Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non–Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01

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Disclosures

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Honoraria	AstraZeneca, Nichi-Iko Pharmaceutical, Astellas Pharma, Takeda Pharmaceutical, MSD, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, Nippon Boehringer Ingelheim, Eli Lilly Japan, Novartis Pharmaceuticals, SymBio Pharmaceuticals, Pfizer Japan, Chugai Pharmaceutical, Clinical Trial Co., NANZANDO, MEDICUS SHUPPAN, Publishers, YODOSHA, Care Net, Nikkei Business Publications, Reno. Medical, Daiichi Sankyo, KYORIN Pharmaceutical, Thermo Fisher Scientific, Medical Review Co., YOMIURI TELECASTING CORPORATION, Roche Diagnostics, Nippon Kayaku, Bayer Yakuhin, Merck Biopharma, Medical Mobile Communications, AbbVie, 3H Clinical Trial
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DESTINY-Lung01: Introduction

An open-label, multicenter, phase 2 study (NCT03505710)

- T-DXd is an antibody–drug conjugate consisting of an anti-HER2 antibody, a cleavable, tetrapeptide-based linker, and a topoisomerase I inhibitor payload
- In a phase 1, open-label, nonrandomized, multiple-dose, 2-part study (NCT02564900) of patients (N = 60) with HER2-expressing or HER2-mutant nonbreast/nongastric solid tumors, T-DXd (6.4 mg/kg) demonstrated promising activity in a heavily pretreated population[1]
- **Here we present the results of the HER2-overexpressing cohort in the DESTINY-Lung01 trial, an open-label, multicenter, phase 2 study**

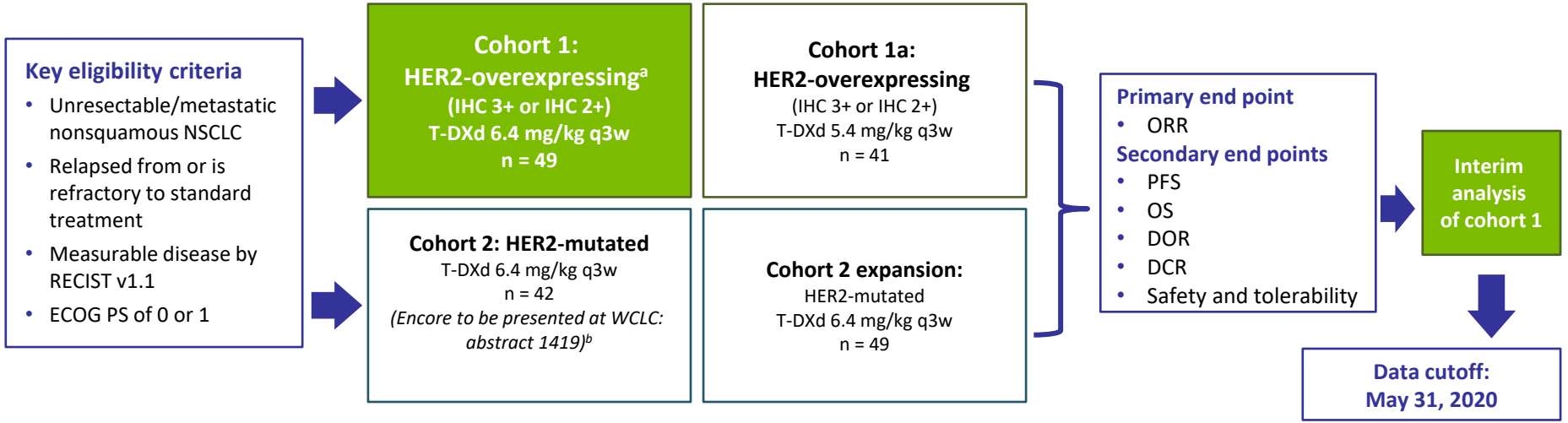
Phase 1 Trial, NSCLC Cohort, (n=18)[1]

