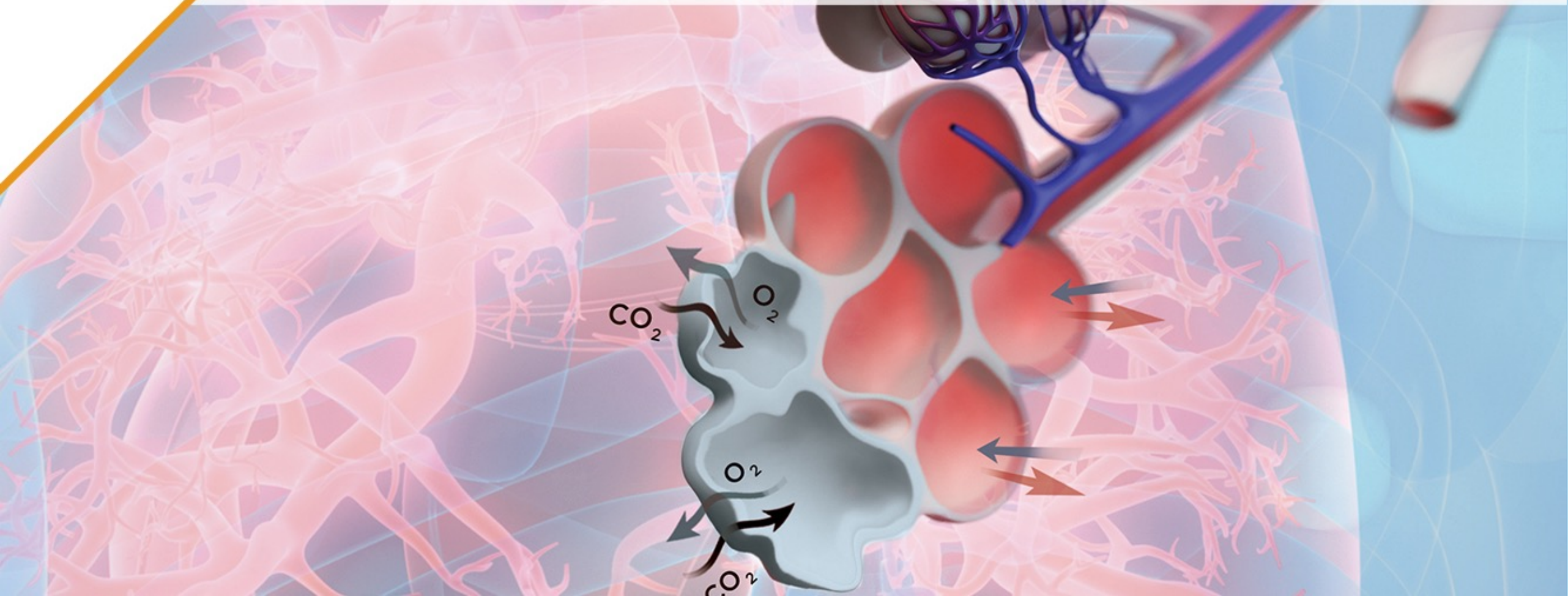
AXIS Medical Education

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



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Disclosure of Conflicts of Interest

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

Learning Objectives

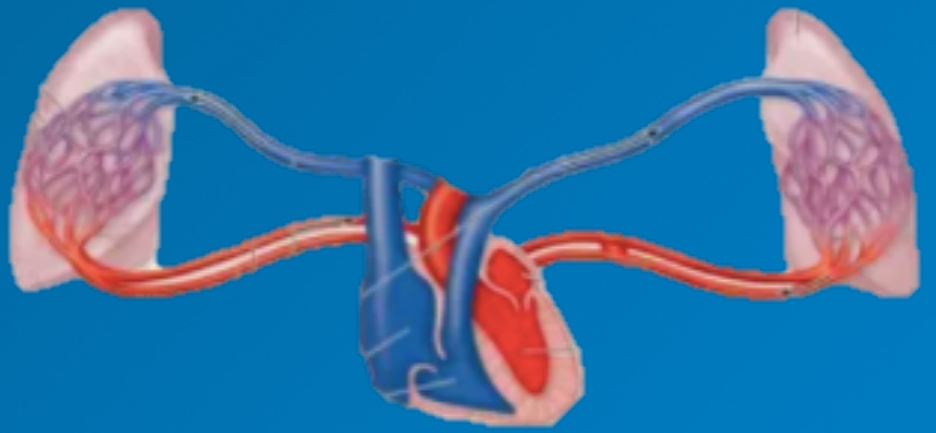
Upon completion of this activity, participants should be better able to:

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

Epidemiology

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

- High prevalence – lungs receive entire blood supply



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

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):528-538.

Variety of Presentations

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

Risk Factors for Drug-induced ILD

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

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, interstitial pulmonary fibrosis.
Skeoch et al. *J Clin Med.* 2018;7(10):356.

Common Signs of ILD

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

Dry, hacking cough that does not produce phlegm

Extreme fatigue and weakness

Unexplained weight loss

Mild chest pain

Shortness of breath

Labored breathing which can be either fast or shallow

No appetite

Bleeding in the lungs

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

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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

Timing

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

Diagnosis and Evaluation

Diagnosis of Exclusion with Highly Variable Presentation

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

Promptly Investigate Evidence of ILD/pneumonitis

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

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.

Radiologic Findings

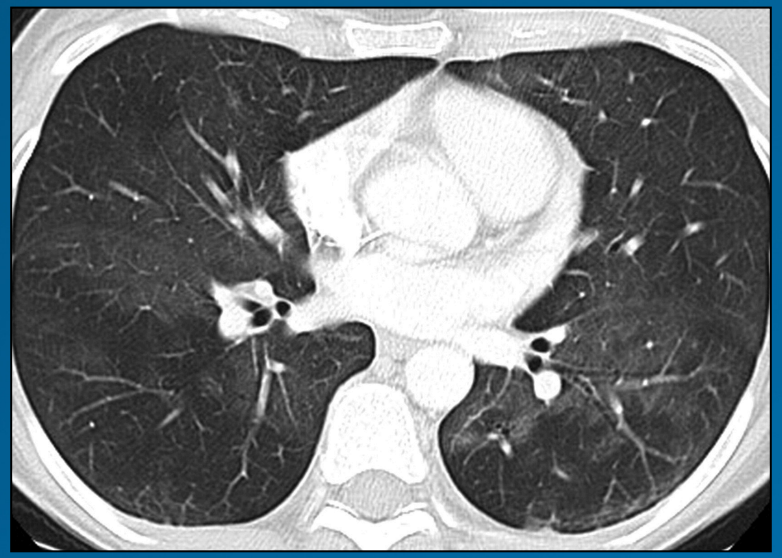
- CT scan the imaging modality of choice, although findings can be non-specific and variable
  - Ground glass opacities with or without consolidation
  - Reticular changes, septal thickening
  - Centrilobular nodules
  - Pulmonary fibrosis – bleomycin (volume loss, traction bronchiectasis, honeycombing)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

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

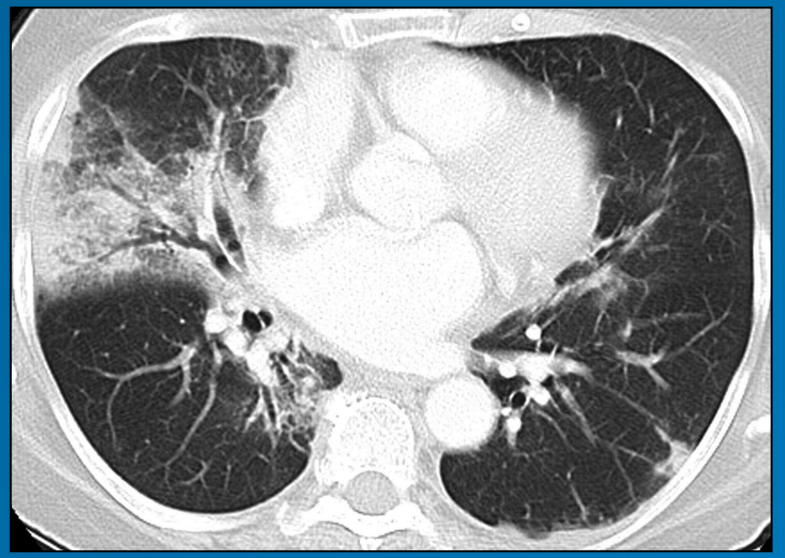
CT, computed tomography; ILD, interstitial lung disease.

