Identifying and Managing Cancer Therapy–Induced Interstitial Lung Disease and Pneumonitis
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Disclosure of Conflicts of Interest

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Nina Thomas, MD, has no real or apparent conflicts of interest to report.
Learning Objectives

Upon completion of this activity, participants should be better able to:

- Identify risk factors and symptoms of drug-induced ILD/pneumonitis in patients treated with anti-cancer therapies known to cause ILD/pneumonitis
- Evaluate newer classes of agents that may contribute to medication-induced ILD/pneumonitis and recommendations for monitoring, detecting, and managing drug-induced ILD/pneumonitis
- Implement close monitoring for signs and symptoms of drug-induced ILD/pneumonitis to improve early detection and effective management of ILD
- Develop patient and caregiver education strategies for symptom monitoring of drug-induced ILD/pneumonitis
Epidemiology

- 10%-20% of all patients receiving antineoplastic agents will develop some form of pulmonary toxicity

- High prevalence – lungs receive entire blood supply

Pathogenesis

- Direct injury to alveolar capillary endothelium → release of cytokines → recruitment of inflammatory cells
- Systemic release of cytokines (gemcitabine) → endothelial dysfunction → capillary leak → noncardiogenic pulmonary edema
- Cell mediated injury – lymphocyte and macrophage activation
- Oxidative injury from free radicals (bleomycin)
- Dysregulation of immune system → T-cell activation (immune checkpoint inhibitors)
- EGFR receptors on type 2 pneumocytes → inhibit alveolar wall repair
- Radiation recall pneumonitis – unclear mechanism

EGFR, epidermal growth factor receptor.
Variety of Presentations

- Acute lung injury/Diffuse alveolar damage
- Acute respiratory distress syndrome (ARDS)
- Capillary leak syndrome
- Non-cardiogenic pulmonary edema
- Interstitial pneumonitis
- Hypersensitivity pneumonitis
- Eosinophilic pneumonia
- Alveolar hemorrhage
- Granulomatous pneumonitis
- Pulmonary fibrosis
- Pulmonary veno-occlusive disease
Risk Factors for Drug-induced ILD

- Increased age
- Male sex
- Pre-existing lung disease
  - ILD
  - IPF
  - COPD
  - Bronchiectasis
- Smoking
- Dose-dependent
  - Some drugs (bleomycin)
- Prior thoracic radiation
  - Especially in lung cancer
- Renal dysfunction
- Genetic susceptibility
  - CYP enzyme polymorphisms
  - HLA allelic variants
- Combination chemotherapy

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, interstitial pulmonary fibrosis.
Common Signs of ILD

If any of the symptoms below arise, experts recommend contacting a health care team.

- Dry, hacking cough that does not produce phlegm
- Extreme fatigue and weakness
- Unexplained weight loss
- Mild chest pain
- Shortness of breath
- Labored breathing which can be either fast or shallow
- No appetite
- Bleeding in the lungs

*This information courtesy of Cedars-Sinai. ILD, interstitial lung disease.*
Symptoms:
(often nonspecific)
- Cough
- Dyspnea
- Low-grade fever
- Hypoxemia
- Less common: chills, sputum production, weight loss

Physical exam:
(can be normal)
- Bibasilar crackles
- Less common: wheezing, morbilliform rash
Timing

- **Highly variable**
  - Onset after initiation of drug
  - May present weeks to months after initiation of therapy
  - Can present with first cycle or with subsequent treatment courses
  - Rare cases of delayed pneumonitis/fibrosis:
    - Bleomycin, nitrosoureas, immunotherapy
## Diagnosis and Evaluation

### Diagnosis of Exclusion with Highly Variable Presentation

- **Differential Diagnosis:**
  - Opportunistic infections
  - Pulmonary metastatic disease
  - Lymphangitic spread of cancer
  - Diffuse alveolar hemorrhage
  - Cardiogenic pulmonary edema

### Promptly Investigate Evidence of ILD/pneumonitis

- **Evaluation may include:**
  - High-resolution CT
  - Pulmonary consultation
  - Blood culture and CBC count
  - Consider bronchoscopy
  - Arterial blood gases if clinically indicated

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**Key to Diagnosis and Treatment of ILD/Pneumonitis**

is Early Recognition of Signs and Symptoms
Radiologic Findings

- CT scan the imaging modality of choice, although findings can be non-specific and variable
  - Ground glass opacities with or without consolidation
  - Reticular changes, septal thickening
  - Centrilobular nodules
  - Pulmonary fibrosis – bleomycin (volume loss, traction bronchiectasis, honeycombing)
  - Distribution pattern:
    - bilateral, basal, peripheral, diffuse affecting multiple lobes
  - Hilar lymphadenopathy or pleural effusions
  - Varying severity

- All episodes of ILD/pneumonitis, regardless of severity, should be tracked until resolution, even after drug discontinuation

CT, computed tomography; ILD, interstitial lung disease.
Examples of Drug-induced Pulmonary Toxicity in Patients with Cancer

Chemotherapy in Breast Cancer

mTOR Inhibitor in Renal Cell Carcinoma

EGFR Inhibitor in Lung Cancer
Pulmonary Function Tests

- Most common decline DLCO (diffusion capacity)
- Can see restrictive pattern on PFTs
  - Decreased FEV1 and FVC with normal ratio
  - Reduced lung volumes
- Does not correlate with worse prognosis and does not predict risk of developing pulmonary toxicity
- Limited utility for serial PFTs

DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 minute; FVC, forced vital capacity; PFTs, pulmonary function tests.