HER2 Status	
HER2 expression/amplification[a]	
HER2 IHC 3+, n (%)	2 (11.1%)
HER2 IHC 2+, n (%)	1 (5.6%)
HER2 IHC 1+, n (%)	8 (44.4%)
HER2 IHC 0, n (%)	5 (27.8%)
HER2 mutations[b], n (%)	11 (61.1%)
Clinical Activity Outcomes by ICR	
ORR, n (95% CI)	55.6% 10 (30.8-78.5)
Median PFS (95% CI)	11.3 months (7.2-14.3)
Median DOR (95% CI)	10.7 months (6.9-11.5)

DOR, duration of response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; NE, nonestimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
[a]Central laboratory assessment was missing for 2 patients. [b]Among the patients with HER2 mutations, 9.1% (1/11) were HER2 IHC 2+, 36.4% (4/11) were HER2 IHC 1+, 36.4% (4/11) were HER2 IHC 0, and 18.2% (2/11) were not evaluated/missing for HER2 IHC.
1. Tsurutani J et al. *Cancer Discov*. 2020;10(5):688-701.

DESTINY-Lung01 Study Design

Phase 2 study of T-DXd, a novel antibody-drug conjugate, in patients with HER2-overexpressing or HER2-mutated metastatic NSCLC (NCT03505710)



- In cohort 1, 11 patients remained on treatment, and 38 patients had discontinued treatment primarily because of PD (n = 22) or AEs (n = 9)[c]
- Median treatment duration was 18.0 weeks (range, 3.0-57.1 weeks)

AE, adverse event; DCR, disease control rate; OS, overall survival; PD, progressive disease; q3w, every 3 weeks.
[a]HER2 overexpression (without known HER2 mutation) was assessed by local assessment of archival tissue and centrally confirmed. [b]Smit EF et al. Presented at: 2020 World Conference on Lung Cancer Singapore, Virtual Meeting; January 28-31, 2021. [c]Other reasons for discontinuation included death (n = 2; unrelated to study treatment), withdrawal of consent (n = 2), investigator decision (n = 2), and other (n = 1).

Baseline Characteristics and Prior Therapies

Demographics and Baseline Characteristics	Patients (N = 49)
Age, median (range), years	63.0 (37-85)
<65 years, n (%) | ≥75 years, n (%)	27 (55.1%) | 2 (4.1%)
Female, n (%)	19 (38.8%)
Region, n (%)	
Asia	12 (24.5%)
North America	19 (38.8%)
Europe	18 (36.7%)
HER2 IHC status, n (%)	
IHC 3+	10 (20.4%)
IHC 2+	39 (79.6%)
IHC 1+ | IHC 0 | missing	0 | 0 | 0

Demographics and Baseline Characteristics	Patients (N = 49)
Other gene abnormality status, n (%)	
EGFR/ALK/ROS1/BRAF	3 (6.1%)
No EGFR/ALK/ROS1/BRAF	14 (28.6%)
Not reported	32 (65.3%)
ECOG performance status, n (%) 0 | 1	14 (28.6%) | 35 (71.4%)
Presence of CNS metastases, n (%)	17 (34.7%)
Prior therapies, n (%)	49 (100.0%)
Platinum-based Anti–PD-1/PD-L1 Docetaxel	45 (91.8%) 36 (73.5%) 12 (24.5%)
Median number of prior lines of therapies (range)	3 (1-8)

