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Trastuzumab Deruxtecan in Asian Patients With Human Epidermal Growth Factor Receptor 2 (*HER2; ERBB2*)-Mutant Metastatic Non–Small Cell Lung Cancer: Subgroup Analysis of DESTINY-Lung02

Presentation 510MO

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Declaration of interests

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Grants: AZK, AbbVie, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Kyorin, Novartis, Ono Pharmaceutical, and Pfizer

Payment or honoraria: Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical Co., Eli Lilly, Merck, MSD, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical Co., Ltd., and Thermo Fisher Scientific

Advisory board compensation: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical Co., Daiichi Sankyo, Eli Lilly, Guardant Health Inc., Illumina, MSD, Novartis, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical Co., Ltd.

Leadership or fiduciary roles: Cancer Net Japan and JAMT

DESTINY-Lung02

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

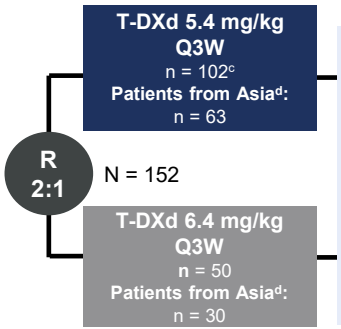
Background

- In DESTINY-Lung02, T-DXd showed clinically meaningful efficacy and manageable safety in patients with previously treated *HER2*m mNSCLC[1]
  - T-DXd 5.4 mg/kg is approved in several countries worldwide for patients with unresectable or metastatic NSCLC with an activating *HER2* mutation, as detected by a locally or regionally approved test, and who have received a prior systemic therapy[2]
- Asia was the largest geographical region represented in DESTINY-Lung02[1]
  - ~60% of all new lung cancer cases occur in Asia[3]
  - *HER2* mutations are slightly more common in Asian patients with NSCLC compared with patients from other regions (1.4-6.7% vs 1-3%)[4,5]
  - It is important to understand the clinical activity and safety of T-DXd in this population

Study Design

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment



Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

Statistical Considerations[e]
- The study was not powered to statistically compare between arms

In this **regional prespecified subgroup analysis** we assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in Asian patients with previously treated *HER2*m mNSCLC

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *HER2*m, human epidermal growth factor receptor 2–mutant; INV, investigator assessment; mNSCLC, metastatic non–small cell lung cancer; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan. [a]Patients with stable baseline brain metastases (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible. [b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [c]1 patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment due to the patient discontinued because of COVID-19 before cycle 1, day 1. [d]Patients were from Japan, South Korea, and Taiwan. [e]Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of confirmed ORR of a T-DXd dose with the benchmark ORR of 26.4%.[1] 1. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863. 2. ENHERTU® approved in the EU as the first HER2-directed therapy for patients with *HER2*-mutant advanced non-small cell lung cancer [press release]. October 23, 2023. Accessed November 1, 2023. 3. Lam DCL et al. *J Thorac Oncol*. 2023;S1556-0864(23)00635. 4. Zhou F. et al. *Transl Lung Cancer Res*. 2018; 7(4):450-463. 5. Ren S. et al. *ESMO Open*. 2022;100395.

Baseline characteristics

Characteristic	Asia[a] Subgroup	
	T-DXd 5.4 mg/kg n = 63	T-DXd 6.4 mg/kg n = 30
Age, median (range), years	56.8 (31-79)	62.3 (28-81)
Female, n (%)	41 (65.1)	21 (70.0)
ECOG PS score, n (%)		
0	18 (28.6)	11 (36.7)
1	45 (71.4)	19 (63.3)
***HER2* mutation kinase domain,[b] n (%)**	61 (96.8)	30 (100)
CNS metastases at baseline, n (%)	17 (27.0)	12 (40.0)
Smoking status (never),[c] n (%)	34 (54.0)	16 (53.3)
Number of lines of prior systemic therapy for advanced/metastatic disease, n (%)		
≤2	37 (58.7)	14 (46.7)
>2	26 (41.3)	16 (53.3)
Number of prior therapy regimens, median (range)	2.0 (1.0-12.0)	3.0 (1.0-7.0)
Renal function at baseline, n (%)		
Normal function	22 (34.9)	9 (30.0)
Mild impairment	26 (41.3)	18 (60.0)
Moderate impairment	15 (23.8)	3 (10.0)
Prior anti–PD-(L)1 therapy, n (%)	44 (69.8)	23 (76.7)
Ongoing study treatment,[d] n (%)	16 (25.8)	8 (26.7)

