



HER2 adverse event navigator: A guide for advanced practice providers

This quick-reference clinical aid provides advanced practice provider (APP)-specific guidance for monitoring and managing adverse events (AEs) associated with human epidermal growth factor receptor 2 (HER2)-targeted therapies in non-small cell lung cancer (NSCLC).

Overview of AEs associated with HER2-targeted therapies

Trastuzumab deruxtecan (T-DXd): Antibody-drug conjugate (ADC)

In the phase II studies DESTINY-Lung01 and DESTINY-Lung02, the safety profile of T-DXd was characterized by hematologic, gastrointestinal, and pulmonary toxicity, with interstitial lung disease (ILD) as the toxicity of greatest clinical concern.^{1,2}

- **DESTINY-Lung01:** The most common treatment-related AEs were nausea (73%), fatigue (53%), alopecia (46%), vomiting (40%), neutropenia (35%), and anemia (33%). Grade ≥ 3 events occurred in approximately 46% of patients, most often neutropenia (19%) and anemia (10%)
- **ILD is the key safety signal:** ILD was observed in approximately 26% of patients overall. Most of these patients experienced grade 1–2 ILD (~20%), with ~4% experiencing grade ≥ 3 ILD and ~2% experiencing fatal (grade 5) ILD. Treatment discontinuation occurred in 25% of patients, largely driven by ILD/pneumonitis
- **DESTINY-Lung02:** This study compared 5.4 mg/kg with 6.4 mg/kg dosing and confirmed that toxicity is dose-dependent.
 - **At 5.4 mg/kg:** Patients experienced nausea (67%), fatigue (45%), neutropenia (43%), and ILD (~15%; adjudicated drug-related ILD was 13%, mostly grade 1–2)
 - **At 6.4 mg/kg:** Patients experienced nausea (82%), neutropenia (56%), fatigue (50%), and ILD (adjudicated drug-related ILD was 28%, mostly grade 1–2), including rare fatal cases. Grade ≥ 3 treatment-related AEs occurred in 39% (5.4 mg/kg) vs 58% (6.4 mg/kg) of patients
 - **Clinical takeaway:** The approved 5.4 mg/kg dose has a better benefit–risk profile than the 6.4 mg/kg dose, but ILD surveillance remains essential at every visit regardless of dose

Sevabertinib: Oral HER2/epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)

In the phase I/II SOHO-01 trial, the safety profile of sevabertinib is characterized by gastrointestinal and dermatologic toxicity, with a favorable pulmonary profile.³

- **Diarrhea is the most common AE:** Diarrhea occurred in approximately 82–84% of patients (n=81 pretreated; n=39 first-line), with 3–24% of patients experiencing grade ≥3 diarrhea
- **Dermatologic effects:** Rash occurred in 49–56% of patients, with paronychia/stomatitis observed in 18–25%. Grade ≥3 treatment-related AEs occurred in 20–38% of patients, depending on cohort
- **No cases of ILD:** No cases were reported in this study population

Zongertinib: Oral HER2-selective TKI

In the Beamion LUNG-1 trial, zongertinib toxicity is generally mild to moderate and is consistent with on-target HER2 inhibition.⁴

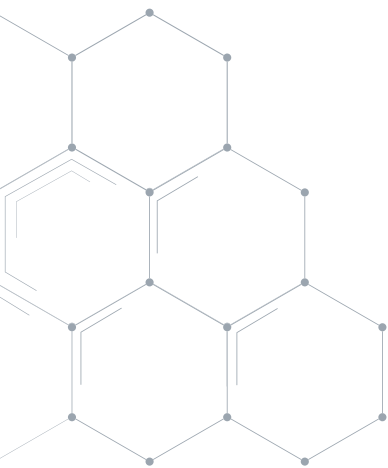
- **Diarrhea is the most common AE:** Common AEs in patients treated with zongertinib at a dose of 120 mg included diarrhea (56%), rash (33%), increased aspartate aminotransferase (24%), increased alanine aminotransferase (21%), and nausea (15%)
 - **Grade ≥3 treatment-related AEs:** These affected ~20–25% of patients; discontinuation due to AEs was relatively uncommon (~6%)
 - **No dominant ILD signal** has been observed to date

Monitoring and early recognition checklist

Early recognition and proactive monitoring are essential across all HER2-targeted therapies. The following checklist highlights key domains that APPs should assess.

