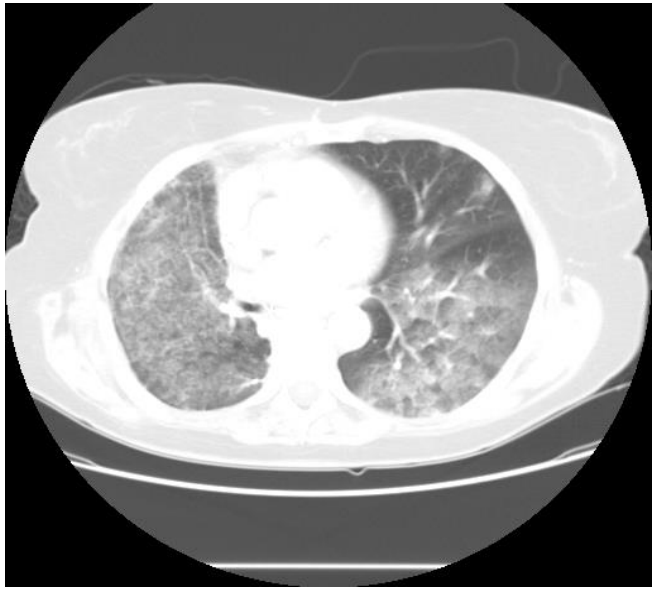
Session 3B: Role of ADCs in Advanced NSCLC

Case: Session 3B: Role of ADCs*

- 52-year-old Caucasian female self-refers to you, with cough and shortness of breath
- Former light smoker (10 pk yrs); PS=1
- CT scan: RUL primary, diffuse “miliary” pulmonary micro-nodules & bone metastases
- CT-guided core needle biopsy: adenoca, TTF1+
- PD-L1 TPS 65%
- Molecular testing elsewhere: EGFR, ALK, ROS1, BRAF V600E: all negative
- Patient is symptomatic but fully functional & highly motivated for therapy



*Cases may have been modified for educational purposes

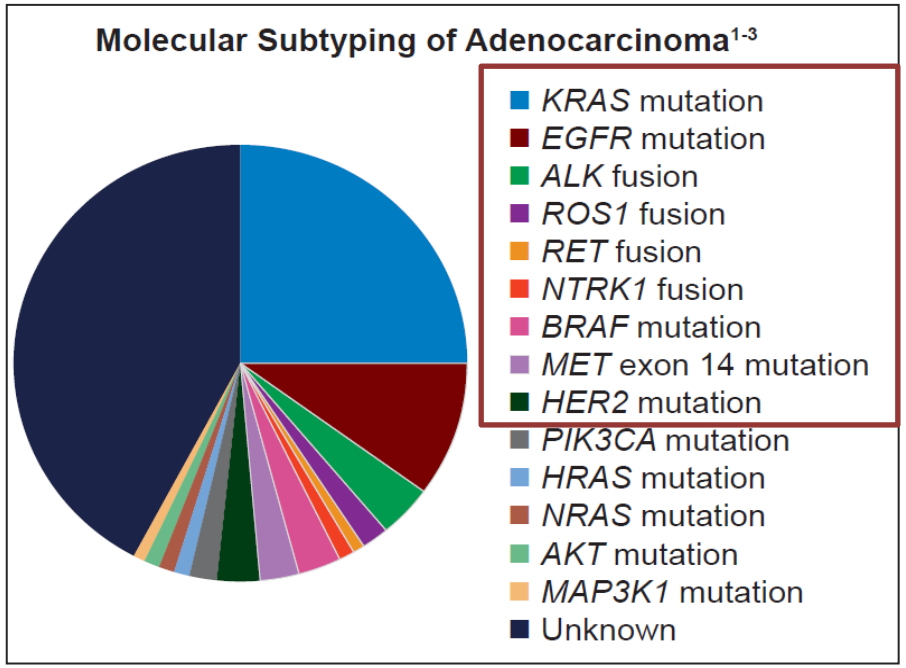
Question

Question 1: What would be your approach in this patient?

