)
1	2 (25.0)	5 (55.6)	7 (41.2)

[a]Other race was not provided.

Results (cont'd)

Daiichi-Sankyo

Table 1. Demographics and baseline clinical characteristics (cont'd)

Characteristic	J101 (N=8)	A104 (N=9)	Pooled (N=17)
HER2 expression (IHC),[a] n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1+	0 (0.0)	0 (0.0)	0 (0.0)
2+	0 (0.0)	1 (11.1)	1 (5.9)
3+	8 (100.0)	3 (33.3)	11 (64.7)
Nonevaluable	0 (0.0)	5 (55.6)	5 (29.4)
HER2 amplification (ISH),[b] n (%)			
Positive	6 (75.0)	0 (0.0)	6 (35.3)
Equivocal	0 (0.0)	0 (0.0)	0 (0.0)
Negative	1 (12.5)	1 (11.1)	2 (11.8)
Missing	1 (12.5)	0 (0.0)	1 (5.9)
Not examined	0 (0.0)	8 (88.9)	8 (47.1)

[a]HER2 status was assessed by a central laboratory according to the American Society of Clinical Oncology/College of American Pathologists guidelines for gastric cancer. [b]Positive, HER2/CEP17 ≥2.0 with any average HER2 copy number or HER2/CEP17 <2.0 with an average HER2 copy number ≥6.0; equivocal, HER2/CEP17 <2.0 with an average HER2 copy number ≥4.0 and <6.0; negative, HER2/CEP17 <2.0 with an average HER2 copy number <4.0.

Results (cont'd)

Daiichi-Sankyo

Table 1. Demographics and baseline clinical characteristics (cont'd)

Characteristic	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Site of primary disease, n (%)			
Parotid gland	4 (50.0)	2 (22.2)	6 (35.3)
Submandibular gland	2 (25.0)	2 (22.2)	4 (23.5)
Glandula sublingualis	0 (0.0)	1 (11.1)	1 (5.9)
Unknown	2 (25.0)	4 (44.4)	6 (35.3)
Visceral disease at baseline, n (%)	7 (87.5)	8 (88.9)	15 (88.2)
Lines of prior systemic therapy,[a] median (range)	2.0 (0–6)	1.0 (1–5)	1.0 (0–6)
Prior cancer therapy, n (%)			
Platinum	1 (12.5)	2 (22.2)	3 (17.6)
Taxane	5 (62.5)	8 (88.9)	13 (76.5)
Trastuzumab	5 (62.5)	8 (88.9)	13 (76.5)
Trastuzumab emtansine	1 (12.5)	0 (0.0)	1 (5.9)

[a]All systemic therapy including adjuvant and locally advanced/metastatic disease.

Results (cont'd)

Table 2. Patient disposition

	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Duration of follow-up, months, median (range)	13.0 (4.4–34.8)	2.8 (2.1–6.3)	5.6 (2.1–34.8)
Ongoing T-DXd, n (%)	1 (12.5)	6 (66.7)	7 (41.2)
Discontinued T-DXd, n (%)	7 (87.5)	3 (33.3)	10 (58.8)
Primary reason for discontinuation of T-DXd, n (%)			
AE	3 (37.5)	1 (11.1)	4 (23.5)
Progressive disease	3 (37.5)	2 (22.2)	5 (29.4)
Withdrawal of consent by patient	1 (12.5)	0 (0.0)	1 (5.9)

Efficacy Results

- The confirmed overall response rate in the pooled analysis was 47.1% (95% confidence interval [CI], 23.0–72.2) (Table 3)

- 15 patients had target lesions per RECIST version 1.1, of whom 93% (14/15) showed tumor shrinkage in 12 weeks post-baseline assessment (Figure 2) and one of case report was presented (Figure 3)

Efficacy Results (cont'd)

Table 3. Clinical activity outcomes

	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Best overall response (confirmed), n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	6 (75.0)	2 (22.2)	8 (47.1)
SD	2 (25.0)	7 (77.8)	9 (52.9)
PD	0 (0.0)	0 (0.0)	0 (0.0)
NE	0 (0.0)	0 (0.0)	0 (0.0)
Confirmed ORR, n (%) [95% CI][a]	6 (75.0) [34.9–96.8]	2 (22.2) [2.8–60.0]	8 (47.1) [23.0–72.2]

Efficacy Results (cont'd)

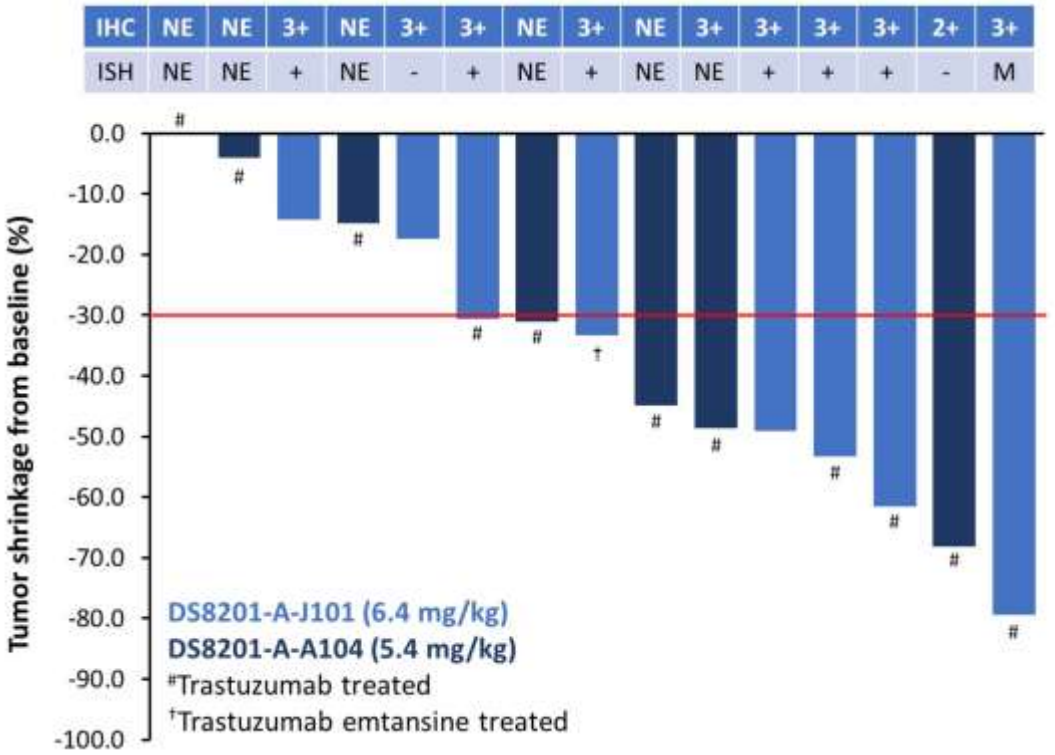
Table 3. Clinical activity outcomes (cont'd)

