AXIS Medical Education

# Expert Answers to Common Questions for Tailoring ADC Therapies Across the HER2 Spectrum in Metastatic Breast Cancer

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

Provided by

AXIS Medical Education

This activity is supported by educational grants from AstraZeneca Pharmaceuticals and Daiichi Sankyo.

# Expert Answers to Common Questions for Tailoring ADC Therapies Across the HER2 Spectrum in Metastatic Breast Cancer

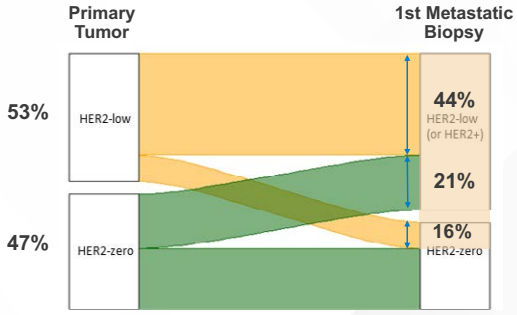
Sara M. Tolaney, MD, MPH


**Sara M. Tolaney, MD, MPH:** Hi, and welcome. My name is Sara Tolaney. I'm a breast medical oncologist at Dana-Farber Cancer Institute. Today I'm going to be answering questions that were asked by clinicians during a recent educational series on antibody–drug conjugate therapies across the HER2 spectrum in metastatic breast cancer. Our questions today will focus on three main topics: 1) Testing and guideline recommendations; 2) Antibody–drug conjugates and their implications in HER2-positive and HER2-low breast cancer; and 3) Treatment-related adverse events. So, let's begin.

# A Practical Definition of HER2-Low Breast Cancer?

Given the complexities of assessing HER2-low and some suggestion of activity of T-DXd irrespective of timepoint of tissue collection, a practical definition of HER2-low is:

- HER2 nonamplified tumor that showed HER2-low expression on any prior specimen in the course of disease

