# Real-world analysis of interstitial lung disease/pneumonitis in patients with HER2-positive unresectable or recurrent breast cancer treated with trastuzumab deruxtecan: All-patient post-marketing surveillance study in Japan

## -Encore presentation from San Antonio Breast Cancer Symposium 2024-

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Daiichi Sankyo Co., Ltd. and AstraZeneca entered into a global development and commercialization collaboration agreement for trastuzumab deruxtecan (T-DXd; DS-8201).

# Conflict of Interest disclosure slide for representative speakers or investigators

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# Background

- T-DXd has been approved for the treatment of HER2-positive unresectable or recurrent breast cancer after prior chemotherapy in Japan.
- While there is accumulating evidence demonstrating the effectiveness of T-DXd in various types of cancers, ILD/p are recognized as important identified risks associated with the use of T-DXd.
- Understanding the risk of ILD/p is crucial for optimizing ILD risk management and promoting the safe use of T-DXd.

Abbreviation: T-DXd, trastuzumab deruxtecan; ILD, interstitial lung disease; ILD/p, ILD/pneumonitis

# Objective

To investigate the incidence of ILD/p and factors associated with the development of ILD/p among breast cancer patients treated with T-DXd in the real-world setting in Japan.

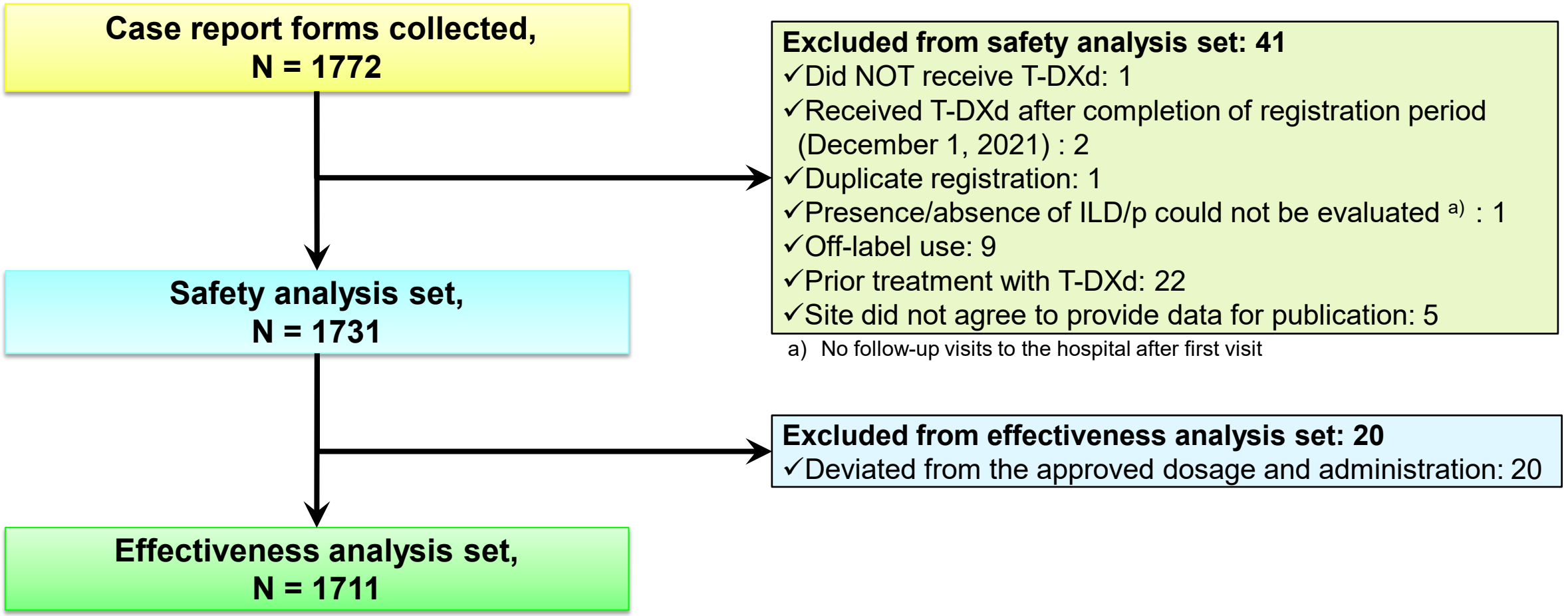
# Method

- This PMS (jRCT1080225197) is a multicenter, observational study with an observation period of 18-months that enrolled all patients treated with T-DXd for breast cancer in Japan in accordance with the GPSP.
- All patients who initiated T-DXd treatment between May 25, 2020 (the day of launch) and November 30, 2021 were enrolled.
- Physician-assessed ILD/p events were retrospectively reviewed by an independent adjudication committee; events adjudicated as drug-related ILD were summarized.
- The factors associated with the development of adjudicated drug-related ILD were investigated using a Cox proportional hazards model.
- The effectiveness endpoints were ORR and intracranial ORR.

Abbreviation: PMS, post-marketing surveillance; GPSP, Good Post-marketing Study Practice; ORR, objective response rate; BOR

# Results

# Patient disposition




a) No follow-up visits to the hospital after first visit

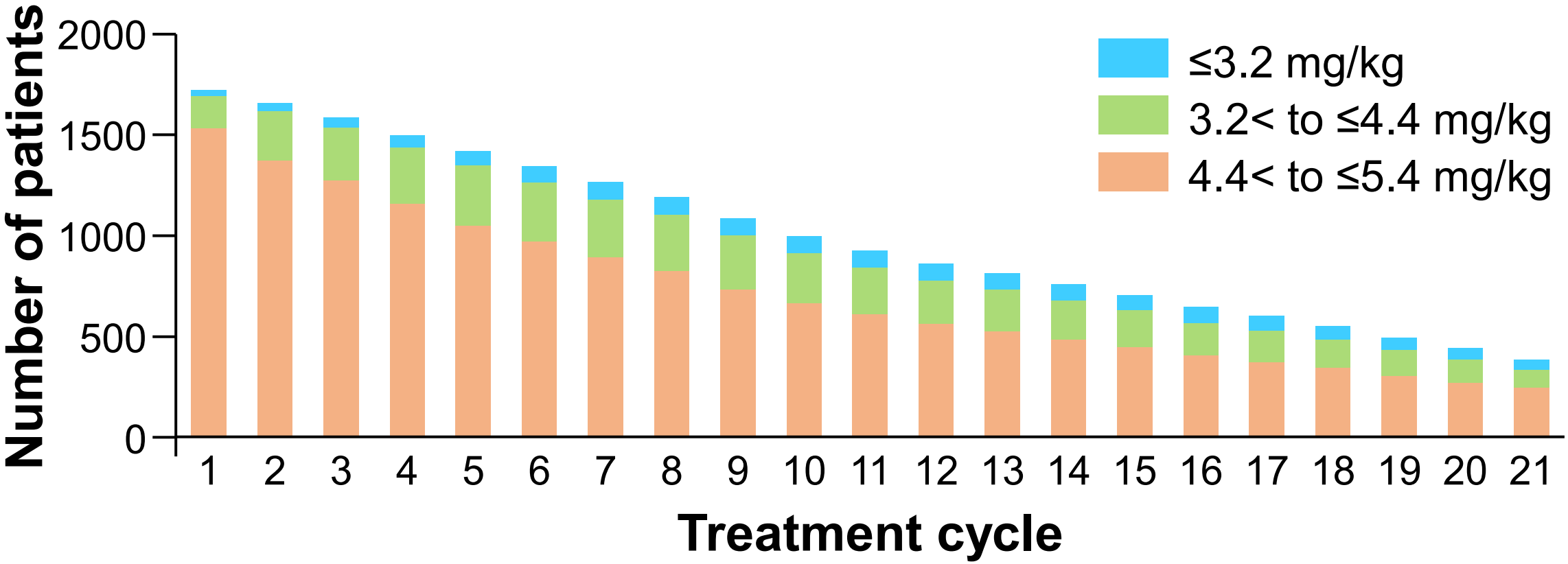
# Patient demographics and clinical characteristics at baseline (safety analysis set)