Examples of Drug-induced Pulmonary Toxicity in Patients with Cancer

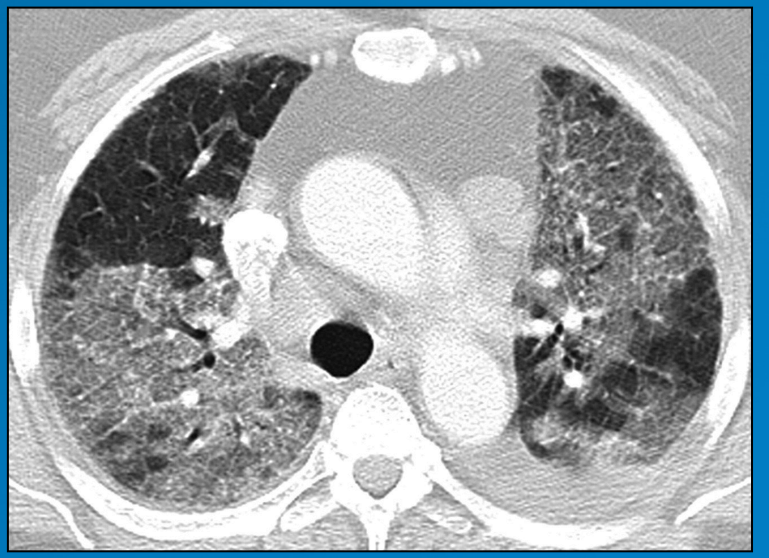
Chemotherapy in Breast Cancer



mTOR Inhibitor in Renal Cell Carcinoma



EGFR Inhibitor in Lung Cancer



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

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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; Hnatiuk *Respiratory Care* 2012;57(1):75-84.

Bronchoscopy

Bronchoalveolar Lavage

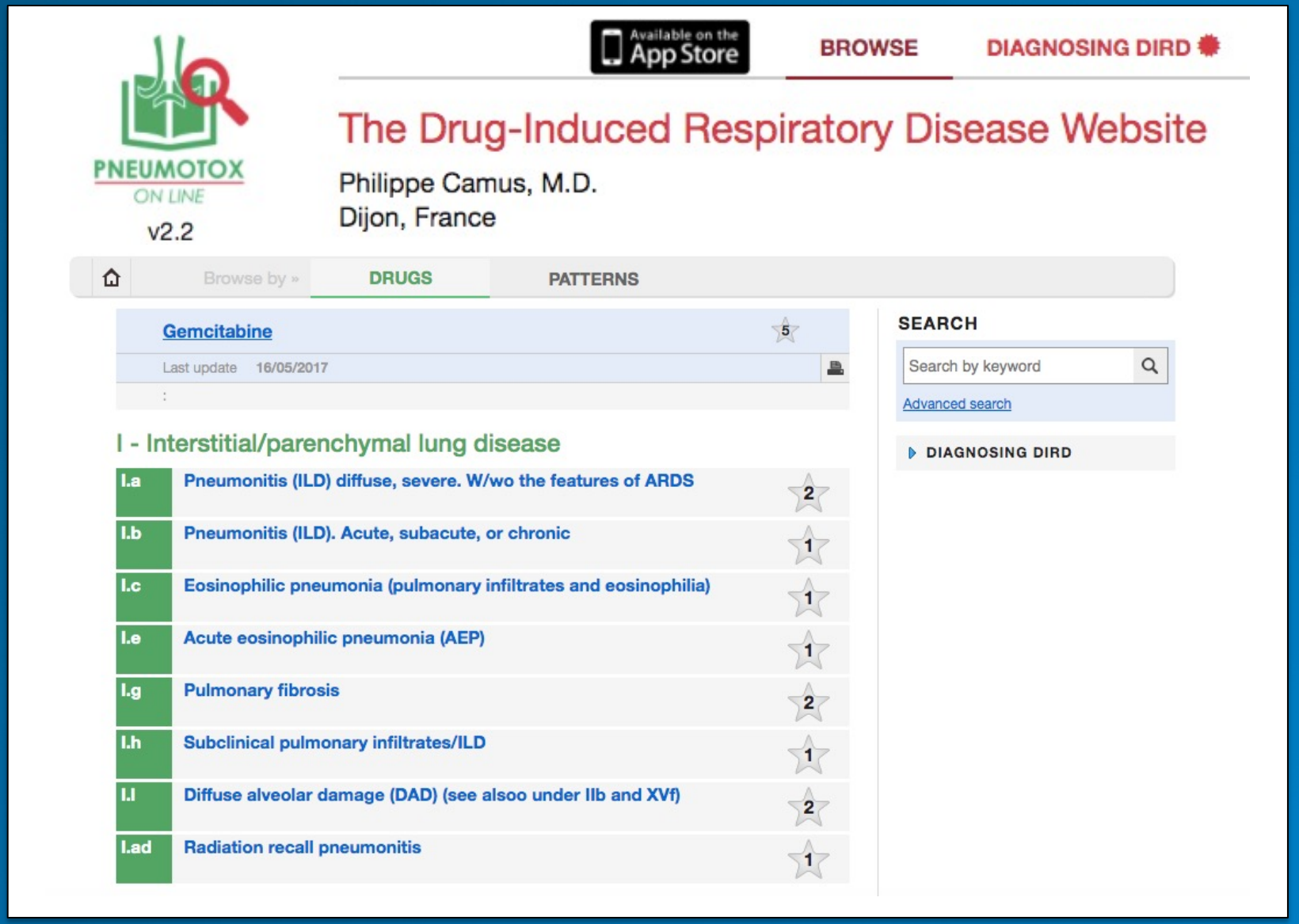
- Blood cell count differential – lymphocytosis, neutrophilia, occasional eosinophilia
- Rule out infection with viral, bacterial, AFB, and fungal cultures
- Cytology to evaluate for malignancy
- Serial aliquots – rule out DAH

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.

Drug-Induced Respiratory Disease Website



Interstitial Lung Disease in Cancer Therapy

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

CDK 4/6, cyclin dependent kinase 4/6; mTOR, mammalian target of rapamycin.

Antibody-Drug Conjugates and Interstitial Lung Disease

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

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

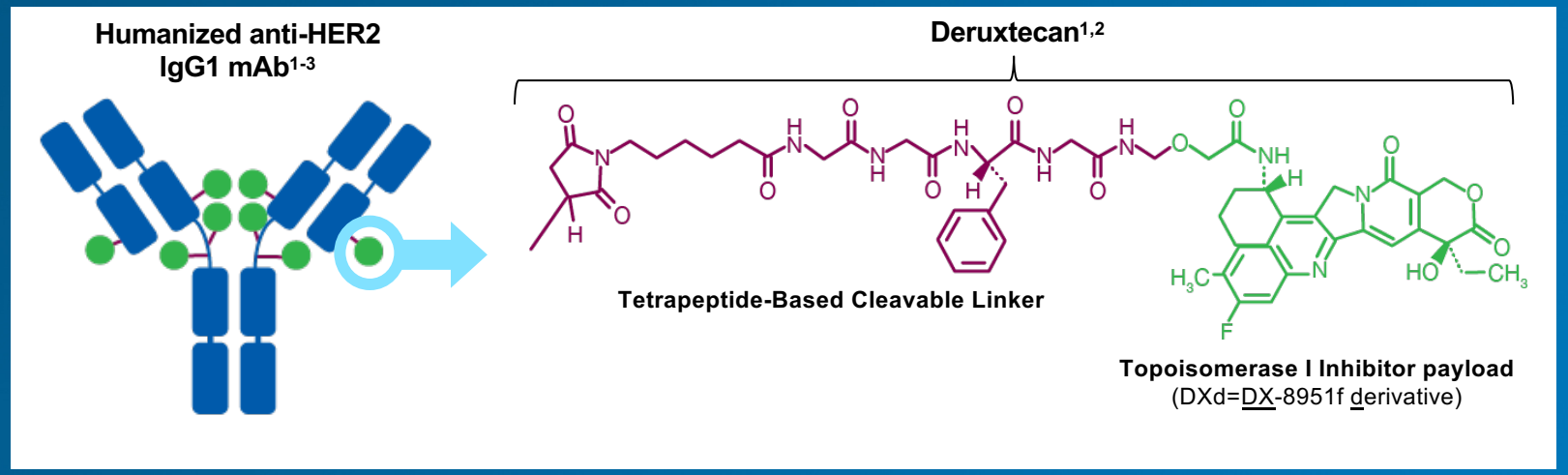
EMA, European Medicines Agency; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Cherri 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.

T-DXd Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 components[1,2]:

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



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

[a]The clinical relevance of these features is under investigation.

1. Nakada et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 2. Ogitani et al. *Clin Cancer Res*. 2016;22(20):5097-5108.
3. Trail et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani et al. *Cancer Sci.* 2016;107(7):1039-1046.