Domain	Monitoring considerations (all HER2-targeted therapies)	Specific monitoring considerations with T-DXd	Specific monitoring considerations with HER2 TKIs (sevabertinib/zongertinib)
General status	▪ Assess weight, unintentional weight loss, ECOG performance status, fatigue, hydration, and nutritional intake at each visit	▪ Evaluate fatigue for underlying anemia or ILD	▪ Evaluate fatigue as potentially secondary to diarrhea, poor oral intake, or cumulative toxicity
Respiratory	▪ Assess for cough and dyspnea ▪ Check oxygen saturation if symptomatic	▪ HIGHEST PRIORITY: ILD/pneumonitis ▪ Screen at every visit for new/worsening cough, dyspnea, fever, or desaturation ▪ Interrupt treatment and evaluate urgently if ILD/pneumonitis is suspected	▪ Carry out routine respiratory monitoring (no significant ILD signal identified to date)

Domain	Monitoring considerations (all HER2-targeted therapies)	Specific monitoring considerations with T-DXd	Specific monitoring considerations with HER2 TKIs (sevabertinib/zongertinib)
Lower GI	Monitor stool frequency, abdominal pain, and hydration status	Monitor as needed (diarrhea typically mild to moderate)	- Diarrhea is the dominant toxicity in this class - Monitor stool frequency, nocturnal diarrhea, dehydration, and electrolytes closely - Initiate early antidiarrheal management as needed
Upper GI	Monitor for nausea, vomiting, and appetite loss	- Monitor for nausea, vomiting, and decreased appetite - Recommend proactive (prophylactic) antiemetic management	- Monitor for nausea, vomiting, and decreased appetite - Use proactive antiemetic management as needed
Weight / nutrition	- Record weight at every visit - Assess appetite and nutritional status	Monitor for weight loss driven by nausea or vomiting	Monitor for weight loss driven by diarrhea, stomatitis, or reduced oral intake
Skin	Perform skin exam for rash and pruritus	Dermatologic toxicity is less common; conduct assessment if symptoms occur	- Regular skin assessment is recommended due to the increased frequency of dermatologic toxicities - Monitor for rash, dry skin, and pruritus
Nails	Assess for periungual pain or inflammation	Nail AEs are rare; conduct assessment if symptoms occur	Monitor for nail disorders/paronychia, particularly with prolonged treatment exposure
Oral mucosa	- Perform oral exam - Assess mouth pain/ulceration	Actively assess for stomatitis/oral mucositis at each visit	Actively assess for stomatitis/oral mucositis at each visit
Hematology	Obtain regular CBC measurements	Monitor closely for neutropenia, anemia, and thrombocytopenia	Severe hematologic toxicity is uncommon; routine monitoring is sufficient
Liver function	Check AST, ALT, and bilirubin levels	Standard monitoring is sufficient	Enhanced/more frequent monitoring is recommended
Infection surveillance	Monitor for fever and signs of infection	Monitor closely for signs of infection, especially if the patient has neutropenia	Watch for secondary infection if severe skin or mucosal toxicity is present
Chest imaging	Carry out imaging according to disease status and respiratory symptoms	Perform prompt chest CT for any new respiratory symptoms	- No additional treatment-specific imaging required - Perform imaging according to standard disease follow-up and clinical indications



AE management, supportive care, and escalation

This section outlines key management steps and escalation pathways to support timely intervention for AEs across HER2-targeted therapies.



