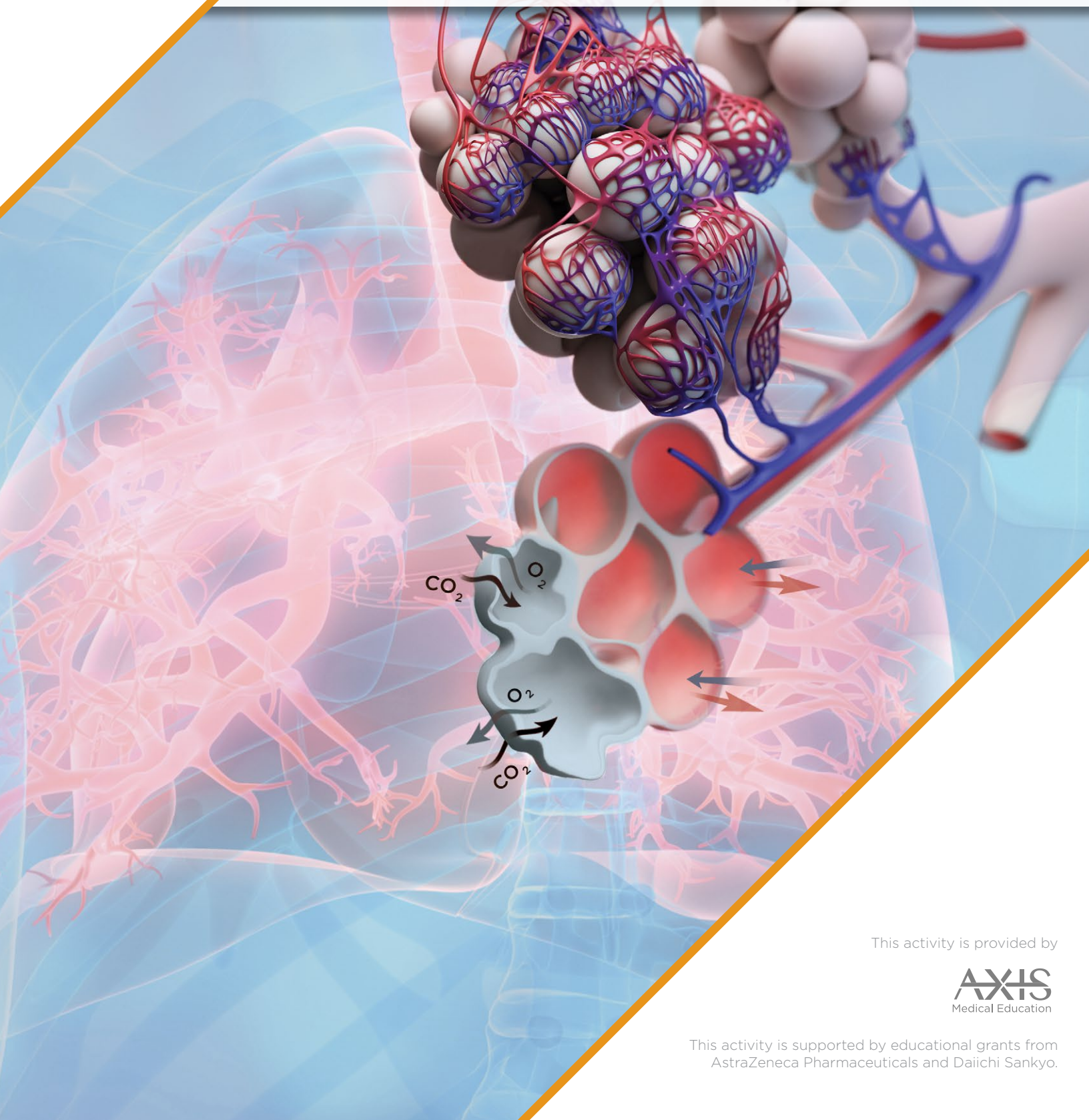


# Identifying and Managing Cancer Therapy–Induced Interstitial Lung Disease and Pneumonitis

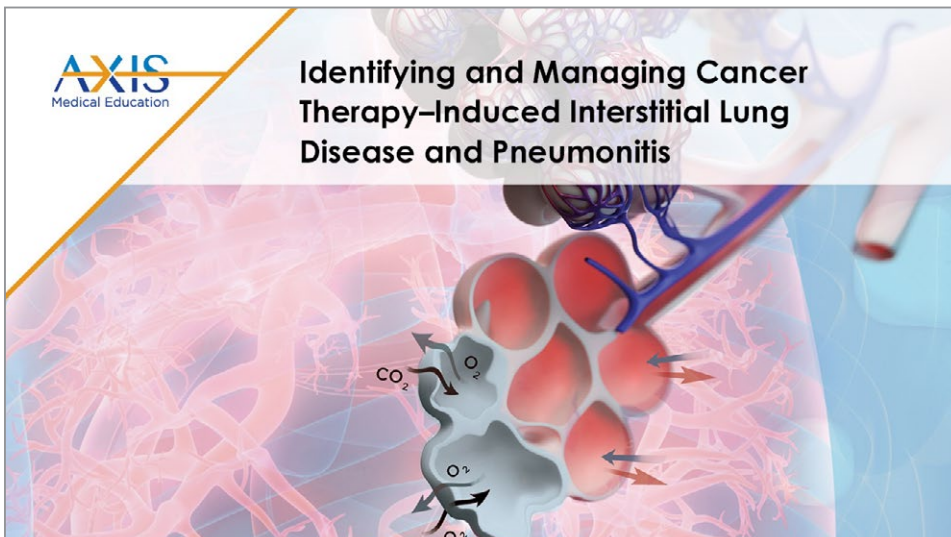
This transcript has been edited for style and clarity and includes all slides from the presentation.



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# Identifying and Managing Cancer Therapy-Induced Interstitial Lung Disease and Pneumonitis

Adam Brufsky, MD, PhD, Nina Thomas, MD



- **Adam Brufsky, MD, PhD:**  
Hello, and welcome to this educational activity entitled *Identifying and Managing Cancer Therapy-Induced Interstitial Lung Disease and Pneumonitis*.

## Introduction

### Adam Brufsky, MD, PhD

Professor of Medicine  
Associate Chief  
Co-Director, Comprehensive Breast Cancer Program  
University of Pittsburgh, UPMC Hillman Cancer Center  
Pittsburgh, Pennsylvania

### Nina A. Thomas, MD

Assistant Professor of Medicine  
Director, Thoracic Malignancy Pillar of Center for Lung and Breathing  
Division of Pulmonary Sciences & Critical Care Medicine  
University of Colorado, Denver

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- I am Dr. Adam Brufsky, a professor of medicine and associate chief of the Division of Hematology/Oncology, and co-director of the Comprehensive Breast Cancer Program at UPMC Hillman Cancer Center of the University of Pittsburgh in Pittsburgh, Pennsylvania.
- I am joined by Nina Thomas, who is assistant professor of medicine and director of the Thoracic Malignancy Pillar of the Center for Lung and Breathing Division of Pulmonary Sciences & Critical Care Medicine at the University of Colorado in Denver, Colorado.



## DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

## DISCLOSURE OF UNLABELED USE

This activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

- Here is a disclaimer and a disclosure indicating that we may be discussing off-label use of approved agents, or agents that are in development.

## Disclosure of Conflicts of Interest

### Adam Brufsky, MD, PhD

Adam Brufsky, MD, PhD, reported a financial interest/relationship or affiliation in the form of Consultant: Pfizer, Inc; Novartis Pharmaceuticals Corp; Lilly USA; AstraZeneca Pharmaceuticals LP; Seagen; and Daiichi Sankyo Co, Ltd.

### Nina Thomas, MD

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



- Here is our financial disclosure information.



## 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



- Upon completion of the activity, you should be better able to identify risk factors and symptoms of interstitial lung disease (ILD) or drug-induced ILD/pneumonitis in patients treated with anti-cancer therapies known to cause ILD and pneumonitis.

In addition, you will evaluate newer classes of agent that may contribute to medication-induced ILD/pneumonitis and recommendations for monitoring, detecting, and managing drug-induced ILD and pneumonitis.

You should be able to implement close monitoring for signs and symptoms of drug-induced ILD/pneumonitis to improve early detection and effective management of ILD.

And finally, you should be able to develop patient and caregiver education strategies for symptom monitoring of drug-induced ILD and pneumonitis.

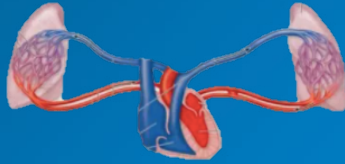


**Nina A. Thomas, MD**

- With that, we'll turn to Dr. Thomas to discuss some of the relevant aspects of ILD and pneumonitis. Dr. Thomas?

## Epidemiology

- 10%-20% of all patients receiving antineoplastic agents will develop some form of pulmonary toxicity
- High prevalence – lungs receive entire blood supply



Dimopoulou et al. *Ann Oncol* 2006;17(3):372-379.

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► **Nina A. Thomas, MD:** Thank you so much, Dr. Brufsky. Drug-induced pneumonitis and ILD are more commonly seen with newer agents now than we previously saw before, so some form of pulmonary toxicity will develop in approximately 10% to 20% of all patients receiving antineoplastic agents during their treatment or even after. And the reason for such high prevalence of drug-induced pneumonitis or pulmonary toxicity is because the lungs receive the entire blood supply, so the exposure is extremely high when patients get these antineoplastic agents.

## 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.  
Vahid and Marik. *Chest* 2008;133(2):526-538.

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► There are multiple different mechanisms of pathogenesis for drug-induced pulmonary toxicity that result in multiple different presentations, and that's what makes it so highly variable. One example of pathogenesis includes direct injury of the alveolar capillary endothelium, which leads to a release of cytokines and recruitment of the inflammatory cells into the lung. Some agents directly signal systemic release of cytokines, like gemcitabine, that result in

endothelial dysfunction, capillary leak, and noncardiogenic pulmonary edema. There are some agents that induce cell-mediated injury, including lymphocyte and macrophage activation.

There's evidence of oxidative injury from free radicals, which we see often with bleomycin—which is an agent that we commonly use to study things like idiopathic pulmonary fibrosis and other ILD; as well as dysregulation of the immune

system and T-cell activation, which we see often with immune checkpoint inhibitors.

Agents that act on EGFR receptors can affect the lungs because there are EGFR receptors on type 2 pneumocytes which actually can result in inhibition of alveolar wall repair. We don't know all of the mechanisms of the pathogenesis that is clearly seen in radiation recall pneumonitis.

## 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

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► Because of the multiple different mechanisms of action for drug-induced pneumonitis, we have a variety of presentations of how it can present. These are just some of the ways that pulmonary toxicity can present with specific lung diagnoses. You can have acute lung injury with diffuse alveolar damage, which is very similar to adult respiratory distress syndrome.

You can have a sort of capillary leak syndrome, and non-cardiogenic pulmonary edema. You can see interstitial pneumonitis, hypersensitivity pneumonitis, organizing pneumonia, eosinophilic pneumonia, diffuse alveolar hemorrhage, granulomatous pneumonitis, pulmonary fibrosis, and even pulmonary veno-occlusive disease, which presents with severe pulmonary hypertension.