	J101 (N=8)	A104 (N=9)	Pooled (N=17)
DOR, months, median [95% CI][a]	12.9 [4.0–NE]	NE [NE–NE]	12.9 [4.0–NE]
Patients with events, n (%)	6 (75.0)	2 (22.2)	8 (47.1)
Patients censored, n (%)	2 (33.3)	2 (100.0)	4 (50.0)
Ongoing without events	1 (16.7)	2 (100.0)	3 (37.5)
Other	1 (16.7)	0 (0.0)	1 (12.5)
PFS, months, median [95% CI][a]	20.5 [5.6–NE]	NE [2.1–NE]	14.1 [5.6–NE]
Patients with events, n (%)	4 (50.0)	2 (22.2)	6 (35.3)
Patients censored, n (%)	4 (50.0)	7 (77.8)	11 (64.7)

[a]Using the Brookmeyer-Crowley method.

Efficacy Results (cont'd)

Figure 2. Best percentage change in tumor size



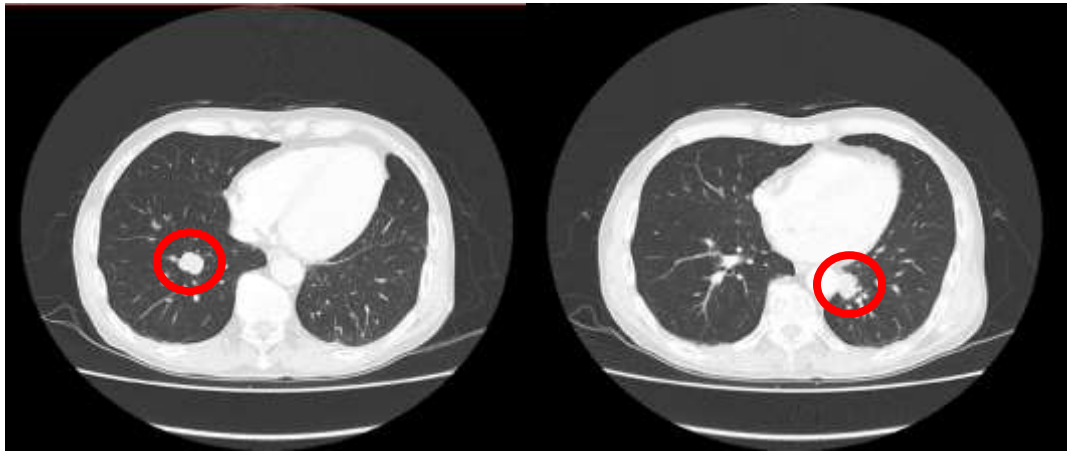
HER2 expression shown is based on central laboratory assessment. HER2 expression status at enrollment was determined via local assessment. The red line denotes a 30% reduction in tumor size.

Efficacy Results (cont'd)

Figure 3. Case report: 69% (Lung left) or 67% (Lung right) regression of a metastatic lung lesion

- 65-year-old man with IHC 2+/ISH negative (central assessment) for HER2 metastatic sublingual gland
- 1 prior line of treatment, including bicalutamide and leuprorelin

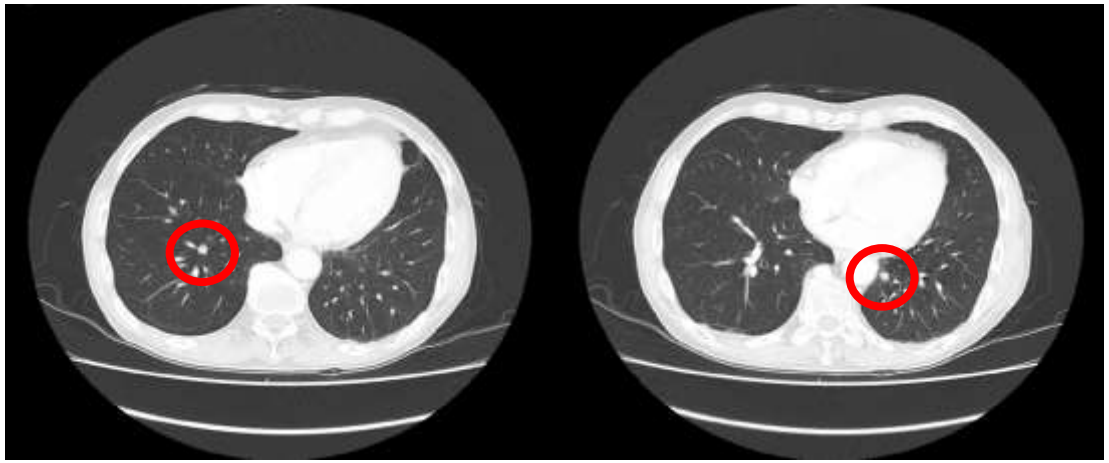
Baseline scan



Lung right lesion was 21 mm

Lung left lesion was 26 mm

6-week scan



Lung right lesion (7 mm) reduced by 67% from baseline

Lung left lesion (8 mm) reduced by 69% from baseline

Safety Results

- Treatment-emergent adverse events (TEAEs) occurred in all 17 patients; 23.5% of patients discontinued treatment and 17.6% and 41.2% of patients experienced dose reduction and dose interruption, respectively, due to TEAEs (Table 4)
- The most common grade ≥3 TEAEs (64.7%) were decreased neutrophil count (47.1%) and decreased white blood cell count (35.3%) (Table 5)
- Three patients (17.6%) had adjudicated drug-related interstitial lung disease but no related death

Safety Results (cont'd)

Table 4. Safety summary

n (%)	Pooled (5.4 or 6.4 mg/kg) (N=17)
All TEAEs	17 (100)
Drug related	17 (100)
TEAE grade ≥3	11 (64.7)
Drug related	9 (52.9)
Serious TEAEs	3 (17.6)
Drug related	1 (5.9)
TEAE associated with discontinuation	4 (23.5)
Drug related	3 (17.6)
TEAE associated with dose reduction	3 (17.6)
Drug related	2 (11.8)
TEAE associated with dose interruption	7 (41.2)
Drug related	7 (41.2)