UNIVERSAL RED FLAGS FOR ANY HER2-TARGETED DRUG

Escalate **immediately** if any of the following are present, regardless of which therapy the patient is receiving:

- New or worsening dyspnea or cough
- Severe diarrhea
- Fever $\geq 38^{\circ}\text{C}$
- Inability to eat or drink
- Rapid clinical decline
- Jaundice / dark urine

Respiratory (critical ILD risk with T-DXd)

	Signs and symptoms	Action
GREEN: Continue treatment	▪ No cough or dyspnea ▪ SpO_2 stable	▪ Continue treatment and routine monitoring
ORANGE: Urgent review ($\leq 24\text{--}48\text{h}$)	▪ New mild cough ▪ Mild exertional dyspnea ▪ Low-grade fever ▪ Slight decrease in SpO_2 from baseline	▪ Interrupt T-DXd until review ▪ Notify oncologist ▪ Consider chest CT
RED: EMERGENCY ACTION	▪ New or worsening dyspnea at rest ▪ $\text{SpO}_2 \leq 90\%$ ▪ Persistent cough + fever ▪ Any suspicion of ILD / pneumonitis on imaging	▪ STOP T-DXd immediately ▪ Emergency CT + hospital admission required ▪ Start corticosteroids under direction of treating physician ▪ Immediate oncology and pulmonary referral required

Diarrhea (main toxicity with TKIs)

	Signs and symptoms	Action
GREEN: Continue treatment	▪ ≤ 3 stools/day above baseline	▪ Hydration advice ▪ Continue treatment
ORANGE: Urgent review ($\leq 24\text{--}48\text{h}$)	▪ ≥ 4 stools/day above baseline ▪ Nocturnal diarrhea ▪ Mild dehydration	▪ Start loperamide immediately ▪ Start oral rehydration ▪ Consider temporary TKI hold ▪ Nurse follow-up in 24h
RED: EMERGENCY ACTION	▪ ≥ 7 stools/day above baseline (Grade ≥ 3) ▪ Signs of dehydration (hypotension, confusion, syncope, dizziness) ▪ Unable to maintain intake ▪ Electrolyte imbalance suspected	▪ STOP HER2 TKI immediately ▪ Administer IV fluids + electrolytes ▪ Same-day medical review required ▪ Consider gastroenterology if refractory

Nausea/vomiting

	Signs and symptoms	Action
GREEN: Continue treatment	Mild nausea only	Perform routine monitoring
ORANGE: Urgent review (≤ 24 –48h)	- Persistent nausea $\pm$ vomiting - Reduced intake	- Intensify antiemetics - Monitor hydration
RED: EMERGENCY ACTION	- Persistent vomiting - Cannot keep fluids down	Interrupt/stop treatment if needed - Administer IV fluids - Urgent medical review required

Skin

	Signs and symptoms	Action
GREEN: Continue treatment	Mild dryness	Recommend emollients
ORANGE: Urgent review (≤ 24 –48h)	- Rash/pruritus - Moderate discomfort	Administer topical steroids $\pm$ antihistamines
RED: EMERGENCY ACTION	- Severe rash - Infection or functional impact	Interrupt treatment - Dermatology referral required

Oral toxicity

	Signs and symptoms	Action
GREEN: Continue treatment	No symptoms	Educate on oral hygiene
ORANGE: Urgent review (≤ 24 –48h)	Mild stomatitis	Recommend mouth rinses and analgesia
RED: EMERGENCY ACTION	Unable to eat or drink	Interrupt treatment - Provide nutritional support

Liver

	Signs and symptoms	Action
GREEN: Continue treatment	Normal LFTs	Perform routine monitoring
ORANGE: Urgent review (≤ 24 –48h)	Mild AST/ALT elevation ($< 3 \times$ ULN)	- Repeat labs - Monitor trends
RED: EMERGENCY ACTION	- AST/ALT ≥ 3–5x ULN - Bilirubin elevation - Jaundice - Dark urine	Stop treatment immediately - Urgent liver work-up required - Refer to hepatology if severe or unclear cause