| | N = 1731, n (%) |
|---|---|
| **Gender** | |
| Male/Female | 8 (0.5) / 1723 (99.5) |
| **Age (years)** | |
| Median (range) | 60.0 (27–87) |
| ≥65 years | 637 (36.8) |
| **ECOG performance status** | |
| 0-1 / 2-4 | 1594 (92.1) / 137 (7.9) |
| **Site(s) of metastasis or recurrence (allowed multiple sites)** | |
| None | 3 (0.2) |
| Local or lymph node / Lung or pleural | 1055 (60.9) / 894 (51.6) |
| Bone / Liver | 744 (43.0) / 609 (35.2) |
| Brain | 367 (21.2) |
| Meninges or spinal fluid / Other | 14 (0.8) / 212 (12.2) |
| **Renal function (CLCr [mL/min])** | |
| Normal: ≥90 | 605 (35.0) |
| Mild impairment: 60≤ to <90 | 767 (44.3) |
| Moderate impairment to end stage: <60 | 332 (19.2) |
| Unknown/missing | 27 (1.6) |

| | N = 1731, n (%) |
|---|---|
| **History of smoking** | |
| Never / Past / Current / Unknown-missing | 1257 (72.6) / 195 (11.3) / 34 (2.0) / 245 (14.2) |
| **$SpO_2$ (%)** | |
| <95 / ≥95 / Not implemented / Unknow or missing | 51 (2.9) / 1297 (74.9) / 369 (21.3) / 14 (0.8) |
| **Prior cancer therapy (regimens)** | |
| ≥2 / ≥3 / ≥6 / ≥10 | 1630 (94.2) / 1212 (70.0) / 426 (24.6) / 95 (5.5) |
| **Medical history / comorbidity** | |
| Respiratory disease | 104 (6.0) / 87 (5.0) |
| ILD | 24 (1.4) / 11 (0.6) |
| Radiation pneumonitis | 40 (2.3) / 31 (1.8) |
| COPD or emphysema | 1 (0.1) / 4 (0.2) |
| Asthma | 29 (1.7) / 23 (1.3) |
| Other respiratory disease | 15 (0.9) / 22 (1.3) |
| History of lung surgery | 76 (4.4) / NA |
| Pleural effusion | NA / 230 (13.3) |
| Malignant tumors other than breast cancer | 58 (3.4) / 26 (1.5) |

Abbreviation: BMI, body mass index; ECOG, European Clinical Oncology Group; CLCr, creatinine clearance calculated using the Cockcroft-Gault equation; $SpO_2$, saturation of percutaneous oxygen; COPD, chronic obstructive pulmonary disease; NA, not applicable

# Dosage change by treatment cycle (safety analysis set)




- A certain number of patients had reduced dosage from the initial administration.
- No cases of dosing above the approved dosage (5.4 mg/kg) were observed.

# T-DXd treatment status at 18-months after treatment initiation

| Status at 18-months after T-DXd initiation | N = 1731, n (%) |
|---|---|
| Ongoing | 434 (25.1) |
| Discontinued | 1297 (74.9) |
| Reason for treatment discontinuation* | |
| Progression of primary disease (including death) | 797 (46.0) |
| Adverse events (other than ILD/p) | 98 (5.7) |
| ILD/p (reported by treating physician) | 280 (16.2) |
| Lost to follow up | 21 (1.2) |
| Refusal or request of the patient | 89 (5.1) |
| Other | 58 (3.4) |