1. **Begin therapy with single agent pembrolizumab**
2. **Begin therapy with pemetrexed-carboplatin + pembrolizumab**
3. **Delay therapy while performing plasma ctDNA by next generation sequencing (NGS); ~TRT about 7 days**
4. **Delay therapy while performing tumor tissue testing by next generation sequencing (NGS); ~TRT about 14 days on available specimen**
5. **Begin platinum-based chemotherapy while awaiting results of plasma ctDNA NGS**

NSCLC is particularly well suited for Precision Oncology Strategies due to Genomic Complexity & Growing Number of Oncogene Targets

- **Genomically complex cancers** with a multitude of potential oncogenes known to drive tumor growth
- Improving the biomarker selection process in individual patients to **individualize therapy** is now possible
- Newer technologies **(Next Gen Sequencing/NGS)** now in the clinic for both tissue & blood-based assays

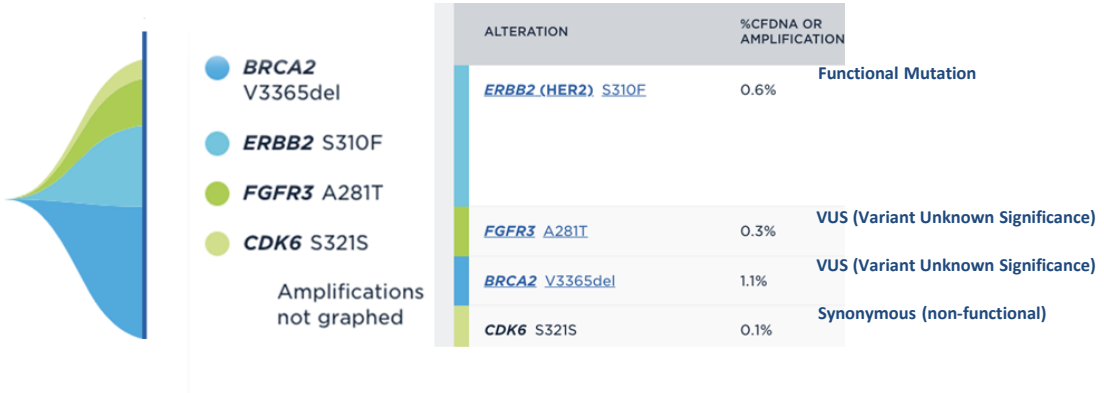


Adapted from Kalemkerian et al. J Clin Oncol. 2018

Question

Due to symptoms, the patient is started on platinum-based chemotherapy with pemetrexed + carboplatin.

Plasma ctDNA by NGS discloses a HER2 Ex20ins mutation as the only clinically applicable abnormality.



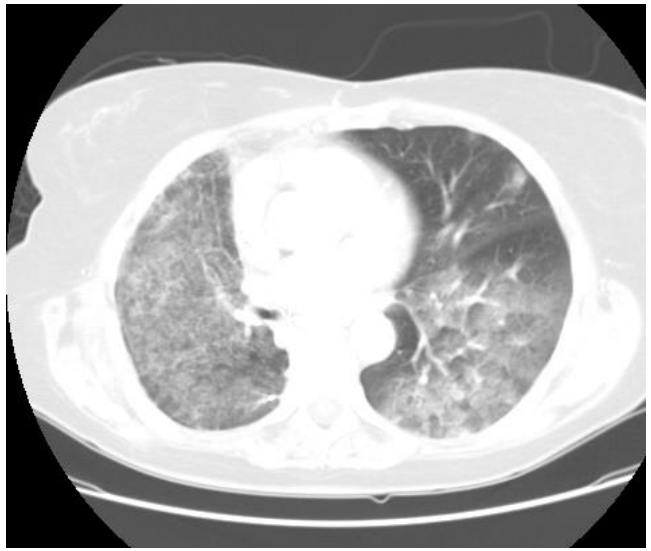
After 2 cycles of chemotherapy, restaging shows stable disease but no reduction in size or number of innumerable pulmonary nodules. She remains symptomatic.