Safety Results (cont'd)

Table 5. Common TEAEs (≥20%) and adjudicated drug-related ILD

TEAEs (≥20%)	Pooled (5.4 or 6.4 mg/kg) (N=17)	
n (%)	All Grades	Grade ≥3
Any TEAE	17 (100)	11 (64.7)
Decreased appetite	15 (88.2)	1 (5.9)
Nausea	15 (88.2)	0 (0.0)
Neutrophil count decreased[a]	13 (76.5)	8 (47.1)
White blood count decreased[a]	10 (58.8)	6 (35.3)
Aspartate aminotransferase increased	9 (52.9)	2 (11.8)
Alanine aminotransferase increased	8 (47.1)	2 (11.8)
Platelet count decreased[a]	8 (47.1)	2 (11.8)
Constipation	8 (47.1)	0 (0.0)

[a]Grouped preferred terms are neutrophil count decreased (neutropenia, neutrophil count decreased), white blood cell count decreased (leukopenia, white blood cell count decreased), platelet count decreased (platelet count decreased, thrombocytopenia).

Safety Results (cont'd)

Table 5. Common TEAEs (≥20%) and adjudicated drug-related ILD (cont'd)

TEAEs (≥20%)	Pooled (5.4 or 6.4 mg/kg) (N=17)	
n (%)	All Grades	Grade ≥3
Any TEAE	17 (100)	11 (64.7)
Malaise	6 (35.3)	0 (0.0)
Alopecia	6 (35.3)	0 (0.0)
Anemia[a]	5 (29.4)	2 (11.8)
Cough	5 (29.4)	0 (0.0)
Diarrhea	5 (29.4)	0 (0.0)
Fatigue[a]	5 (29.4)	0 (0.0)
Vomiting	4 (23.5)	0 (0.0)
Stomatitis[a]	4 (23.5)	0 (0.0)
Adjudicated drug-related ILD	3 (17.6)	1 (5.9)

[a]Grouped preferred terms are fatigue (asthenia, fatigue), anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased), stomatitis (aphthous ulcer, mouth ulceration, oral mucosa erosion, oral musosal blistering, stomatitis).

Conclusions

- T-DXd 5.4 and 6.4 mg/kg showed promising antitumor activity in HER2-expressing SDC with durable responses
  - Confirmed objective response rate: 47.1%
  - Median duration of response: 12.9 months
  - Median progression-free survival: 14.1 months
- The safety profile was generally consistent with previous results of studies with other solid tumors and no new safety signals were reported
- Interpretation of these results is limited by the short follow-up in DS8201-A-A104 and the small patient number
- Our results support further investigation of T-DXd in HER2-expressing SDC

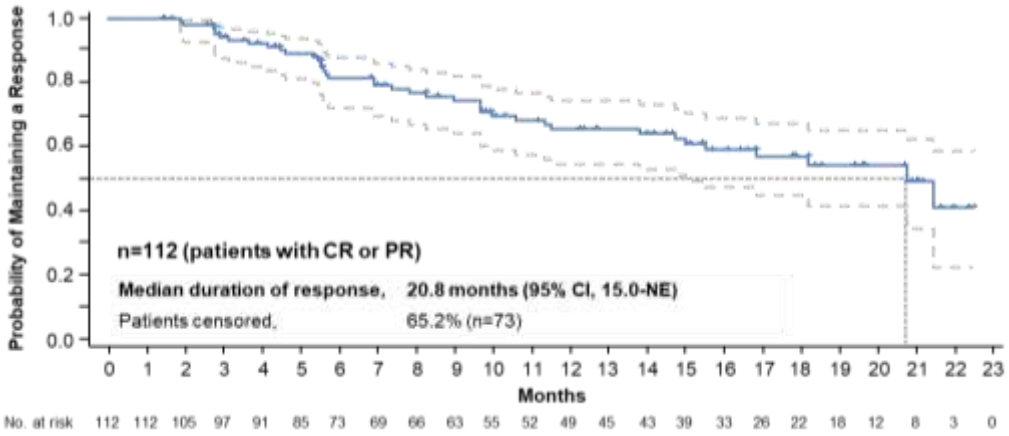
Background

- T-DXd has been approved for use in patients with HER2-positive metastatic breast cancer that has progressed on ≥2 prior anti-HER2 therapies (US, EU, UK) or after chemotherapy (Japan) and in patients with HER2-positive metastatic gastric cancer who have received a prior trastuzumab-based regimen (US) or progressed after chemotherapy (Japan)

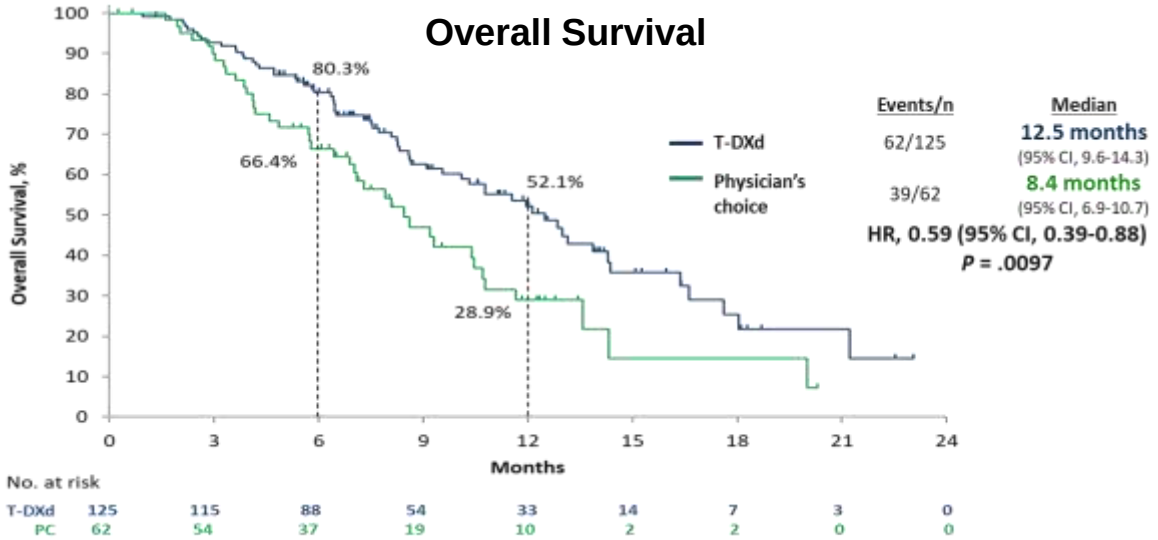
DESTINY-Breast01: June 2020 Data Cutoff[1]	T-DXd 5.4 mg/kg (N=184)
Objective response rate, n (%)	113 (**61.4**)