* Not mutually exclusive

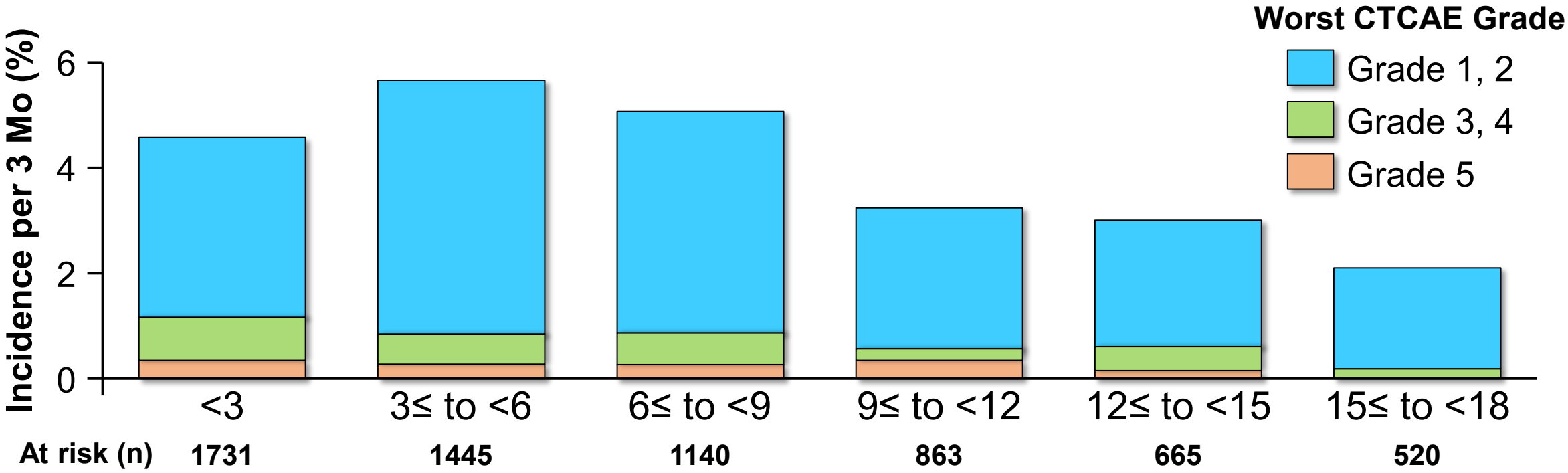
- At 18-months after treatment initiation, 25.1% of patients continued treatment with T-DXd.
- The most common reason for treatment discontinuation was disease progression.

# Incidence of adjudicated drug-related ILD

Median duration of T-DXd treatment in safety analysis set: **9.40 months (range: 0.7-17.9)**

| N | Worst CTCAE Grade, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade | Grade ≥3 |
| 1731 | 125 (7.22%) | 101 (5.83%) | 34 (1.96%) | 1 (0.06%) | 17 (0.98%) | 278 (16.06%) | 52 (3.00%) |

# Time to adjudicated drug-related ILD




- Median time to first ILD onset: 5.1 months (range: 0.5-17.3)
- Observed the development of adjudicated drug-related ILD throughout the observation period, showing a higher incidence during the first 9 months of treatment, with no specific peak

# Outcome of adjudicated drug-related ILD (by worst Grade)

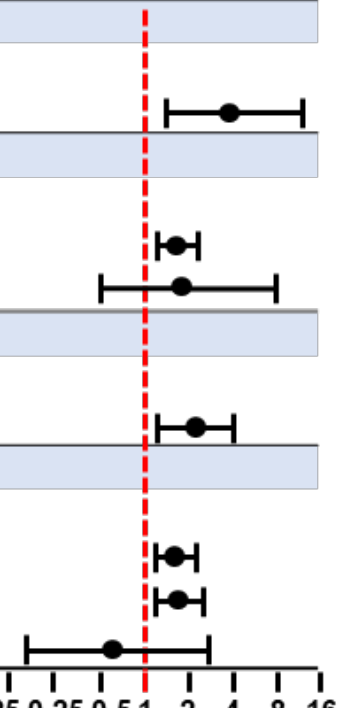
| Worst Grade | N | Outcome (up to 6 months of follow-up after onset of ILD), n (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Resolved | Resolving | Resolved with sequelae | Not resolved | Fatal | Unknown/ missing |
| Any Grade | 278 | 146 (52.52) | 69 (24.82) | 15 (5.40) | 26 (9.35) | 17 (6.12) | 5 (1.80) |
| Grade 1 | 125 | 78 (62.40) | 28 (22.40) | 0 (0) | 15 (12.00) | 0 (0) | 4 (3.20) |
| Grade 2 | 101 | 60 (59.41) | 29 (28.71) | 5 (4.95) | 6 (5.94) | 0 (0) | 1 (0.99) |
| Grade 3 | 34 | 8 (23.53) | 12 (35.29) | 9 (26.47) | 5 (14.71) | 0 (0) | 0 (0) |
| Grade 4 | 1 | 0 (0) | 0 (0) | 1 (100) | 0 (0) | 0 (0) | 0 (0) |
| Grade 5 | 17 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 17 (100) | 0 (0) |
| Grade ≥3 | 52 | 8 (15.38) | 12 (23.08) | 10 (19.23) | 5 (9.62) | 17 (32.69) | 0 (0) |

The CTCAE grades of adjudicated drug-related ILD at the onset for the 17 patients with a fatal outcome were as follows: Grade 1 for 3 patients, Grade 2 for 3 patients, and Grade 3 for 11 patients.