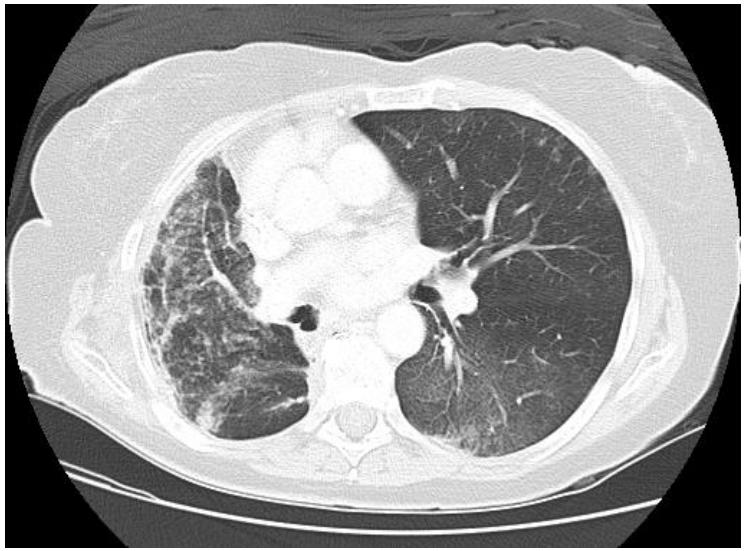
Question 2: What would be your therapeutic approach in this patient?

1. **Add pembrolizumab & continue platinum-based chemotherapy**
2. **Add trastuzumab & continue platinum-based chemotherapy**
3. **Switch to ado-trastuzumab emtansine (T-DM1)**
4. **Switch to trastuzumab deruxtecan (T-DXd)**

Case

- The patient is started on an ADC targeting HER2 (trastuzumab deruxtecan)
- Symptoms resolve after initiating therapy
- Restaging demonstrates an excellent response