DESTINY-Gastric01: November 2019 Data Cutoff[2]	T-DXd 6.4 mg/kg (N=119)	Physician's choice (N=56)
Objective response rate, n (%)	61 (**51.3**)	8 (14.3)

Duration of Response



Overall Survival

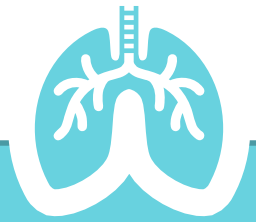


- Interstitial lung disease (ILD) is an important identified risk for patients treated with T-DXd[3-8]
- Here we further characterize ILD and assess potential associated factors in a pooled analysis of 8 single arm phase 1 and 2 T-DXd monotherapy studies, including the first-in-human study

1. Modi S, et al. SABCS 2020 [abstract PD3-06]; 2. Shitara K, et al. *N Engl J Med*. 2020;382;2419-2430; 3. Doi T, et al. *Lancet*. 2017;18(11):1512-22; 4. Shitara K, et al. *Lancet*. 2019;20(6):827-36; 5. Tamura K, et al. *Lancet*. 2019;20(6):816-26; 6. Modi S, et al. *J Clin Oncol*. 2020;38(17):1887-96; 7. Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701; 8. Modi S, et al. *N Engl J Med*. 2020;382(7):610-21.

Methods

Data as of 08 June 2020 were pooled from 879 patients who received ≥1 dose of T-DXd monotherapy at 5.4, 6.4, 7.4, or 8.0 mg/kg across 8 phase 1 or 2 studies representing all available single-arm monotherapy studies in the T-DXd developmental program.



An independent adjudication committee retrospectively reviewed all potential ILD cases using imaging and clinical data (from baseline through the time of the potential ILD case) to assess whether the reported event was a case of ILD and, if such, if it was related to the study drug; **events adjudicated as study drug related are reported**. In addition, ILD cases with a fatal outcome were assessed to determine if the cause of death was due to ILD

A multivariate stepwise Cox regression model was used to explore the association between baseline factors and the time to occurrence of the outcome with stepwise variable selection entry criterion of $P<.05$ and remain criterion of $P<.10$. This analysis is exploratory and hypothesis generating in nature.

Baseline characteristics and T-DXd treatment

Patients were heavily pretreated with advanced disease

	N=879
Age, median (range), years	58.0 (23-96)
≥ 65 years, n (%)	271 (30.8)
Female, n (%)	674 (76.7)
Japanese, n (%)	364 (41.4)
ECOG PS, n (%)	
0	476 (54.2)
1 / 2	401 (45.6) / 2 (0.2)
Tumor type, n (%)[a]	
Breast cancer	510 (58.0)
Gastric cancer	78 (8.9)
Lung cancer	148 (16.8)
Colorectal cancer	107 (12.2)
Other	34 (3.9)
Lung comorbidities, n (%)[b]	101 (11.5)

	N=879
No. of prior regimens, median (range)	5.0 (1-27)
T-DXd dose, n (%)	
5.4 mg/kg	315 (35.8)
6.4 mg/kg	537 (61.1)
> 6.4 mg/kg	27 (3.1)
Duration of treatment, median (range), mo	6.90 (0.7-50.1)
0 to 6 mo, n (%)	407 (46.3)
> 6 to 12 mo, n (%)	223 (25.4)
> 12 to 24 mo, n (%)	192 (21.8)
> 24 mo, n (%)	57 (6.5)
No. of treatment cycles, median (range)	9.0 (1-67)

ECOG PS, Eastern Cooperative Oncology Group performance status. [a] Tumor type was missing for 2 patients. [b] Includes asthma, COPD, prior interstitial lung disease/pneumonitis, pulmonary fibrosis, pulmonary emphysema, pleural effusion, and radiation pneumonitis.

Investigator-assessed ILD onset date vs adjudication committee

	Adjudicated drug-related ILD events (n=148)
Concordant, n (%)	**72 (48.6%)**
Discordant, n (%)	
Earlier than the adjudication committee	**5 (3.4%)**
Median difference (range), days	**7.0 (1-44)**
Later than the adjudication committee	**71 (48.0%)**
Median difference (range), days	**49.0 (1-288)**

Scans occurred every 6 weeks (42 days).

The adjudication committee frequently identified ILD onset earlier than investigators

Summary of steroid use

Systemic steroid use by grade of adjudicated drug-related ILD

	Grade 2-4	Events leading to Grade 5
No. of events	80	21
Events treated with systemic steroids, n (%)	48 (60.0)	16 (76.1)

Defined as any systemic steroids initiated within 90 days of the adjudicated ILD onset date.
Steroids were recommended for grade ≥2 ILD.

- Median time from adjudicated ILD onset date (any grade) to start of systemic steroid treatment was long, 21.0 days (range, 1-87 days)
- 141 of 148 (95%) adjudicated ILD events occurred prior to 15 December 2019 when updated toxicity management guidelines were implemented in clinical trials
  - Updated guidelines included information on optimal steroid dosing and duration

Assessment of factors potentially associated with ILD

A stepwise multivariate Cox regression model evaluated the association of potential factors with the time to occurrence of any-grade ILD, and the following 6 were identified as factors of interest:

- Patients treated in Japan vs non-Japan
- Dose of ≥ 7.4 mg/kg vs 5.4 mg/kg
- Baseline SpO2 < 95% vs ≥ 95%
- Moderate/severe renal impairment at baseline vs no impairment
- Presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis)
- Time since initial diagnosis of ≥ 3.9 years vs <3.9 years

Notably, when accounting for other factors, lung cancer or lung metastases/ lymphangitic carcinomatosis at baseline and prior chest/lung radiotherapy were not associated with ILD in this analysis

Given the limitations of the present analysis (extensive prior treatment, differences in treatment durations, and heterogeneity of the patient population), the identified factors of interest remain to be confirmed and will be further evaluated with future data in a larger, more homogenous patient population

Factors included in the model were: age group, sex, tumor type, ECOG Performance Status, lung cancer or lung metastases/lymphangitic carcinomatosis at baseline, prior chest/lung radiotherapy, lung comorbidities, baseline renal function, number of prior regimens category, baseline white blood cell count ($x10^9$/L), baseline albumin (g/L), time since initial disease diagnosis (year) category, time since the end date of last anticancer therapy to first infusion of T-DXd (months) category, dose (mg/kg) category and baseline SpO2 (%) category.