All of these different presentations make it very difficult to diagnose this, especially with the variety of other things on the differential diagnosis when patients present.

## 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. Skeoch et al. *J Clin Med*. 2018;7(10):356.

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► We found risk factors that predispose patients to developing drug-induced pulmonary toxicity. Some of those include older age, male sex, any sort of preexisting lung disease; for example, ILD, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and bronchiectasis, along with a history of smoking or actively currently smoking.

Some pulmonary toxicities are dose-dependent for some drugs; for example, bleomycin. A history of thoracic radiation especially for lung cancer, because the radiation is directed specifically at the lung, or for radiation to places around the chest, for example, breast cancer. A history of renal dysfunction.

There are also some examples of genetic susceptibility to pulmonary toxicity, including CYP enzyme polymorphisms as well as HLA allelic variants. And then also if they are on combination chemotherapy, the risk is higher.

## 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



Shortness of breath



Extreme fatigue and weakness



Labored breathing which can be either fast or shallow



Unexplained weight loss



No appetite



Mild chest pain



Bleeding in the lungs

\*This information courtesy of Cedars-Sinai.  
ILD, interstitial lung disease.

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► So patients will often present for drug-induced pneumonitis with very vague symptoms. Some of the more common symptoms are cough, dyspnea, some low-grade fevers, hypoxemia, less commonly you'll see chills, sputum production, and weight loss. Most of the time the cough is nonproductive, but sometimes they will have some sputum production.

And on physical exam, a lot of times it can be a very normal physical exam, but you can sometimes hear things like bibasilar crackles, wheezing, rales, and occasionally a morbilliform rash if they have a hypersensitivity reaction.

## Presentation

### 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

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## 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

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▶ The timing for a presentation for pulmonary toxicity from antineoplastic agents is highly variable, which makes it very difficult to diagnose. At the very least, the onset should happen after initiation of the drug, but when after initiation is somewhat variable. It can present within weeks to months of initiating therapy, it can present with the first cycle or any subsequent treatment courses, and for some agents you can have delayed pneumonitis or fibrosis even after the agent has been discontinued. And we see that sometimes with agents like bleomycin, nitrosoureas, and 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

**Key to Diagnosis and Treatment of ILD/Pneumonitis is Early Recognition of Signs and Symptoms**

CBC, complete blood cell; CT, computed tomography; ILD, interstitial lung disease.  
Enhertu™ (trastuzumab deruxtecan) [prescribing information]. April 2021. <https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/enhertu-product-monograph-en.pdf>.  
Modi et al. *N Engl J Med*. 2020;382(7):610-621.

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▶ The diagnosis of acute pneumonitis, or pulmonary toxicity, or ILD from an antineoplastic agent is very difficult. The diagnosis is usually a diagnosis of exclusion with a highly variable presentation. There's a large differential diagnosis when they present, including opportunistic infections, metastatic disease to the lungs, lymphangitic spread of cancer in the lungs, diffuse alveolar hemorrhage which can also be a presentation of pulmonary toxicity but can be totally unrelated, cardiogenic pulmonary edema.

Some of the tools that we use to help with diagnosis are a high-resolution computed tomography (CT), consultation with your local pulmonologist. You can get blood cultures and a complete blood cell count, which can sometimes be helpful if there's an underlying infection. And with your consultant pulmonologist you can discuss bronchoscopy as an adjuvant diagnostic test, as well as an arterial blood gas if it's clinically indicated to evaluate for hypoxemia, especially when they are clinically sick enough to be in the hospital.



## 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.

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► I think one of the most important tools for evaluating for the diagnosis of pulmonary toxicity is high-resolution CT. It's the imaging modality of choice, and unfortunately the findings can be somewhat nonspecific and variable because of all the different ways that it can present, but at least with the CT there are certain patterns that we sometimes look for to help identify pulmonary toxicity. Some of those patterns are things like ground-glass opacities with or without some consolidation, you can see reticular changes or septal thickening,

centrilobular nodules; which we see frequently with hypersensitivity pneumonitis, even pulmonary fibrosis; so, for example, with bleomycin you might see lung volume loss, traction bronchiectasis, and honeycombing.

The distribution is usually bilateral, basilar predominant, and very peripheral, and it's usually very diffuse, so affecting multiple lobes. There are some exceptions to that; for example, with recall radiation pneumonitis you can get it locally in one lobe as opposed to the other lobes, and then sometimes just they present in one

lobe or in one part of the lung for unknown reasons. Sometimes you can have some hilar lymphadenopathy or mediastinal lymphadenopathy, as well as pleural effusions, and they can present with varying severities.

Any time you get a patient with ILD or pneumonitis that is drug-induced, regardless of how serious it is or how severe, you should always follow them with serial CTs and evaluations until resolution, including after you've discontinued the drug, and that's to make sure that there's no continued progression of the disease.

# Examples of Drug-induced Pulmonary Toxicity in Patients with Cancer

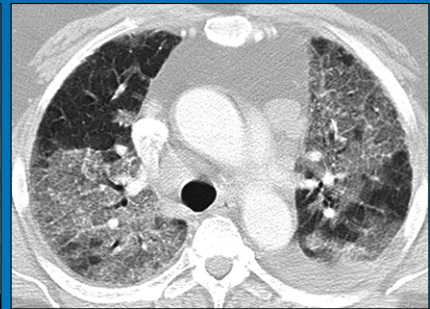
**Chemotherapy  
in Breast Cancer**



**mTOR Inhibitor  
in Renal Cell Carcinoma**



**EGFR Inhibitor  
in Lung Cancer**



mTOR, mechanistic target of rapamycin.  
Torrisi et al. *Radiology* 2011;258(1):41-56.

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► I just wanted to go over a few examples of what you might see with patients and the variability of patients' presentations, and their CT patterns that you might see. This is a patient who has breast cancer and was treated with paclitaxel and after only 2 doses, fevers as well as shortness of breath developed, and you see on the CT scan some bilateral subtle ground-glass opacities that's pretty diffuse in all lobes. Basically this patient was treated by discontinuing the drug and there was resolution.

This is another patient who had a history of metastatic renal cancer, came in with mild shortness of breath and some intermittent fevers during the first 3 months of therapy. This is the CT after 2 months, which shows consolidation in the right middle lobe. This patient underwent transbronchial biopsy with bronchoscopy, which showed interstitial inflammation and organizing pneumonia without any evidence of infection. The infiltrates actually improved and cleared with cessation of therapy and starting prednisone.

This is a patient with a little bit more severe disease. This is a patient who had lung cancer and was a former smoker, and you can see evidence of emphysema in the spared lung on the CT scan; he was treated with erlotinib. The CT scan shows pretty extensive ground-glass opacities in bilateral lungs, as well as some septal thickening and a pleural effusion. This was identified in the fourth week of treatment with erlotinib, and despite discontinuation of the drug and treatment with prednisone the patient, unfortunately, had disease progression and died.

## 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. Castro Chest 1996;109(4):939; Hnatluk Respiratory Care 2012;57(1):75-84.

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- ▶ One of the other tools that is sometimes brought up for evaluation for pulmonary toxicity are pulmonary function tests, and the use of pulmonary function tests (PFTs) for prediction of developing pulmonary toxicity is, unfortunately, not well studied or established.

If you were to get PFTs, the patterns you would see are occasionally they could be normal, or most commonly you might see a decline in the diffusion capacity or DLCO, as well as a restrictive pattern on PFTs; so decreased FEV1 and FVC with a normal ratio, as well as reduced lung volumes if you were to assess that with PFTs.

Unfortunately, PFTs don't really correlate with the worst prognosis and don't predict the risk of developing pulmonary toxicities, so there's very limited utility for serial PFTs, not to mention there are multiple other diseases and acute illnesses that can alter your PFTs.

# 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.  
Vahid and Marik. *Chest* 2008;133(2):528-538.

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▶ A tool that can be very useful, however, is bronchoscopy in consultation with a pulmonologist. There are a couple techniques that we can use to help with diagnosis, depending on the CT patterns that we see. You can use bronchoalveolar lavage to collect cultures as well as a blood cell count with differential to see if there are other etiologies that you can rule out; for example, infectious etiologies—so you can collect viral, bacterial, acid-fast bacteria, and fungal cultures. The blood cell count differential often shows lymphocytosis but can also show neutrophilia and eosinophilia.

You can also get cytology from a bronchoalveolar lavage (BAL) to evaluate for malignancy. Now, the diagnostic yield for cytology from just a BAL is not very good, however in the setting of concern for lymphangitic carcinomatosis can have a diagnostic yield anywhere up to 60%. So, it can sometimes be useful. You can also do serial aliquots of BALs to rule out diffuse alveolar hemorrhage.

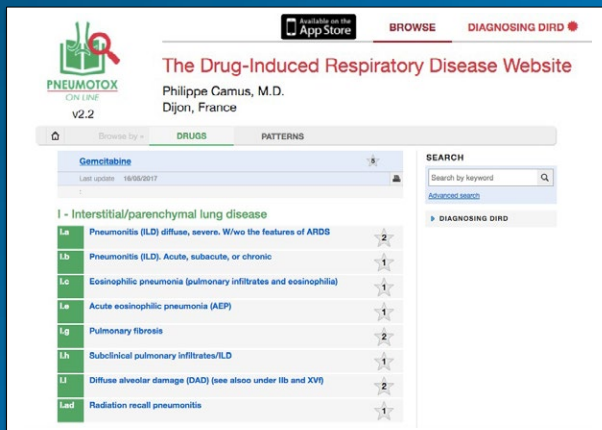
Transbronchial biopsy is another tool that we can use to help exclude things like lymphangitic carcinomatosis, vasculitis, or certain pneumonias; for example, certain fungal pneumonias as

well as organizing pneumonia. That being said, most of the time transbronchial biopsy does not necessarily rule out but can rule in other diseases.

There's significant risk that comes with transbronchial biopsies, including bleeding and pneumothorax, so it's definitely something that we respect and hold off on unless it's absolutely necessary. Often, too, the pathologic diagnosis that you get with transbronchial biopsy can be very nonspecific. For example, you can get granulomas that can be associated with infections, but also drug-induced pneumonitis, as well as other ILDs.



## Drug-Induced Respiratory Disease Website



► So, a common tool that we use very frequently in the pulmonary realm is pneumotox (pneumotox.com). This is a website that was developed by Philippe Camus and is free for everyone to use. You can search certain antineoplastic agents, and it will show you if it's associated with pulmonary toxicity, as well as what patterns that are most commonly seen. So, if you are worried about gemcitabine, you can search gemcitabine and see the common patterns that are associated with it.



Adam Brufsky, MD, PhD

► I will turn it back over to Dr. Brufsky to continue to discuss some of the more specific agents associated with pulmonary toxicity.

**Brufsky:** Thank you very much, Dr. Thomas. I'm going to go through a variety of agents that have a known ILD, and these agents are used in cancer therapy.

## 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.

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- ▶ There are antibody-drug conjugates, mTOR inhibitors, checkpoint inhibitors, tyrosine kinase inhibitors, and CDK 4/6 inhibitors, and they each have an individual differential type of pulmonary toxicity.