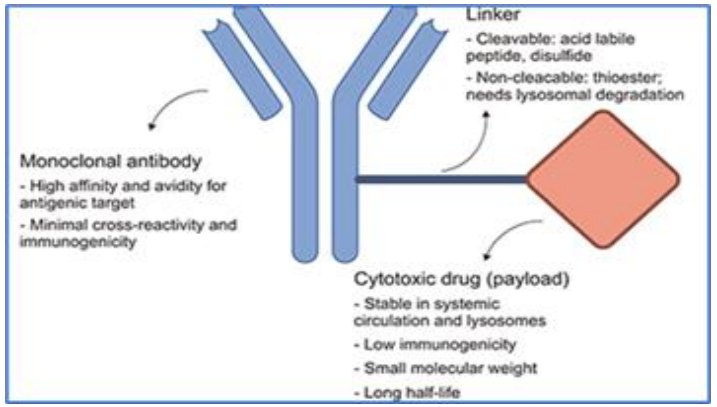


Antibody-drug conjugates in NSCLC

Drug	Target	Payload	ClinicalTrials.gov (Study Name)	Other solid tumors in clinical trials	FDA Approval Status in NSCLC
Trastuzumab Emtansine (TDM1)	HER2	Emtansine (DM1)	NCT02289833	Breast	
Trastuzumab Deruxtecan (DS-8201)	HER2	Deruxtecan (DXd)	NCT04644227 (DESTINY-LUNG02)	Breast, gastric, gastro-esophageal, osteosarcoma, biliary tract, cervical, endometrial, ovarian, pancreas	FDA-approved
ARX788HE	HER2	Monomethyl Auristatin F (MMAF)	NCT03255070 (ACE-Pan Tumor 01)	Breast, gastric	
Trastuzumab-Duocarmazine (SYD985)	HER2	Duocarmazine	NCT04235101	Breast, ovarian, endometrial	
Patritumab Deruxtecan	HER3	Deruxtecan (DXd)	NCT04619004 (HERTHENA-Lung01)	Breast, colon, head & neck cancer	FDA Priority Review
Telisotuzumab Vedotin (ABBV-399)	c-MET	Vedotin (MMAE)	NCT03539536	Solid tumors	FDA Breakthrough Status
Datopotamab-Deruxtecan (DS-1062)	Trop2	Deruxtecan (DXd)	NCT04656652 (TROPION-Lung01) NCT04484142 (TROPION-Lung05) NCT03401385 (TROPION-PanTumor01)	Breast (triple-negative, hormone receptor positive/HER2-negative breast cancer), urothelial, gastric, esophageal	
Sacituzumab Govitecan (IMMU-132, hRS7-SN-38)	Trop2	Govitecan (SN-38)	NCT03964727 (TROPiC S-03) NCT03337698 (Morpheus Lung)	Breast, head & neck, endometrial, gastric, esophageal, hepatocellular, ovarian, prostate, bladder, renal cell, cervical, pancreas, GBM	
Enapotamab-Vedotin (HuMax-AXL-ADC)	AXL	Vedotin (MMAE)	NCT02988817	Ovarian, cervical, endometrial, thyroid, melanoma, sarcoma	
CAB-AXL-ADC (BA3011)	AXL	Vedotin (MMAE)	NCT04681131	Pancreas, melanoma, sarcoma	
CX2029	CD71	Vedotin (MMAE)	NCT03543813 (PROCLAIM-CX-2029)	Head & neck, diffuse large b-cell lymphoma, esophageal	
Tusamitamab-Ravtansine (SAR408701)	CEACAM5	Ravtansine (DM4)	NCT04154956 (CARMEN-LC03) NCT04524689 (CARMEN-LC05)	Breast, pancreas	

Coleman N *et al. npj Precis. Onc.* **7**, 5 (2023). https://doi.org/10.1038/s41698-022-00338-9

Key Characteristics of Antibody Drug Conjugates (ADCs)



Requisites for ADC development

- **Target antigen**: present in tumor, absent in normal tissues
- **Antibody**
  - High antigen specificity
  - Internalization efficiency
- **Linker:** Cleavable vs Non-Cleavable
- **Payload**
  - Drug Class variability determines toxicity profile
  - Highly cytotoxic (nM IC50)
  - Hydrophobic & membrane permeable

	IgG1	IgG2	IgG3	IgG4
Antibodies				
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

	Cleavable			Non-cleavable
Linkers	Hydrazone	Disulfide	Dipeptide	MC*, MCC*
	Acid cleavable	Reducible	Protease cleavable	

Payloads	Auristatins	Maytansinoids	Calicheamicins	Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