Bronchoscopy

**Bronchoalveolar Lavage**
- Blood cell count differential – lymphocytosis, neutrophilia, occasional eosinophilia
- Rule out infection with viral, bacterial, AFB, and fungal cultures
- Cytology to evaluate for malignancy
- Serial aliquots – rule out DAH

**Transbronchial Biopsy**
- Exclude: lymphangitic carcinomatosis, vasculitis, pneumonias
- Pathologic diagnosis – often nonspecific

AFB, acid-fast bacteria; DAH, diffuse alveolar hemorrhage.
Drug-Induced Respiratory Disease Website

The Drug-Induced Respiratory Disease Website
Philippe Carus, M.D.
Dijon, France

1 - Interstitial/parenchymal lung disease

La. Pneumonitis (ILD) diffuse, severe. W/wo the features of ARDS
Lb. Pneumonitis (ILD). Acute, subacute, or chronic
Lc. Eosinophilic pneumonia (pulmonary infiltrates and eosinophilia)
Le. Acute eosinophilic pneumonia (AEP)
Lg. Pulmonary fibrosis
Lh. Subclinical pulmonary infiltrates/ILD
Li. Diffuse alveolar damage (DAD) (see also under llb and XVI)
Lad. Radiation recall pneumonitis
Interstitial Lung Disease in Cancer Therapy

- Antibody-drug conjugates
- mTOR inhibitors
- Checkpoint inhibitors
- Tyrosine kinase inhibitors
- CDK 4/6 inhibitors

CDK 4/6, cyclin dependent kinase 4/6; mTOR, mammalian target of rapamycin.
Antibody-Drug Conjugates and Interstitial Lung Disease
Incidence of Pneumonitis with Targeted Cancer Therapies Approved by the FDA and EMA in the Treatment of Solid Tumors

<table>
<thead>
<tr>
<th>Antibody-Drug Conjugate</th>
<th>Tumor Type</th>
<th>Incidence of Lung Toxicity (any grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab emtansine</td>
<td>HER2+ breast cancer</td>
<td>9%</td>
</tr>
<tr>
<td>Trastuzumab deruxtecan</td>
<td>HER2+ breast cancer</td>
<td>9-17%</td>
</tr>
<tr>
<td></td>
<td>Gastric cancer</td>
<td>10%</td>
</tr>
<tr>
<td>Enfortumab vedotin</td>
<td>Urothelial cancer</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Sacituzumab govitecan</td>
<td>TNBC</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.
T-DXd Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 components:\(^1,2\):

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to
2. A topoisomerase I inhibitor payload, an exatecan derivative, via
3. A tetrapeptide-based cleavable linker

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### Key Attributes

1. **Payload MOA:**
   - topoisomerase I inhibitor\(^1,2,a\)
2. **High potency of payload\(^1,2,a\)**
3. **High drug to antibody ratio \(\approx 8\)**
4. **Payload with short systemic half-life\(^1,2,a\)**
5. **Stable linker-payload\(^1,2,a\)**
6. **Tumor-selective cleavable linker\(^1,2,a\)**
7. **Membrane-permeable payload\(^1,4,a\)**

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*The clinical relevance of these features is under investigation.*

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MOA, mechanism of action; T-DXd, trastuzumab deruxtecan.
 DESTINY-Breast01: Study Design

An Open-Label Multicenter Phase 2 Study of T-DXd\textsuperscript{1,2}

**Endpoints**

- **Primary:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK, and safety

**Population**

- \(\geq 18\) years of age
- Unresectable and/or metastatic BC
- HER2 positive (centrally confirmed in archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Pretreated and stable brain metastases were allowed

**Median Duration of Follow-Up**

- **August 1, 2019 data cutoff:** 11.1 months (range, 0.7-19.9 mo)\textsuperscript{1}
- **June 8, 2020 data cutoff:** 20.5 months (range, 0.7-31.4 mo)\textsuperscript{2}
- **March 26, 2021 data cutoff:** 26.5 months (range, 0.7-39.1 mo)\textsuperscript{3}

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\textsuperscript{a}All 184 patients received \(\geq 1\) dose of T-DXd. \textsuperscript{b}HER2 status was centrally assessed on the most recent archival tissue according to the ASCO-CAP guidelines.


BC, breast cancer; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
By independent central review. A total of 169 patients from the enrolled analysis set (N=184) had both baseline and postbaseline target lesion assessments by independent central review and are included in this analysis.

DESTINY-Breast01
Adverse Events of Special Interest: ILD/Pneumonitis

<table>
<thead>
<tr>
<th>Interstitial Lung Disease, n (%)(^a)</th>
<th>August 2019 DCO T-DXd 5.4 mg/kg (N = 184)</th>
<th>June 2020 DCO T-DXd 5.4 mg/kg (N = 184)</th>
<th>March 2021 DCO T-DXd 5.4 mg/kg (N = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>5 (2.7)</td>
<td>6 (3.3)</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>15 (8.2)</td>
<td>16 (8.7)</td>
<td>16 (8.7)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 5</td>
<td>4 (2.2)</td>
<td>5 (2.7)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>Any grade/total</td>
<td>25 (13.6)</td>
<td>28 (15.2)</td>
<td>29 (15.8)</td>
</tr>
</tbody>
</table>

Since June 2020 cutoff date, 1 new case of T-DXd-related ILD reported, as determined by the independent adjudication committee.