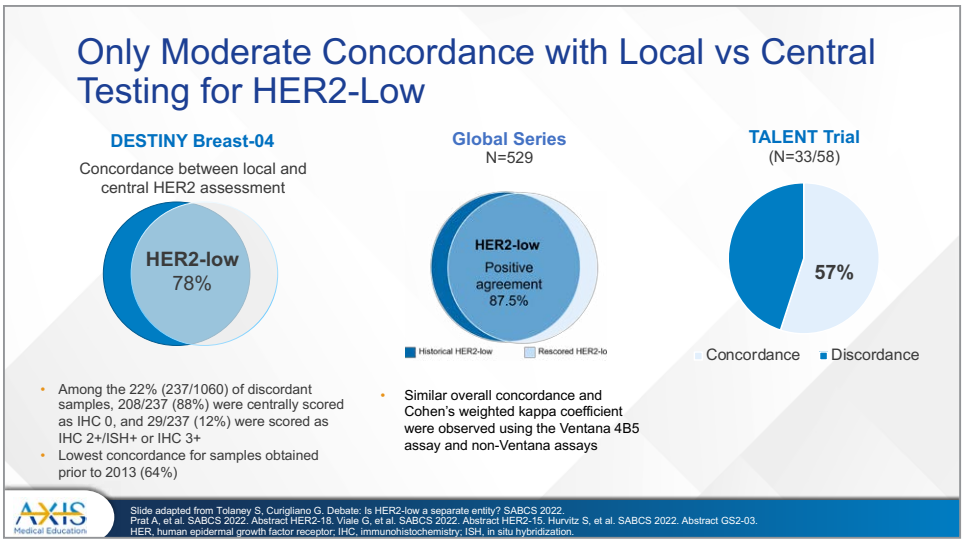



**= 81% HER2 low according to the practical definition**

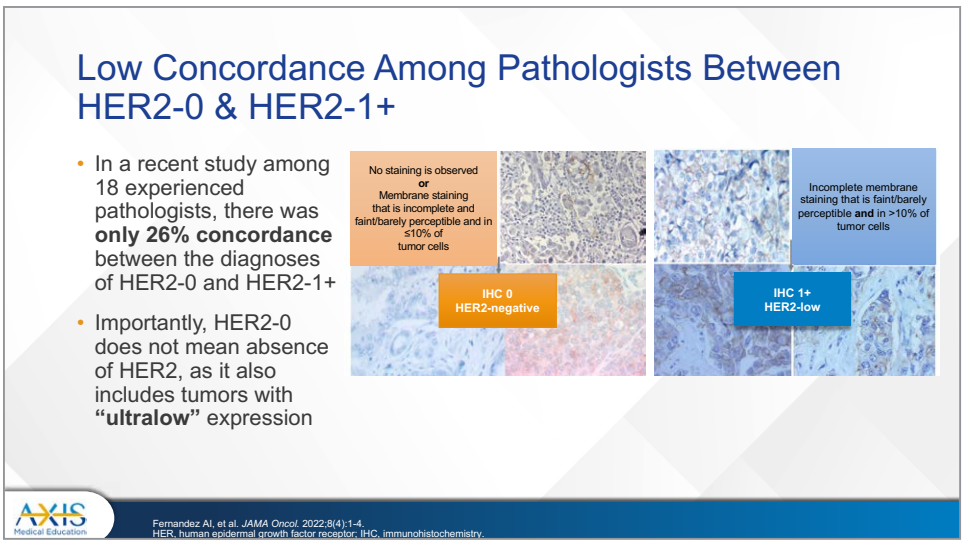
Adapted based on work by Paolo Tarantino, MD
Tarantino P, et al. *Eur J Cancer.* 2022;163:35-43.
HER, human epidermal growth factor receptor; T-DXd, Fam-trastuzumab deruxtecan-nxki.

So, the first topic for today's discussion is really thinking about testing issues. So, I think one of the most common questions we get is how can you tell if a tumor is really HER2-low? What sample do you actually utilize to make a determination if that tumor – if that patient has a HER2-low cancer? And so, this is challenging because we know HER2-low status is dynamic. So, someone can have a tumor that started off, for example, in their primary tumor as HER2-low, and when they recurred, it became HER2-0, or vice versa, it could start off HER2-0 and become HER2-low. And then to make it even more complicated in the metastatic setting, we can see that it even changes over time if they've had several biopsies, you can see someone could be HER2-low at one time point and then later HER2-0, and then become HER2-low again.

And so, if you're seeing a patient at that moment in clinic, what do you call them? Do you call them having HER2-low tumor or HER2-0 tumor? And in truth, the most practical answer I have to that is you would count them as having a HER2-low tumor if they've had a tumor at any point in time that was defined as HER2-low, meaning 1+ or 2+ and not amplified by FISH. And so, that means even if their primary tumor was HER2-low and their most recent metastatic biopsy is HER2-0, I still count them as being HER2-low and still consider them a candidate for T-DXd.




And this is really based on data that emerged from DESTINY-Breast04, where they found that whatever time point you utilized to define that patient as having a HER2-low breast cancer, the benefit of T-DXd was always greater than the benefits for chemotherapy, irrespective of the sample utilized. So, again, it doesn't completely answer the question, if, for example, someone who would have greater benefit if their most recent biopsy was HER2-low compared to HER2-0 because we don't really have data exactly like that. But generally suggests that benefit is likely to be there. And so, even though this is a dynamic marker, again, you could count any time point to make them eligible.




The other challenge we have is that HER2-low is not so reproducible. So, for example, if you showed a pathologist a slide that was 1+ or HER2-0, and you showed several pathologists the slide, you'd see that they don't usually agree on calling the slide 0 or 1+; in fact, there's only a 26% concordance rate in this type of setting, which, you know, does suggest it is challenging to have good reproducibility of this read. And so, you know, sometimes if you have a patient who's HER2-0, I know a lot of clinicians will go back and ask their pathologist, you know, could you reread this? Particularly if it was done in an era prior to the availability of T-DXd because originally, the ASCO CAP Guidelines were built really to select patients for trastuzumab, not so much for T-DXd.

So, I think this is something you can do. I think we also think about rebiopsying a patient who's always been HER2-0. I do like to rebiopsy them and retest because, again, this is a dynamic marker, and again, doesn't have very good reproducibility in the read. And so, I do think about every biopsy in that situation where someone's always had HER2-0 result.