More than 80% of ILD had resolved, were resolving, or resolved with sequelae within 24 weeks from the onset, while the proportion decreases to less than 60% in the cases of Grade ≥3.

# Factors of interest for the development of adjudicated drug-related ILD

| Variables | Patients N = 1730 | ILD case N = 277 | Hazard ratio [95% CI] a) |
|---|---|---|---|
| **Gender** | | | |
| Female (reference) | 1722 | 273 | - |
| Male | 8 | **4** | **3.634 [1.299, 10.163]** |
| **BMI (kg/m$^2$)** | | | |
| <21.3 (Median) (reference) | 858 | 118 | - |
| ≥21.3 (Median) | 857 | **157** | **1.649 [1.275, 2.133]** |
| Unknown/missing | 15 | 2 | 1.987 [0.465, 8.499] |
| **ILD (medical history and/or comorbidity)** | | | |
| No (reference) | 1697 | 266 | - |
| Yes b) | 33 | **11** | **2.237 [1.210, 4.134]** |
| **Renal function (CLCr [mL/min])** | | | |
| Normal: ≥90 (reference) | 605 | 77 | - |
| Mild impairment: 60≤ to <90 | 766 | **140** | **1.719 [1.272, 2.322]** |
| Moderate impairment to End stage: <60 b) | 332 | **58** | **1.850 [1.240, 2.761]** |
| Unknown/missing | 27 | 2 | 0.648 [0.149, 2.819] |




a) Calculated using a multivariate Cox proportional hazards model
b) "Potential risk factor of interest" for ILD/p identified in the published literature (Powell et al., 2022)

Baseline factors included in the model were gender, ECOG-PS, serum albumin levels, $SpO_2$, age, body weight, BMI, history of smoking, time since the diagnosis of recurrent/unresectable breast cancer, the stage of unresectable/recurrent breast cancer, hormone receptor expression status, HER2 receptor expression status, lung or pleura metastasis or recurrence, liver metastasis or recurrence, brain metastasis or recurrence, prior cancer therapy for unresectable or recurrent breast cancer, the number of regimens for all prior treatments against breast cancer, prior chest radiation therapy, and other medical history and/or comorbidity (ILD, radiation pneumonitis, COPD, emphysema, asthma, pleural effusion, and history of lung surgery), renal function, and hepatic function.

# Effectiveness

Median duration of T-DXd treatment: 9.23 months (range: 0.7-17.9)

| Effectiveness in the effectiveness analysis set | | | | | | | |
|---|---|---|---|---|---|---|---|
| N | ORR (CR + PR) | | BOR [a], n (%) | | | | |
| | n (%) | 95% CI | CR | PR | SD | PD | NE |
| 1711 | 1036 (60.5) | 58.2, 62.9 | 98 (5.7) | 938 (54.8) | 448 (26.2) | 155 (9.1) | 72 (4.2) |
| **Effectiveness among patients with brain metastasis** | | | | | | | |
| N | Intracranial ORR (CR + PR) | | Intracranial BOR [a], n (%) | | | | |
| | n (%) | 95% CI | CR | PR | SD | PD | NE |
| 365 | 133 (36.4) | 31.5, 41.4 | 31 (8.5) | 102 (27.9) | 135 (37.0) | 20 (5.5) | 74 (20.3) |

ORR, objective response rate; BOR, best objective response;
CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable

# Discussion

# Strength and Limitations

- This study was non-blinded, non-randomized, and there was no control arm (all of which can lead to inherent risks for bias).
- One of the identified factors of interest (male gender) had a small sample size (n=8); this can reduce the validity of this finding.
- This study was conducted in Japan; the study findings must be interpreted with caution when generalizing to other populations outside of Japan.

# Conclusions

- The incidence of adjudicated drug-related ILD was “Any Grade: 16.06%; Grade ≥3: 3.00%; Grade 5: 0.98%” which was not notably different from that in clinical studies, suggesting no new safety concerns were identified in this PMS, despite the fact that these were real-world patients with higher ECOG performance status and more comorbidities than those in clinical studies.
- Clinical factors of interest for the development of adjudicated drug-related ILD may include male gender, higher BMI, medical history and/or comorbidity of ILD, and renal impairment. Further investigation is warranted to confirm risk factors for ILD/p.