\(^a\)As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

DCO, data cutoff; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

**Patients**
- Unresectable or metastatic HER2-positive\(^a\) breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting\(^b\)
- Could have clinically stable, treated brain metastases

**Stratification factors**
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

**Primary endpoint**
- PFS (BICR)

**Key secondary endpoint**
- OS

**Secondary endpoints**
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

**Interim analysis for PFS (data cutoff: May 21, 2021)**
- Efficacy boundary for superiority: \( P < 0.000204 \) (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

**Key secondary endpoint, OS**: boundary for efficacy: \( P < 0.000265 \) (based on 86 events)

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\(^a\)HER2 IHC3+ or IHC2+/ISH+ based on central confirmation.

\(^b\)Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.

# ADC Characteristic Differences Between T-DXd and T-DM1

<table>
<thead>
<tr>
<th>T-DXd&lt;sup&gt;1&lt;/sup&gt;</th>
<th>T-DXd&lt;sup&gt;1-4.a&lt;/sup&gt;</th>
<th>ADC Attributes</th>
<th>T-DM1&lt;sup&gt;3-5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topoisomerase I inhibitor</td>
<td>Payload MoA</td>
<td>Anti-microtubule</td>
<td></td>
</tr>
<tr>
<td>~8:1</td>
<td>Drug-to-antibody ratio</td>
<td>~3.5:1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Tumor-selective cleavable linker?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Evidence of bystander anti-tumor effect?</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

ADC, antibody-drug conjugate; MoA, mechanism of action; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

*aThe clinical relevance of these features is under investigation.*

DESTINY-Breast03
Secondary Endpoint: PFS by Investigator Assessment

Patients Still at Risk:

<table>
<thead>
<tr>
<th>Patients Still at Risk:</th>
<th>T-DXd (261)</th>
<th>T-DM1 (263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DXd</td>
<td>261</td>
<td>263</td>
</tr>
<tr>
<td>T-DM1</td>
<td>256</td>
<td>253</td>
</tr>
</tbody>
</table>

### Table: PFS Results

<table>
<thead>
<tr>
<th></th>
<th>T-DXd</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, mo (95% CI)</td>
<td>25.1 (22.1-NE)</td>
<td>7.2 (6.8-8.3)</td>
</tr>
<tr>
<td>12-mo PFS rate, % (95% CI)</td>
<td>76.3 (70.4-81.2)</td>
<td>34.9 (28.8-41.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.27 (0.20-0.35)</td>
<td>P = 6.5 × 10^{-24}</td>
</tr>
</tbody>
</table>

PFS, progression-free survival.
DESTINY-Breast03: Adverse Events of Special Interest

### Adjudicated as drug-related ILD/pneumonitis

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Any Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DXd (N = 257)</td>
<td>7 (2.7)</td>
<td>18 (7.0)</td>
<td>2 (0.8)</td>
<td>0</td>
<td>0</td>
<td>27 (10.5)</td>
</tr>
<tr>
<td>T-DM1 (N = 261)</td>
<td>4 (1.5)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (1.9)</td>
</tr>
</tbody>
</table>

There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd.

### ↓ LVEF

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Any Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DXd (N = 257)</td>
<td>1 (0.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (2.3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>T-DM1 (N = 261)</td>
<td>0</td>
<td>1 (0.4)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

In the T-DXd arm, all LVEF adverse events reported were asymptomatic and no cases of cardiac failure occurred.

ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

<sup>a</sup>Patients with prior history of ILD/pneumonitis requiring steroids were excluded. <sup>b</sup>Left ventricular dysfunction. <sup>c</sup>Decreased ejection fraction.

DESTINY-Gastric01: Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

In the primary analysis of 101 OS events and 54% maturity, and in this updated analysis of 133 OS events and 71% maturity, T-DXd showed superior antitumor activity compared to PC.
DESTINY-Gastric01: T-DXd–related ILD/Pneumonitis

- 9.6% (n = 12) patients had T-DXd–related ILD/pneumonitis as determined by an independent adjudication committee
  - Median time to first onset: 84.5 days
  - Most were Grade 1 (n = 3) or 2 (n = 6)
  - Grade 3 (n = 2)
  - Grade 4 (n = 1)
  - No Grade 5 events
- Majority of ILD cases (8/12) had resolved/were resolving at time of analysis
  - Median duration: 57 days
  - 3 had not resolved (1 each Grades 1, 2, 4)
  - 1 was unknown (Grade 2)
- No cases of ILD occurred in the physician’s choice arm
DESTINY-CRC01: Study Design

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

Patients
- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- RAS/BRAF wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

Primary endpoint
Confirmed ORR by independent central review (ICR) in Cohort A

Cohort A (n=53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

T-DXd 6.4 mg/kg q3w

A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n = 7)
HER2 IHC 2+/ISH-

Cohort C (n = 18)
HER2 IHC 1+

Data cutoff: August 9, 2019
- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

IHC, immunohistochemistry; ISH, in-situ hybridization; HER2, human epidermal growth factor receptor 2; ORR, objective response rate.
DESTINY-CRC01: Best Change in Tumor Size

Cohort A: Best Change in Tumor Size

IHC, immunohistochemistry; ISH, in-situ hybridization; HER2, human epidermal growth factor receptor 2.
DESTINY-CRC01: AEs of Special Interest