**AXIS**

## Antibody-Drug Conjugates and Interstitial Lung Disease

- ▶ We'll start with antibody-drug conjugates and ILD.

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

Antibody-Drug Conjugate	Tumor Type	Incidence of Lung Toxicity (any grade)
Trastuzumab emtansine	HER2+ breast cancer	9%
Trastuzumab deruxtecan	HER2+ breast cancer	9-17%
	Gastric cancer	10%
Enfortumab vedotin	Urothelial cancer	<1%
Sacituzumab govitecan	TNBC	Unknown

EMA, European Medicines Agency; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.  
Chen et al. *Cancers* (Basel). 2021;13(5):1052.  
Enhertu™ (trastuzumab deruxtecan) [prescribing information]. April 2021. <https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/enhertu-product-monograph-en.pdf>.

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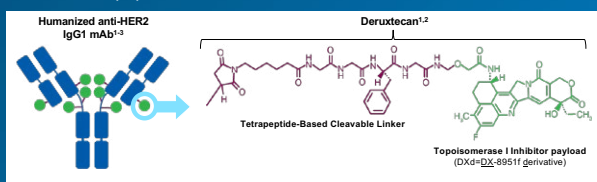
► This is a summary from the EMA and FDA that was published in *Cancers* and shows the various antibody-drug conjugates and their incidence of lung toxicity of any grade. Two are for HER2-positive metastatic breast cancer, trastuzumab emtansine and trastuzumab deruxtecan, and you can see here an incidence of trastuzumab emtansine of 9%, trastuzumab deruxtecan of about 9% to 14% in breast cancer, and about 10% in HER2-positive gastric cancer. Enfortumab vedotin in urothelial cancer has an incidence of lung toxicity of less than 1%, sacituzumab govitecan in triple-negative breast cancer is unknown.

This is interesting because it's not necessarily the payload of these antibody-drug conjugates, but actually a potential interaction with payload as well as the antigen. Most of the toxicity of these antibody-drug conjugates appears to be limited to HER family monoclonal antibodies as the antibody, and not necessarily the payload or potentially the linker.

## T-DXd Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 components<sup>1,2</sup>:

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



- 1 Payload MOA: topoisomerase I inhibitor<sup>1,2,a</sup>
- 2 High potency of payload<sup>1,2,a</sup>
- 3 High drug to antibody ratio  $\approx 8$
- 4 Payload with short systemic half-life<sup>1,2,a</sup>
- 5 Stable linker-payload<sup>1,2,a</sup>
- 6 Tumor-selective cleavable linker<sup>1,2,a</sup>
- 7 Membrane-permeable payload<sup>1,4,a</sup>

<sup>a</sup>The clinical relevance of these features is under investigation.

1. Nakada et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogilani et al. *Clin Cancer Res*. 2016;22(20):5097-5108.

3. Trail et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogilani et al. *Cancer Sci*. 2016;107(7):1039-1048.

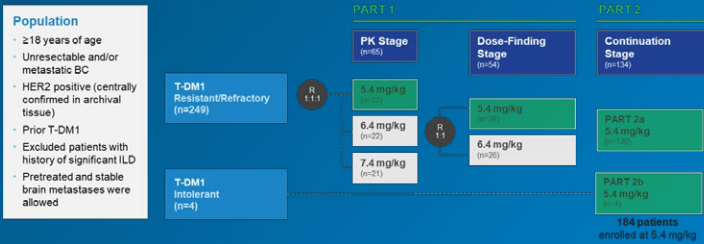
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MOA, mechanism of action; T-DXd, trastuzumab deruxtecan.

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► So trastuzumab deruxtecan, or T-DXd was designed with several key attributes. It's a humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab linked with a cleavable linker to tetrapeptide-cleavable linker that has a total topoisomerase inhibitor payload, and it has 8:1 antibody payload to antibody ratio and has a cleavable linker that allows the payload to be cleaved in the extracellular space as well as inside of the cancer cell.

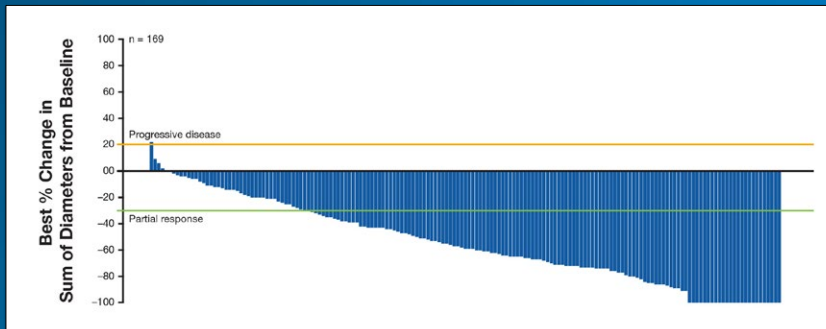
## DESTINY-Breast01: Study Design

An Open-Label Multicenter Phase 2 Study of T-DXd<sup>1,2</sup>



Several trials have been performed and published in major journals. This is the DESTINY-01 breast study where women with unresectable or metastatic breast cancer that already progressed on several regimens, including trastuzumab emtansine, and they were treated initially with a pharmacokinetic dose-finding stage and then a continuation stage, and 184 patients were enrolled at a dose of 5.4 mg/kg.

## DESTINY-Breast01: Best Percent Change From Baseline in Target Lesions



This was fairly a dramatic response, fully 96% to 97% of the patients had either stable disease or a response to this therapy, with a median of 6 regimens.

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. Modi et al. *N Engl J Med*. 2020; 382(7):610-621; Modi et al. SABCS 2020 Virtual. Poster Spotlight PD3-06.

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

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

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

<sup>a</sup>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. Saura et al. *Ann Oncol*. 2021;32(5):S485-S486.

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► Now, the interesting thing about this trial is that initially ILD was seen very early when the trial was started in Japan, and the initial report in August 2019 had 4 grade 5 episodes of interstitial lung disease for a total of 13.6 of all grades. This was updated and an additional fatal toxicity grade 5 was seen, making it 5 of 184 patients, or 2.7% of patients had interstitial lung disease, not really unstable approximately 10 months in later March 2021 at the final analysis.

So most of the ILD in this phase 2 trial appeared to occur within the first year of therapy, and the total percentage of adverse events appeared to remain stable across all three endpoints of the trial, and this was independently adjudicated with a group of oncologists and pulmonologists.

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

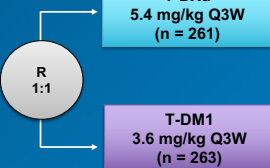
An open-label, multicenter study (NCT03529110)

### Patients

- Unresectable or metastatic HER2-positive<sup>a</sup> breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting<sup>b</sup>
- 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)

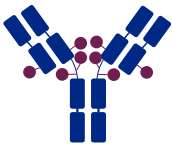
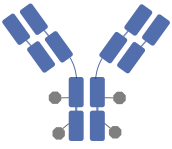
**Key secondary endpoint, OS:** boundary for efficacy:  $P < 0.000265$  (based on 86 events)

BICR, blinded independent central review; DOR, duration of response; IDMC, Independent Data Monitoring Committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan. <sup>a</sup>HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. <sup>b</sup>Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane. Cortes et al. *Ann Oncol*. 2021;32 (suppl\_5):S1283-S1346.

**AXIS**  
Medical Education

► Now, this trial was recently presented at the ESMO meeting, and this was again a trial in a second line. Patients had progressed on standard first-line therapy for HER2-positive metastatic breast cancer and were randomized to T-DXd or trastuzumab deruxtecan versus T-DM1 or trastuzumab- emtansine.

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

T-DXd <sup>1</sup>	T-DXd <sup>1-4,a</sup>	ADC Attributes	T-DM1 <sup>3-5</sup>	T-DM1 <sup>5</sup>
	Topoisomerase I inhibitor	Payload MoA	Anti-microtubule	
	~8:1	Drug-to-antibody ratio	~3.5:1	
	Yes	Tumor-selective cleavable linker?	No	
	Yes	Evidence of bystander anti-tumor effect?	No	

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

<sup>a</sup>The clinical relevance of these features is under investigation.

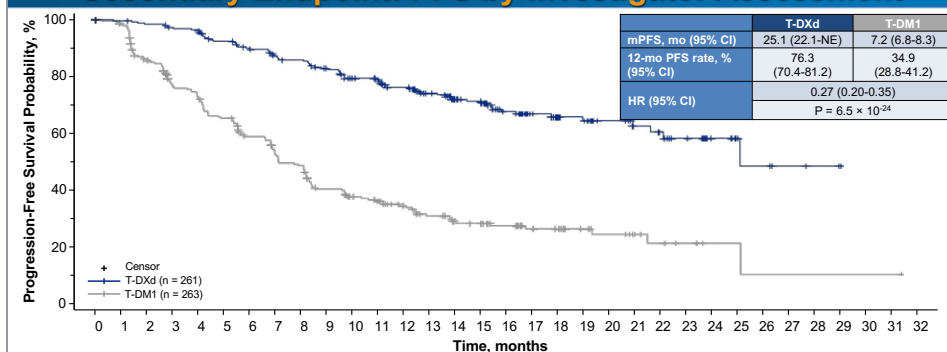
1. Nakada et al. *Chem Pharm Bull (Tokyo)*. 2019;67:172-185. 2. Ogilanti et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trail et al. *Pharmacol Ther*. 2016;161:126-42.

4. Ogilanti et al. *Cancer Sci*. 2016;107:1039-46. 5. LoRusso et al. *Clin Cancer Res*. 2011;17:9437-47.

**AXIS**  
Medical Education

► The differences are shown here where T-DXd had an 8:1 antibody-to-drug ratio where T-DM1 had a 3.5:1 antibody-to-drug ratio. But T-DXd had a cleavable linker and these potential bystander effects, so the thought was that it was a better ADC than T-DM1, and in fact that was borne out in this randomized trial.

## DESTINY-Breast03 Secondary Endpoint: PFS by Investigator Assessment



Patients Still at Risk:

T-DXd (261) 261 256 252 247 244 230 221 209 205 195 179 176 158 140 120 113 85 64 53 48 37 31 27 20 11 7 5 3 2 0  
T-DM1 (263) 263 253 216 185 175 156 136 119 110 88 78 72 61 51 43 39 34 25 23 16 13 9 7 5 2 2 1 1 1 1 1 0

PFS, progression-free survival.

Cortes et al. *Annals of Oncology* (2021) 32 (suppl\_5): S1283-S1346.

**AXIS**  
Medical Education

► The progression-free survival in second-line therapy was 25.1 months versus 7.2 months from T-DM1, and this likely will now become the standard second-line therapy for HER2-positive metastatic breast cancer.