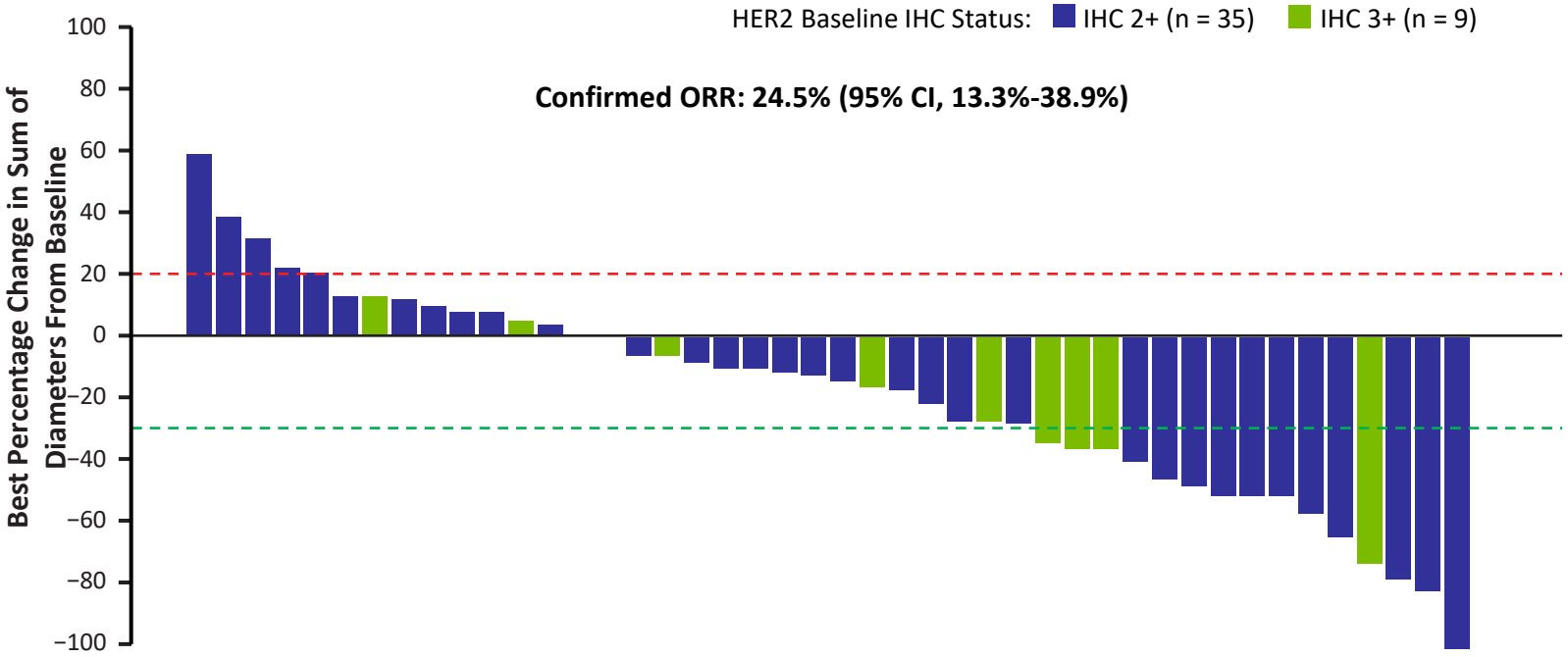
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed death 1; PD-L1, programmed death ligand 1.
Full analysis set data are shown.

Efficacy Results With T-DXd

Response Assessment by ICR	IHC 3+ (n = 10)	IHC 2+ (n = 39)	Overall (N = 49)
Confirmed ORR, n (95% CI)	**20.0%** 2 (2.5-55.6)	**25.6%%** 10 (13.0-42.1)	**24.5%** 12 (13.3-38.9)
CR, n (%)	0	1 (2.6%)	1 (2.0%)
PR, n (%)	2 (20.0%)	9 (23.1%)	11 (22.4%)
SD, n (%)	6 (60.0%)	16 (41.0%)	22 (44.9%)
PD, n (%)	1 (10.0%)	10 (25.6%)	11 (22.4%)
Not evaluable, n (%)	1 (10.0%)	3 (7.7%)	4 (8.2%)
DCR, n (95% CI)	**80.0%** 8 (44.4-97.5)	**66.7%** 26 (49.8-80.9)	**69.4%** 34 (54.6-81.8)
Median DOR, months (95% CI)	**6.0 (NE-NE)**	**5.8 (3.2-NE)**	**6.0 (3.2-NE)**