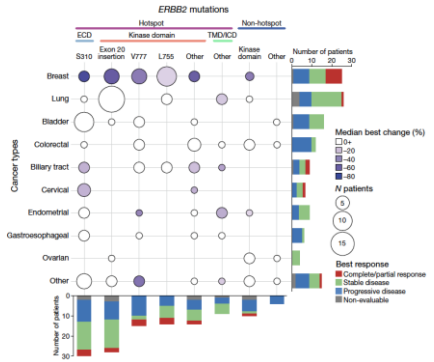
Drago. Nat Rev Cancer 2021

Differing Relevance of the Target with ADCs

HER2-directed ADCs

HER2 alterations in NSCLC

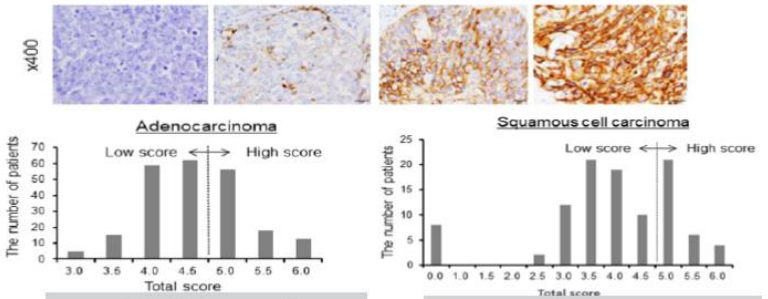
- **Over-expression (≥2+) -15-30%**
- **Over-expression (3+) -2-6%**
- **Amplification -2-5%**
- **Mutation -1-3%**



TROP2-directed ADCs

Trophoblast Cell-surface Antigen 2 (TROP2)

Surgically Detected NSCLC



Trop2⁺ cancer cell score	
Low score (n = 141,62%)	High score (n = 87,38%)

Any expression: 100%

Trop2⁺ cancer cells score	
Low score (n = 67,65%)	High score (n = 36,35%)

Any expression: 92%

YR. Mito et a, Pathology International, 2020

Metastatic NSCLC

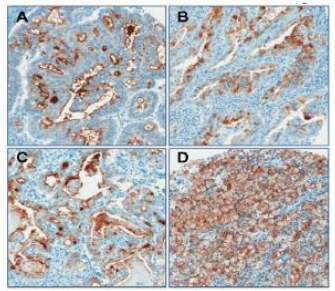
- >10% any intensity: NSCLC (90%; n=26); SCLC (92%; n=29)

R. Heist, J Clin Oncol. 2017; J. Grav. Clin Can Res. 2017.

CEACAM5-directed ADCs

CEA-related Cell Adhesion Molecule 5 (CEACAM5)

Surgically Detected NSCLC



Tumor Tissue	Any Staining	Strong-to-moderate
Adenocarcinoma	22/58 (38%)	28%
Squamous Cell Ca	28/143 (20%)	13%

Decary et al, Clin Cancer Res, 2020

HER2 expression or mutation in NSCLC

- HER2 is an Oncogene
- Relevant for HER2-directed ADCs
- Expression variably present in NSCLC
- HER2 mutation is uncommon (~1-3%)
- High expression & mutation are less frequent in Squamous