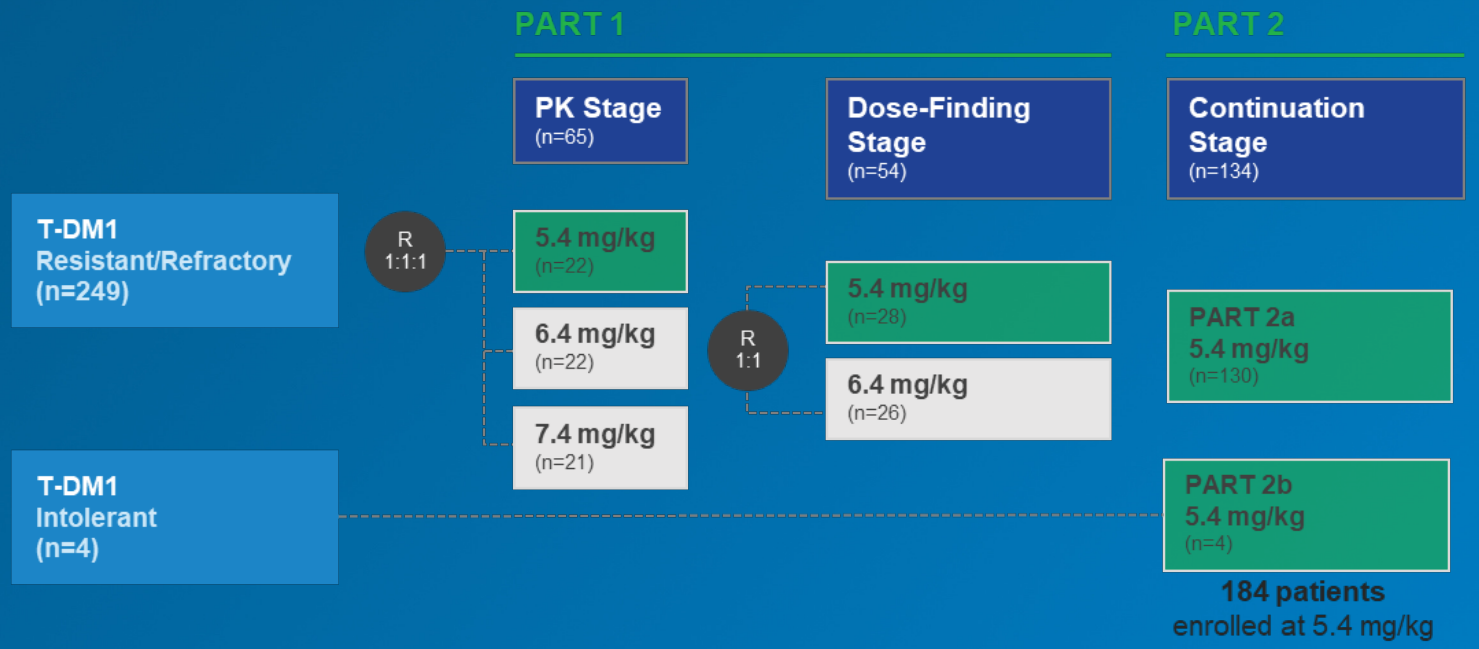
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MOA, mechanism of action; T-DXd, trastuzumab deruxtecan.

DESTINY-Breast01: Study Design

An Open-Label Multicenter Phase 2 Study of T-DXd[1,2]

Population

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



Endpoints

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

Median Duration of Follow-Up

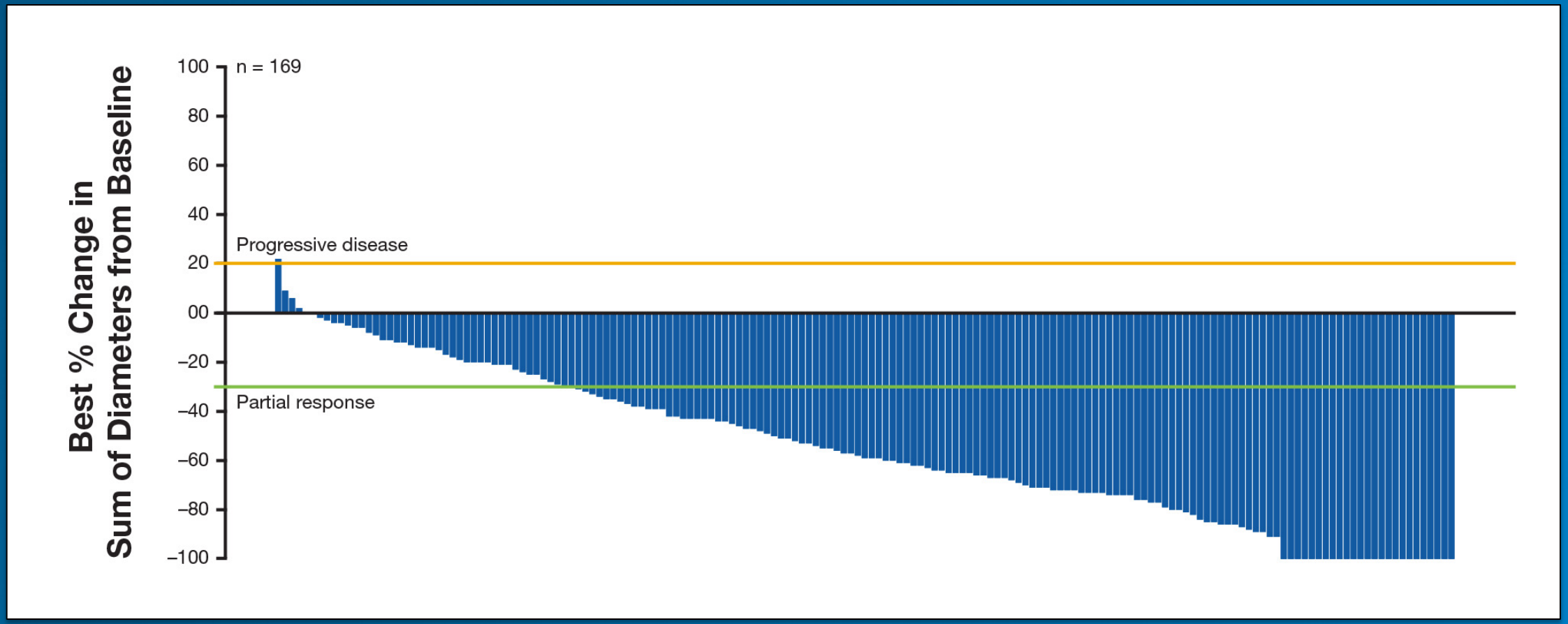
- **August 1, 2019 data cutoff:** 11.1 months (range, 0.7-19.9 mo)[1]
- **June 8, 2020 data cutoff:** 20.5 months (range, 0.7-31.4 mo)[2]
- **March 26, 2021 data cutoff**: 26.5 months (range, 0.7-39.1 mo)[3]

[a]All 184 patients received ≥1 dose of T-DXd. [b]HER2 status was centrally assessed on the most recent archival tissue according to the ASCO-CAP guidelines.

1. Modi et al. *N Engl J Med*. 2020; 382(7):610-621. 2. Modi et al. SABCS 2020 Virtual. Poster Spotlight PD3-06. 3. Saura et al. *Ann Oncol*. 2021;32(5):S485-S486.

BC, breast cancer; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

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



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 (%)[a]	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

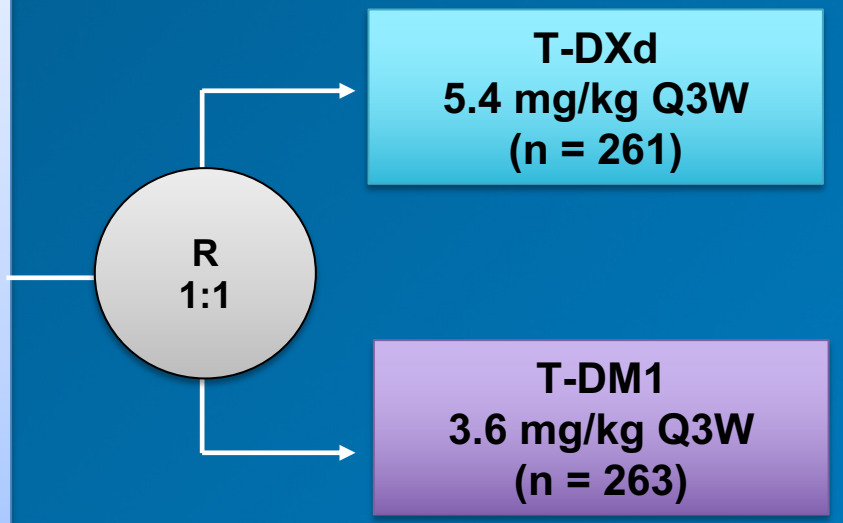
[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.
DCO, data cutoff; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
Saura et al. *Ann Oncol*. 2021;32(5):S485-S486.

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

An open-label, multicenter study (NCT03529110)

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

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



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

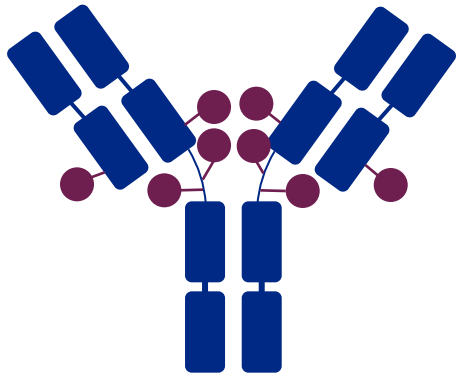
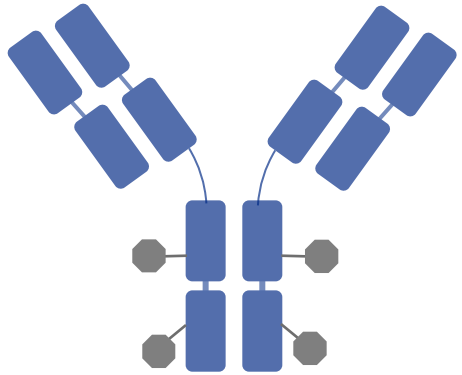
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