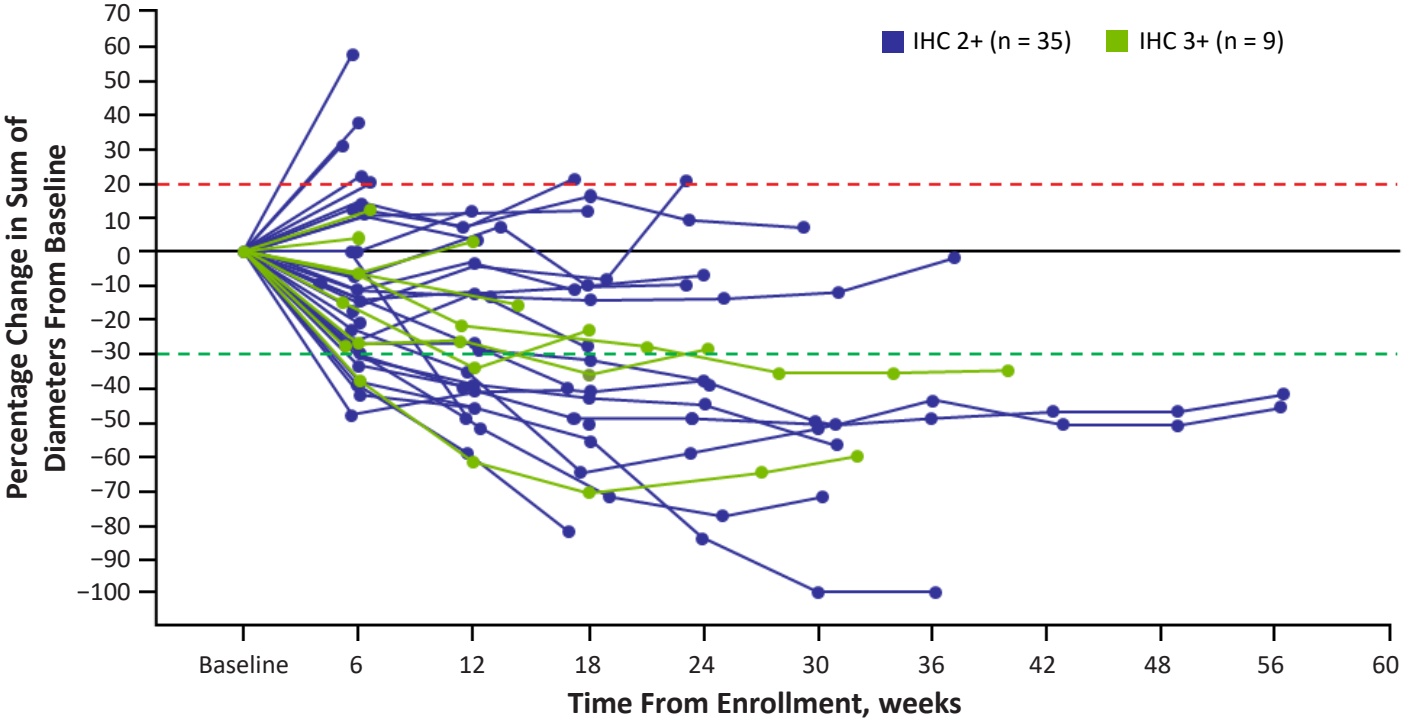
CR, complete response; PR, partial response; SD, stable disease.
Full analysis set data are shown.

Best Percentage Change in Tumor Size[a] With T-DXd



[a]Best (minimum) percentage change from baseline in the sum of diameters for all target lesions, based on ICR. Baseline was last measurement taken before enrollment. Red line at 20% indicates PD, and green line at −30% indicates PR (when considering only target lesions). Full analysis set data are shown.