Conclusions

- **T-DXd had shown significant antitumor activity in HER2-positive metastatic breast[1] and gastric cancer,[2] as well as other tumor types[3]**
- **The majority of independently adjudicated ILD cases (78%) were low grade**
- **ILD risk may decrease after ≈12 months of treatment; longer follow-up is needed to confirm the observed trend**
- **Optimal steroid management was not observed, with delay in detection of ILD and underdosing of steroids; new toxicity guidelines have now been implemented and education provided**
  - After implementation of these guidelines, data suggest a lower rate of high-grade ILD events
- **Potential clinical factors of interest associated with ILD may include low oxygen saturation, lung comorbidities, and renal insufficiency**
  - Identification of specific risk factors requires confirmation in larger trials
- **This pooled analysis further supports the benefit/risk profile of T-DXd in advanced cancer**
  - Phase 3 randomized controlled trials across multiple tumor types are ongoing

1. Modi S, et al. SABCS 2020 [abstract PD3-06]; 2. Shitara K, et al. *N Engl J Med*. 2020;382;2419-2430; Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701.

Patient Disposition

Treatment status, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Ongoing study treatment	15 (30)	13 (26)	10 (13)
Discontinued from study treatment	35 (70)	37 (74)	70 (88)
Progression[a]	26 (52)	27 (54)	42 (53)
Adverse events	6 (12)	4 (8)	16 (20)
Death	1 (2)	2 (4)	4 (5)
Follow-up, median (range), mo	9.2 (4.3-25.9)	6.6 (3.1-24.0)	13.9 (7.3-22.0)
Exposure, median (range), mo	4.1 (0.7-24.1)	3.5 (0.7-23.4)	3.3 (0.7-17.1)

[a] Includes progressive disease per Response Evaluation Criteria in Solid Tumors v1.1 and clinical progression.

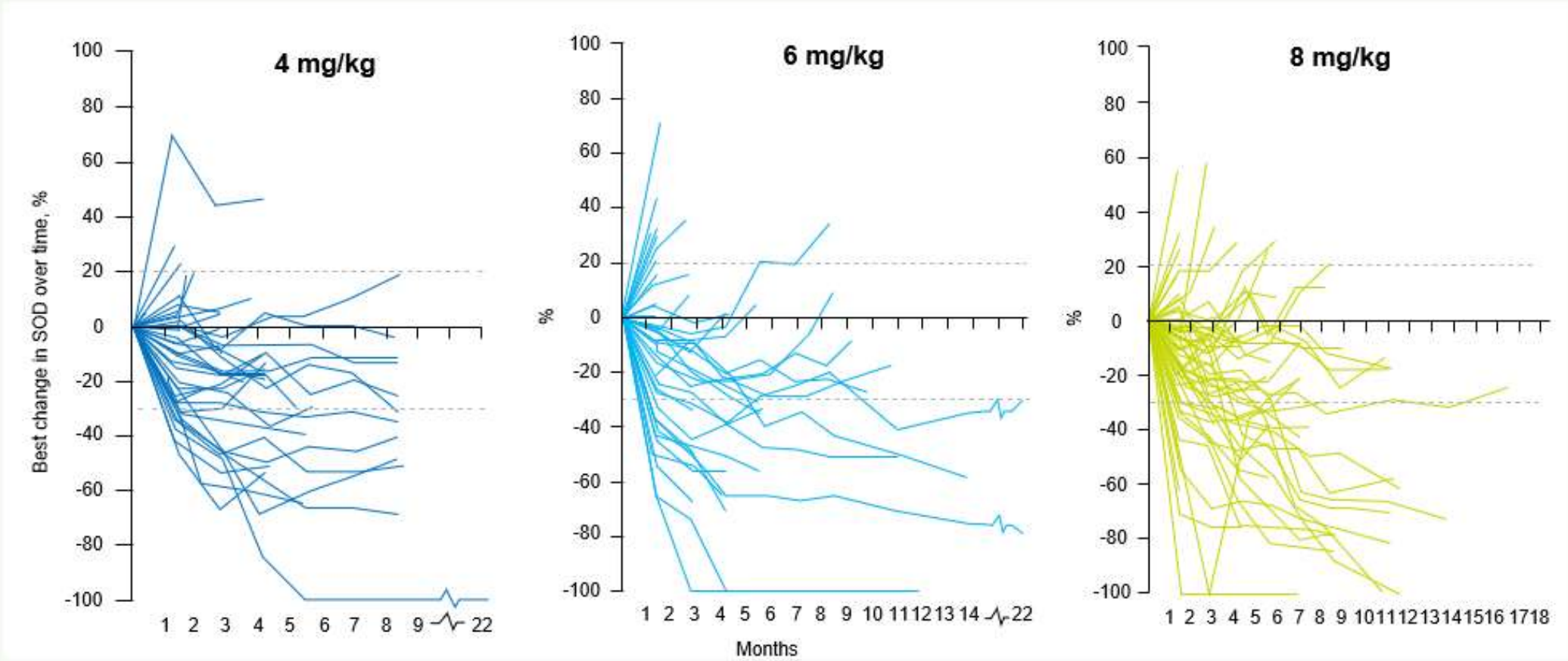
Due to later time of enrollment, follow-up was shorter for patients treated with the 4- and 6-mg/kg doses than the 8-mg/kg dose

Patient Demographics and Baseline Characteristics

Characteristic	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Age, ≥ 65 years, %	36	40	46
Weight, median (range), kg	72 (38-156)	66 (39-104)	70 (38-115)
Sex, male, %	54	56	51
Country, %			
United States	58	76	79
Japan	42	24	21
Histology, %			
Nonsquamous	82	90	88
Squamous	18	10	13
≥3 Prior lines of therapy, %	58	62	65
Previous systemic treatment, %			
Immunotherapy	86	74	88
Platinum-based chemotherapy	94	96	98
Tyrosine kinase inhibitor	20	18	18
***EGFR* mutations, %**	16	16	20

Baseline characteristics were generally balanced across dosing cohorts

Efficacy: Change in Sum of Diameters for Target Lesions (BICR) Over Time



BICR, blinded independent central review; SOD, sum of diameters.