## DESTINY-Breast03: Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis <sup>a</sup> , n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (N = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (N = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

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

↓ LVEF, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (N = 257)	1 (0.4) <sup>b</sup>	6 (2.3) <sup>c</sup>	0	0	0	7 (2.7)
T-DM1 (N = 261)	0	1 (0.4) <sup>c</sup>	0	0	0	1 (0.4)

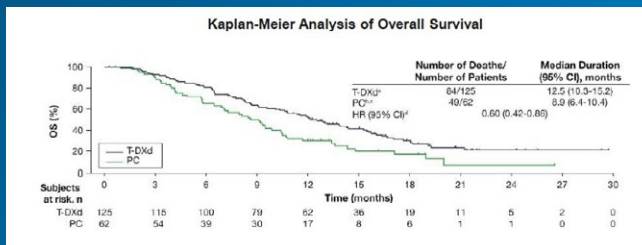
In the T-DXd arm, all LVEF adverse events reported were asymptomatic and no cases of cardiac failure occurred

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.  
 Cortes et al. *Ann Oncol*. 2021;32 (suppl. 5): S1293-S1346.

**AXIS**  
Medical Education

▶ Looking at the adverse events, the ILD/pneumonitis rates in this trial—and by this point we had already had the phase 2 trial, so there was a lot of awareness of how to manage this and recognize this early, as Dr. Thomas mentioned earlier. What you can see is that the all-grade incidence was 10.5%, and there were only 2 cases of grade 3 pneumonitis and 7% grade 2, which essentially, as we're going to find out, are CT abnormalities with symptoms, whereas T-DM1 had a much lower incidence, only 5 of 261 patients. And there was no grade 4 or 5 adjudicated ILD or pneumonitis in this trial.

## 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

OS, overall survival; PC, Physician's choice; T-DXd, trastuzumab deruxtecan.  
 Shitara et al. *N Engl J Med*. 2020;382:2419-2430; Yamaguchi et al. *J Clin Oncol*. 2021;39(15):4048.

**AXIS**  
Medical Education

▶ There were other trials. Gastric cancer has a certain percentage of patients that had HER2-positive disease, and again this is a trial published in *The New England Journal of Medicine*, DESTINY-Gastric01, which was a T-DXd or trastuzumab deruxtecan versus a physician's choice of therapy.

The median overall survival in this trial was 12.5 months versus 8.9 months with physician's choice of therapy, for a hazard ratio of 0.6, and this likely will also become a standard of care for HER2-positive gastric cancer.

## 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

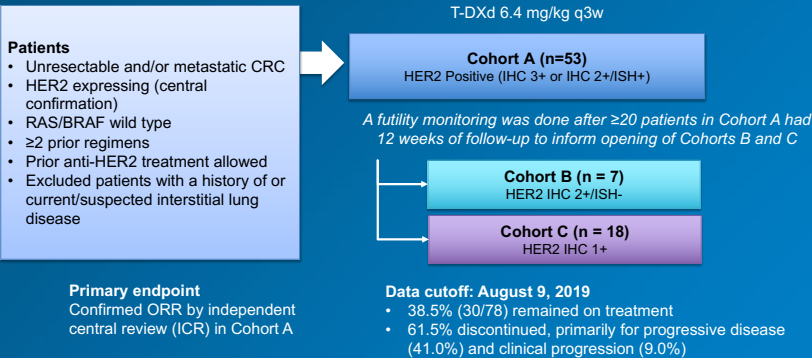
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.  
Shitara et al. *N Engl J Med*. 2020;382:2419–2430.

**AXIS**  
Medical Education

► In this trial, 9.6% had a treatment-related ILD/pneumonitis and the median time to onset was about a little under 3 months. Most were grade 1, there were a few that were grade 3 or 4, there were no grade 5 events. What's nice is that the majority—8 of 12—of these cases had resolved or were resolving at the time of analysis, with median duration or resolution of that a little under 2 months. Three had not resolved, and 1 was unknown. Obviously, because there was not an antibody-drug conjugate used, no cases of ILD occurred in the physician's choice arm.

## DESTINY-CRC01: Study Design

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



IHC, immunohistochemistry; ISH, in-situ hybridization; HER2, human epidermal growth factor receptor 2; ORR, objective response rate.  
Siena et al. *J Clin Oncol*. 2020;38(15):4000–4000; Siena et al. *Lancet Oncol*. 2021;22(6):779–789.

**AXIS**  
Medical Education

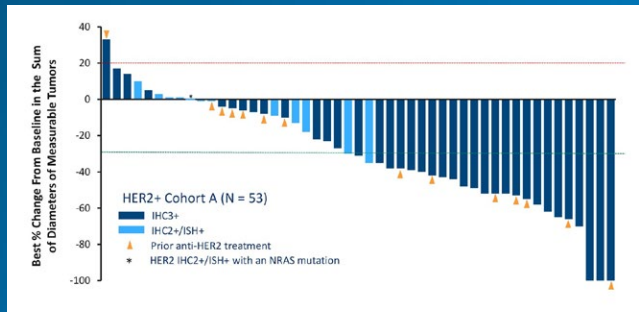
► DESTINY-CRC01 looked at unresectable or metastatic colorectal cancer that was HER2-expressing; again, that's about probably 10% of all colorectal cancer. The *RAS* and *BRAF* were wild type, it was a median of 2 prior regimens, and again this trial excluded patients with a history of current or suspected ILD. The primary endpoint was confirmed overall response rate.

The drug was actually given at a slightly higher dose, 6.4 mg/kg every 3 weeks. There was an initial cohort where futility monitoring was done, and if greater than 20 patients had a pre-adjudicated response rate, two further cohorts were treated, one with HER2-positive disease that was IHC 2-plus as opposed to IHC 3-plus or fluorescence in situ hybridization-positive, and cohort C was actually IHC 1-plus in this trial.



## 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.  
Siena et al. *J Clin Oncol*. 2020;38(15):4000-4000; Siena et al. *Lancet Oncol*. 2021;22(6):779-789.

AXIS  
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- ▶ And like the other trials of trastuzumab deruxtecan in colon cancer, it was a fairly dramatic response as well as stable disease in this trial.

Interestingly enough, a few patients with IHC 3-plus disease or IHC 2-plus actually responded as well.

## 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)

### Adjudicated Drug-Related ILD

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

AEs, adverse events; ILD, interstitial lung disease.  
Siena et al. *Lancet Oncol*. 2021;22(6):779-789.

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- ▶ The ILD in this trial again adjudicated. The median time to onset was about 2 months. All patients received corticosteroids. Four of the patients with grade 2 recovered, 1 patient with grade 3 did not recover and was actually felt to have died because of disease progression.

The median onset to the initiation of steroids in this trial when ILD was recognized was 3.5 days, and the 3 fatal cases, of the 86 patients, or 3.5%, the median time to onset was anywhere from 9 to 120 days with median of 22 days, and death occurred about 1 to 3 weeks after diagnosis.

And again, it's not surprising, I think, that the incidence of grade 5 pneumonitis was a little bit higher, mainly I think because of the dose of the drug, and perhaps at the time this was not as recognized a side effect of trastuzumab deruxtecan in colorectal cancer.

## 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

### Cohort 1 (n = 42)

HER2 expressing (IHC 3+ or IHC 2)

### Cohort 2 (n = 42)

HER2 mutated

T-DXd 6.4 mg/kg q3w

### Primary endpoint

Confirmed ORR  
by independent central review

### 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.  
Smit et al. *J Clin Oncol*. 2020;38(15):9504-9504; Li et al. *N Engl J Med*. 2021 Sept 16; doi:10.1056/NEJMoa2112431; *Ann Oncol*. 2021;32(suppl\_5): S1283-S1346.

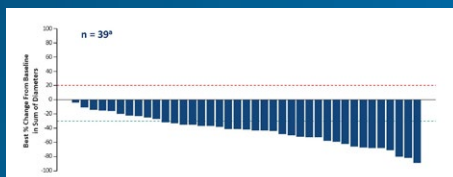
AXIS  
Medical Education

- There was also a trial of lung cancer published in *The New England Journal of Medicine*. These were patients with unresectable or metastatic nonsquamous non-small cell lung cancer that was refractory to standard treatment, with a HER2-expressing or HER2-activating mutation, with an endpoint of overall response rate.

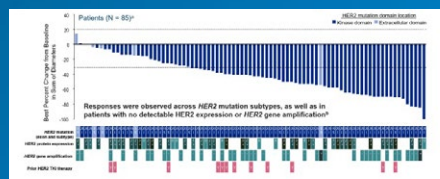
Again there were two cohorts, one that was HER2-mutated and not amplified, and one that was HER2-expressing either IHC 3-plus or IHC 2-plus. And in this particular trial, just like the others, in this trial of 85 patients actually updated at ESMO 2021.

## DESTINY-Lung01: Best Change in Tumor Size

### HER2-Mutated NSCLC Best Change in Tumor Size



### ESMO 2021: Best Percentage Change of Tumor Size from Baseline



HER2, human epidermal growth factor receptor 2; ESMO, European Society of Medical Oncology; NSCLC, non-small cell lung cancer.  
Li et al. *N Engl J Med*. 2021 Sept 16; doi:10.1056/NEJMoa2112431; *Ann Oncol*. 2021;32(suppl\_5): S1283-S1346.

AXIS  
Medical Education

- Most patients, like the other therapies, responded quite nicely. Some had actually had prior therapy with HER2 tyrosine kinase inhibitors, and either had HER2 protein expression or amplification, or a HER2 mutation. Just about everybody responded to this therapy.

## 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  $\geq 1$  dose of glucocorticoids
- At time of data cutoff, 54% (13/24) of investigator-reported cases had fully resolved

### Adjudicated Drug-Related ILD

	n (%)
Grade 1	3 (3.3)
Grade 2	15 (16.5)
Grade 3	4 (4.4)
Grade 4	0
Grade 5	2 (2.2)
Any Grade/Total	24 (26.4)

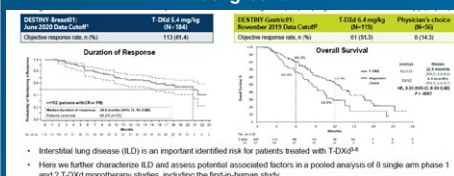
AEs, adverse events; ILD, interstitial lung disease.  
Li et al. *N Engl J Med*. 2021 Sept 18; doi:10.1056/NEJMoa2112431; *Ann Oncol*. 2021;32(suppl\_5): S1283-S1346.

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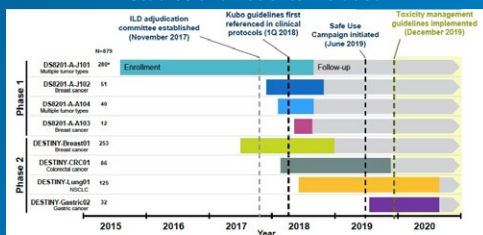
- Looking at the ILD, because this was also a higher dose, the median time to onset in this trial was 141 days with a duration of 43 days, the vast majority being low grade, and the vast majority, 21 of 24 patients, received at least 1 dose of glucocorticoids – 54% had resolved at the time of the report, and again there were 2 incidences of grade 5 or fatal interstitial lung disease in this analysis.

## Pooled Analysis: Drug-related ILD in 8 Single-Arm Trastuzumab Deruxtecan Studies Across Various Tumor Types

### Background



### Studies and Patients Included



\* Only patients who received T-DXd 5.4, 6.4, 7.4, or 8.4 mg/kg are included. All studies listed here are active but no longer recruiting, except for DESTINY-CRC01, which was completed in September 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 grey is follow-up.

ILD, interstitial lung disease.  
Powell et al. *Cancer Res*. 2021;81(13):CT167.