Adjudicated drug-related ILDs:
- Median time to onset: 61.0 days
- 8/8 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 onset to initiation of steroid treatment in 8 ILD cases: 3.5 days
- In 3 fatal cases, onset was from 9 to 120 days (median: 22 days), and death occurred 6-19 days after diagnosis (median: 6 days)

<table>
<thead>
<tr>
<th>Grade</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (N=86)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
<tr>
<td>Grade 5</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Any Grade/Total</td>
<td>8 (9.3)</td>
</tr>
</tbody>
</table>

DESTINY-Lung01: Study Design

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

Patients
- Unresectable/metastatic non-squamous NSCLC
- Relapsed/refractory to standard treatment
- HER2-expressing or HER2-activating mutation
- No prior HER2-targeted therapy, except pan-HER TKIs

Primary endpoint
Confirmed ORR by independent central review

Cohort 1 (n = 42)
HER2 expressing (IHC 3+ or IHC 2)

Cohort 2 (n = 42)
HER2 mutated

T-DXd 6.4 mg/kg q3w

Data cutoff: November 25, 2019
- 45.2% of patients (19/42) in Cohort 2 remained on treatment
- 54.8% discontinued, primarily for progressive disease and adverse events (21.4% each)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

HER2-Mutated NSCLC
Best Change in Tumor Size

ESMO 2021: Best Percentage Change of Tumor Size from Baseline

Responses were observed across HER2 mutation subtypes, as well as in patients with no detectable HER2 expression or HER2 gene amplification.

HER2, human epidermal growth factor receptor 2; ESMO, European Society of Medical Oncology; NSCLC, non-small cell lung cancer.
DESTINY-Lung01: AEs of Special Interest

Adjudicated drug-related ILD:

- Median time to onset: 141 days
- Median duration: 43 days
- 75% were low grade (Grade 1-2)
- 21/24 patients received ≥1 dose of glucocorticoids
- At time of data cutoff, 54% (13/24) of investigator-reported cases had fully resolved

<table>
<thead>
<tr>
<th>Adjudicated Drug-Related ILD</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>15 (16.5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
<tr>
<td>Grade 5</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Any Grade/Total</td>
<td>24 (26.4)</td>
</tr>
</tbody>
</table>
Pooled Analysis: Drug-related ILD in 8 Single-Arm Trastuzumab Deruxtecan Studies Across Various Tumor Types

Background

- Interstitial lung disease (ILD) is an important identified risk for patients treated with T-DXd.
- 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.

Studies and Patients Included

- ILD adjudication committee established (November 2017)
- Kubo guidelines first referenced in clinical protocols (1Q 2018)
- Safe Use Campaign Initiated (June 2019)
- Toxicity management guidelines implemented (December 2019)

*Only patients who received T.01W 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.

ILD, interstitial lung disease.
Pooled Analysis: 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 $\geq 7.4$ mg/kg vs $5.4$ mg/kg
- Baseline SpO2 $< 95\%$ vs $\geq 95\%$
- 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 $\geq 3.9$ 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.
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.
### Pooled Analysis: Drug-related ILD

**Adjudicated Drug-related ILD by Tumor Type and Grade**

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

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

**Steroid Use by Grade of Adjudicated Drug-related ILD**

<table>
<thead>
<tr>
<th>No. of events</th>
<th>Grade 2-4</th>
<th>Events leading to Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events treated with systemic steroids, n (%)</td>
<td>48 (60.0)</td>
<td>16 (76.1)</td>
</tr>
</tbody>
</table>

**Incidence of ILD After Implementation of Toxicity Management Guidelines**

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

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

**Updated toxicity management guidelines implemented (Dec 2019)**

ILD, interstitial lung disease.
Trastuzumab Deruxtecan Pooled Analysis: Summary Points

- T-DXd has shown significant antitumor activity in HER2+ metastatic breast and gastric cancers, and other tumor types.
- Majority of independently adjudicated ILD cases were low grade (78%).
- ILD risk may decrease after ≈12 months of treatment.
- Optimal steroid management not observed, with delay in detection of ILD and underdosing of steroids.
  - New toxicity guidelines
  - Data suggest lower rate of high-grade ILD events after implementation of guidelines.

- Potential clinical factors of interest associated with ILD may include:
  - Low oxygen saturation
  - Lung comorbidities
  - Renal insufficiency

HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
An ILD Management Program for T-DXd Clinical Studies Has Been Established

**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 & CBC (other blood tests could be considered as needed)
- Consider bronchoscopy & bronchoalveolar lavage if clinically indicated and feasible
- PFTs & pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD 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 from date of onset, maintain dose
  - If resolved in >28 days from date of onset, reduce dose one level
  - If Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, drug should be discontinued

- **Grades 2-4:** Permanently discontinue treatment
  - Refer to toxicity management guidelines for trastuzumab deruxtecan

CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; PFTs, pulmonary function tests; PK, pharmacokinetics; T-DXd, trastuzumab deruxtecan.