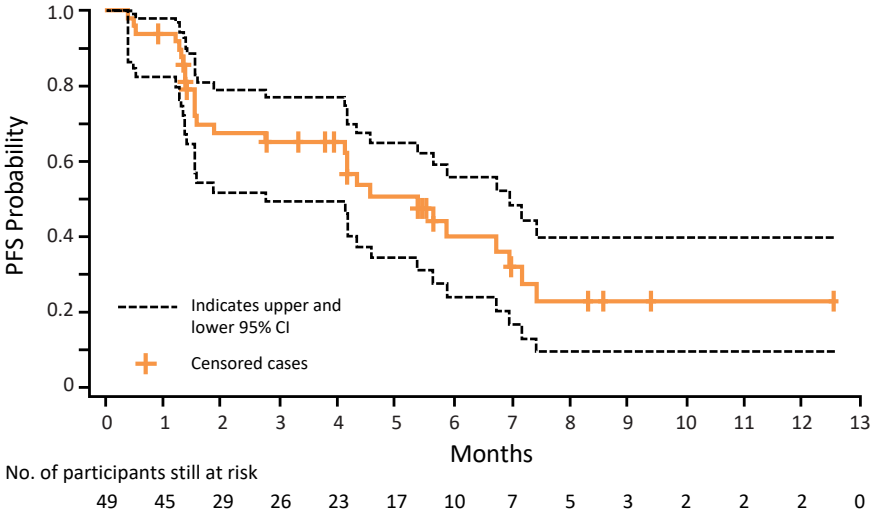
Change in Tumor Size Over Time With T-DXd



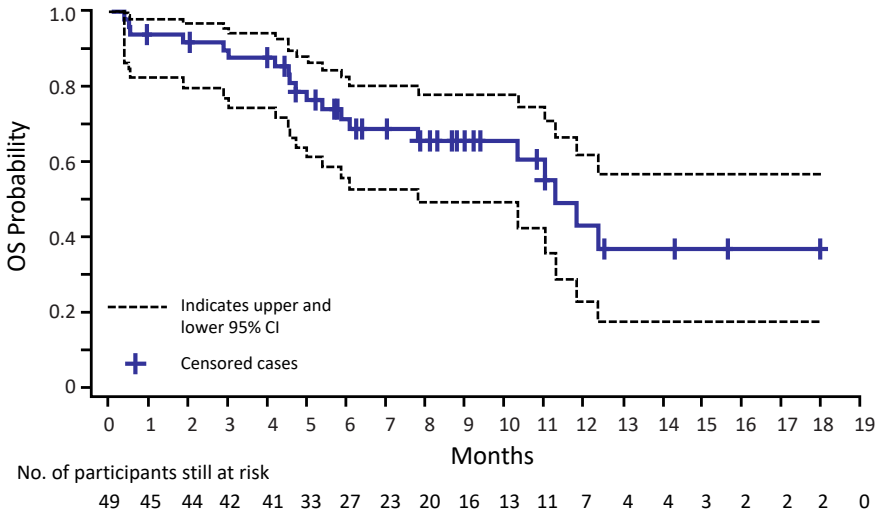
Baseline is defined as the last measurement taken before enrollment. Data beyond first determination of PD or start of new antineoplastic therapy are not displayed. Red line at 20% indicates PD, and green line at −30% indicates PR (when considering only target lesions). Plot is based on ICR and in the full analysis set.

PFS and OS With T-DXd

PFS (N = 49)
Median: 5.4 months (95% CI, 2.8-7.0 months)



OS (N = 49)
Median: 11.3 months (95% CI, 7.8-NE)



Progressive disease was assessed by ICR using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). The median was based on Kaplan-Meier estimate; 95% CI for the median was computed using the Brookmeyer-Crowley method.
Median follow-up was 6.1 months (range, 0.4-18.0 months). Full analysis set data are shown.

Overall Safety Summary

Type of Adverse Event[a]	Patients, n (%) N = 49
Any TEAE	49 (100.0%)
Drug related	44 (89.8%)
TEAE grade ≥3	36 (73.5%)
Drug related	27 (55.1%)
Serious TEAE	22 (44.9%)
Drug related	8 (16.3%)
TEAE associated with dose discontinuation	11 (22.4%)
Drug related	6 (12.2%)
TEAE associated with dose reduction	17 (34.7%)
Drug related	16 (32.7%)
TEAE associated with dose interruption	26 (53.1%)
Drug related	17 (34.7%)