- **Baseline characteristics were similar across the T-DXd 5.4 mg/kg and 6.4 mg/kg arms of the Asia subgroup as well as the full analysis set[1,e]**
- In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms of the full analysis set:[1]
  - Patients were predominantly female (63.7% and 68.0%) and had a median age of 59.4 years and 61.3 years, respectively
  - *HER2 (ERBB2)* mutations were predominantly in the kinase domain (97.1% and 100%) and 34.3% and 44.0% of patients had baseline CNS metastases, respectively

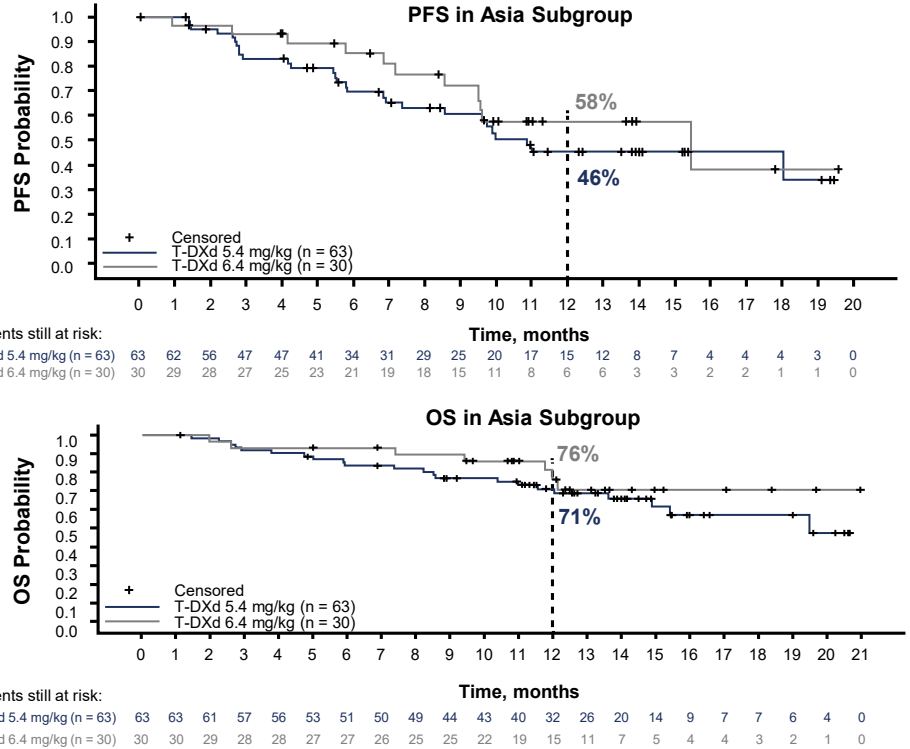
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed death (ligand) 1; T-DXd, trastuzumab deruxtecan.
[a]Patients were from Japan, South Korea, and Taiwan. [b]The rest of the *HER2* mutations were in the extracellular domain. [c]The rest of the patients were former smokers. [d]Percentage calculated based on number of patients in the Asia subgroup who received ≥1 dose of T-DXd: 5.4 mg/kg (n = 62), 6.4 mg/kg (n = 30). [e]The full analysis set comprised all patients for whom study treatment was assigned by randomization (overall population).

1. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863.

Efficacy summary

	Asia Subgroup	
	T-DXd 5.4 mg/kg n = 63	T-DXd 6.4 mg/kg n = 30
Confirmed ORR,[a] % (95% CI)	50.8 (37.9-63.6)	73.3 (54.1-87.7)
Median DoR,[b,c] months (95% CI)	16.8 (7.1-NE)	NE (6.8-NE)
Median PFS,[b,d] months (95% CI)	10.8 (7.4-NE)	15.4 (9.5-NE)
12-month PFS rate, % (95% CI)	45.5 (30.6-59.2)	57.8 (35.2-74.9)
Median OS,[e] months (95% CI)	19.5 (14.9-NE)	NE (12.1-NE)
12-month OS rate, % (95% CI)	71.3 (57.8-81.2)	76.3 (53.9-88.8)