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry</td>
<td>• Promptly start treatment with systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until clinical improvement, followed by gradual taper over at least 4 weeks</td>
<td>• Hospitalization required</td>
</tr>
<tr>
<td>• Consider follow-up imaging in 1-2 weeks (or as clinically indicated)</td>
<td>• Monitor symptoms closely</td>
<td>• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1,000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) for at least 14 days until clinical improvement, followed by gradual taper over at least 4 weeks</td>
</tr>
<tr>
<td>• Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks</td>
<td>• Re-image as clinically indicated</td>
<td>• Re-image as clinically indicated</td>
</tr>
<tr>
<td>• If worsening of diagnostic observations despite initiation of corticosteroids, then follow grade 2 guidelines*</td>
<td>• If worsening or no improvement in clinical or diagnostic observations in 5 days:</td>
<td>• If still no improvement within 3-5 days:</td>
</tr>
<tr>
<td></td>
<td>- Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)</td>
<td>- Re-consider additional work-up for alternative etiologies as described above</td>
</tr>
<tr>
<td></td>
<td>- Re-consider additional work-up for alternative etiologies as described above</td>
<td>- Consider other immunosuppressants and/or treat per local practice</td>
</tr>
<tr>
<td></td>
<td>- Escalate care as clinically indicated</td>
<td></td>
</tr>
</tbody>
</table>

*If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given.

ILD, interstitial lung disease.

mTOR Inhibitors and ILD
BOLERO-2 Primary Endpoint: Final PFS Analysis With Everolimus + Exemestane in NSAI-Refractory Advanced BC

<table>
<thead>
<tr>
<th></th>
<th>Events (Local), n/N</th>
<th>Median PFS (Local), mo</th>
<th>Median PFS (Central), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus + exemestane</td>
<td>310/485</td>
<td>7.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Placebo + exemestane</td>
<td>200/239</td>
<td>3.2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

HR: 0.45 (P < .0001)
HR: 0.38 (P < .0001)

ORR at 18 mo: 12.6% with everolimus + exemestane vs 1.7% with placebo + exemestane (P < .0001)

BC, breast cancer; EVE, everolimus; EXE, exemestane; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; PFS, progression-free survival.

Incidence of Pneumonitis With Targeted Cancer Therapies Approved by the FDA and EMA in the Treatment of Solid Tumors

<table>
<thead>
<tr>
<th>mTOR Inhibitor</th>
<th>Tumor Type</th>
<th>Incidence of Lung Toxicity (Any Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>Advanced HR+ breast cancer</td>
<td>12%-38%</td>
</tr>
<tr>
<td></td>
<td>Advanced RCC</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Advanced NET</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Advanced pancreatic NET</td>
<td>17%</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Advanced RCC</td>
<td>2%-22%</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; FDA, US Food & Drug Administration; HR, hormone receptor; mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; RCC, renal cell carcinoma.
## Proposed Clinical Management of mTOR Inhibitor-induced ILD

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>mTOR Inhibitor Treatment</th>
<th>Further Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway disease</td>
<td>Continue mTOR inhibitor, watchful waiting</td>
<td>Start inhaled steroids (i.e., ciclesonide 320 mcg BID). Reduce dose every 2 weeks if symptoms allow</td>
</tr>
<tr>
<td>Suspected ILD</td>
<td>Continue mTOR inhibitor, watchful waiting</td>
<td>In case of quick deterioration of clinical condition: treat as ILD</td>
</tr>
<tr>
<td>ILD</td>
<td>Interrupt mTOR inhibitor until resolution of symptoms to CTCAE grade 1 (≥3 weeks). Restart at reduced dose. In case of life-threatening ILD: permanently discontinue mTOR inhibitor.</td>
<td>Start prednisolone 40 mg qd orally. Reduce dose by 10 mg every 2 weeks. From 20 mg, reduce by 5 mg every week until stop. Add PCP prophylaxis until stop of prednisolone. Combine with empiric antibiotic therapy while results of diagnostic procedures are pending</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>In case of grade 3 or 4 symptoms: interrupt mTOR inhibitor pending analysis of differential diagnosis</td>
<td>Analyze for other possible causes of symptoms</td>
</tr>
</tbody>
</table>

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; mTOR, mammalian target of rapamycin. Willemsen et al. *Int J Cancer* 2016;138:2312-2321.
Everolimus-related Pneumonitis in Breast Cancer

Radiology Assessment by CT Scan

<table>
<thead>
<tr>
<th>Radiographic findings consistent with pneumonitis</th>
<th>Patients on Everolimus (n = 86), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>29 (33.7)</td>
</tr>
<tr>
<td>Postbaseline</td>
<td>62 (72.1)</td>
</tr>
<tr>
<td>Everolimus-related pneumonitis</td>
<td>45 (52.3)</td>
</tr>
<tr>
<td>Newly occurring</td>
<td>38 (44.2)</td>
</tr>
<tr>
<td>Worsened</td>
<td>7 (8.1)</td>
</tr>
<tr>
<td>Clinically diagnosed with NIP</td>
<td>22 (25.6)</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>14 (16.3)</td>
</tr>
</tbody>
</table>

Cumulative Probability of Radiographic Everolimus-related Pneumonitis in Patients with mBC