Type of Adverse Event[a]	Patients, n (%) N = 49
TEAE grade ≥3 (>15%)	
Decreased neutrophil count	10 (20.4%)
TEAE associated with dose discontinuation[b]	
Pneumonitis	5 (10.2%)
TEAEs associated with dose reduction[b]	
Decreased neutrophil count	5 (10.2%)
Fatigue	4 (8.2%)
Nausea	3 (6.1%)
TEAEs associated with dose interruption[b]	
Decreased neutrophil count	5 (10.2%)
Nausea	3 (6.1%)
TEAE grade 5[c] | Drug related	7 (14.3%) | 1 (2.0%)

- Median treatment duration was 18 weeks (range, 3.0-57.1 weeks)

TEAE, treatment-related adverse event.
[a]Relationship to study drug was determined by the treating investigator. [b]Most common occurring in more than 2 patients. [c]The grade 5 TEAEs included disease progression (n = 4), hydrocephalus, pneumonitis, and bronchospasm (n = 1 each).
Safety analysis set data are shown.

AEs of Special Interest: ILD

All Patients (N = 49)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade/Total**
Adjudicated drug-related ILD[a]	2 (4.1%)	3 (6.1%)	0	0	3 (6.1%)	8 (16.3%)

Adjudicated drug-related ILDs[b]

- Median time to onset was 64.5 days (range, 2-126 days)
- All patients had drug withdrawn
- Steroid treatment was used in patients who had grade 2 (n = 3) and those who had grade 5 ILDs (n = 3)
- 3 patients recovered (grade 1 [n = 1] and grade 2 [n = 2]) and 2 patients had not recovered by data cutoff (grade 1 [n = 1] and grade 2 [n = 1])
- 4 of 8 patients had immune checkpoint inhibitors included in their prior lines of therapy

Grade 5 ILD[c] events

- Medical history of the 3 patients included
  1. Pulmonary embolism, productive cough, dyspnea, pleural effusion, and lobectomy; 4 prior lines of therapy
  2. Cough, dyspnea, pleural effusion, and pulmonary embolism; 5 prior lines of therapy
  3. Dyspnea, SLE without lung involvement, and TTP; 1 prior line of therapy
- Steroid treatment was initiated within 5 days after the event was reported by the investigator[d]
- All had previously received immune checkpoint inhibitors
- Primary cause of death was PD in 2 patients and pneumonitis in 1 patient

ILD, interstitial lung disease; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.
[a]Drug-related ILD was determined by an independent ILD adjudication committee based on 44 preferred terms. [b]All potential cases of ILD that occurred before the data cutoff were adjudicated. [c]The 3 cases of grade 5 ILD were initially reported by the investigator as grade 4 pneumonitis and grade 4 respiratory failure (n = 1), grade 4 respiratory failure (n = 1), and grade 5 pneumonitis (n = 1). [d]Steroid treatment was initiated 2 days later for case 1, 5 days later for case 2, and on the same day for case 3. Safety analysis set data are shown

T-DXd Showed Preliminary Evidence of Antitumor Activity in Patients With HER2-Overexpressing NSCLC

Efficacy Results

- In extensively pretreated patients who had previously received a median of 3 lines of therapies (range, 1-8), T-DXd 6.4 mg/kg demonstrated
  - A confirmed ORR of 24.5%, with no apparent difference in ORR by HER2 expression (IHC 3+ vs 2+)
  - A DCR of 69.4% and median OS of 11.3 months

Safety Results

- The safety profile was generally consistent with previous trials[1-5]
- In this interim analysis of 49 patients, drug-related ILD occurred in 16.3% of patients with fatal outcomes observed in 6.1% of patients; ILD continues to be closely monitored and proactively managed, with further investigation as more follow-up data become available

Future Studies

- These encouraging early efficacy results support the continued exploration of T-DXd in patients with HER2-overexpressing NSCLC

1. Tsurutani J et al. *Cancer Discov*. 2020;10(5):688-701. 2. Tamura K et al. *Lancet Oncol*. 2019;20(6):816-826. 3. Modi S et al. *N Engl J Med*. 2020;382(7):610-621. 4. Modi S et al. *J Clin Oncol*. 2020;38(17):1887-1896. 5. Shitara K et al. *Lancet Oncol*. 2019;20(6):827-836.

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