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

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

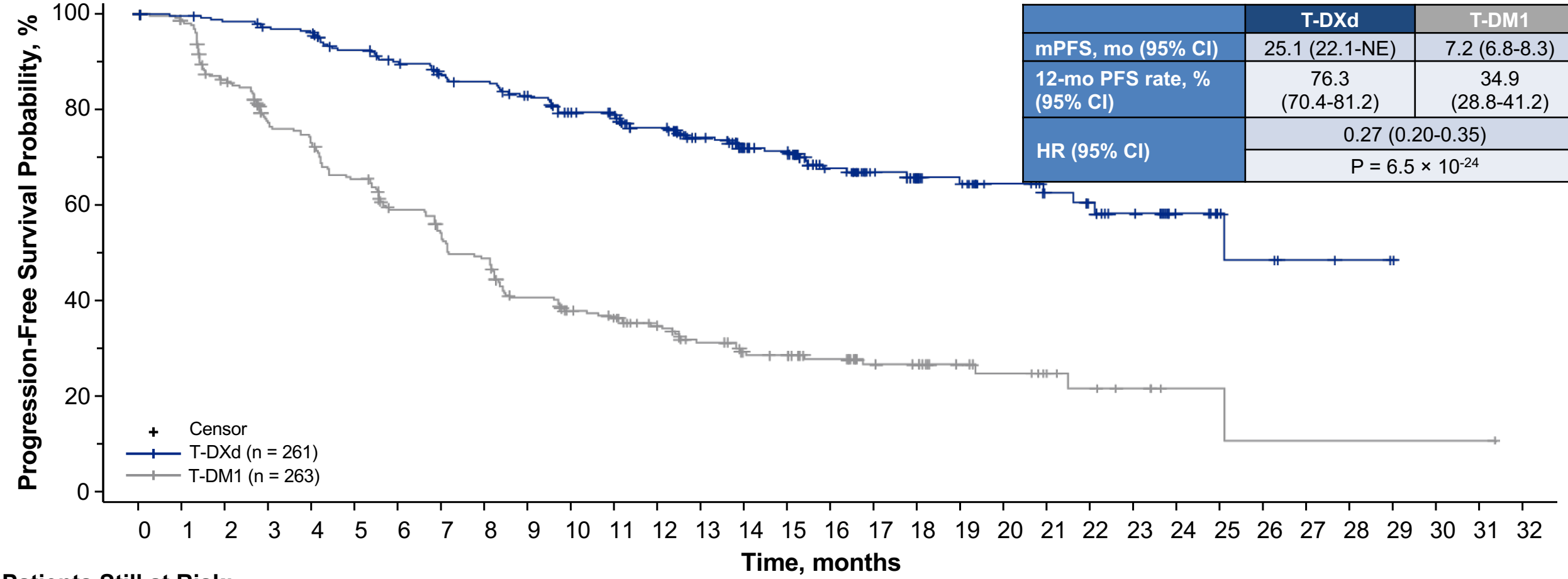
BICR, blinded independent central review; DOR, duration of response; IDMC, Independent Data Monitoring Committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.
Cortes et al. *Ann Oncol.* 2021;32 (suppl_5):S1283-S1346.

ADC Characteristic Differences Between T-DXd and T-DM1

T-DXd[1]	T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]	T-DM1[5]
	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.
[a]The clinical relevance of these features is under investigation.
1. Nakada et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Ogitani et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast03
Secondary Endpoint: PFS by Investigator Assessment



	T-DXd	T-DM1
mPFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)
HR (95% CI)	0.27 (0.20-0.35)	
	$P = 6.5 \times 10^{-24}$	

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	1	0

PFS, progression-free survival.

Cortes et al. *Annals of Oncology* (2021) 32 (suppl_5): S1283-S1346.

DESTINY-Breast03: Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], 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)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (N = 261)	0	1 (0.4)[c]	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.
[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.
Cortes et al. *Ann Oncol.* 2021;32 (suppl_5): S1283-S1346.

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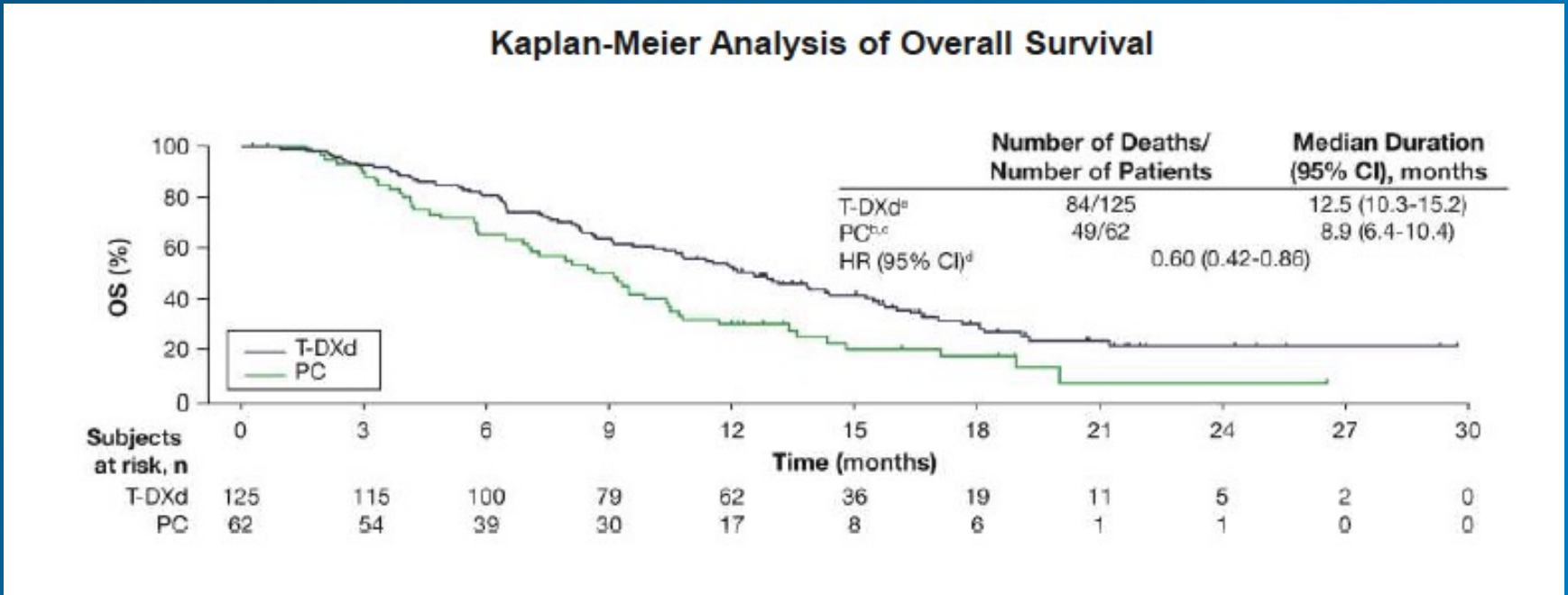
DESTINY-Gastric01: Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer



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.

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.

DESTINY-CRC01: Study Design

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

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

T-DXd 6.4 mg/kg q3w

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

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

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

Cohort C (n = 18)
HER2 IHC 1+

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

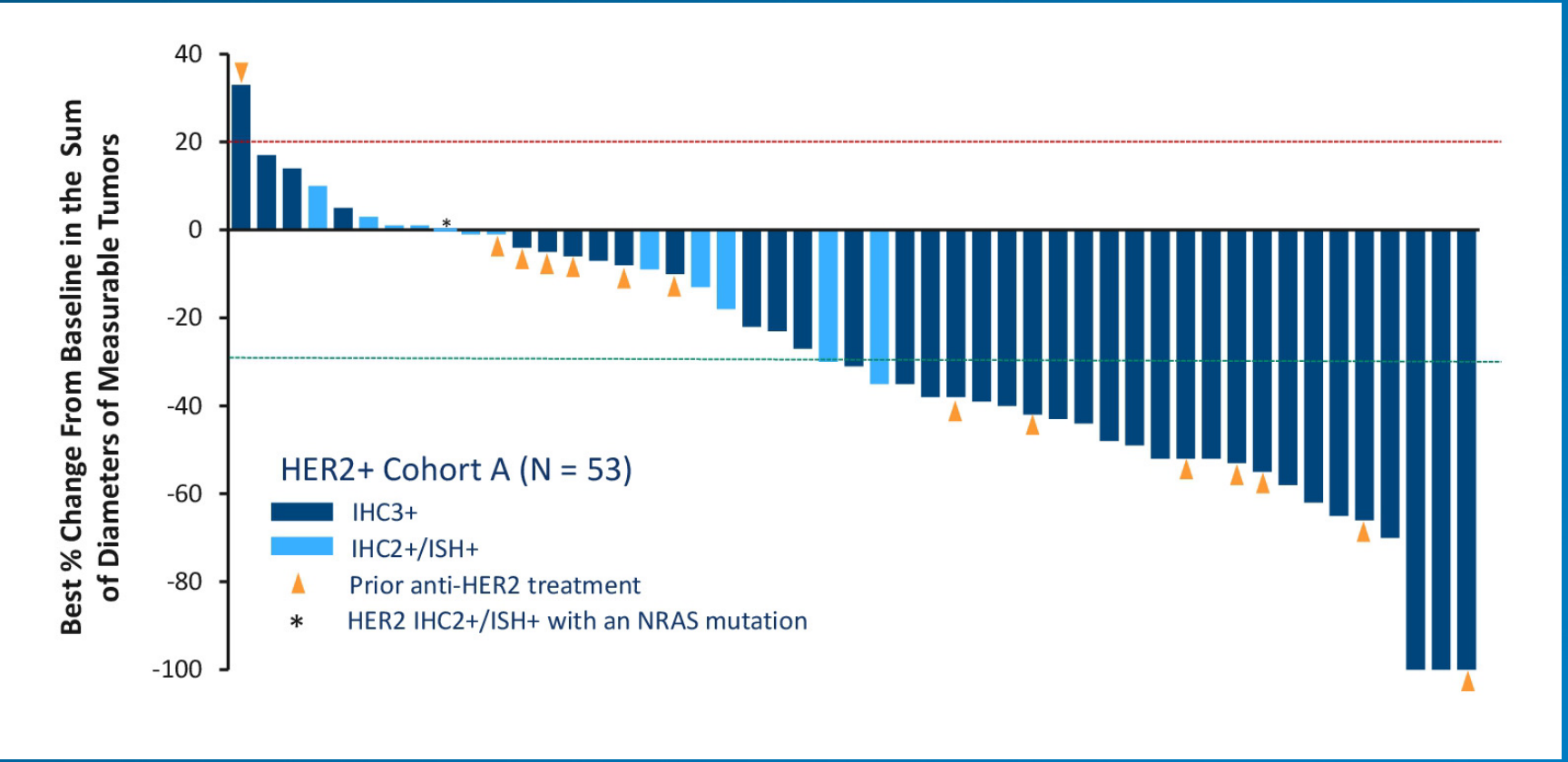
Data cutoff: August 9, 2019
- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