PFS and OS in Patients With and Without Everolimus-related Pneumonitis

CT, Computed Tomography; ERP, everolimus-related pneumonitis; mBC, metastatic breast cancer; NIP, noninfectious pneumonitis; OS, overall survival; PFS, progression-free survival.
Checkpoint Inhibitors and ILD
<table>
<thead>
<tr>
<th>Immune Checkpoint Inhibitors</th>
<th>Tumor Type</th>
<th>Incidence of Lung Toxicity (Any Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Melanoma</td>
<td>1.3%-1.5%</td>
</tr>
<tr>
<td></td>
<td>Squamous NSCLC</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Non-squamous NSCLC</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>HNSCC</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>RCC</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Urothelial carcinoma</td>
<td>3%</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>Melanoma</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>RCC</td>
<td>6.2%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1+ HNSCC</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>HNSCC</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>NSCLC PD-L1 ≥50%</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td>NSCLC PD-L1 ≥1%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>1.8%-3.3%</td>
</tr>
<tr>
<td></td>
<td>Urothelial carcinoma</td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>PD-L1+ urothelial carcinoma</td>
<td>2%</td>
</tr>
<tr>
<td>Pembrolizumab + chemotherapy</td>
<td>NSCLC</td>
<td>4.4%-6.5%</td>
</tr>
<tr>
<td></td>
<td>PD-L1+ HNSCC</td>
<td>5%</td>
</tr>
<tr>
<td>Pembrolizumab + axitinib</td>
<td>RCC</td>
<td>2.8%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Urothelial carcinoma</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>1%</td>
</tr>
<tr>
<td>Atezolizumab + nab-paclitaxel</td>
<td>TNBC</td>
<td>3.1%</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1 ≥1% NSCLC</td>
<td>12.6%</td>
</tr>
<tr>
<td>Durvalumab + chemotherapy</td>
<td>SCLC</td>
<td>3%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>MCC</td>
<td>1%</td>
</tr>
<tr>
<td>Avelumab + axitinib</td>
<td>RCC</td>
<td>0.6%</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Melanoma</td>
<td>2%</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; FDA, US Food & Drug Administration; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

Pneumonitis in Patients Treated With Anti–PD-1/PD-L1 Therapy

Patients who received anti–PD-1/PD-L1 therapy

<table>
<thead>
<tr>
<th>Demographic Characteristics and Treatment &amp; Response Data for Patients With Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from first dose of anti–PD-1/PD-L1 therapy to date of pneumonitis event stratified by grade</td>
</tr>
</tbody>
</table>

Pneumonitis in Patients Treated With Anti–PD-1/PD-L1 Therapy

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.
Tyrosine Kinase Inhibitors and ILD
## Incidence of Pneumonitis with Targeted Cancer Therapies Approved by the FDA and EMA in the Treatment of Solid Tumors

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Tumor Type</th>
<th>Incidence of Lung Toxicity (Any Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR TKI</strong></td>
<td>Gefitinib</td>
<td><strong>EGFR</strong>-mutated NSCLC</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td><strong>EGFR</strong>-mutated NSCLC</td>
<td>0.8%-1.6%</td>
</tr>
<tr>
<td></td>
<td><strong>EGFR</strong>-mutated NSCLC</td>
<td>Pancreatic cancer</td>
<td>1.6%-2.5%</td>
</tr>
<tr>
<td></td>
<td>Afatinib</td>
<td><strong>EGFR</strong>-mutated NSCLC</td>
<td>0.7%-1.6%</td>
</tr>
<tr>
<td></td>
<td>Osimertinib</td>
<td><strong>EGFR</strong>-mutated NSCLC <strong>EGFR T790M</strong>-mutated NSCLC</td>
<td>4%</td>
</tr>
<tr>
<td><strong>ALK TKI</strong></td>
<td>Crizotinib</td>
<td>ALK+ and ROS1+ NSCLC</td>
<td>1.2%-1.8%</td>
</tr>
<tr>
<td></td>
<td>Ceritinib</td>
<td>ALK+ NSCLC</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>Alectinib</td>
<td>ALK+ NSCLC</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td>Lorlatinib</td>
<td>ALK+ NSCLC</td>
<td>1.8%</td>
</tr>
<tr>
<td></td>
<td>Brigatinib</td>
<td>ALK+ NSCLC</td>
<td>4.5%-7%</td>
</tr>
<tr>
<td><strong>HER2 TKIs</strong></td>
<td>Lapatinib</td>
<td>HER2+ breast cancer</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Tucatinib</td>
<td>HER2+ breast cancer</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>Neratinib</td>
<td>HER2+ and HR+ breast cancer</td>
<td>0.07%-0.1%</td>
</tr>
<tr>
<td><strong>Multikinase and angiogenesis TKIs</strong></td>
<td>Sorafenib</td>
<td>Hepatocellular carcinoma (HCC)</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differentiated thyroid cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td>GIST</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal cell carcinoma (RCC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic neuroendocrine tumor (NET)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>RCC</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soft-tissue sarcoma (STS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>Kit+ gastrointestinal stromal tumor (GIST)</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatofibrosarcoma protuberans</td>
<td></td>
</tr>
<tr>
<td><strong>BRAF and MEK TKIs</strong></td>
<td>Trametinib</td>
<td>V600 <strong>BRAF</strong>-mutated melanoma</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Trametinib + dabrafenib</td>
<td>V600 <strong>BRAF</strong>-mutated melanoma</td>
<td>≤1%</td>
</tr>
<tr>
<td><strong>PI3K TKI</strong></td>
<td>Alpelisib</td>
<td>HR+ <strong>HER2</strong>- breast cancer with PIK3CA mutation</td>
<td>0.7%-1.8%</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2. MEK, mitogen-activated protein/extracellular signal-regulated kinase; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol 3-kinase; TKIs, tyrosine kinase inhibitors.