## Case Presentation

- 55-year-old woman
- History
  - Hormone receptor positive HER2-low metastatic BC
  - Diagnosed 4 years ago
- Treatment
  - Has gone through several lines of therapy in the metastatic setting
    - Endocrine based therapies
    - Prior exposure to CDK 4/6 inhibition
    - One prior line of chemotherapy
  - Developed progressive disease on capecitabine
- Biopsy Results
  - Primary breast tumor was HER2-low
  - Bone biopsy was HER2-0

So, what about another question? So, I think another area that we think about are the clinical implications. And so, I think a case really puts this into perspective. So, let's say you had a 55-year-old woman who had a hormone receptor-positive HER2-low metastatic cancer that was originally diagnosed 4 years ago and had, you know, been progressing through several lines of therapy in the metastatic setting. So, had had different endocrine-based therapies, including prior exposure to CDK4/6 inhibition, and had had one prior line of chemotherapy. But the patient did develop progressive disease on capecitabine, and so you're now faced with the question about what treatment to give her. And so, this patient in the metastatic setting had only had a bone biopsy. And so you really only have results from a primary breast tumor which was HER2-low and from a bone biopsy that was HER2-0.

And so, how do you then make a decision, again, because the most recent biopsy is not HER2-low? One thing to keep in mind is that bone biopsies have not been validated for defining a cancer as a HER2-low cancer. So, you should not reliably utilize the results of a bone biopsy to make a decision about calling a tumor HER2-low or HER2-0. So instead, if the only tissue I had available was a bone biopsy, I would go back to the primary tumor to determine if this cancer is HER2-low. Or I would think about, if this patient had another site that could be biopsied that was not bone, to consider a repeat biopsy to determine HER2-low status.

## DESTINY-Breast04:T-DXd in Previously Treated HER2-Low MBC (NCT03734029)

- Phase 3 study of patients with HER2-low MBC who had received 1 or 2 lines of chemotherapy
- HER2-low defined as IHC1+ or IHC2+/ISH-
- 557 patients randomized 2:1 to receive T-DXd or physician's choice of chemotherapy
  - Primary endpoint: PFS in HR+ cohort
  - Secondary endpoints: PFS in all patients, OS in HR+ cohort, OS in all patients

Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.
HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, fam-trastuzumab deruxtecan-nxki

In this particular case, the patient's primary tumor was HER2-low. And so, even though the bone biopsy was read as HER2-0, again, I would count that as not being a reliable read for determining HER2-low. So, I would have thought about this patient as having HER2-low cancer. And in this setting, they've had one line of chemotherapy, so would have been eligible, for example, for DESTINY-Breast04, and would think about T-DXd in this setting.

## Treatment Considerations

- HER2-low: T-DXd
- HER2-0: Sacituzumab govitecan

AXIS Medical Education

## Sacituzumab Govitecan

- Phase III TROPiCS-02 study[1]
  - 543 patients with HR positive, locally recurrent inoperable or metastatic breast cancer
  - Heavily pretreated cohort (median 3 previous lines of chemotherapy)
  - Patients randomized to sacituzumab govitecan (TROP-2 directed ADC) or chemotherapy of physician's choice
    - > Median PFS: 5.5 months with SG vs. 4.0 months with chemotherapy (HR 0.66, 95% CI 0.53-0.83, *P* = 0.0003)
    - > Median OS: 14.4 months with SG vs. 11.2 months with chemotherapy (HR 0.79, 95% CI 0.65-0.96, *P* = 0.02)[2]
    - > Objective response rates: 21% with SG, 14% with chemotherapy