IHC, immunohistochemistry; ISH, in-situ hybridization; HER2, human epidermal growth factor receptor 2; ORR, objective response rate.

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

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.

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.

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

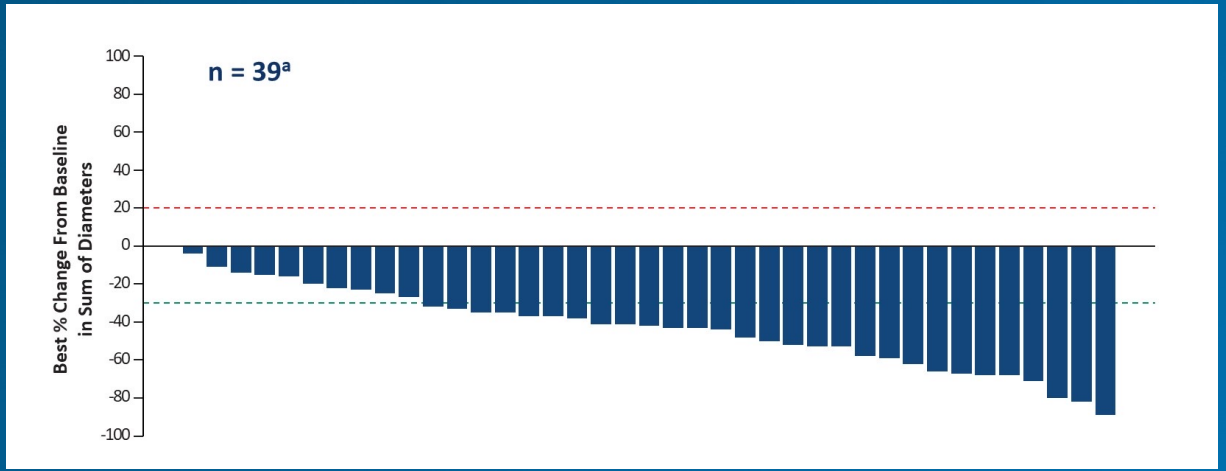
Data cutoff: November 25, 2019
- 45.2% of patients (19/42) in Cohort 2 remained on treatment
- 54.8% discontinued, primarily for progressive disease and adverse events (21.4% each)

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

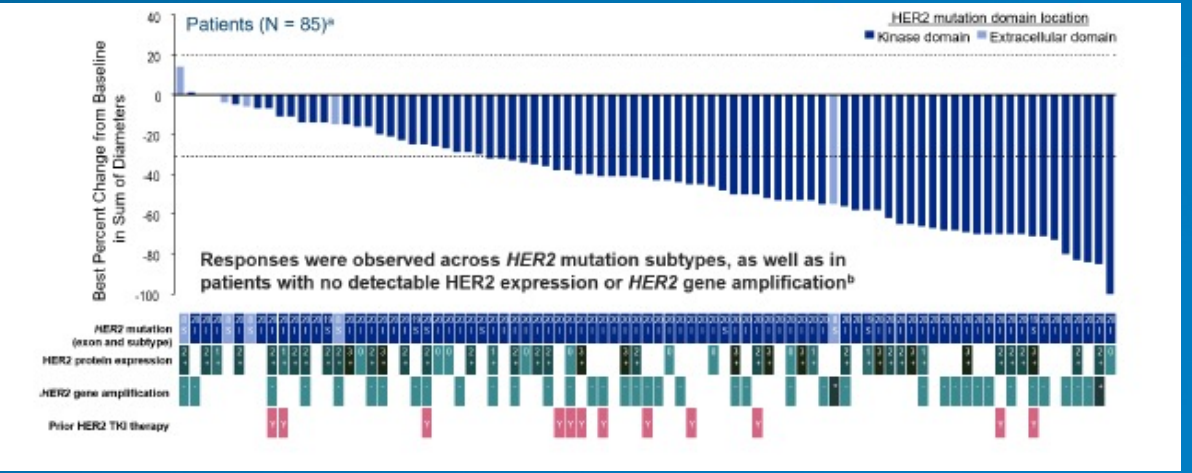
Smit et al. *J Clin Oncol*. 2020;38(15):9504-9504; Li et al. *N Engl J Med*. 2021 Sept 18; doi:10.1056/NEJMoa2112431; *Ann Oncol*. 2021;32(suppl_5): S1283-S1346.

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 18; doi:10.1056/NEJMoa2112431; *Ann Oncol*. 2021;32(suppl_5): S1283-S1346.

DESTINY-Lung01: AEs of Special Interest

Adjudicated drug-related ILD:

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

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.

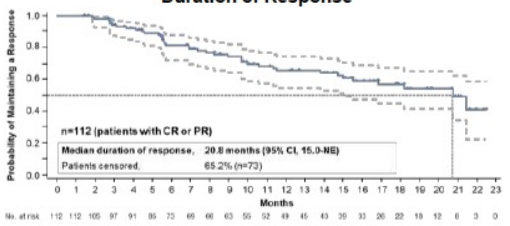
Li et al. *N Engl J Med*. 2021 Sept 18; doi:10.1056/NEJMoa2112431; *Ann Oncol*. 2021;32(suppl_5): S1283-S1346.

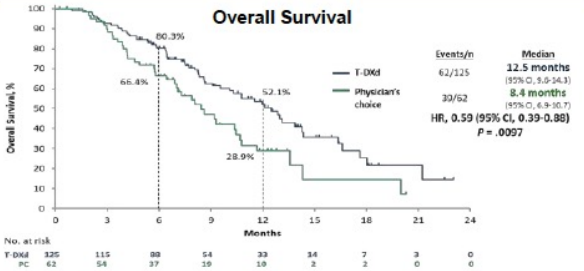
Pooled Analysis: Drug-related ILD in 8 Single-Arm Trastuzumab Deruxtecan Studies Across Various Tumor Types

Background

DESTINY-Breast01: June 2020 Data Cutoff[1]	T-DXd 5.4 mg/kg (N=184)
Objective response rate, n (%)	113 (61.4)

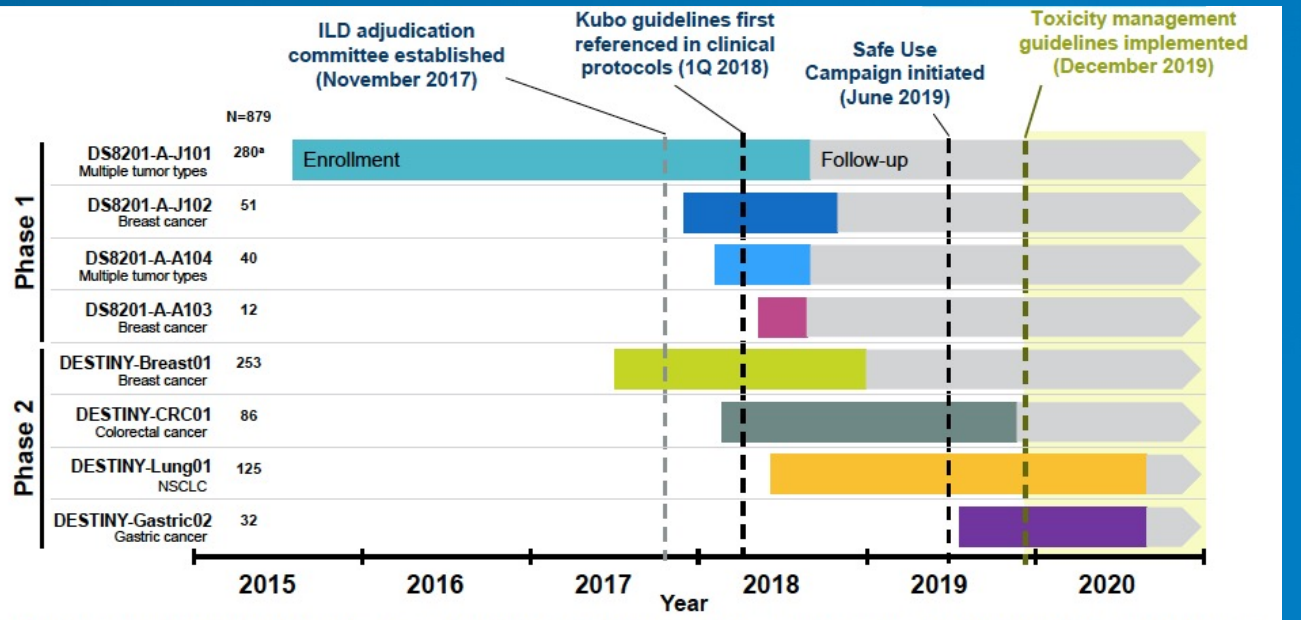
DESTINY-Gastric01: November 2019 Data Cutoff[2]	T-DXd 6.4 mg/kg (N=119)	Physician's choice (N=56)
Objective response rate, n (%)	61 (51.3)	8 (14.3)