CDK 4/6 Inhibitors andILD
Incidence of Pneumonitis with Targeted Cancer Therapies Approved by the FDA and EMA in the Treatment of Solid Tumors

<table>
<thead>
<tr>
<th>CDK 4/6 Inhibitor</th>
<th>Tumor Type</th>
<th>Incidence of Lung Toxicity (Any Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abemaciclib</td>
<td>HR+/HER2- Metastatic Breast Cancer</td>
<td>1-3%</td>
</tr>
<tr>
<td>Palbociclib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribociclib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relative Risk for Pneumonitis or ILD Associated with CDK 4/6 Inhibitors: Meta-analysis of Phase 3 RCTs

<table>
<thead>
<tr>
<th>CDK 4/6 Inhibitor</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade ILD/pneumonitis</td>
<td>1.64%</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>0.28%</td>
</tr>
</tbody>
</table>

Pooled RR for Any Grade Pneumonitis or ILD Associated with CDK 4/6 Inhibitors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CDK 4/6 Inhibitor Events</th>
<th>Control arm Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MONALEESA-3</td>
<td>6</td>
<td>483</td>
<td>2</td>
<td>241</td>
<td>1.53 (0.90, 2.60)</td>
</tr>
<tr>
<td>MONALEESA-7</td>
<td>1</td>
<td>335</td>
<td>0</td>
<td>337</td>
<td>3.02 (0.12, 73.82)</td>
</tr>
<tr>
<td>MONARCH plus</td>
<td>14</td>
<td>309</td>
<td>4</td>
<td>352</td>
<td>1.72 (0.58, 5.14)</td>
</tr>
<tr>
<td>Monarch</td>
<td>75</td>
<td>2791</td>
<td>33</td>
<td>2800</td>
<td>2.28 (1.52, 3.42)</td>
</tr>
<tr>
<td>PALLAS</td>
<td>15</td>
<td>2840</td>
<td>5</td>
<td>2905</td>
<td>3.07 (1.12, 8.43)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6758</td>
<td>6433</td>
<td>100%</td>
<td></td>
<td>2.26 (1.60, 3.19)</td>
</tr>
<tr>
<td>Total events</td>
<td>111</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 4 (P = 0.93); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.62 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pooled RR for Grade 3/4 Pneumonitis or ILD Associated with CDK 4/6 Inhibitors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CDK 4/6 Inhibitor arm Events</th>
<th>Control arm Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MONALEESA-3</td>
<td>1</td>
<td>483</td>
<td>0</td>
<td>241</td>
<td>25.1% 1.50 (0.06, 36.68)</td>
</tr>
<tr>
<td>MONALEESA-7</td>
<td>0</td>
<td>335</td>
<td>0</td>
<td>337</td>
<td>Not estimable</td>
</tr>
<tr>
<td>MONARCH plus</td>
<td>1</td>
<td>309</td>
<td>1</td>
<td>352</td>
<td>30.8% 0.49 (0.03, 7.81)</td>
</tr>
<tr>
<td>Monarch</td>
<td>9</td>
<td>2791</td>
<td>3</td>
<td>2800</td>
<td>44.1% 9.03 (1.14, 71.22)</td>
</tr>
<tr>
<td>PALLAS</td>
<td>0</td>
<td>2840</td>
<td>0</td>
<td>2903</td>
<td>0.09 (0.01, 1.68)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3918</td>
<td>3530</td>
<td>100%</td>
<td></td>
<td>2.35 (0.37, 15.08)</td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.93; Chi² = 3.01, df = 2 (P = 0.22); I² = 34%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.90 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA Warns About Rare but Severe Lung Inflammation With CDK 4/6 Inhibitors for Breast Cancer (Sept 2019)

Patients
- Notify HCP right away for any new or worsening symptoms involving lungs, as they may indicate a rare but life-threatening condition that can lead to death
- Symptoms to watch for include:
  - Difficulty or discomfort with breathing
  - Shortness of breath while at rest or with low activity

Healthcare Professionals
- Monitor patients regularly for pulmonary symptoms indicative of ILD and/or pneumonitis
- Signs and symptoms may include:
  - Hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded
- Interrupt CDK 4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms
- Permanently discontinue treatment in patients with severe ILD and/or pneumonitis
Best Practice Recommendations for Monitoring, Identifying, and Managing Cancer Therapy Induced ILD/Pneumonitis: A Team-Based Approach
### Grading: DI-ILD and Pneumonitis

#### Grading of DI-ILD based on NCI-CTCAE

<table>
<thead>
<tr>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
<th>Grade 4 (life-threatening or disabling)</th>
<th>Grade 5 (fatal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, radiographic findings only</td>
<td>Symptomatic, not interfering with activities of daily living</td>
<td>Symptomatic, interfering with activity of daily life or oxygen indicated</td>
<td>Life-threatening, or ventilator support required</td>
<td>Fatal</td>
</tr>
</tbody>
</table>