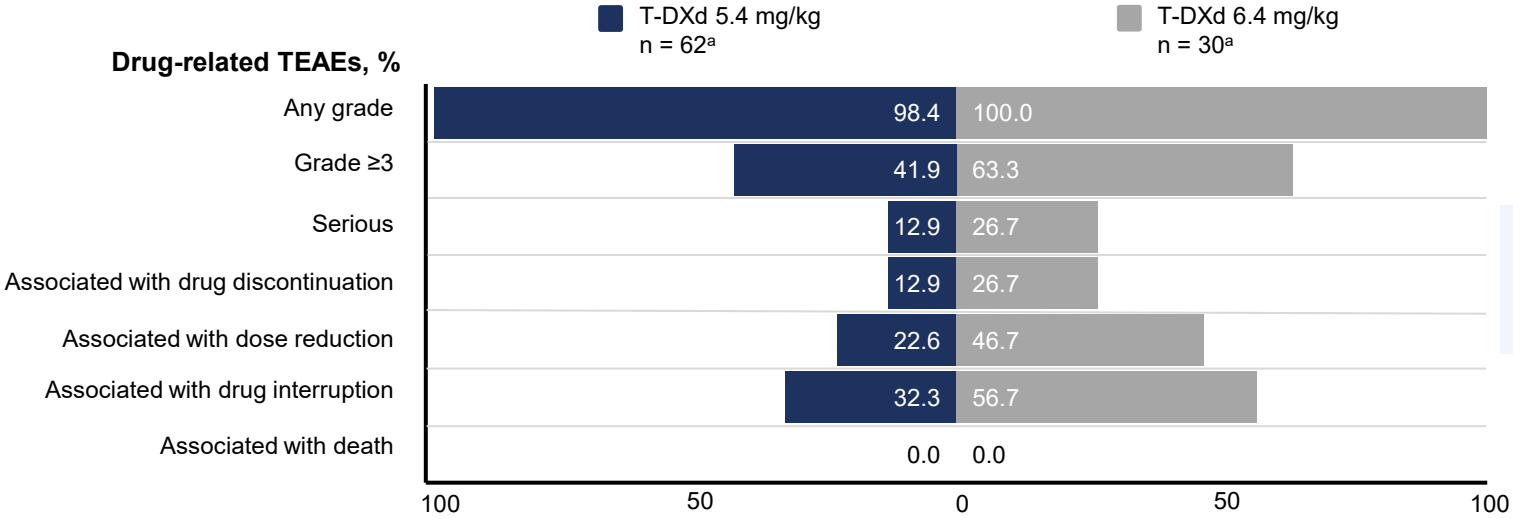
- **Efficacy results in the Asia subgroup were mostly consistent with the full analysis set[1,f]**



BICR, blinded independent central review; CR, complete response; DoR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan. [a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]Assessed by BICR. [c]Time from the initial response (CR or PR) by BICR until documented tumor progression or death from any cause. [d]Time from date of randomization until first objective radiographic tumor progression or death from any cause. [e]Time from date of randomization until death from any cause. [f]The full analysis set comprised all patients for whom study treatment was assigned by randomization (overall population).

1. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863.

Safety summary



Median treatment duration (range), months:
- 5.4 mg/kg: 8.4 (1.4-20.8)
- 6.4 mg/kg: 8.5 (0.7-20.3)

- In the Asia subgroup, the incidence of drug-related TEAEs associated with drug discontinuation, dose reduction, and drug interruption was lower with T-DXd 5.4 mg/kg than 6.4 mg/kg, consistent with the safety analysis set[1,b]
- The most common (≥20% of patients) TEAEs in the Asia subgroup were gastrointestinal or hematologic in nature
  - In the T-DXd 5.4 mg/kg arm, the most frequently reported TEAEs were nausea (66.1%), neutropenia (43.5%), and thrombocytopenia (40.3%)
  - In the T-DXd 6.4 mg/kg arm, the most frequently reported TEAEs were nausea (83.3%), neutropenia (60.0%), and anemia (56.7%)
- Any-grade TEAEs with a higher frequency (≥10% difference) in the Asia subgroup than in the safety analysis set[1] were:
  - Thrombocytopenia (40.3% vs 27.7%) in the T-DXd 5.4 mg/kg arms and leukopenia (46.7% vs 34.0%) in the T-DXd 6.4 mg/kg arms

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.
[a]Randomly assigned patients who received ≥1 T-DXd dose in the Asia subgroup. [b]The safety analysis set comprised all randomly assigned patients who received ≥1 T-DXd dose .
1. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863.