- Interstitial lung disease (ILD) is an important identified risk for patients treated with T-DXd[3-8]
- Here we further characterize ILD and assess potential associated factors in a pooled analysis of 8 single arm phase 1 and 2 T-DXd monotherapy studies, including the first-in-human study

Studies and Patients Included



[a] Only patients who received T-DXd 5.4, 6.4, 7.4, or 8.0 mg/kg are included. All studies noted here are active but no longer recruiting, except for DESTINY-CRC01, which was completed in November 2020. Note that most patients were enrolled prior to the implementation of toxicity management guidelines. The color bar on each arrow indicates the time of patient enrollment and the gray is follow-up.

ILD, interstitial lung disease.

Powell et al. *Cancer Res*. 2021;81(13):CT167.

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 ≥ 7.4 mg/kg vs 5.4 mg/kg
- Baseline SpO2 < 95% vs ≥ 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 ≥3.9 years vs <3.9 years

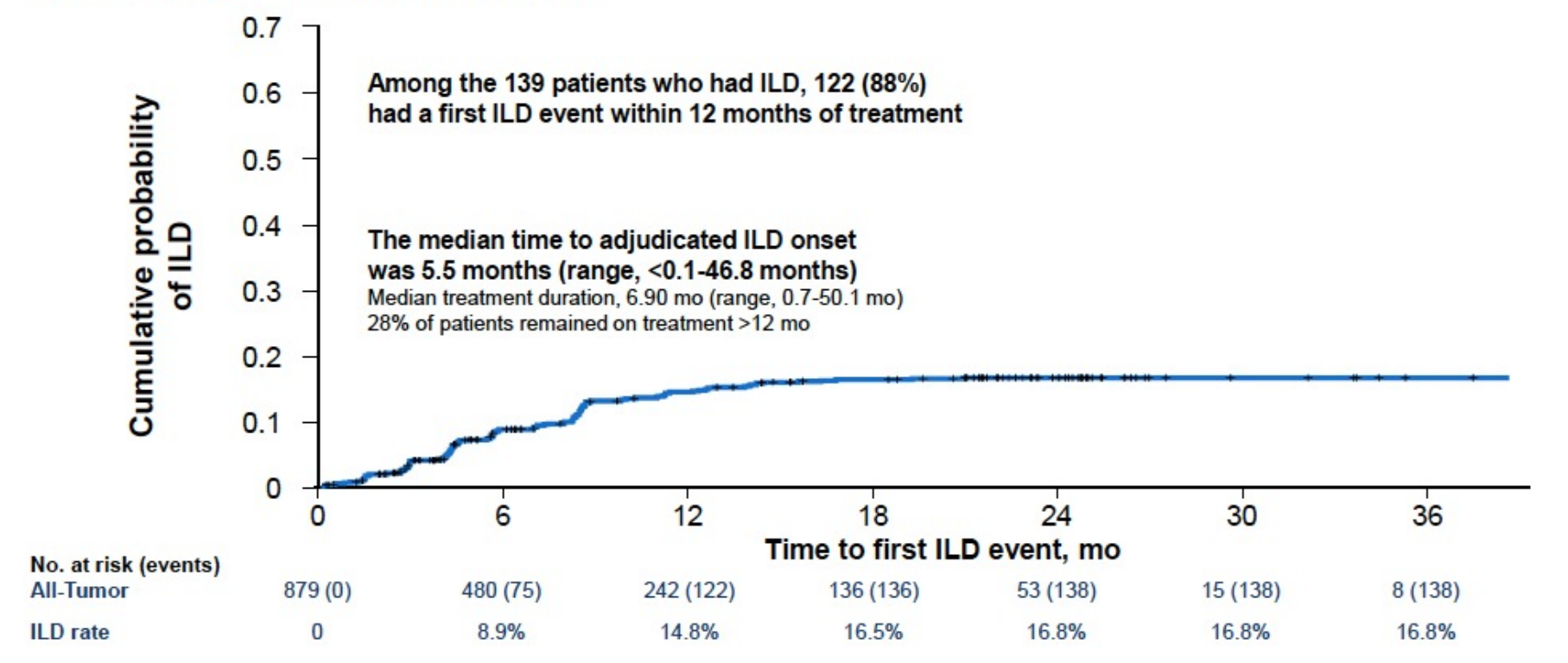
Notably, when accounting for other factors, lung cancer or lung metastases/lymphangitic carcinomatosis at baseline and prior chest/lung radiotherapy were not associated with ILD in this analysis

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 ($x10^9$/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 SpO2 (%) category.
ILD, interstitial lung disease; SpO2, oxygen saturation pulse oximetry.
Adapted from Powell et al. *Cancer Res*. 2021;81(13):CT167.

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.

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%).

Updated toxicity management guidelines implemented (Dec 2019)

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.

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.

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.

Recommended Guidelines for the Management of Trastuzumab Deruxtecan-Induced ILD

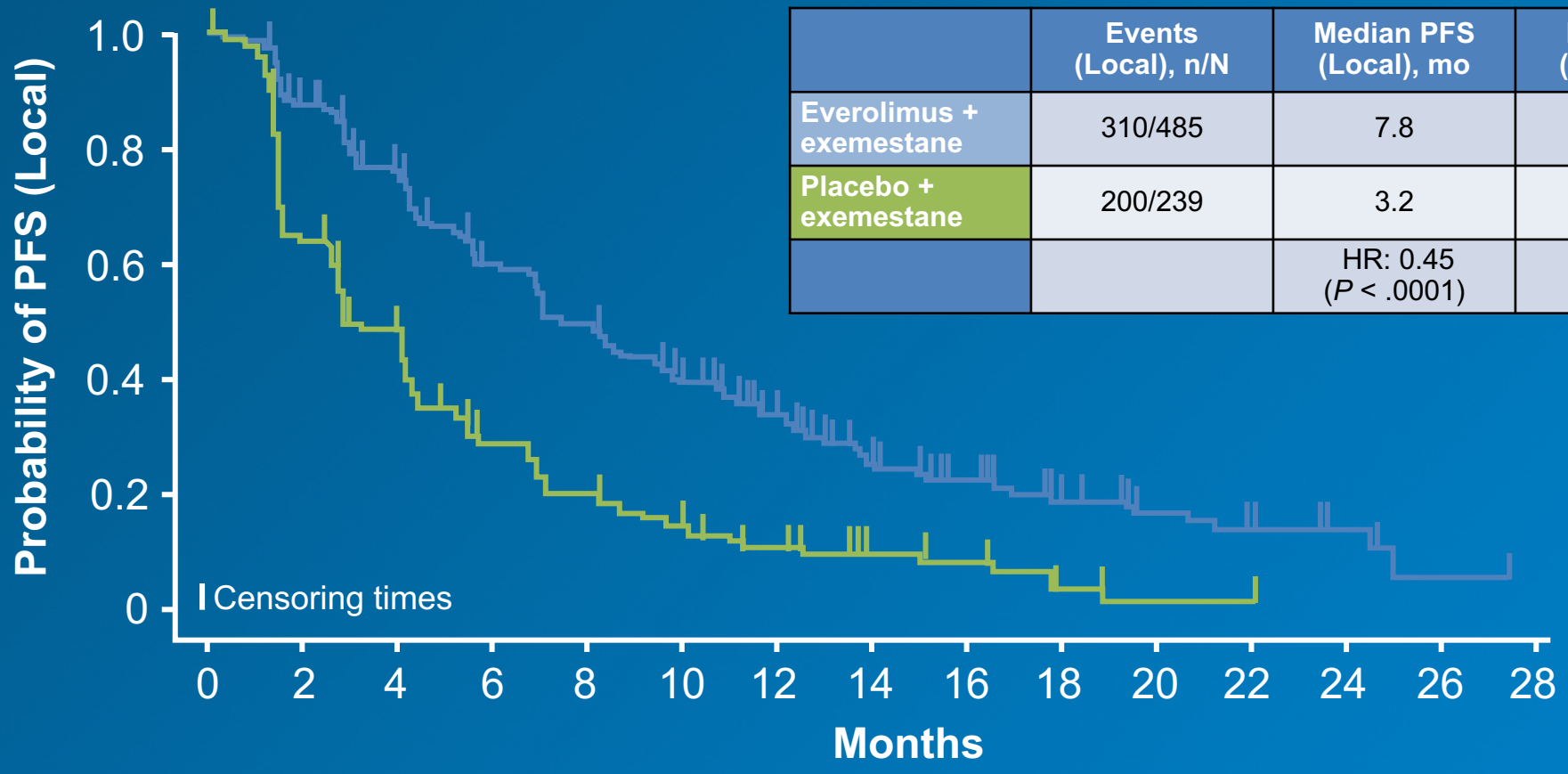
Grade 1	Grade 2	Grade 3/4
• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated) • **Consider starting systemic steroids** (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement,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

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

AXIS Medical Education

mTOR Inhibitors and ILD

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



	Events (Local), n/N	Median PFS (Local), mo	Median PFS (Central), mo
Everolimus + exemestane	310/485	7.8	11.0
Placebo + exemestane	200/239	3.2	4.1
		HR: 0.45 ($P < .0001$)	HR: 0.38 ($P < .0001$)

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

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

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

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 Cherri et al. *Cancers (Basel)*. 2021;13(5):1052.