TROP2 expression in NSCLC

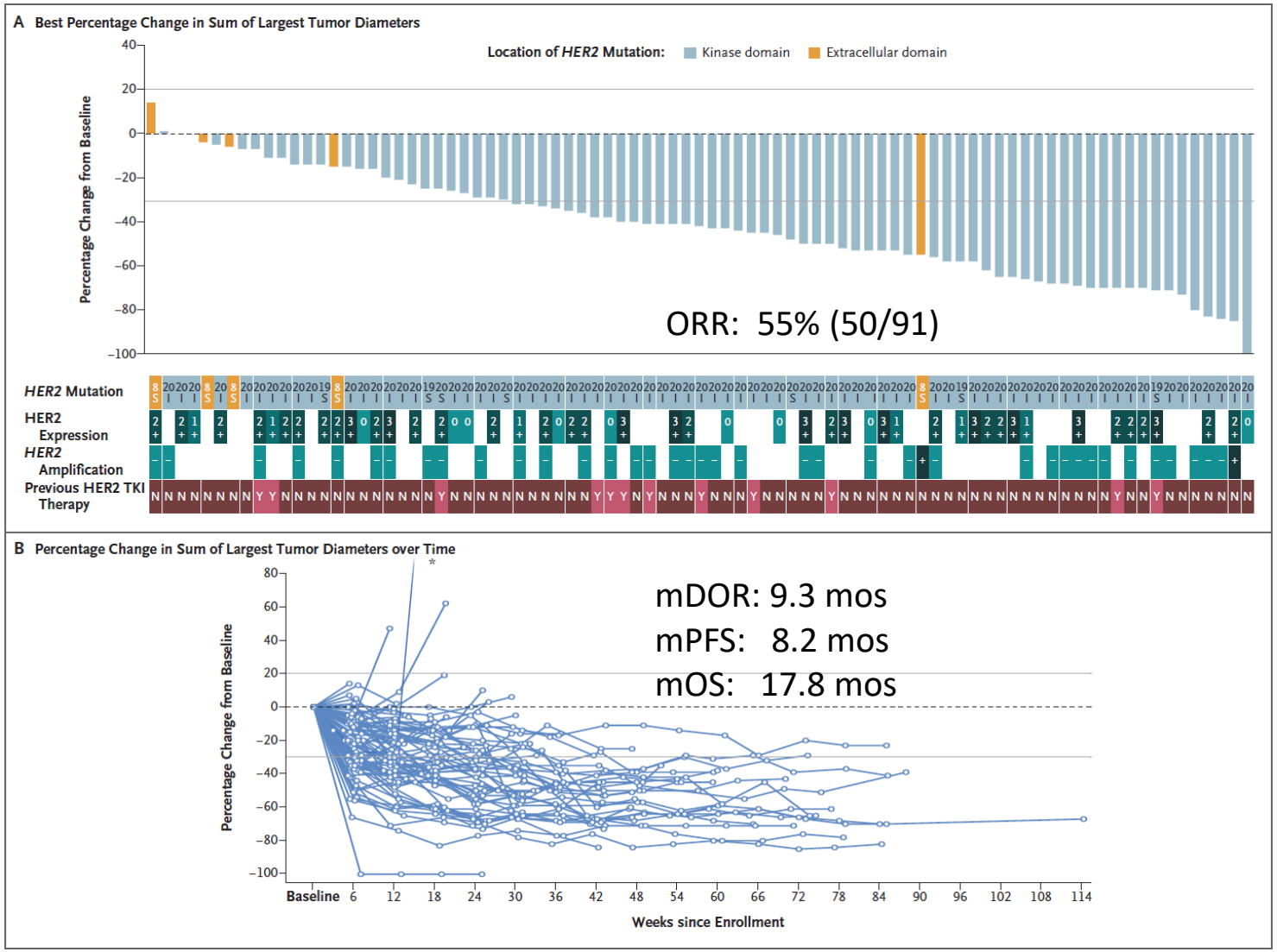
- TROPS2 not an Oncogene
- Unclear relevance for TROP2 ADCs
- Present in almost all NSCLC
- High expression less frequent in Squamous

CEACAM5 expression in NSCLC

- CEACAM5 is not an Oncogene
- Highly Relevant to CEACAM5 ADCs
- Variably present in NSCLC
- Strong expression less frequent in Squamous

Pillai RN et al. *Cancer.* 2017; Wistuba IASLC TTLC 2023

Activity of Trastuzumab Deruxtecan (T-DXd) in HER2-mutated NSCLC



Li et al. NEJM 2022

Case/Question

After 4 months on T-DXd, the patient develops cough and mild shortness of breath.
Repeat CT scan shows continued response in pulmonary nodules but a new patchy infiltrate in the left lung. O2 saturation is 96% at rest and with exercise. Pulmonary medicine is consulted.
Biopsy is consistent with drug-induced interstitial lung disease (ILD), without evidence of cancer.
T-Dxd is held and she is given prednisone at 60 mg/day, with a slow taper.

4 weeks later, symptoms have resolved and CT scan is improved.
She remains on prednisone at 5 mg/day.