**AXIS**  
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- Looking at a pooled analysis presented at AACR of single-arm trastuzumab deruxtecan studies across the various tumor types, what you can see is it's an important identified risk factor in patients treated with T-DXd. And in this trial, again they looked at the timing. The guidance was initiated in the first quarter of 2018. There was a safe use campaign initiated that looked to see exactly what happened over time.

# 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 SpO<sub>2</sub> < 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

Factors included in the model were: age group, sex, tumor type, ECOG Performance Status, lung cancer or lung metastases/lymphangitic carcinomatosis at baseline, prior chest/lung radiotherapy, lung comorbidities, baseline renal function, number of prior regimens category, baseline white blood cell count ( $\times 10^9/L$ ), baseline albumin (g/L), time since initial disease diagnosis (year) category, time since the end date of last anticancer therapy to first infusion of T-DXd (months) category, dose (mg/kg) category and baseline SpO<sub>2</sub> (%) category. ILD, interstitial lung disease; SpO<sub>2</sub>, oxygen saturation pulse oximetry. Adapted from Powell et al. *Cancer Res.* 2021;81(13):CT167.

**AXIS**  
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► And they identified several factors that were potentially associated with ILD based on a multivariate Cox regression model and they were shown here. The patients were treated in Japan versus non-Japan, suggesting potentially there were some pharmacogenomic aspects to ILD; patients receiving a higher dose versus a standard 5.4 mg/kg appeared to be patients that were more prone to ILD; patients who had a baseline O<sub>2</sub> saturation of less than 95%; moderate or severe renal impairment at baseline versus no impairment.

The presence of lung comorbidities including asthma, chronic obstructive pulmonary disease, prior ILD, pulmonary fibrosis, emphysema, or radiation pneumonitis appeared to be associated with ILD, and the time since initial diagnosis. Patients who had a longer disease course before receiving the T-DXd appeared to have a slightly higher incidence of ILD.

When accounting for other factors, baseline lung cancer or lymphangitic carcinomatosis and/or prior chest radiotherapy was not

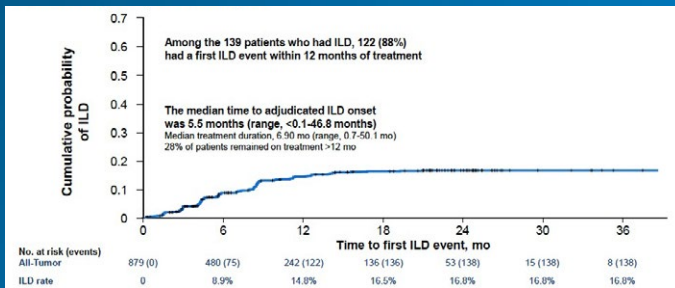
associated with ILD.

At the end of the day, given that this was a fairly heterogeneous analysis the identified factors of interest remain to be confirmed, and I think future data in larger, more homogeneous populations are necessary to confirm these factors that are associated with ILD.



## Pooled Analysis: Time to First ILD Event

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



Treatment discontinuations due to reasons other than ILD were included as competing event.  
ILD, interstitial lung disease.  
Powell et al. Cancer Res. 2021;81(13):CT167.

**AXIS**  
Medical Education

► The time to the first ILD event in this analysis is shown here. The median time appeared to be 5.5 months, and most of the ILD events occurred within the first 12 months of treatment. This gives us a little bit of an idea of what to expect, that generally within the first 5 to 6 months, and really within the first 12 months, most of the events should be seen, and if you make it through that 12-month period—and there probably is still a lot of censoring in this study—there still could be some events that occur after 12 months, but it appears that after about 12 months most of the ILD will occur in this.

## Pooled Analysis: Drug-related ILD

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

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

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

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

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

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

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

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

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

ILD, interstitial lung disease.  
Adapted from Powell et al. Cancer Res. 2021;81(13):CT167.

**AXIS**  
Medical Education

► Again, looking at the drug-related ILD by tumor type and grade, I think that again the overall grade 5 ILD in all patients, about 2.4%, and again the majority, other than those 21 fatal cases out of 879, the vast majority appeared to be grade 1 and grade 2, and there didn't seem to be any really preferential difference depending on the tumor type at least initially.

The other important thing shown in this table is that once the guidelines were implemented, the incidence at least of grade 5 ILD appeared to go down, and in 2020 there were only 2 cases out of 160 patients analyzed. And the vast majority of patients, whether they had grade 2 to 4 or grade 5, received corticosteroids as part of the therapy to try to ameliorate the 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. Powell et al. *Cancer Res*. 2021;81(13):CT167. Shitara et al. *N Engl J Med*. 2020;382:2419-2430; Tsurutani et al. *Cancer Discov*. 2020;10(5):688-701.

**AXIS**  
Medical Education

► There's obviously, as I said before, significant antitumor activity, the majority of independently adjudicated ILD were low grade, the risk may decrease after about 12 months. Optimal steroid management was not really observed, the big problem was delay in detection of the interstitial lung disease and under-dosing of steroids.

New toxicity guidelines have been implemented which suggest a lower rate of high-grade ILD events after implementation of the guidelines, and I think that potential risk factors include low O2 sat, lung comorbidities, and renal insufficiency.

This supports a beneficial benefit/risk profile of T-DXd in advanced cancers, and that's really important because these drugs seem to work very well, but early recognition, early discontinuation of drug, and institution of relatively high doses of steroids early adjudicates some of the more severe grades of interstitial lung disease.

# 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. Adapted from Modi et al. *N Engl J Med.* 2020;382(7):610-621.

**AXIS**  
Medical Education

- ▶ This shows you the ILD management program for T-DXd. If you suspect ILD, which is basically developing radiographic changes and/or acute onset of pulmonary symptoms such as dyspnea or cough or fever, I tell this to all my patients who are on trastuzumab deruxtecan that any new shortness of breath, any cough, any fever, they need to contact us immediately.

If we're looking at a CT scan, any kind of ground-glass opacities, that needs to be evaluated and not simply

blown off as background noise that we often before really recognition of ILD used to do. The evaluation should really be a high-resolution CT, a pulmonologist consultation where available, blood cultures and complete blood cell count. We would consider a bronchoscopy in some patients, as Dr. Thomas said, to try to rule out other causes. I think again pulmonary function test, pulse ox, and rarely arterial blood gases. I think that generally that's what we do. We should follow this regardless of severity or

seriousness should be followed until resolution, including after drug discontinuation.

And then finally, a grade 1 you interrupt the dose, and if it resolves within 28 days or less you can maintain the dose. If it takes greater than 21 days you reduce one dose level. If it has not resolved within 49 days, generally the drug should be discontinued, and if you have higher grades, grades 2 to 4, you should permanently discontinue treatment.

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

Grade 1	Grade 2	Grade 3/4
<ul style="list-style-type: none"> <li>Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry</li> <li>Consider follow-up imaging in 1-2 weeks (or as clinically indicated)</li> <li><b>Consider starting systemic steroids</b> (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by <b>gradual taper over at least 4 weeks</b></li> <li>If worsening of diagnostic observations despite initiation of corticosteroids, then follow grade 2 guidelines*</li> </ul>	<ul style="list-style-type: none"> <li>Promptly start <b>treatment with systemic steroids</b> (eg, at least 1 mg/kg/day prednisone or equivalent) <b>for at least 14 days</b> or until clinical improvement, followed by <b>gradual taper over at least 4 weeks</b></li> <li>Monitor symptoms closely</li> <li>Re-image as clinically indicated</li> <li>If worsening or no improvement in clinical or diagnostic observations in 5 days: <ul style="list-style-type: none"> <li><b>Consider increasing dose of steroids</b> (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)</li> <li>Re-consider additional work-up for alternative etiologies as described above</li> <li>Escalate care as clinically indicated</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Hospitalization required</li> <li>Promptly <b>initiate empiric high-dose methylprednisolone IV treatment</b> (eg, 500-1,000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) <b>for at least 14 days</b> until clinical improvement, followed by gradual taper over at least 4 weeks</li> <li>Re-image as clinically indicated</li> <li>If still no improvement within 3-5 days: <ul style="list-style-type: none"> <li>Re-consider additional work-up for alternative etiologies as described above</li> <li>Consider other immunosuppressants and/or treat per local practice</li> </ul> </li> </ul>

\*If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given.  
ILD, interstitial lung disease.  
Adapted from Modi et al. *N Engl J Med*. 2020;382(7):610-621.

AXIS  
Medical Education

► And these are the guidelines for therapeutic management. For grade 1, monitor closely and consider starting systemic steroids at 0.5 mg/kg/day until improvement followed by a taper over 2 weeks.

For grade 2, really you need to start steroids with at least 1 mg/kg/day for at least 14 days followed by a gradual taper, and if there's no improvement increase the dose of steroids to 2 mg/kg/day. I think at that point, a lot of us would obtain a pulmonary consult to try to determine if there are other etiologies.

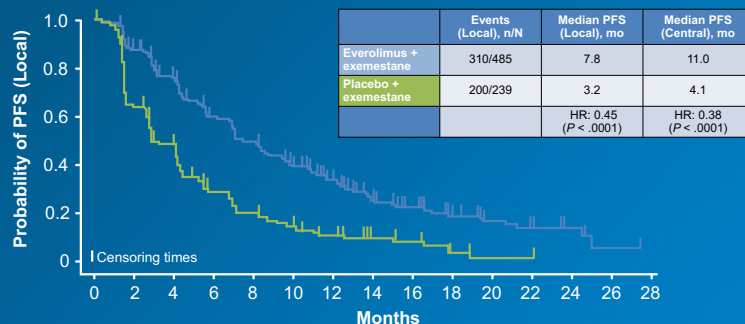
Finally, if it's grade 3 or 4, the hospitalization is required with empiric high-dose methylprednisolone at a fairly substantial dose for at least 14 days followed by a gradual taper. And again, if there's no improvement within 3 to 5 days, generally we'll reconsider additional workup for alternative etiologies.

► So that's generally trastuzumab deruxtecan for which we recognize the ILD upfront to try to figure out the risk/benefit ratio, but what about other drugs? Well, there are mTOR inhibitors in ILD.

AXIS

## mTOR Inhibitors and ILD

## BOLERO-2 Primary Endpoint: Final PFS Analysis With Everolimus + Exemestane in NSAI-Refractory Advanced BC



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. Yardley. *Adv Ther*. 2013;30:870.

**AXIS**  
Medical Education

► This is the BOLERO-2 trial, which is everolimus, an mTOR inhibitor with exemestane (aromatase inhibitor). We all tend to use this as second- or third-line therapy for hormone receptor-positive metastatic breast cancer because it essentially more than doubles the progression-free survival, as shown here, 4.1 months to 11 months, and so this is a successful therapy that's been used for a long time.

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

mTOR Inhibitor	Tumor Type	Incidence of Lung Toxicity (Any Grade)
Everolimus	Advanced HR+ breast cancer	12%-38%
	Advanced RCC	14%
	Advanced NET	12%
	Advanced pancreatic NET	17%
Temsirolimus	Advanced RCC	2%-22%

EMA, European Medicines Agency; FDA, US Food & Drug Administration; HR, hormone receptor; mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; RCC, renal cell carcinoma. Adapted from Cheri et al. *Cancers (Basel)*. 2021;13(5):1052.