AXIS Medical Education

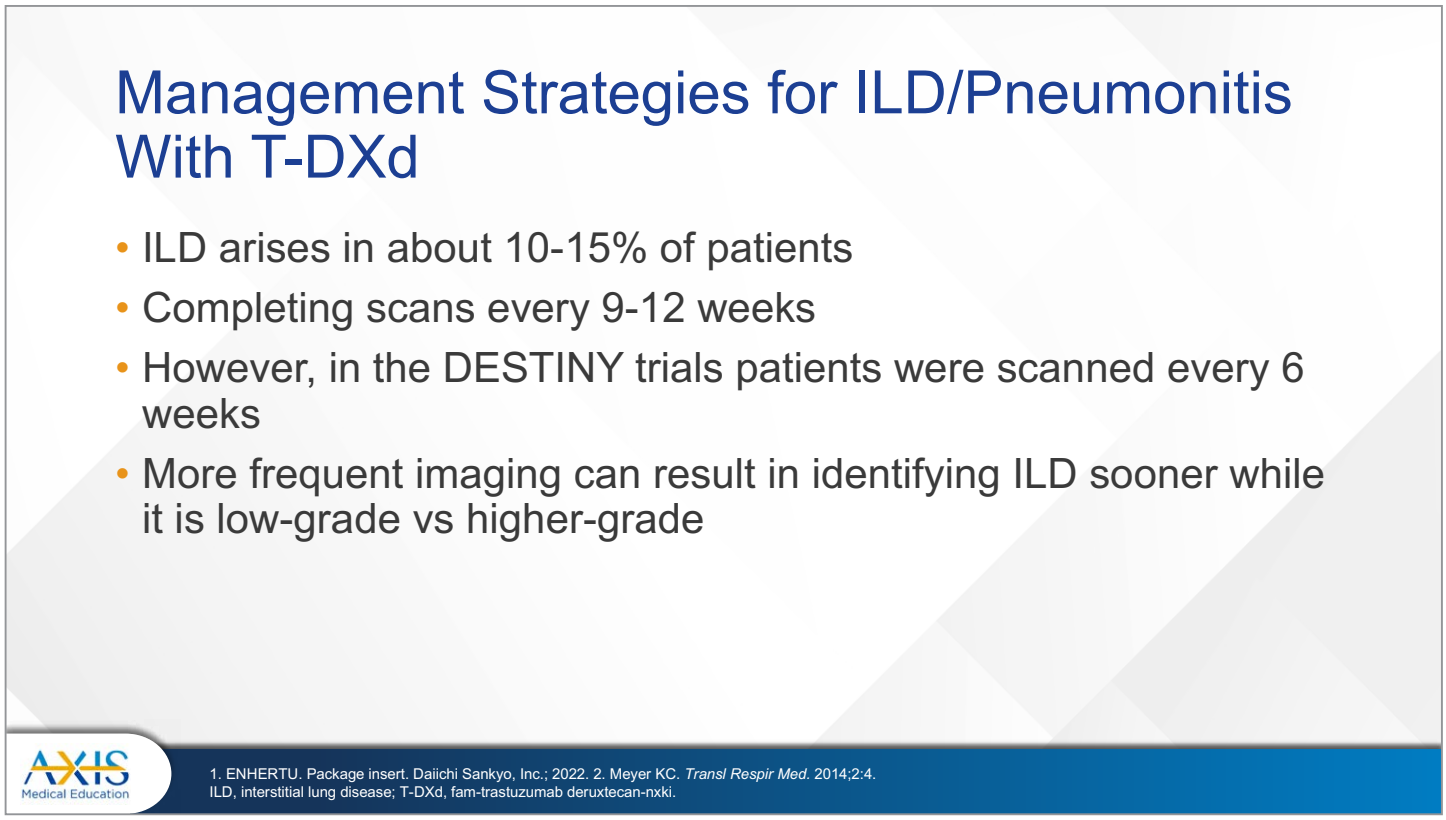
1. Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376. 2. Rugo HS, et al. ESMO Congress 2022. Abstract LBA76.
HR, hormone receptor; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

Let's have her switch the case slightly and say that that original primary tumor was HER2-0 and the bone biopsy was HER2-0, what do you do then? Then I would say you would want to think about getting another biopsy. And so, in this case, if the patient, for example, had liver metastases, I would think about getting a biopsy of the liver metastasis to understand if the patient could have a HER2-low tumor. If it was HER2-low, then I would think about T-DXd.