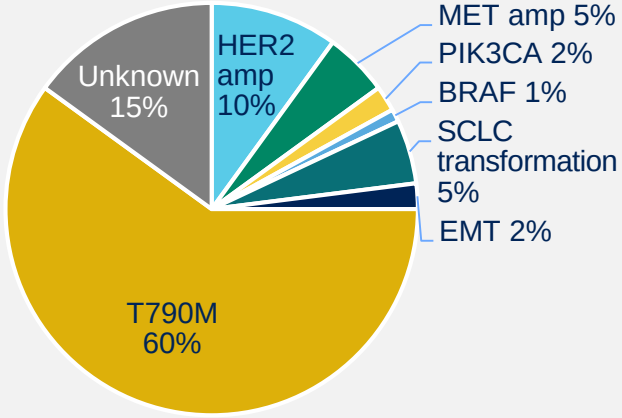
Most responses were durable over time

Broad Range of Resistance Mechanisms in *EGFR*m NSCLC Following the Failure of EGFR Tyrosine Kinase Inhibitor (TKI) Therapy

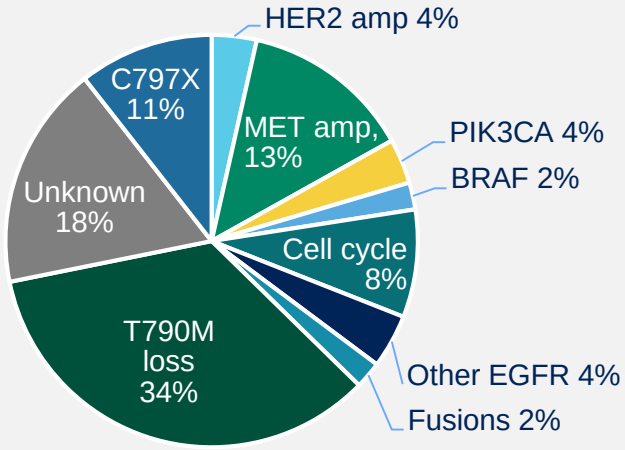
- Efficacy of EGFR TKI in *EGFR*m NSCLC has been established; however, the development of various resistance mechanisms commonly leads to disease progression[1-2]
- Platinum-based chemotherapy following EGFR TKI failure has limited efficacy (ORR, 25%–44%; PFS, 2.7–6.4 months)[3]
- Salvage therapies after EGFR TKI and platinum-based chemotherapy have not been effective (PFS, 2.8–3.2 months)[4]

Wide variety of genomic alterations associated with EGFR TKI resistance[1,2]

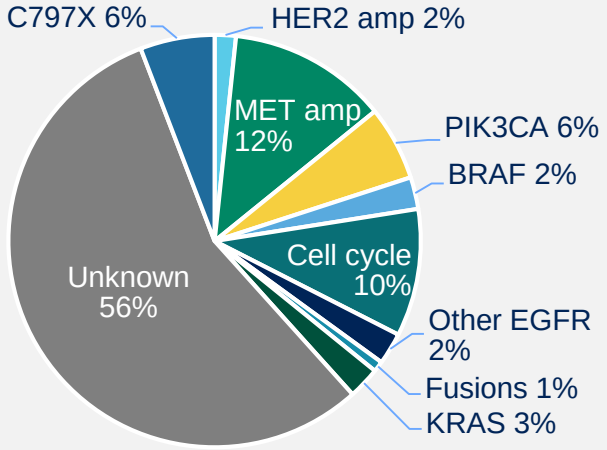
First-line erlotinib, gefitinib, afatinib



Second-line osimertinib



First-line osimertinib



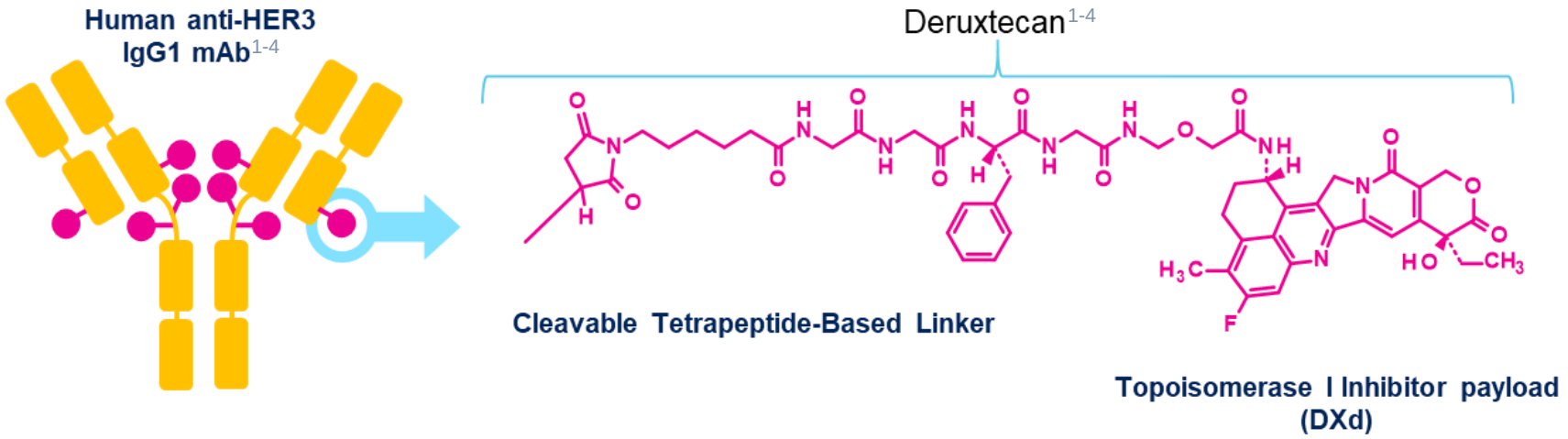
1. Engelman JA, et al. *Science*. 2007;316:1039-1043. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15:18-21. 3. Han B, et al. *Onco Targets Ther*. 2018;11:2121-9. 4. Yang CJ, et al. *BMC Pharmacol Toxicol* 2017;18(1).

Patritumab Deruxtecan (HER3-DXd)—Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer

HER3 is expressed in 83% of NSCLC tumors[7,a]

HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC



[a] HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046. 7. Scharpenseel H et al, *Sci Rep* 2019;9(1):7406.