Adjudicated drug-related ILD

Adjudicated drug-related ILD, n (%)	Asia Subgroup	
	T-DXd 5.4 mg/kg n = 62[a]	T-DXd 6.4 mg/kg n = 30[a]
Total	8 (12.9)	12 (40.0)
Grade 1	2 (3.2)	4 (13.3)
Grade 2	6 (9.7)	8 (26.7)
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0

- In the T-DXd 5.4 mg/kg arm of the Asia subgroup, rates of adjudicated drug-related ILD were lower than in the 6.4 mg/kg arm and consistent with the safety analysis set[1,b]
  - **Safety analysis set**, 5.4 mg/kg arm: 13 (12.9%) total; 4 (4.0%) grade 1, 7 (6.9%) grade 2, 1 (1.0%) grade 3, and 1 (1.0%) grade 5 event
- In the T-DXd 6.4 mg/kg arm of the Asia subgroup, adjudicated drug-related ILD rates were higher than in the safety analysis set[1]
  - **Safety analysis set**, 6.4 mg/kg arm: 14 (28.0%) total; 4 (8.0%) grade 1, 9 (18.0%) grade 2, and 1 (2.0%) grade 5 event
- There were no grade ≥3 adjudicated drug-related ILD events in the Asia subgroup at either dose of T-DXd

ILD, interstitial lung disease; T-DXd trastuzumab deruxtecan.
[a]Randomly assigned patients who received ≥1 T-DXd dose in the Asia subgroup. [b]The safety analysis set comprised all randomly assigned patients who received ≥1 T-DXd dose .
1. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863.

Conclusions

- Both T-DXd 5.4 mg/kg and 6.4 mg/kg demonstrated **strong and durable responses** and **manageable safety** in the **Asia subgroup** of DESTINY-Lung02
  - Limitations of this subgroup analysis include its descriptive nature and the limited sample size
- A numerically higher response rate was observed in the T-DXd 6.4 mg/kg arm of the Asia subgroup compared with the full analysis set;[1] however, T-DXd 6.4 mg/kg was associated with a higher incidence of grade ≥3 TEAEs compared with the safety analysis set[1]
- Patients in the T-DXd 5.4 mg/kg arm of the Asia subgroup had numerically lower incidence rates of drug discontinuation, drug interruption, dose reduction, and adjudicated drug-related ILD than patients in the 6.4 mg/kg arm
- T-DXd 5.4 mg/kg was associated with a more favorable benefit/risk profile in the Asia subgroup, consistent with the safety analysis set[1]

Overall, data from this subgroup analysis support the use of T-DXd 5.4 mg/kg for Asian patients with previously treated *HER2*m mNSCLC and reinforce T-DXd as the standard of care in this patient population

*HER2*m, human epidermal growth factor receptor 2–mutant; ILD, interstitial lung disease; mNSCLC, metastatic non–small cell lung cancer; T-DXd, trastuzumab deruxtecan.

1. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863.

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Prior therapies

n (%)	Asia Subgroup	
	T-DXd 5.4 mg/kg n = 63	T-DXd 6.4 mg/kg n = 30
Prior systemic cancer therapy	63 (100)	30 (100)
Platinum-based therapy	63 (100)	30 (100)
Docetaxel treatment	25 (39.7)	14 (46.7)
Anti–PD-(L)1 treatment	44 (69.8)	24 (80.0)
Number of prior therapy regimens		
0	0	0
1	16 (25.4)	3 (10.0)
2	19 (30.2)	11 (36.7)
3	6 (9.5)	5 (16.7)
4	7 (11.1)	9 (30.0)
5	7 (11.1)	0
>5	8 (12.7)	2 (6.7)

PD-(L)1, programmed death (ligand) 1; T-DXd, trastuzumab deruxtecan

Overall safety summary

TEAEs, n (%)	Asia Subgroup	
	T-DXd 5.4 mg/kg n = 62[a]	T-DXd 6.4 mg/kg n = 30[a]
Any grade	62 (100)	30 (100)
Drug-related	61 (98.4)	30 (100)
Grade ≥3	31 (50.0)	21 (70.0)
Drug-related	26 (41.9)	19 (63.3)
Serious TEAEs	18 (29.0)	13 (43.3)
Drug-related	8 (12.9)	8 (26.7)
TEAEs associated with drug discontinuation	9 (14.5)	11 (36.7)
Drug-related	8 (12.9)	8 (26.7)
TEAEs associated with drug interruption	28 (45.2)	21 (70.0)
Drug-related	20 (32.3)	17 (56.7)
TEAEs associated with dose reduction	15 (24.2)	14 (46.7)
Drug-related	14 (22.6)	14 (46.7)
TEAEs associated with death	4 (6.5)	0
Drug-related	0	0