Question 3: What would you do next in this patient (prior treatment with pemetrexed-carboplatin and grade 2 ILD on T-DXd)? PD-L1 65%

1. **Observation and close monitoring with CT scans.**
2. **Restart T-DXd at full dose**
3. **Restart T-DXd at ½ dose**
4. **Switch therapy to docetaxel +/- ramucirumab**
5. **Switch therapy to nivolumab-ipilimumab**

Management of T-DXd–induced ILD

TABLE 1. T-DXd Prescribing Information and DESTINY-Breast03 and DESTINY-Breast04 Protocol-Recommended Dose Modifications for Pneumonitis/ILD[4,7,9]

Severity	Treatment	
Asymptomatic pneumonitis/ILD (grade 1)	Interrupt T-DXd until resolved to grade 0, then If resolved in 28 days or less from date of onset, maintain dose If resolved in >28 days from date of onset, reduce dose 1 level per the recommendations below However, if the grade 1 pneumonitis/ILD event occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued Consider corticosteroid treatment (eg, ≥0.5 mg/kg/d prednisolone or equivalent) as soon as pneumonitis/ILD is suspected	
	Dose reduction schedule	Breast cancer
	Recommended starting dose	5.4 mg/kg
	First dose reduction	4.4 mg/kg
	Second dose reduction	3.2 mg/kg
	Requirement for further dose reduction	Discontinue treatment
Symptomatic pneumonitis/ILD (grade 2 or greater)	Permanently discontinue T-DXd Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg/d prednisolone or equivalent and continue for ≥14 days, followed by gradual taper for ≥4 weeks) as soon as pneumonitis/ILD is suspected	

Abbreviations: ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

TABLE 2. Recommended Guidance for Toxicity Management of T-DXd–Induced Pneumonitis/ILD From the DESTINY-Breast03 and DESTINY-Breast04 Protocols[7,9]

Clinical Approach	Grade 1	Grade 2	Grades 3 and 4
Monitoring	Monitor and closely follow up in 2-7 days for onset of clinical symptoms and pulse oximetry	Monitor symptoms closely	Hospitalization required
Corticosteroid treatment	Consider starting systemic corticosteroids (eg, ≥0.5 mg/kg/d prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks	Promptly start systemic corticosteroids (eg, ≥1 mg/kg/d prednisone or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks	Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1,000 mg/d for 3 days), followed by ≥1 mg/kg/d of prednisone or equivalent for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks
Imaging	Consider follow-up imaging in 1-2 weeks (or as clinically indicated)	Reimage as clinically indicated	
Worsening of or no improvement in pneumonitis/ILD	If worsening of diagnostic observations despite initiation of corticosteroids, then follow grade 2 guidelines (if the patient is asymptomatic, then they should still be considered as grade 1, even if corticosteroid treatment is given)	If worsening or no improvement in clinical or diagnostic observations in 5 days: Consider increasing dose of corticosteroids (eg, 2 mg/kg/d prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone) Reconsider additional workup for alternative etiologies, as described above Escalate care as clinically indicated	If still no improvement within 3-5 days: Reconsider additional workup for alternative etiologies, as described above Consider other immunosuppressants and/or treat per local practice

NOTE. Pneumonitis/ILD management in the DESTINY-Breast03 and DESTINY-Breast04 studies was managed per protocol with dose interruptions, reductions, or discontinuations; corticosteroids; and supportive care. A summary of pneumonitis/ILD toxicity management is included. A brief summary of the CTCAE grading categories for pneumonitis is given.[40,a]

Abbreviations: CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; IV, intravenous; T-DXd, trastuzumab deruxtecan.

[a]Grade 1, asymptomatic; grade 2, symptomatic; grade 3, severe symptoms; grade 4, life-threatening respiratory compromise; and grade 5, death.

Rugo et al. JCO Oncol Practice 2023

In this patient with HER2-mutated NSCLC, response to T-DXd but complicated by ILD, would you consider another ADC for further therapy?

Question 4: Would you consider another ADC, and if so, what criteria would to use to select the ADC?

1. **No, I would not consider another ADC. I would choose a different drug class**
2. **Yes, if the target was relevant (i.e. HER family-related)**
3. **Yes, if the target was different (i.e. Trop2)**
4. **Yes, if the payload drug class was different (i.e. not a topoisomerase-related like T-DXd)**
5. **Yes, if the target and payload were different**