HER3-DXd Antitumor Activity by History of CNS Metastases

In Patients Previously Treated with an EGFR TKI and Platinum-based Chemotherapy

Outcomes (BICR per RECIST 1.1) Median Follow Up: 9.6 (range, 5.2-19.9) mo[a]	History of Brain Metastases HER3-DXd 5.6 mg/kg (N=52)[a] Yes (N=25)	 No (N=27)
Confirmed ORR, % (95% CI)	32 (15-54)	41 (22-61)
Best overall response, n (%)		
CR	1 (4)	0
PR	7 (28)	11 (41)
SD, Non-CR/Non-PD	12 (48)	7 (26)
PD	4 (16)	4 (15)
Not evaluable	1 (4)	5 (19)
PFS, median (95% CI), mo	8.2 (4.0-NE)	8.3 (3.0-NE)

The response rate and PFS were similar in patients with and without prior brain metastases

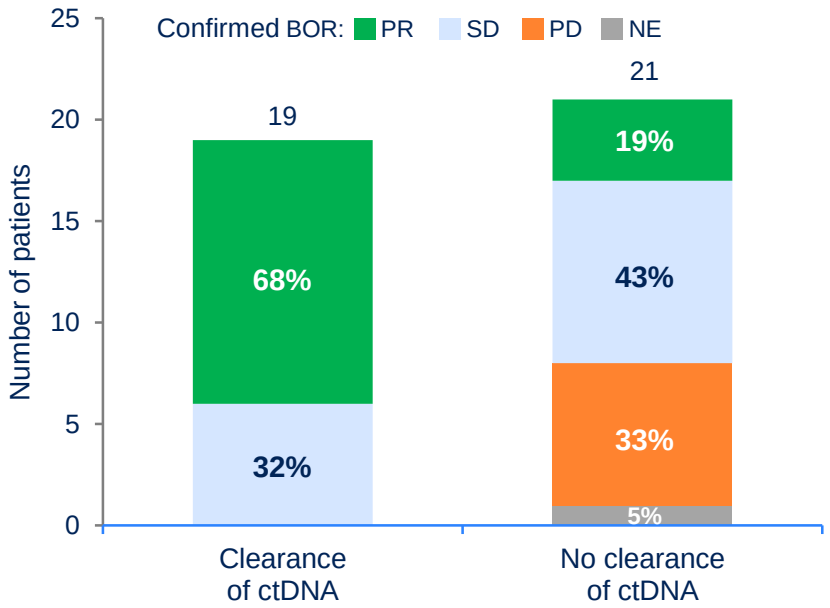
BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.

[a] For patients treated with the recommended dose for expansion of HER3-DXd who had prior treatment with any EGFR TKI and platinum-based chemotherapy.

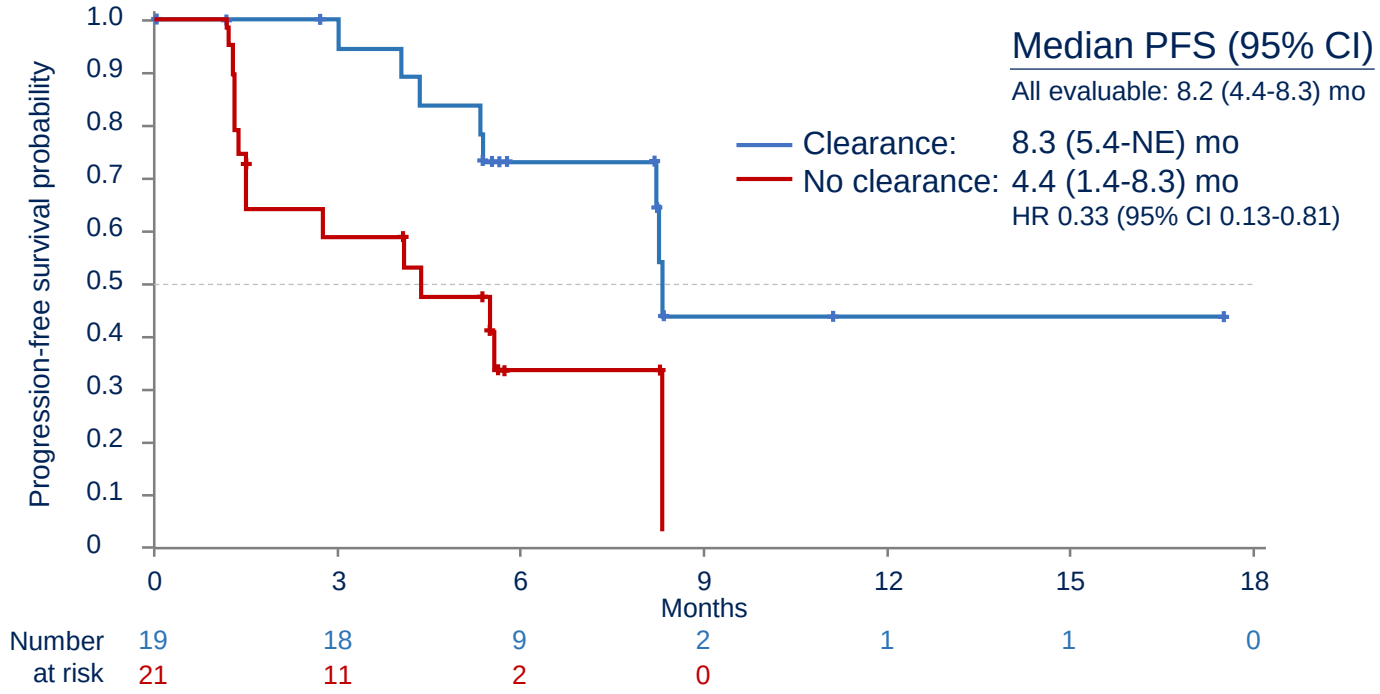
Early Clearance of *EGFR* Ex19del or L858R Mutations in ctDNA is Associated With Favorable BOR and PFS

Early clearance of ctDNA was defined as non-detectable plasma of either *EGFR* Ex19del or *EGFR* L858R at Week 3 or 6, where either mutation was detectable at baseline (evaluable in 40/57 patients[a])