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Randomly assigned patients who received ≥1 T-DXd dose

Most common (≥20% of patients) TEAEs

	Asia Subgroup			
	T-DXd 5.4 mg/kg n = 62[a]		T-DXd 6.4 mg/kg n = 30[a]	
Preferred Term, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	41 (66.1)	2 (3.2)	25 (83.3)	2 (6.7)
Neutropenia[b]	27 (43.5)	13 (21.0)	18 (60.0)	12 (40.0)
Thrombocytopenia[b]	25 (40.3)	5 (8.1)	11 (36.7)	4 (13.3)
Decreased appetite	24 (38.7)	1 (1.6)	15 (50.0)	2 (6.7)
Constipation	24 (38.7)	0	9 (30.0)	0
Leukopenia[b]	22 (35.5)	2 (3.2)	14 (46.7)	7 (23.3)
Fatigue[b]	22 (35.5)	4 (6.5)	11 (36.7)	4 (13.3)
Anemia[b]	21 (33.9)	7 (11.3)	17 (56.7)	6 (20.0)
Vomiting	19 (30.6)	0	11 (36.7)	0
Alopecia	14 (22.6)	0	12 (40.0)	0
Transaminases increased[b]	14 (22.6)	1 (1.6)	5 (16.7)	0
Diarrhea	10 (16.1)	0	10 (33.3)	1 (3.3)

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Randomly assigned patients who received ≥1 T-DXd dose. [b]Grouped terms include neutropenia (neutrophil count decreased, neutropenia), fatigue (fatigue, asthenia, malaise, lethargy), anemia (hemoglobin decreased, red blood cell decreased, anemia, hematocrit decreased), leukopenia (white blood cell decreased, leukopenia), thrombocytopenia (platelet count decreased, thrombocytopenia), and transaminases increased (transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyl transferase increased, liver function test abnormal, hepatic function test abnormal, liver function test increased, hypertransaminasemia).

Plain language summary

Why did we perform this research?

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate designed to target and kill cancer cells that express the human epidermal growth factor receptor 2 (HER2) protein and is the only approved HER2-directed treatment for patients with previously treated *HER2*-mutant metastatic non–small cell lung cancer (mNSCLC).[1,2] In the DESTINY-Lung02 study, T-DXd 5.4 mg/kg and 6.4 mg/kg showed strong, long-lasting reduction in tumor size and manageable side effects in these patients.[3] As Asia was the largest geographic representation in DESTINY-Lung02, in this regional subgroup analysis we investigated how effective and safe the 5.4 mg/kg and 6.4 mg/kg doses of T-DXd were for Asian patients with previously treated *HER2*-mutant mNSCLC.

How did we perform this research?

In DESTINY-Lung02, 152 patients were randomly assigned 2:1 to receive either T-DXd 5.4 mg/kg (n = 102; n = 63 patients from Asia) or T-DXd 6.4 mg/kg (n = 50; n = 30 patients from Asia). The effectiveness and safety of T-DXd was assessed in each arm of the Asia subgroup.

What were the findings of this research and what are the implications?

Our study showed that at both the 5.4 mg/kg and 6.4 mg/kg doses, T-DXd showed strong, long-lasting tumor shrinkage and manageable side effects in Asian patients with previously treated *HER2*-mutant mNSCLC. Although better tumor shrinkage was observed with T-DXd 6.4 mg/kg, the 5.4 mg/kg dose was associated with a more favorable benefit/risk profile, which was generally consistent with the overall population.

Where can I access more information?

DESTINY-Lung02: ClinicalTrials.gov. Trastuzumab deruxtecan in participants with *HER2*-mutated metastatic non-small cell lung cancer (NSCLC) (DESTINY-Lung02) https://clinicaltrials.gov/ct2/show/NCT04644237

1. Liu S et al. *Clin Cancer Res.* 2018;24:2594-2604. 2. Enhertu. Summary of product characteristics. Daiichi Sankyo Europe GmbH; 2022. 3. Goto K et al. *J Clin Oncol.* 2023;41:4852-4863.