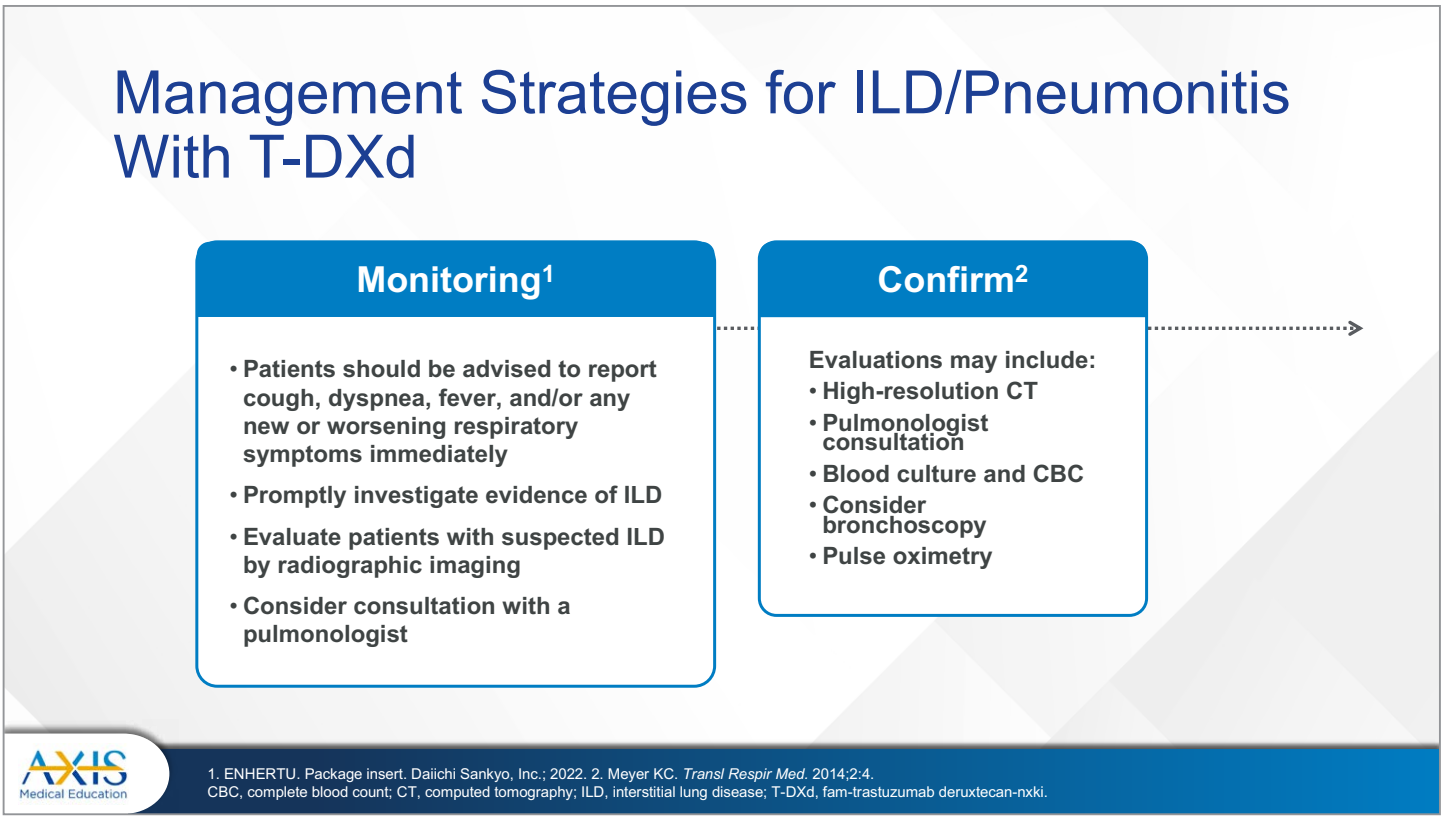
But if it remained HER2-0, then I would think about sacituzumab govitecan, given the data that we have from TROPiCS-02 that suggested that sacituzumab did better than chemotherapy in patients with pretreated metastatic hormone receptor-positive disease.

So again, I think trying to understand the context of whether or not you need to do a repeat biopsy is pretty important. Because again, you don't want to miss out on the opportunity to give that patient T-DXd. And so, getting a repeat biopsy, if they've always been HER2-0, I think can be quite critical.