Hematology

	Signs and symptoms	Action
GREEN: Continue treatment	Stable CBC	Perform routine monitoring
ORANGE: Urgent review (≤ 24 –48h)	- Mild cytopenia - Severe asymptomatic cytopenia (no fever or bleeding)	- Monitor / delay T-DXd treatment cycle if needed - Perform prompt evaluation and monitoring of cytopenia
RED: EMERGENCY ACTION	- Febrile neutropenia - Severe cytopenia with fever or active bleeding	Immediate hospitalization required - Febrile neutropenia requires urgent assessment; hospitalization is needed for most patients, with outpatient management in low-risk patients only - Administer IV antibiotics if febrile - Hematology input required for G-CSF / transfusion

Patient counseling and education tips

Effective patient counseling is essential to ensure safe and consistent use of HER2-targeted therapies. The following tips help APPs to reinforce key self-management behaviors.

- **Understanding treatment goals:** Explain the purpose of treatment, expected benefits, and the importance of taking therapy as prescribed or attending scheduled infusion appointments
- **Communication with the care team:** Encourage patients to report new symptoms early rather than waiting until the next scheduled visit. Early intervention can prevent complications and avoid treatment interruptions
- **Symptom diary:** Recommend keeping a daily record of symptoms, bowel movements, appetite, weight changes, temperature, and any new medications taken
- **Medication adherence:** For oral HER2 TKIs, stress the importance of taking medication exactly as prescribed, at the same time each day, and not modifying doses without consulting the healthcare team
- **Missed doses (oral drugs):** Instruct patients to follow the treatment-specific guidance provided by their care team and not to double doses if a dose is missed
- **Hydration:** Encourage adequate fluid intake, particularly if diarrhea, vomiting, or reduced oral intake occurs
- **Nutrition:** Advise patients to eat small, frequent meals and maintain adequate calorie and protein intake. Referral to a dietitian may be beneficial if appetite decreases or weight loss occurs
- **Fatigue management:** Encourage regular light physical activity as tolerated, adequate rest, and reporting of fatigue that interferes with daily activities

INSTRUCT PATIENTS TO CONTACT THEIR HEALTHCARE TEAM IMMEDIATELY IF THEY EXPERIENCE:

- New or worsening shortness of breath
- New or worsening cough
- Fever $\geq 38^{\circ}\text{C}$ (100.4°F)
- Severe or persistent diarrhea
- Inability to eat or drink adequately
- Persistent vomiting
- Significant weight loss
- Severe rash or painful nail changes
- Mouth sores affecting eating or drinking
- Yellow eyes/skin or dark urine

References

1. Li BT, Smit EF, et al. Trastuzumab deruxtecan in *HER2*-mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386(3):241–251.
2. Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with *HER2*-mutant metastatic non-small-cell lung cancer: Primary results from the randomized, phase II DESTINY-Lung02 trial. *J Clin Oncol* 2023;41(31):4852–4863.
3. Loong HH, et al. Safety and antitumor activity of BAY 2927088 (sevabertinib), a *HER2*/EGFR tyrosine kinase inhibitor, in *HER2*-mutant NSCLC: the SOHO-01 trial. *J Clin Oncol*. 2025;43(16_suppl):8504).
4. Heymach JV, et al. Zongertinib in previously treated *HER2*-mutant non-small cell lung cancer. *N Engl J Med*. 2025;392(23):2321–2333.

Abbreviations

ADC, antibody-drug conjugate

AE, adverse event

ALT, alanine aminotransferase

APP, advanced practice provider

AST, aspartate aminotransferase

CBC, complete blood count

CT, computed tomography

ECOG, Eastern Cooperative Oncology Group

EGFR, epidermal growth factor receptor

G-CSF, granulocyte colony-stimulating factor

GI, gastrointestinal

HER2, human epidermal growth factor receptor 2

ILD, interstitial lung disease

IV, intravenous; LFT, liver function test

NSCLC, non-small cell lung cancer

SpO₂, peripheral oxygen saturation

T-DXd, trastuzumab deruxtecan

TKI, tyrosine kinase inhibitor

ULN, upper limit of normal