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 grade1 (≥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

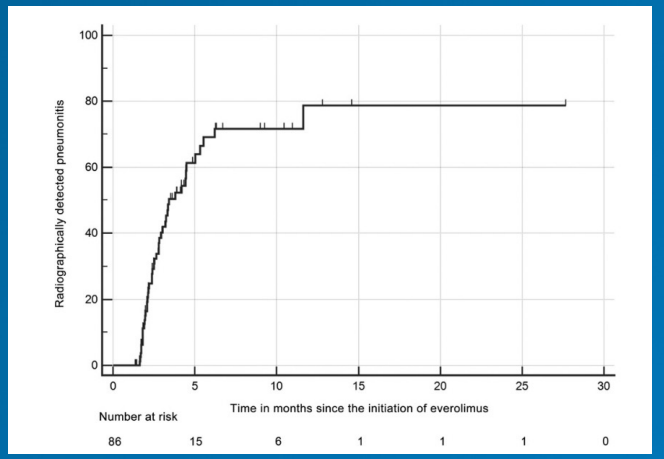
CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; mTOR, mammalian target of rapamycin.
Willemsen et al. *Int J Cancer* 2016;138:2312-2321.

Everolimus-related Pneumonitis in Breast Cancer

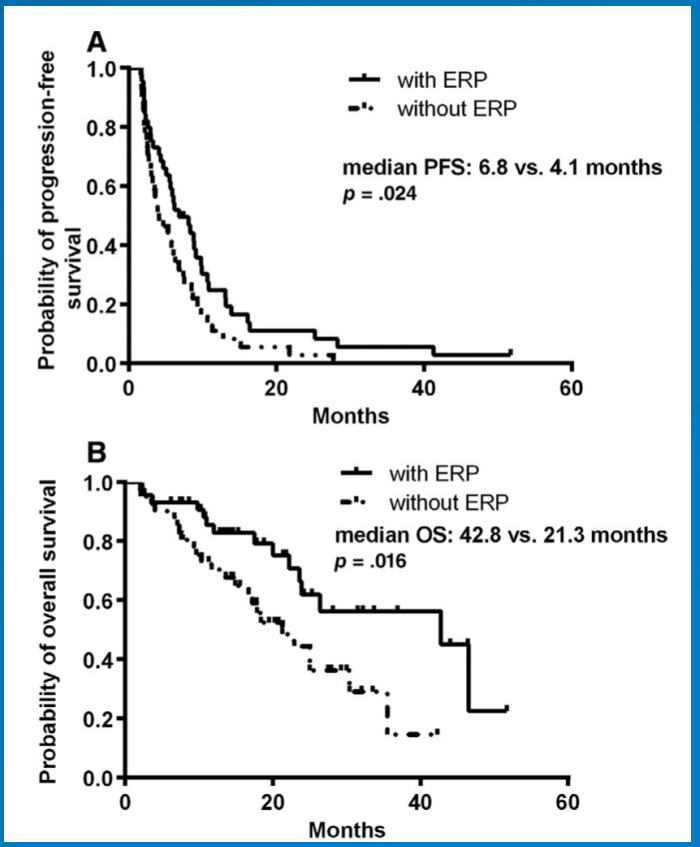
Radiology Assessment by CT Scan

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

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%
	Urothelial carcinoma	3%
Nivolumab + ipilimumab	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%
	PD-L1+ urothelial carcinoma	2%
Pembrolizumab + chemotherapy	NSCLC	4.4%-6.5%
	PD-L1+ HNSCC	5%
Pembrolizumab + axitinib	RCC	2.8%
Atezolizumab	Urothelial carcinoma	2%
	NSCLC	1%
Atezolizumab + nab-paclitaxel	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 Cherri et al. *Cancers (Basel)* 2021;13(5):1052.

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

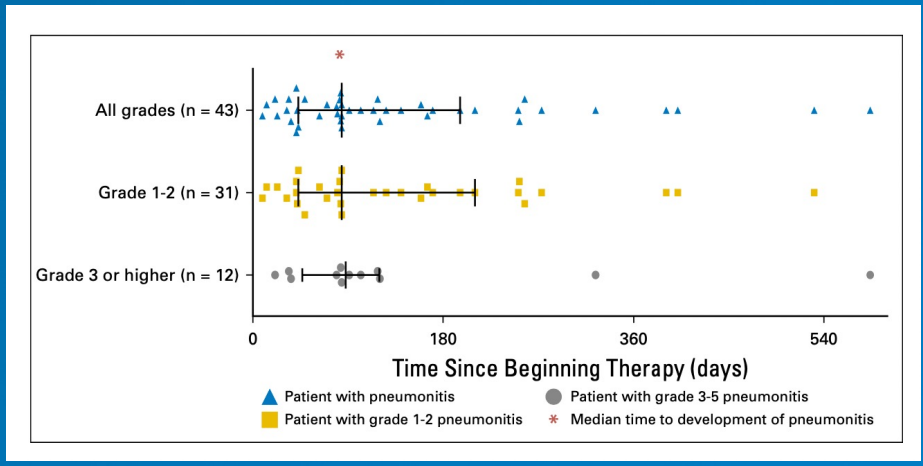
Patients who received anti–PD-1/PD-L1 therapy

	MSKCC, No. (%)	MIA, No. (%)
No. of patients	578	337
Single agent *v* combination		
Monotherapy	441 (76)	275 (82)
Combination	137 (24)	62 (18)
PD-1 *v* PD-L1		
PD-1	405 (70)	337 (100)
PD-L1	173 (30)	0
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

Clinical Feature	No. (%)
Patient feature	
Median age, years (range)	67 (36-89)
Smoking status	
Current/former	24 (56)
Never*	19 (44)
Single agent *v* combination therapy	
Monotherapy	24 (56)
Combination	19 (44)
Underlying lung condition	
None	27 (63)
Asthma	4 (9)
Bronchiectasis	1 (2)
COPD	1 (2)
Interstitial lung disease	1 (2)
Pleural effusion	2 (5)
Pulmonary embolus	4 (9)
Pleural effusion and pulmonary embolus	1 (2)
Sleep apnea	2 (5)
Primary disease type	
NSCLC	9 (20)
Malignant melanoma	26 (60)
Hematologic malignancy	4 (9)
Bladder carcinoma	1 (2)
Breast carcinoma	1 (2)
Head and neck squamous cell carcinoma	1 (2)
Pancreatic carcinoma	1 (2)
Line of therapy	
1	14 (33)
2	17 (40)
≥ 3	12 (27)
Prior chest radiation therapy	
No	27 (63)
Yes	16 (37)
Prior immune checkpoint blockade	
No	32 (74)
Yes	11 (26)
Anti–PD-1/PD-L1 treatment data	
Single agent *v* combination therapy	
Combination	19 (44)
Monotherapy	24 (56)
PD-1 *v* PD-L1	
PD-1	40 (93)
PD-L1	3 (7)
Median No. of doses (range)	4 (1-38)
Best objective response†	
CR/PR	25
PD	2
SD	14

Time from first dose of anti–PD-1/PD-L1 therapy to date of pneumonitis event stratified by grade



MIA, Melanoma Institute of Australia; MSKCC, Memorial Sloan Kettering Cancer Center; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

Naidoo. *J Clin Oncol*. 2017; 35:709-717.