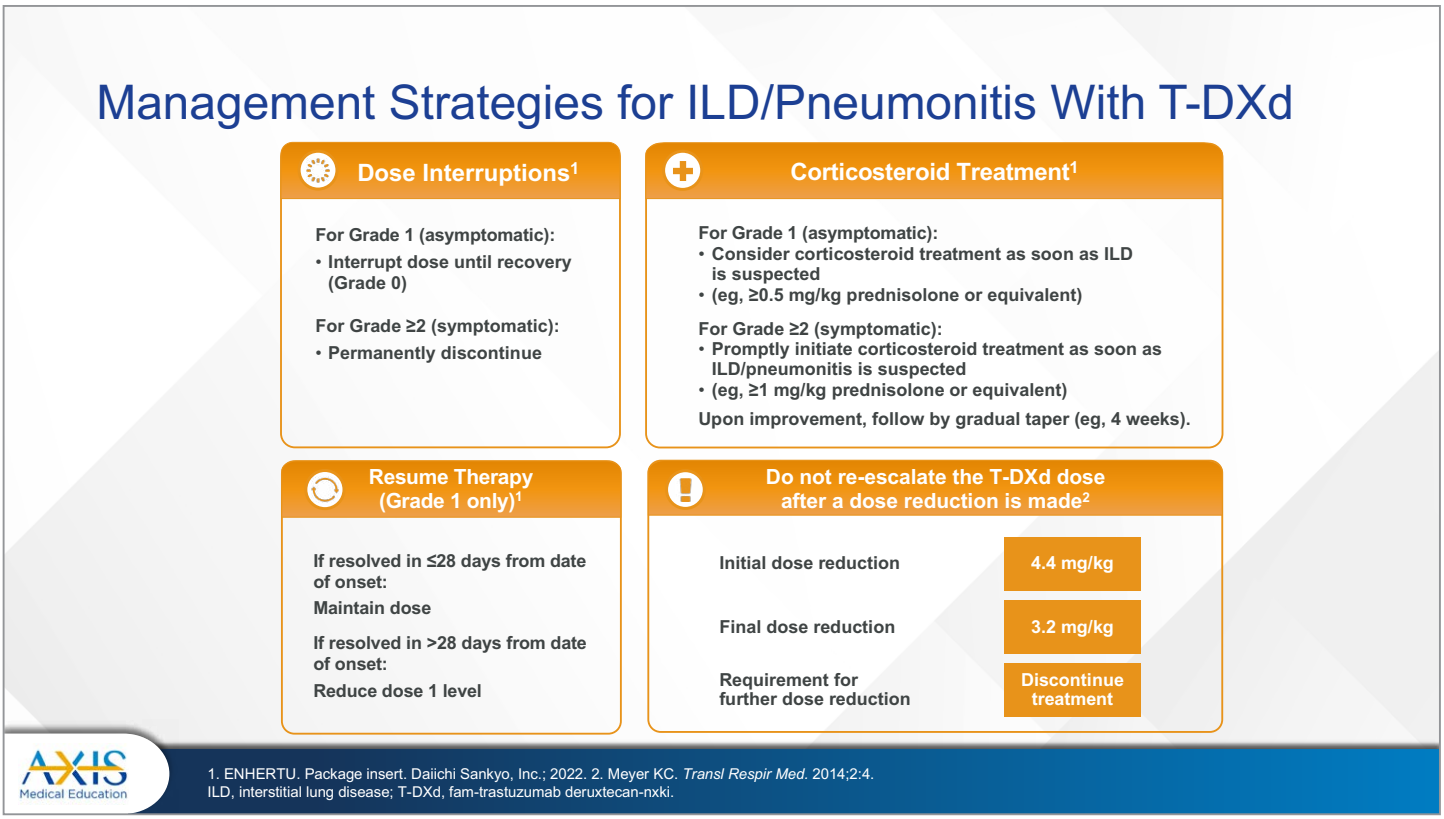
In fact, there was a series, that was looked at from the Mass General Hospital where they looked at patients who had had serial biopsies over time, and they found that by biopsy number 5, for example, everyone was determined to be HER2-low. So, if you do enough biopsies, at some point in time, you're likely to find that the patient has a HER2-low tumor. This was in the triple-negative breast cancer setting, but certainly does go to show why a repeat biopsy may be important.




So, what about another area that comes up when thinking about antibody–drug conjugates, that's the toxicities that arise. And how do we think about monitoring and preventing these side effects? So, one particular side effect of interest is interstitial lung disease that can result from T-DXd. We know this arises in about 10 to 15% of patients. And so, the question is, how often do we need to do imaging to screen patients for potential ILD? Normally, when we're restaging patients in the metastatic setting, we're often doing scans more on the every, you know, 9- to 12- week mark rather than, you know, more frequently. However, in the DESTINY trials looking at T-DXd, all of these trials utilized imaging every 6 weeks. And the idea is that if you do more frequent imaging, it's potentially possible that you'll pick up low-grade ILD before it maybe becomes a higher-grade ILD event. And so, maybe if you pick it up early, you could potentially treat it and allow that patient to be able to continue on T-DXd, rather than have a higher-grade event that could require discontinuation or become a much more serious side effect.