**AXIS**  
Medical Education

► However, the incidence of pneumonitis with either everolimus or temsirolimus, which is used for renal cell carcinoma and even neuroendocrine tumors, is about 12% to 17% averaging across all of these trials. So, there is pneumonitis with this therapy.

## Proposed Clinical Management of mTOR Inhibitor-induced ILD

Conclusion	mTOR Inhibitor Treatment	Further Management
Airway disease	Continue mTOR inhibitor, watchful waiting	Start inhaled steroids (i.e., ciclesonide 320 mcg BID). Reduce dose every 2 weeks if symptoms allow
Suspected ILD	Continue mTOR inhibitor, watchful waiting	In case of quick deterioration of clinical condition: treat as ILD
ILD	Interrupt mTOR inhibitor until resolution of symptoms to CTCAE grade 1 ( $\geq 3$ weeks). Restart at reduced dose In case of life-threatening ILD: permanently discontinue mTOR inhibitor	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
Inconclusive	In case of grade 3 or 4 symptoms: interrupt mTOR inhibitor pending analysis of differential diagnosis	Analyze for other possible causes of symptoms

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.

**AXIS**  
Medical Education

► And the proposed clinical management is a little bit different than the ILD from antibody-drug conjugates. Generally, if there's airway disease or suspected ILD with minimum symptoms, I think people will continue the mTOR, I think we consider steroids, but if someone deteriorates fairly quickly the mTOR has to

be stopped until it resolves to a grade 1 or less, and a lot of people will start at a reduce dose.

Obviously, in a case of life-threatening ILD, grade 3 or 4, the mTOR inhibitor needs to be interrupted and potentially and probably discontinued. And if there is higher-grade, generally the therapy is

prednisolone reduced on a slow taper, and if there are other suspected etiologies such as *Pneumocystis jiroveci* pneumonia (PCP) or other bacterial potential etiologies in the differential, one should consider antimicrobial therapy while we're awaiting the results of diagnostic procedures. So, it's a little bit different.

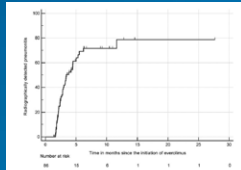


## Everolimus-related Pneumonitis in Breast Cancer

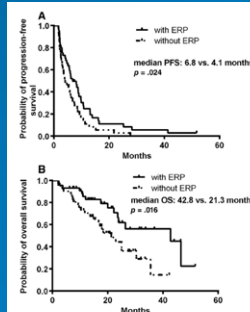
Radiology Assessment by CT Scan

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

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. Gong et al. *Oncologist* 2021;26:e580-e587.

AXIS  
Medical Education

- ▶ What's interesting and actually was published this year in the *Oncologist* in 2021, that everolimus-related pneumonitis in breast cancer actually was associated with a response. The cumulative probability of this happening, looking at Figure 1 of this particular paper, was about 80% if it's going to happen within the first 12 months, and the incidence of developing clinical symptoms was about 16.3%.

The interesting thing, though, is that if you had some everolimus-related pneumonitis, your survival actually was better, which is really kind of interesting. The median overall survival was 42 months if you had everolimus-induced pneumonitis versus 23.1 months, and I think people are trying to figure out how one relates to the other. I think it's an interesting observation.

AXIS

## Checkpoint Inhibitors and ILD

- ▶ But what about checkpoint inhibitors and ILD?

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

Immune Checkpoint Inhibitors	Tumor Type	Incidence of Lung Toxicity (Any Grade)
Nivolumab	Melanoma	1.3%-1.5%
	Squamous NSCLC	5%
	Non-squamous NSCLC	3%
	HNSCC	2.1%
	RCC	4%
Nivolumab + ipilimumab	Urothelial carcinoma	3%
	Melanoma	6.4%
	RCC	6.2%
Pembrolizumab	PD-L1+ HNSCC	6%
	HNSCC	4%
	NSCLC PD-L1 ≥50%	2.6%
	NSCLC PD-L1 ≥1%	5%
	Melanoma	1.8%-3.3%
	Urothelial carcinoma	4.1%
Pembrolizumab + chemotherapy	PD-L1+ urothelial carcinoma	2%
	NSCLC	4.4%-6.5%
Pembrolizumab + axitinib	PD-L1+ HNSCC	5%
Atezolizumab	RCC	2.8%
	Urothelial carcinoma	2%
Atezolizumab + nab-paclitaxel	NSCLC	1%
	TNBC	3.1%
Durvalumab	PD-L1 ≥1% NSCLC	12.6%
Durvalumab + chemotherapy	SCLC	3%
Avelumab	MCC	1%
Avelumab + axitinib	RCC	0.6%
Ipilimumab	Melanoma	2%

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. Adapted from Cherni et al. *Cancers (Basel)* 2021;13(5):1052.

**AXIS**  
Medical Education

Again, the incidence of pulmonary toxicity across all the known checkpoint inhibitors and all tumor types appears to be somewhat lower than that from everolimus, as well as that from trastuzumab deruxtecan. You can see here the incidence appears anywhere from 1.3% to about 5% across all of these agents. I think most of the agents, with the exception maybe of the combination of nivolumab and ipilimumab, appear to be relatively the same regardless of the agent, regardless of the combination whether chemotherapy or axitinib, durvalumab, avelumab, atezolizumab, nivolumab, or pembrolizumab. All appear to be about the same here. There was one with durvalumab that had about 12.6%, but that seems to be an outlier in these studies.

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

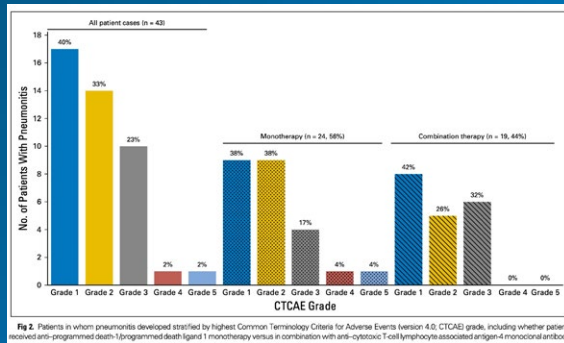
### Patients who received anti-PD-1/PD-L1 therapy

	MSKCC, No. (%)	MIA, No. (%)
No. of patients	578	337
Single agent v combination	441 (76)	275 (82)
Combination	137 (24)	62 (18)
PD-1 v PD-L1	405 (70)	337 (100)
PD-1	173 (30)	0
PD-L1	232 (40)	337 (100)
Primary cancer type		
Non-small-cell lung carcinoma	209	0
Metastatic melanoma	195	337
Renal cell carcinoma	24	0
Hematologic malignancy	35	0
Bladder carcinoma	30	0
Pancreatic carcinoma	18	0
Breast carcinoma	14	0
Head and neck squamous carcinoma	10	0
Sarcoma	7	0
Colorectal carcinoma	6	0
Gastroesophageal carcinoma	12	0
Ovarian carcinoma	7	0
Hepatocellular carcinoma	4	0
Prostate carcinoma	3	0
Anal carcinoma	2	0
Small-cell lung carcinoma	2	0
Pneumonitis		
No	551 (95)	321 (95)
Yes	27 (5)	16 (5)

### Demographic Characteristics and Treatment & Response Data for Patients With Pneumonitis

	No. (%)
Median age, years (range)	61 (26-88)
Smoking status	
Current/former	24 (88)
Never	3 (12)
Single agent v combination therapy	
Monotherapy	24 (88)
Combination	3 (12)
Combining lung medication	
Tyrosine kinase inhibitors	27 (100)
Anti-VEGF	4 (15)
Anti-EGFR	1 (4)
Anti-HER2	1 (4)
Anti-PD-1/PD-L1	1 (4)
Anti-CTLA-4	1 (4)
Anti-CD47	1 (4)
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## Pneumonitis in Patients Treated With Anti-PD-1/PD-L1 Therapy



► You can see when you look at all patients' cases, again the vast majority was grade 1 and grade 2, and it didn't really matter whether you had monotherapy or combination. I think some of the combination therapies, such as with the combination of ipilimumab or chemotherapy, if you're going to have pneumonitis, the incidence of grade 3 was a little bit higher with the anti-PD-1 or PD-L1 therapy.



## Tyrosine Kinase Inhibitors and ILD

► What about tyrosine kinase inhibitors and ILD?

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

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

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. Adapted from Chern et al. *Cancers (Basel)* 2021;13(5):1352.

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► Again, it's really not standard in non-small cell lung cancer, hepatocellular cancer, renal cell carcinoma, melanoma, really the tyrosine kinase inhibitors it's across. I think with sunitinib and pazopanib and imatinib it's fairly rare, and in the other ones it also is fairly rare, about 1% averaging across all the trials. Brigatinib appeared to be about 4.5% to 7%, that seems to be the highest, but short of that it really appears to be probably the less than 1% to about 1.5% to 2% across all the trials.



## CDK 4/6 Inhibitors and ILD

► Finally, CDK 4/6 inhibitors and ILD.

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

CDK 4/6 Inhibitor	Tumor Type	Incidence of Lung Toxicity (Any Grade)
Abemaciclib	HR+/HER2-Metastatic Breast Cancer	1-3%
Palbociclib		
Ribociclib		

EMA, European Medicines Agency; FDA, US Food & Drug Administration; HER2, human epidermal growth factor 2; HR, hormone receptor.

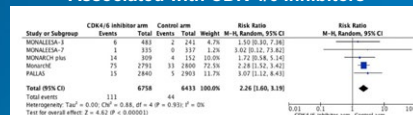
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- This has been now recently recognized as a side effect. The FDA and EMA did a post-marketing analysis and an analysis of all the trials of both abemaciclib, palbociclib, and ribociclib in hormone receptor-positive/HER2-negative metastatic breast cancer, and very similar to the other tyrosine kinases the CDK 4/6 inhibitors had an incidence of about 1% to 3%, and averages about 1.5% when you look across the trials.

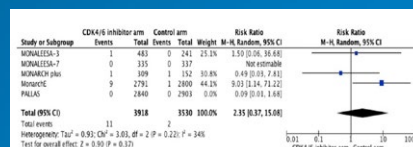
## Relative Risk for Pneumonitis or ILD Associated with CDK 4/6 Inhibitors: Meta-analysis of Phase 3 RCTs

	CDK 4/6 Inhibitor	Control
All grade ILD/pneumonitis	1.64%	0.68%
Grade 3/4	0.28%	0.06%

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



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



ILD, interstitial lung disease; RCTs, randomized controlled trials; RR, risk ratio.  
Jahan et al. J Clin Oncol. 2021;39:1072.

AXIS  
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- And, in fact, this is an analysis recently published showing across all of the trials that have been done, both in the metastatic and in the adjuvant setting—MonarchE and PALLAS are adjuvant uses of CDK 4/6 inhibitors—the incidence appears to be about 1.64% with a CDK4/6 versus about 0.68 with the control arms of the trial, which is roughly doubling, or a little more than doubling of the rate using the CDK 4/6. The incidence of grade 3 or 4 was gratifyingly fairly low, about 0.28% with the CDK 4/6 versus about 0.06% with the control in this pooled meta-analysis.