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

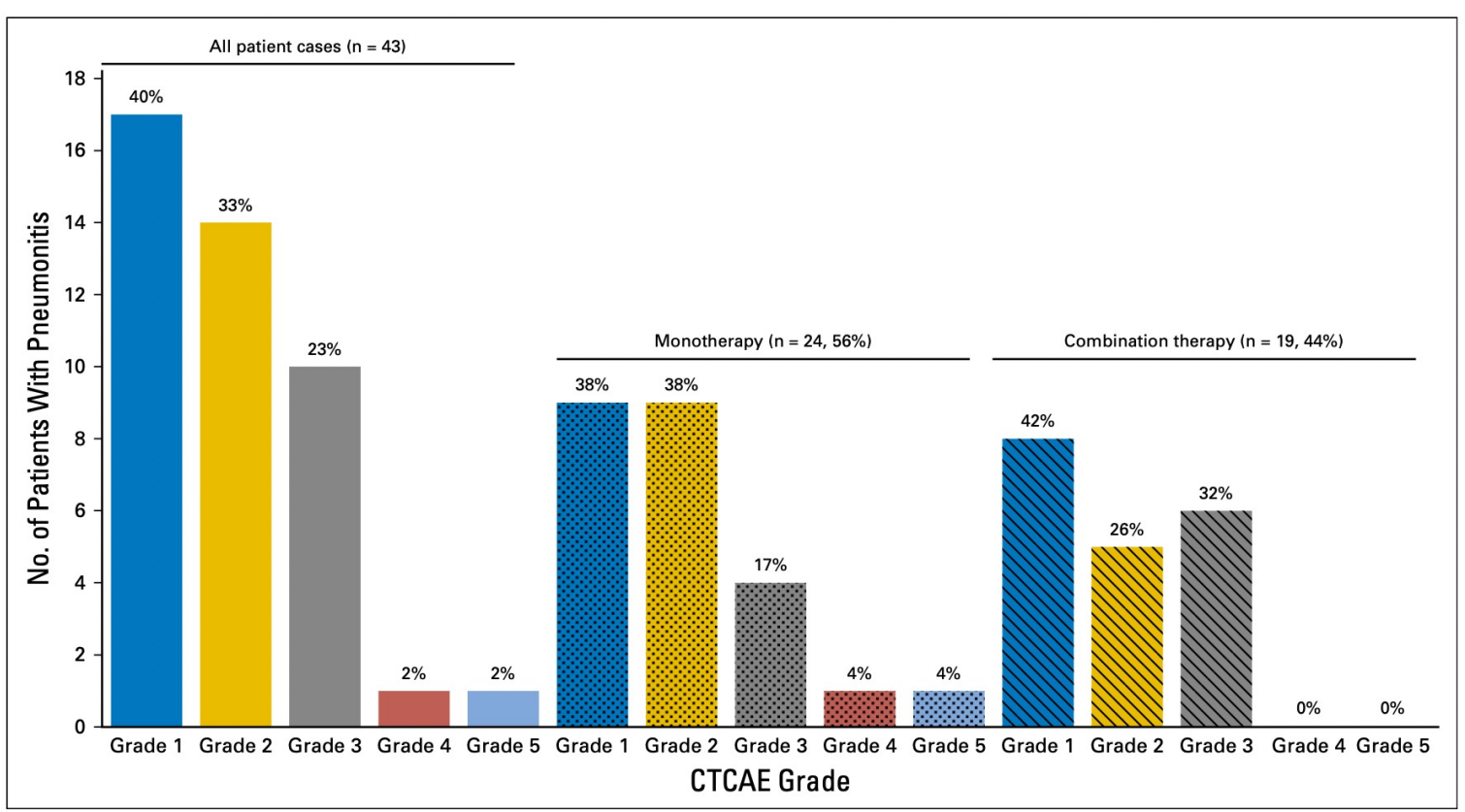


Fig 2. Patients in whom pneumonitis developed stratified by highest Common Terminology Criteria for Adverse Events (version 4.0; CTCAE) grade, including whether patients received anti–programmed death-1/programmed death ligand 1 monotherapy versus in combination with anti–cytotoxic T-cell lymphocyte associated antigen-4 monoclonal antibody.

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

Naidoo. *J Clin Oncol*. 2017; 35:709-717.

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)	
	Imatinib	Kit+ gastrointestinal stromal tumor (GIST)	Rare
		Dermatofibrosarcoma protuberans	
BRAF and MEK TKIs	Trametinib	V600 *BRAF*-mutated melanoma	2.4%
	Trametinib + dabrafenib	V600 *BRAF*-mutated melanoma	≤1%
PI3K TKI	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 Cherri et al. *Cancers (Basel)* 2021;13(5):1052.

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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

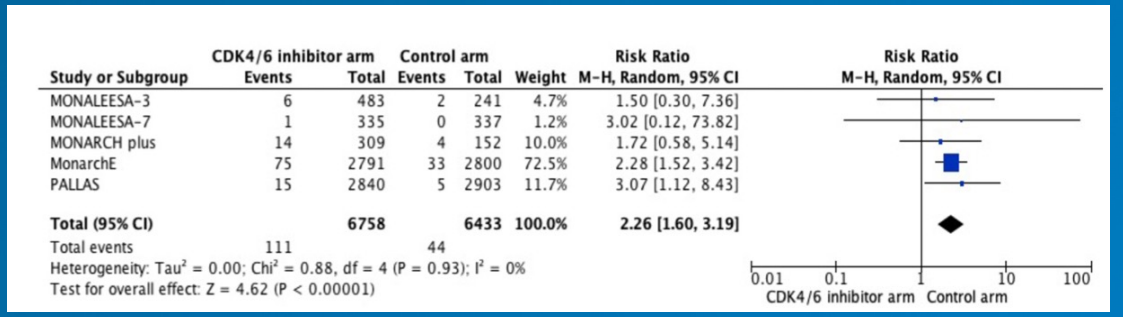
CDK 4/6 Inhibitor	Tumor Type	Incidence of Lung Toxicity (Any Grade)
Abemaciclib	HR+/HER2- Metastatic Breast Cancer	1-3%
Palbociclib		
Ribociclib		

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

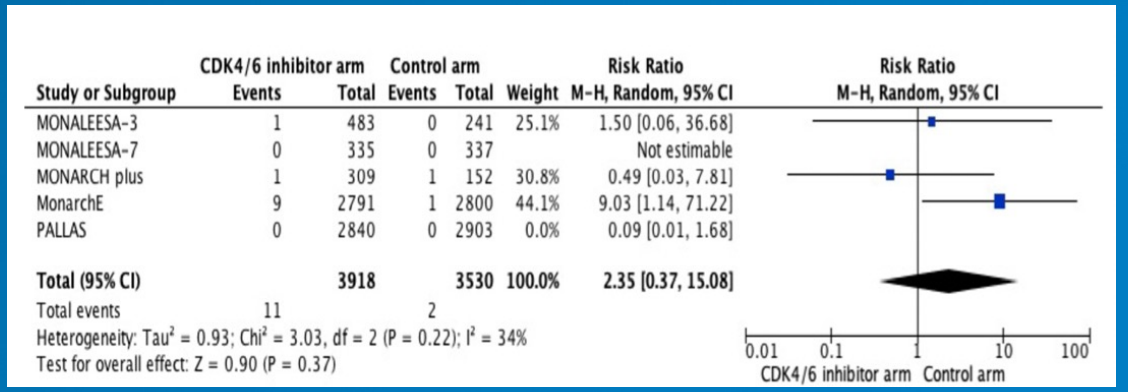
Relative Risk for Pneumonitis or ILD Associated with CDK 4/6 Inhibitors: Meta-analysis of Phase 3 RCTs

	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.

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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

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

Grading: DI-ILD and Pneumonitis

Grading of DI-ILD based on NCI-CTCAE	
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 indicted • 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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Close and Early Monitoring Techniques for Cough, Dyspnea, Fever, New or Worsening Respiratory Symptoms

Advise patients to contact their healthcare provider immediately for any symptoms

Inform patients of the risks of severe, life-threatening, or fatal ILD

Considerations With Steroid Treatment

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

Management of Pneumonitis According to Severity

Grade 1	Continue treatment Monitor the patient	• Corticosteroids not needed
Grade 2	Discontinue treatment (possibility to restart when G 0-1)	• Oral corticosteroids (prednisone 1-2 mg/kg/day) • Consider empirical antibiotics or BAL • If no improvement after 48-72 hours, treat as Grade 3
Grades 3-4	Permanently discontinue treatment	• Hospitalize patient • Intravenous corticosteroids (methylprednisolone 1-2 mg/kg/day to 4 mg/mg/day) • Empiric antibiotics • Bronchoscopy with BAL +/- transbronchial biopsy • Immunosuppressive drugs if steroid-refractory (e.g. infliximab, mycophenolate, cyclophosphamide, IVIG)

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

An ILD Management Program for T-DXd Clinical Studies Has Been Established

STEP 1: **Monitor**

Suspected ILD

Interrupt drug

Rule out ILD if a patient develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever.

STEP 2: **Confirm**

Evaluations should include:

- High-resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture & CBC (other blood tests could be considered as needed)
- Consider bronchoscopy & bronchoalveolar lavage if clinically indicated and feasible
- PFTs & pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD suspected, if feasible

All events of ILD, regardless of severity or seriousness should be followed until resolution including after drug discontinuation.

STEP 3: **Manage**

Drug must be interrupted for any ILD events regardless of grade

- **Grade 1: Interrupt until fully resolved, then:**
  - If resolved in ≤28 days from date of onset, maintain dose
  - If resolved in >28 days from date of onset, reduce dose one level
  - If Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, drug should be discontinued
- **Grades 2-4: Permanently discontinue treatment**
  - Refer to toxicity management guidelines for trastuzumab deruxtecan

CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; PFTs, pulmonary function tests; PK, pharmacokinetic; T-DXd, trastuzumab deruxtecan.
Adapted from Modi et al. *N Engl J Med*. 2020;382(7):610-621.

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Recommended Guidelines for the Management of Trastuzumab Deruxtecan-Induced ILD

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

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

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Practical Application
Patient Case

Case Study: Patient Presentation and Treatment

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

CT, computed tomography; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; PR, progesterone receptor; RUQ, right upper quadrant.

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.

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.

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.

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