#### Pneumonitis Severity Classification According to NCI-CTCAE and ASCO Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE Version 5.0</td>
<td>Asymptomatic • Clinical or diagnostic observations only • Intervention not indicated</td>
<td>Symptomatic • Medical intervention indicated • Limiting instrumental ADL</td>
<td>Severe symptoms • Limiting self-care ADL • Oxygen indicated</td>
<td>Life-threatening respiratory compromise • Urgent intervention indicated (trachetomy or intubation)</td>
</tr>
<tr>
<td>ASCO Guidelines 2018</td>
<td>Asymptomatic • Confined to one lobe of the lung of &lt;25% or lung parenchyma • Clinical or diagnostic observations only</td>
<td>Symptomatic • Involves ≥1 lobe of the lung, or 25%-50% of lung parenchyma • Medical intervention indicated • Limiting instrumental ADL</td>
<td>Severe symptoms • Hospitalization required • Involves all lung lobes or &gt;50% of lung parenchyma • Limiting self-care ADL • Oxygen indicated</td>
<td>Life-threatening respiratory compromise • Urgent intervention indicated (intubation)</td>
</tr>
</tbody>
</table>

ADL, activity of daily living; ASCO, American Society of Clinical Oncology; DI-ILD, drug-induced interstitial lung disease; CTCAE, Common Terminology Criteria for Adverse Events; G, grade; NCI, National Cancer Institute; Instrumental ADL, activities of daily living such as shopping, preparing food, using the telephone, managing money, etc.

Close and Early Monitoring Techniques for Cough, Dyspnea, Fever, New or Worsening Respiratory Symptoms

Advise patients to contact their healthcare provider immediately for any symptoms.

Inform patients of the risks of severe, life-threatening, or fatal ILD.
Considerations With Steroid Treatment

-Severity and rapidity of worsening pulmonary impairment
  - Grade 3 or 4
- Pattern (histologic or radiologic) responsive to glucocorticoids
- Exclude infectious etiologies – bronchoscopy
-Dosing:
  - Prednisone 40-60 mg tapered over 1-2 months
  - IV methylprednisolone 1 gram daily x 3 days for respiratory failure on mechanical ventilation
  - Consider *Pneumocystis jirovecii* pneumonia prophylaxis
Management of Pneumonitis According to Severity

**Grade 1**
- Continue treatment
- Monitor the patient
- **•** Corticosteroids not needed

**Grade 2**
- Discontinue treatment
- (possibility to restart when G 0-1)
- **•** Oral corticosteroids (prednisone 1-2 mg/kg/day)
- **•** Consider empirical antibiotics or BAL
- **•** If no improvement after 48-72 hours, treat as Grade 3

**Grades 3-4**
- Permanently discontinue treatment
- **•** Hospitalize patient
- **•** Intravenous corticosteroids (methylprednisolone 1-2 mg/kg/day to 4 mg/mg/day)
- **•** Empiric antibiotics
- **•** Bronchoscopy with BAL +/- transbronchial biopsy
- **•** Immunosuppressive drugs if steroid-refractory (e.g. infliximab, mycophenolate, cyclophosphamide, IVIG)

**Adapted from Cherri et al. Cancers (Basel). 2021;13(5):1052.**
An ILD Management Program for T-DXd Clinical Studies Has Been Established

**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 & CBC (other blood tests could be considered as needed)
- Consider bronchoscopy & bronchoalveolar lavage if clinically indicated and feasible
- PFTs & pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD 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 from date of onset, maintain dose
  - If resolved in >28 days from date of onset, reduce dose one level
  - If Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, drug should be discontinued

- **Grades 2-4:** Permanently discontinue treatment
  - Refer to toxicity management guidelines for trastuzumab deruxtecan

CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; PFTs, pulmonary function tests; PK, pharmacokinetic; T-DXd, trastuzumab deruxtecan.

### Recommended Guidelines for the Management of Trastuzumab Deruxtecan-Induced ILD

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3/4</th>
</tr>
</thead>
</table>
| • 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** (eg, 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* |  
  • Promptly start **treatment with systemic steroids** (eg, at least 1 mg/kg/day prednisone or equivalent) **for at least 14 days or until clinical improvement**, followed by **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** (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, 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** (eg, 500-1,000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) **for at least 14 days** until clinical improvement, followed by gradual taper over at least 4 weeks  
  • Re-image as clinically indicated  
  • If still no improvement within 3-5 days:  
    - Re-consider additional work-up for alternative etiologies as described above  
    - Consider other immunosuppressants and/or treat per local practice |

*If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given.

ILD, interstitial lung disease.

Practical Application
Patient Case
Case Study: Patient Presentation and Treatment

- 56-year-old woman
- Presents with right breast mass and RUQ pain
- CT scan of chest, abdomen and pelvis: multiple liver lesions consistent with metastases, largest 3 cm
- Biopsy of breast mass: IDC, ER 0% PR 0%, HER2 3+
Case Study: Patient Presentation and Treatment

- Started on paclitaxel, trastuzumab, pertuzumab
- Liver lesions and breast lesion reduced by 80%
- Two years later, now has tumor progression in liver
- Starts T-DM1 with 50% tumor reduction in liver lesions
- 12 months later, had tumor progression in liver lesions
Case Study:  
Patient Presentation and Treatment

- Started on trastuzumab-deruxtecan
- Initial diarrhea controlled with loperamide
- Response in liver (50% reduction of liver lesions) within 9 weeks
- Presents with dry cough x 2 weeks
- CT chest shows ground glass infiltrate in upper lobe of left lung
Case Study Question

How would you manage this patients’ ILD?

a) Continue treatment with close monitoring
b) Continue treatment with close monitoring and initiate steroids
c) **Interrupt drug with close monitoring**
d) Interrupt drug and treat with systemic steroids
e) Permanently discontinue treatment

ILD, interstitial lung disease.
Identifying and Managing Cancer Therapy–Induced Interstitial Lung Disease and Pneumonitis