## 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

FDA, US Food & Drug Administration; HCP, healthcare professional; ILD, interstitial lung disease.  
<https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer>

**AXIS**  
Medical Education

► The FDA put out a warning about 2 years ago about severe lung inflammation with CDK 4/6 inhibitors. And I think again like with the antibody-drug conjugates and the other agents, if there's any worsening symptoms involving the lungs, like a new cough, shortness of breath, this has to really be evaluated fairly quickly. And again, patients should really be monitored for pulmonary symptoms indicative of interstitial lung disease and pneumonitis, and the symptoms are what we would expect, as Dr. Thomas talked about before. And CDK 4/6 inhibitor treatment should be interrupted, and if patients have severe, like say grade 3 or 4 ILD, the treatment really needs to be discontinued at that point.

**AXIS**

## Best Practice Recommendations for Monitoring, Identifying, and Managing Cancer Therapy Induced ILD/Pneumonitis: A Team-Based Approach

► At this point, we'll talk about best practice recommendations for monitoring, identifying, and managing cancer therapy-induced ILD/pneumonitis.



## Grading: DI-ILD and Pneumonitis

Grading of DI-ILD based on NCI-CTCAE	
Grade 1 (mild)	Asymptomatic, radiographic findings only
Grade 2 (moderate)	Symptomatic, not interfering with activities of daily living
Grade 3 (severe)	Symptomatic, interfering with activity of daily live or oxygen indicated
Grade 4 (life-threatening or disabling)	Life-threatening, or ventilator support required
Grade 5 (fatal)	Fatal

Pneumonitis Severity Classification According to NCI-CTCAE and ASCO Guidelines				
Guideline	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE Version 5.0	Asymptomatic • Clinical or diagnostic observations only • Intervention not indicated	Symptomatic • Medical intervention indicated • Limiting instrumental ADL	Severe symptoms • Limiting self-care ADL • Oxygen indicated	Life-threatening respiratory compromise • Urgent intervention indicated (tracheotomy or intubation)
ASCO Guidelines 2018	Asymptomatic • Confined to one lobe of the lung of <25% or lung parenchyma • Clinical or diagnostic observations only	Symptomatic • Involves ≥1 lobe of the lung, or 25%-50% of lung parenchyma • Medical intervention indicated • Limiting instrumental ADL	Severe symptoms • Hospitalization required • Involves all lung lobes or >50% of lung parenchyma • Limiting self-care ADL • Oxygen indicated	Life-threatening respiratory compromise • Urgent intervention indicated (intubation)

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.  
Adapted from Skeoch J Clin Med 2018; 7(10): 356 and Cherri et al. Cancers (Basel), 2021;13(5):1052.

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- These are the grades of medication-induced ILD. Mild is asymptomatic with radiographic findings only. Grade 2 is symptomatic but not interfering with activities of daily living. Grade 3 is interfering with activities and/or oxygen as indicated. Finally, grade 4 is life-threatening with or without the need for ventilator support. And grade 5 is fatal.

## 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

- ▶ Close and early monitoring techniques for cough, dyspnea, fever, and new or worsening respiratory symptoms. The key is to advise patients to contact their healthcare provider immediately, and to inform the patients of risks of severe, life-threatening, or fatal ILD.

Dr. Thomas, do you have any comment on this particular topic?

**Thomas:** I agree that it's very important to warn patients ahead of time to look for these symptoms, because they are the ones that are going to notice it first as well as their caregivers. It's an indication for workup, and can certainly be indications of other acute illnesses, too, that need to be further evaluated. This can be a little bit more difficult for patients, for example, with lung cancer because they may have underlying cough, dyspnea, and even fever that may worsen. So you need to be very careful noticing how subtle changes can actually be an indication of pneumonitis.

**Brufsky:** Good. How important is radiographic imaging; should we get a CT on everybody that comes in the door, Dr. Thomas?

**Thomas:** It depends on the severity of illness and their baseline. I think one big clinical indicator is if they're suddenly newly hypoxic or have an increase in their oxygen requirements, that's probably a pretty good indication to get radiographic imaging, and to go ahead and start with the CT, a chest radiograph is going to be very limited in giving you any information.

And then it's sort of on follow-up when you evaluate these patients. If there's very close follow-up, you can see if it's just the sniffles one day and then it's progressed into cough and dyspnea, then you might take that more seriously and get a CT at that point.

**Brufsky:** When do we involve a pulmonologist; should we involve a pulmonologist for all cases or just severe cases?

**Thomas:** I think it's tough because of the variability that these present with, and all the other things that are on the differential. If you have the benefit of a tumor board that's multidisciplinary, this can be very helpful, and you can often review cases with the radiologist or the pulmonologist that is this just straightforward pneumonitis or is there something else that we can worry about. And your radiologist and pulmonologist can give their feedback into, well, this certain infection can have a similar pattern, maybe we should do a bronchoscopy. The earlier that you get a pulmonologist and radiologist involved, the better.

For severe or very severe disease, a higher grade, more likely than not you'll already have a pulmonologist involved either as a consultant on the floor if they're hospitalized or even in the ICU. Early detection and early involvement of your consultants are pretty important.

## 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



► **Brufsky:** Great. The next question is when to do corticosteroid treatment. When would you use steroids in somebody with suspected ILD, Dr. Thomas?

**Thomas:** I think if they have grade 3 or 4, it's pretty much a no-brainer to use steroids and stop the agent. If they have grade 1, you can sometimes get away with just stopping the agent, but if the disease is progressing you might consider. And then grade 2 can sometimes be a gray area and depending on the age and pattern on the CT, you might consider steroids, and this is going to be different for each agent that we see.

Sometimes the pattern can be helpful to decide whether

it's going to be responsive to glucocorticoids. So, for example, eosinophilic pneumonia or organizing pneumonia tends to be much steroid-responsive. But it's also going to be difficult just that, for example, organizing pneumonia tends to take a longer taper of steroids because there's a high rate of recurrence for organizing pneumonia if you taper off the steroids too quickly.

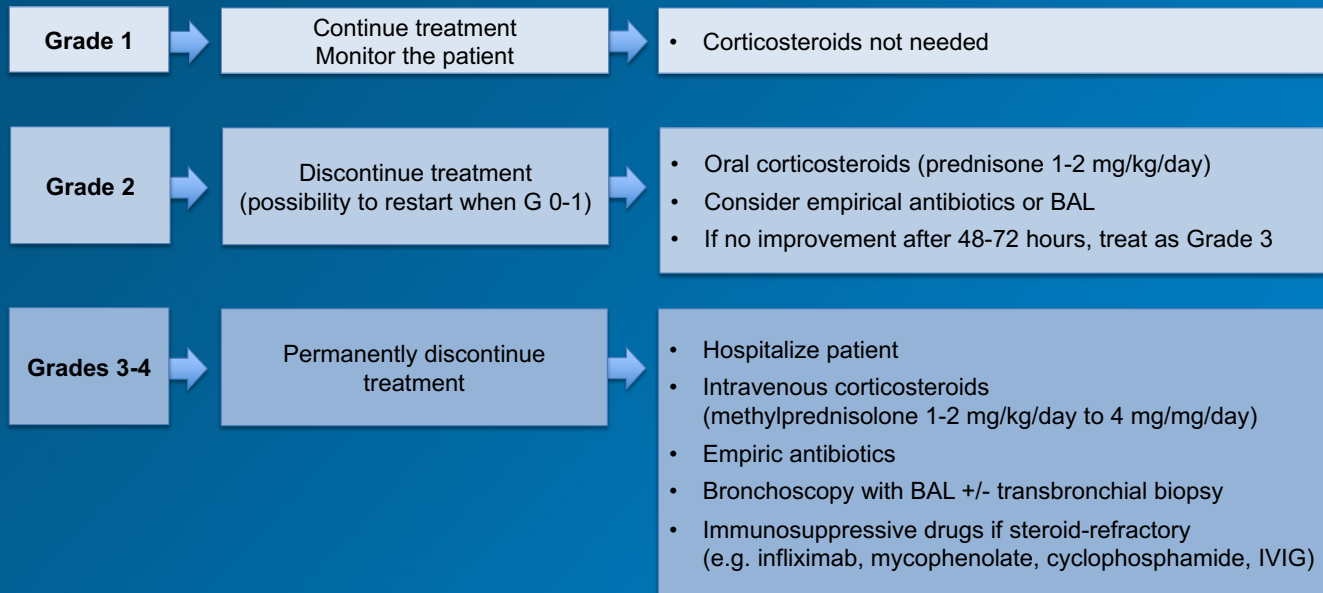
And then finally, I think if there's any sort of infectious symptoms, which if they have the regular symptoms of pulmonary toxicity that's almost identical to infectious etiologies. You might consider bronchoscopy if it's safe, or sometimes, like you alluded to before, just empiric antibiotics

to cover them while you are treating them with steroids.

**Brufsky:** What about if you're giving high-dose steroids, do you consider prophylaxis for PCP?

**Thomas:** Yeah, definitely. If you have high-dose steroids, and usually we provide prophylaxis for PCP if you're on prednisone greater than 20 mg for over 1 month, then you might consider PCP prophylaxis with either sulfamethoxazole and trimethoprim or dapsone, or whatever agent that you might choose or is appropriate for the patient. If it's just a pretty short course, for example, less than 14 days, and they're going to be on tapering doses that go under 20 mg, you may not necessarily need PCP prophylaxis.

# Management of Pneumonitis According to Severity



BAL, bronchoalveolar lavage.  
Adapted from Cherri et al. *Cancers (Basel)*. 2021;13(5):1052.

**AXIS**  
Medical Education

► **Brufsky:** We'll talk about an overview of recommended management protocols, and there's actually several. And I'll go through them, and I'll ask you, Dr. Thomas, what you think after I go through these.

The first one is pneumonitis actually from a publication

in 2021 in *Cancers*. Grade 1, you continue treatment and monitor the patient. Grade 2, you discontinue the treatment and possibly restart when the grade becomes 0 to 1, and this point you would start oral corticosteroids with possible empiric antibiotics. If there's no improvement after about 2 to

3 days, then I would treat it as grade 3.

For grade 3 and 4, you discontinue the treatment and hospitalize the patient for high-dose corticosteroids, potentially consider other options with a bronchoscopy or other potential agents.

# 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  $\leq 28$  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. Adapted from Modi et al. *N Engl J Med*. 2020;382(7):610-621.

**AXIS**  
Medical Education

► Now specifically, an ILD management program for T-DXd. Generally, if you have grade 1 you would interrupt the drug. Step 1 is you interrupt the drug and look for radiographic change. Step 2, you'd confirm that with a high-resolution CT, a pulmonary consultation, and again a potential bronchoscopy if other etiologies are suspected, and generally you have to follow until drug discontinuation and even beyond.

And the drug needs to be interrupted, that's the management. In grade 1, you interrupt until fully resolved, and if it resolves within 28 days you can reduce one dose level. However, if the ILD has not resolved within 49 days, the drug should be discontinued. And grade 2 to 4, you permanently discontinue treatment.