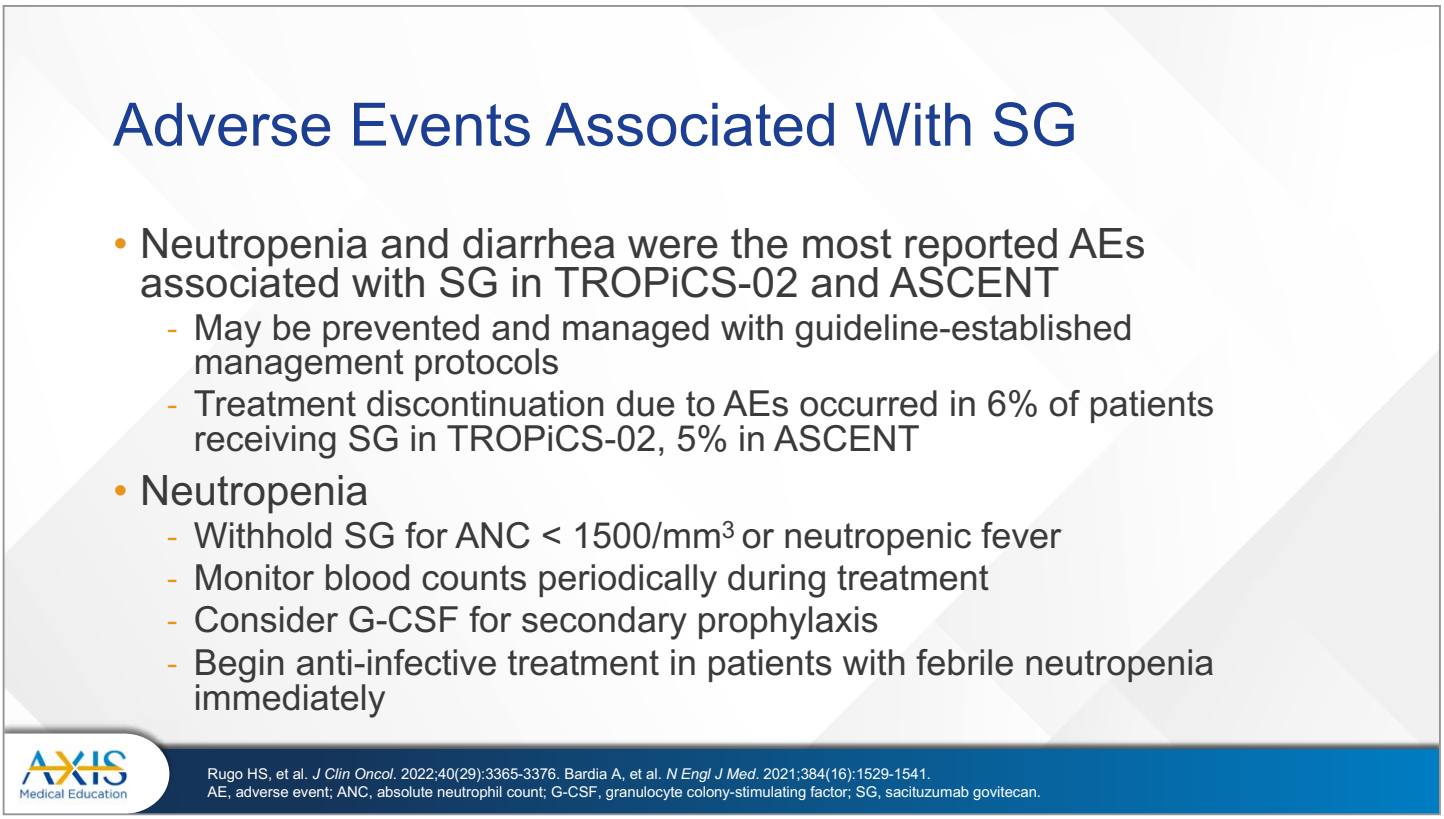

And so, given this, my preference has been to do imaging more frequent. So, I do try to screen patients , and I just do restaging scans every 6 weeks for most of my patients for the first year on T-DXd. We do know that the rates of ILD do plateau at that 12-month mark, so I'm a little more willing to separate out the scans once they get to the year point. However, a lot of insurance won't cover that scan every 6 weeks, and so, sometimes I am doing them every 9 weeks. And again, it totally depends on the clinical situation, and insurance coverage. But I would say it is pretty important to do scans either every 6 to 9 weeks, particularly for that first year that patients are on T-DXd so that you could pick up the ILD, if it arises.




So, the question is what if you do pick up the ILD? So, what if you see on imaging that there are ground-glass changes, but the patient is totally asymptomatic? We would think of this as grade 1 ILD. And in that case, you do need to hold the T-DXd and you do consider administration of steroids. I will say that I do treat all these patients with grade 1 ILD with steroids. I'm hoping that by doing that maybe I speed up the recovery time from the grade 1 ILD. And then I usually reimage at the 3- to 4-week mark to see if those ILD changes have resolved on imaging. If they resolve prior to 28 days, you can restart the T-DXd at the same dose.