Confirmed ORR higher with early clearance of ctDNA



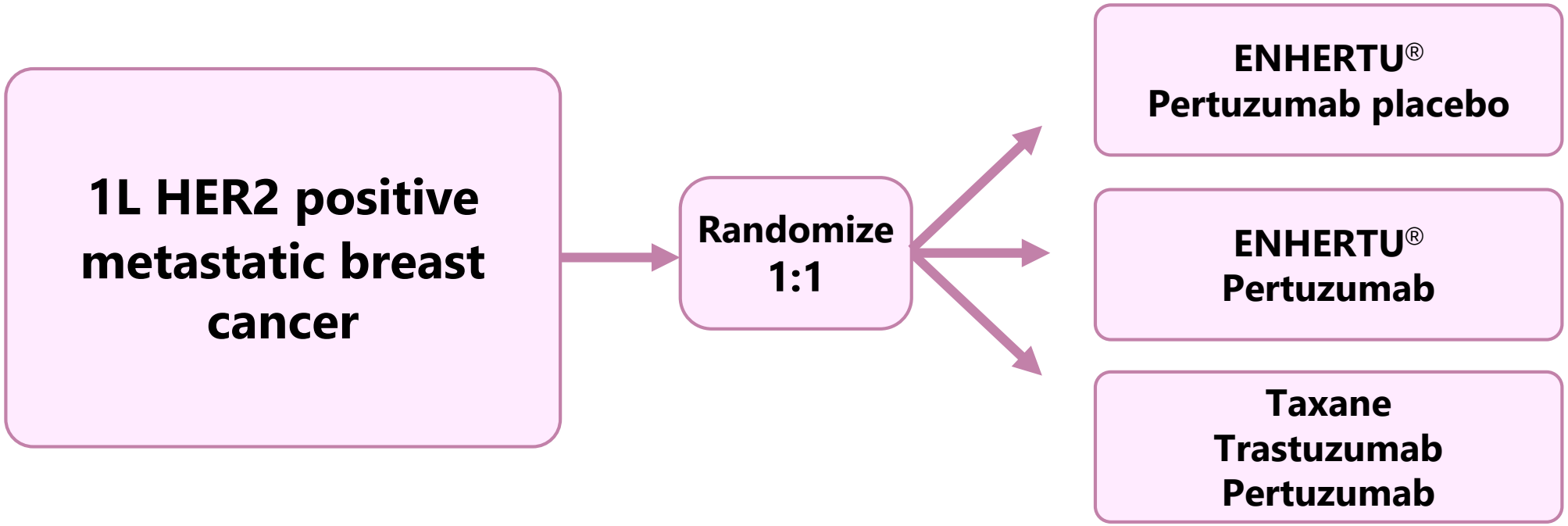
PFS prolonged in patients with early clearance of ctDNA



BOR, best overall response; PR, partial response; NE, not evaluable; PD, progressive disease; SD stable disease.
[a] Serial ctDNA samples were collected from 45 patients, but 5 did not have evaluable ctDNA data for either Weeks 3 or 6.

ENHERTU®: DESTINY-Breast09 Study

ENHERTU® with or without pertuzumab compared to taxane+ trastuzumab+pertuzumab in 1L HER2+ metastatic breast cancer



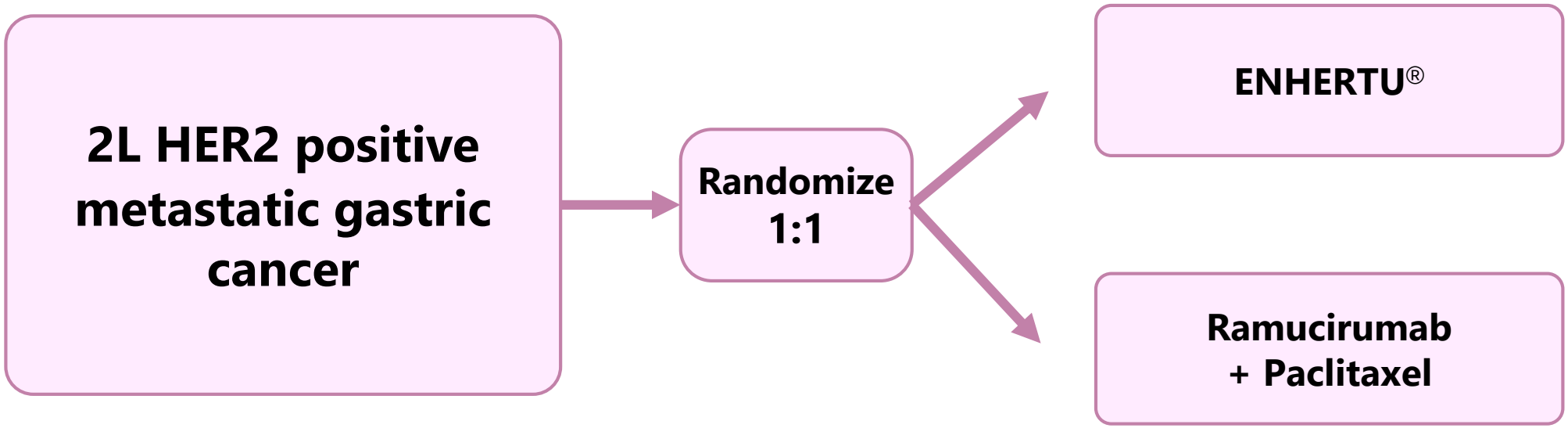
Endpoints: PFS as well as other endpoints

Study started: Jun 2021

ClinicalTrials.gov Identifier: NCT04784715

ENHERTU®: DESTINY-Gastric04 Study

ENHERTU® vs ramucirumab+paclitaxel in 2L HER2+ metastatic gastric cancer



Endpoints: OS as well as other endpoints

Study start: FY2021 1H planned

ClinicalTrials.gov Identifier: NCT04704934

HER3-DXd: Significance and Future Direction

EGFRm NSCLC

Post-TKI Post-PBC

Clear medical need in a difficult to treat patient population

- Salvage therapy is minimally effective, and offers short durations of efficacy (PFS, 2.8–3.2 months)
- HER3-DXd offers clinically meaningful, durable efficacy in a heavily pretreated population (ORR, 39%; median PFS, 8.2 months)
- Efficacy shown across multiple EGFR TKI resistance mechanisms and a broad range of baseline membrane HER3 expression

Post-TKI Pre-PBC

Potential to displace platinum-based chemotherapy

- Pt-based chemotherapy (PBC) is often used following EGFR TKI failure
- High activity observed in post-TKI/post-PBC and preliminary evidence suggests promising efficacy in chemotherapy-naïve patients

Other Indications

Transform treatment across HER3 expressing tumors

- NSCLC: Ongoing Ph1 study in EGFRwt
- CRC: Ongoing Ph2 study in 3L+
- BC: Ongoing Ph1/2 study in 2L+; collaborations ongoing with GRCC, SCRI, SOLTI
- Ongoing assessment of multiple additional HER3 expressing malignancies

BC: breast cancer, CRC: colorectal cancer, GRCC: Gustave Rossy Cancer Center. NSCLC: non-small cell lung cancer, PBC: platinum based chemotherapy, SCRI: Sarah Cannon Research Institute, SOLTI: Spanish Breast Cancer Research Group, TKI: tyrosine kinase inhibitor

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