This is really interesting, because we have a lot of people with minimal

symptomatic disease and radiographic changes that rapidly go back to 0 or 1, and I think this is kind of a gray area; you're grade 1.5, you're not quite severely symptomatic. And I think a lot of us are really trying to figure out whether we should retreat patients with trastuzumab deruxtecan that have become minimally symptomatic, and I'll ask for your comments on that in a minute.

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

Grade 1	Grade 2	Grade 3/4
<ul style="list-style-type: none"> <li>Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry</li> <li>Consider follow-up imaging in 1-2 weeks (or as clinically indicated)</li> <li><b>Consider starting systemic steroids</b> (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by <b>gradual taper over at least 4 weeks</b></li> <li>If worsening of diagnostic observations despite initiation of corticosteroids, then follow grade 2 guidelines*</li> </ul>	<ul style="list-style-type: none"> <li>Promptly start <b>treatment with systemic steroids</b> (eg, at least 1 mg/kg/day prednisone or equivalent) <b>for at least 14 days</b> or until clinical improvement, followed by <b>gradual taper over at least 4 weeks</b></li> <li>Monitor symptoms closely</li> <li>Re-image as clinically indicated</li> <li>If worsening or no improvement in clinical or diagnostic observations in 5 days: <ul style="list-style-type: none"> <li><b>Consider increasing dose of steroids</b> (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)</li> <li>Re-consider additional work-up for alternative etiologies as described above</li> <li>Escalate care as clinically indicated</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Hospitalization required</li> <li>Promptly <b>initiate empiric high-dose methylprednisolone IV treatment</b> (eg, 500-1,000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) <b>for at least 14 days</b> until clinical improvement, followed by gradual taper over at least 4 weeks</li> <li>Re-image as clinically indicated</li> <li>If still no improvement within 3-5 days: <ul style="list-style-type: none"> <li>Re-consider additional work-up for alternative etiologies as described above</li> <li>Consider other immunosuppressants and/or treat per local practice</li> </ul> </li> </ul>

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

ILD, interstitial lung disease.

Adapted from Modi et al. *N Engl J Med*. 2020;382(7):610-621.

**AXIS**  
Medical Education

- ▶ But finally, these are the recommended guidelines. For grade 1, you closely follow and consider starting systemic steroids with a gradual taper over 4 weeks. If you have grade 2, you promptly start, you don't wait, you start the systemic steroids and give for at least 14 days, with a taper over 2 weeks, and if there's no improvement in 5 days, you increase the steroids. And finally, grade 3 to 4 requires hospitalization and empiric high-dose methylprednisolone for at least 14 days with a gradual taper.

So let me ask you a question about this. If you have someone referred to you, Dr. Thomas, say I have a patient with breast cancer that's getting trastuzumab deruxtecan comes in with a minimal, comes in with a minimal cough—and we're going to have a case, but I'm curious how you'd manage this now—comes in with a minimal cough, and has a pattern on the CT that suggests interstitial or

pneumonitis. If I sent her to you, what would your management recommendations be at that point?

**Thomas:** Obviously, you would definitely discontinue the drug and see if there is resolution of the symptoms. Depending on the pattern on the CT and their clinical presentation, you may or may not consider if there's any other underlying diagnoses; for example, infection that you'd be worried about, or metastatic disease, etc. If they have significant enough symptoms, get a CT to evaluate that.

And then if they resolve with mild symptoms with just discontinuing the drug, I'd probably hold off on any steroid therapy, but if they're progressing or their symptoms get worse, I might consider it in that arena.

But one thing is I definitely defer to my oncology colleagues of whether or not

to retreat the drug, especially it's going to be more patient-specific on what line of therapy that they're on and what options they have. But for mild disease, I would probably just recommend discontinuing the drug and following with serial CTs and visits to see if their symptoms resolve.

**Brufsky:** Right. And in clinical practice it's usually what happens. I think if someone is symptomatic, I think we really should stop the drug and discontinue. But if someone's responding dramatically and it's much later lines of therapy and they're minimally symptomatic, maybe just a really mild cough, I think that some of us may actually restart the drug. And I think that's really a matter of some debate amongst oncologists, is with that kind of grade 1.5-plus what do you do? It's not quite grade 2. They're interstitial pattern on CT, but the patient's responding. It's an interesting question.





## ILD/Pneumonitis Patient Educational Video

Provided as a tool to improve communication between patients and their healthcare team to detect therapy-induced ILD at early onset for more effective management

► Going now to finally, what strategies and tools that we can employ for patient and caregiver education? I would like to mention that a brief educational video for patients is available as an added resource. In the video I review risk factors, common signs and symptoms, monitoring, and management of cancer therapy-induced interstitial lung disease/pneumonitis, as well as what patients should do when experiencing symptoms. This resource is provided as a tool to improve communication between patients and their healthcare team to detect therapy-induced ILD at early onset for more effective management. We encourage you to access and use this resource in your clinical practice with your patients.

## ILD/Pneumonitis Patient Video Study: Call for Site Champions What Does Being a Champion in this Project Entail?

1. Complete post-assessment & evaluation for this activity
2. Participate in orientation & technology training on use of pre-loaded educational video on AXIS-provided tablet
3. View 10-minute patient educational video on pre-loaded tablet with ≥10 patients who will or are currently receiving targeted anti-cancer agents with known risk factors for ILD/P
  - o Request patient to complete anonymous survey provided by AXIS
4. After completing 10 patient educational video reviews, site Champion re-takes post-assessment and completes a post-project short survey
5. Receive \$1,000 Honorarium

**If you are interested in participating as a Site Champion:**

Email AXIS at:  
**[ILDPA@AXISMedEd.com](mailto:ILDPA@AXISMedEd.com)**

More information available at:  
**<http://ok.cx/1777>**

► AXIS Medical Education is also implementing a study to assess whether utilizing the educational video can improve prompt recording of ILD signs and symptoms by patients to their healthcare team. If you are interested in using this video resource with your patients, please sign up to be a Site Champion for this study. Site Champions will be required to view the video with patients receiving targeted anticancer agents with known risk factors for ILD and pneumonitis, and complete a survey.

ILD/P, interstitial lung disease/pneumonitis.



## Practical Application Patient Case

► So now we'll talk about one 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+

► This is a 56-year-old woman who presented with a right breast mass and right upper quadrant pain. She had a CT scan of the chest, abdomen, and pelvis that showed multiple liver lesions consistent with metastases, the largest 3 cm. And the biopsy showed an ER/PR-negative, HER2 3-plus infiltrating ductal carcinoma in the right breast mass, and it was presumed that the liver lesions were metastatic.

### 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

T-DM1, trastuzumab emtansine.

**AXIS**  
Medical Education

► She was treated with the typical therapy of paclitaxel, trastuzumab, and pertuzumab, which resulted in her liver lesions and breast lesions reduced by about 80%. This lasted for about 2 years, she's now had liver progression. She was then started on a T-DM1 or trastuzumab emtansine with another 50% reduction in her liver lesions; however, 12 months later she had disease progression.

### 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

CT, computed tomography.

**AXIS**  
Medical Education

► She was started on trastuzumab deruxtecan. She had diarrhea from this, which is a relatively common side effect, and controlled with loperamide. She did have a great response very quickly in her liver within 9 weeks on CT scan, but she now presented with a minimal dry cough for 2 weeks and had a chest CT that showed a ground-glass infiltrate in the upper lobe of the 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.

**AXIS**  
Medical Education

► The question is what do we do, and I'll bring this to Dr. Thomas. So immediately I refer to you 1 day later and I'm asking for what you would do, so what advice would you give me at this point?

**Thomas:** I would certainly evaluate the patient and see other than the dry cough were there any other infection signs or symptoms? It sounds like a pretty mild disease if it's just a dry cough for 2 weeks, but on physical exam are they having evidence of hypoxia, how severe is their disease, is it impairing their activities of daily living (ADLs) at home?

And then looking at the CT, what's interesting is that it's localized in just the upper lobe of the left lung, so you might consider if there's a certain pattern of consolidation at all, or if there's any concern for infectious etiology, but it sounds like not if it's just ground glass.

At the very least, I would recommend at least discontinuing the drug to see if there's resolution of these symptoms, and then close monitoring with evaluation in the clinic, and maybe a follow-up CT in about 4 to 6 weeks to see if the ground-glass infiltrates are resolved.

If there's progression, we might start thinking about other etiologies with the ground glass and the patient's symptoms. But that's probably where I would start.

**Brufsky:** Would you treat the patient with steroids at that point?

**Thomas:** I think with mild disease, I would hold off unless there's any progression of the disease.

**Brufsky:** Great. I think a lot of us would do that. I think, again, this is kind of the stage 1.5; it's not quite 2, her ADLs are completely fine. And I think

that it's reasonable to follow her symptoms very closely and redo her scans in about 3 to 4 weeks and see if things have improved. And if they have, I think a lot of us would potentially retreated her at that point, consider she's a stage 1, not really a 2, although she does have symptoms, but her ADLs are not being compromised.

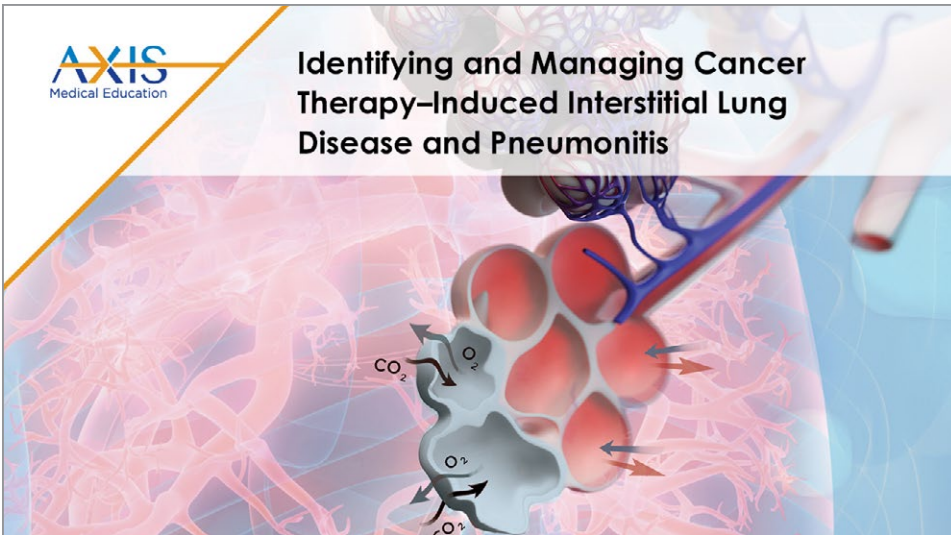
It's kind of that soft debate whether you should stop it permanently. She's responding, she's third- or fourth-line therapy already, and you're really trying to balance the potential benefit of the drug versus toxicity. Obviously, if she progresses either symptomatically or on CT, then we start steroids and discontinue the drug permanently. That's how we would manage this patient.

## Thank You

Thank you for participating in this activity!

- ▶ With that, I want to thank everybody for participating in this activity. I want to thank Dr. Thomas for her very excellent presentation and insightful comments that she's given about the management of ILD.

## Identifying and Managing Cancer Therapy-Induced Interstitial Lung Disease and Pneumonitis



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