However, if it takes longer than 28 days for those ground-glass changes to go away, then you do need to dose reduce once the ground-glass changes have resolved when you restart. You do need to wait to restart until those ground-glass changes have resolved, which is frustrating because sometimes it does take a while, and obviously I start then getting anxious about leaving the patient off therapy for a while. And so, you know it is a tricky situation.

However, for grade 2 ILD, this means that they had changes on imaging consistent with ILD, but they were also symptomatic. So, you know, the patient may have, for example, a dry cough, some shortness of breath, some dyspnea on exertion. And so, if they have grade 2 ILD, you actually have to permanently discontinue the T-DXd and not retry, even when that ILD is resolved. And the reason the guidelines are so strict is because there have been deaths due to ILD, and that is, again, you know, why we just don't think about rechallenging right now. We don't have data to know about the safety of doing that. And so, it's tough because this drug is so effective, but you do have to stop with grade 2 ILD and again, treat with steroids.




Another question that comes up is how to manage side effects from sacituzumab govitecan, where we do see quite a bit of neutropenia. And so, I will say that, you know, in the ASCENT trial and TROPiCS-02 trials, almost 50% of patients did require utilization of growth factor support. But I don't use growth factor prophylactically with sacituzumab, I will use it only at onset of neutropenia. And so, once the neutropenia arises that requires a dose hold, I wait for that neutropenia to resolve, and then when reinitiating the sacituzumab, I do give it with growth factors. The trick is, how do you use the growth factors, because you can use GCSF for example, on days 2, 3, 4, and then use a long-acting pegfilgrastim on day 9. Sometimes you can get away with just the day 9 pegfilgrastim depending on the timing that that neutropenia developed. But I would say I'm not, again, using prophylactic growth factor support with sacituzumab, but again, using it at onset of neutropenia.

So, you know, I realize there are lots of questions that do arise when treating patients with these antibody–drug conjugates. We're fortunate to have these agents to really expand our armamentarium of treatment options for patients and really improve their outcomes. But I appreciate you listening in today, and goodbye.

## REFERENCES


Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384(16):1529-1541.

ENHERTU. Package insert. Daiichi Sankyo, Inc.; 2022.

Fernandez AI, Liu M, Bellizzi A, et al. Examination of low ERBB2 protein expression in breast cancer tissue. *JAMA Oncol*. 2022;8(4):1-4.

Hurvitz SA, Bardia A, Press MF, et al. TRIO-US B-12 TALENT: Neoadjuvant trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early stage breast cancer. Abstract presented at: The 2022 San Antonio Breast Cancer Symposium; San Antonio, TX; December 7, 2022. Abstract GS2-03.

Meyer KC. Diagnosis and management of interstitial lung disease. *Transl Respir Med*. 2014;2:4.

Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387(1):9-20.

Prat A, Modi S, Tsurutani J, et al. Determination of HER2-low status in tumors of patients with unresectable and/or metastatic breast cancer in DESTINY-Breast04. Abstract presented at: The 2022 San Antonio Breast Cancer Symposium; San Antonio, TX; December 7, 2022. Abstract HER2-18.

Rugo HS, Bardia A, Marmé F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022;40(29):3365-3376.

Rugo HS, Bardia A, Marmé F, et al. Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC). Abstract presented at: European Society for Medical Oncology Congress 2022; Paris, France; September 9, 2022. Abstract LBA76.

Tarantino P, Gandini S, Nicolò E, et al. Evolution of low HER2 expression between early and advanced-stage breast cancer. *Eur J Cance*r. 2022;163:35-43.

Tolaney S, Curigliano G. Debate: Is HER2-low a separate entity? Abstract presented at: The 2022 San Antonio Breast Cancer Symposium; San Antonio, TX; December 7, 2022.

Viale G, Basik M, Niikura N, et al. Retrospective Study to Estimate the Prevalence and Describe the Clinicopathological Characteristics, Treatment Patterns, and Outcomes of HER2-Low Breast Cancer. Abstract presented at: The 2022 San Antonio Breast Cancer Symposium; San Antonio, TX; December 7, 2022. Abstract HER2-15.

**About AXIS Medical Education, Inc.**

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

AXIS Medical Education