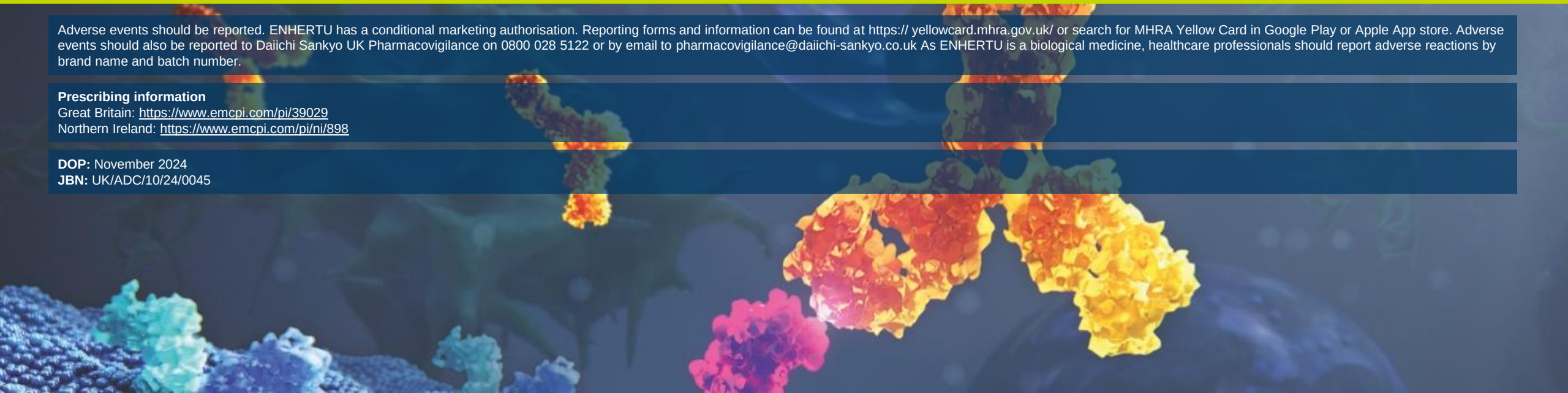
UK Guidance for the monitoring and management of ENHERTU®▼(trastuzumab deruxtecan)-related ILD (interstitial lung disease)

The funding and facilitation of this promotional material was organised and funded by Daiichi Sankyo and AstraZeneca and is intended for UK healthcare professionals only.

These guidelines have been developed by the UK Breast Cancer Group (UKBCG) in collaboration with national ILD experts. The scope, content and final wording in the recommendation has been generated and agreed by all named authors.

The summary of product characteristics (SmPC) should always be consulted for management guidance of patients on ENHERTU.



Adverse events should be reported. ENHERTU has a conditional marketing authorisation. Reporting forms and information can be found at https:// yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in Google Play or Apple App store. Adverse events should also be reported to Daiichi Sankyo UK Pharmacovigilance on 0800 028 5122 or by email to pharmacovigilance@daiichi-sankyo.co.uk As ENHERTU is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Prescribing information
Great Britain: https://www.emcpi.com/pi/39029
Northern Ireland: https://www.emcpi.com/pi/ni/898

DOP: November 2024
JBN: UK/ADC/10/24/0045

Disclaimers

This content is intended for healthcare professionals based in Great Britain and/or Northern Ireland.

This deck should not be used for patient education.

These recommendations are based on discussions between specialist breast oncologists, representing the UK Breast Cancer Group (UKBCG) (Prof. Mark Beresford, Dr Catherine Harper-Wynne, Dr Mukesh Mukesh, Prof. Iain MacPherson and Dr Judy King), and National Interstitial Lung Disease Specialists (Dr Lisa Spencer and Dr Peter George).

These recommendations are the opinions of the authors with no input from AstraZeneca or Daiichi Sankyo.

The development of these recommendations was funded and organised by AstraZeneca.

AstraZeneca and Daiichi Sankyo recommend that ENHERTU- ILD management decisions should be directed by the summary of product characteristics (SmPC) and clinical discretion.

Monitoring and management of ENHERTU®-related ILD

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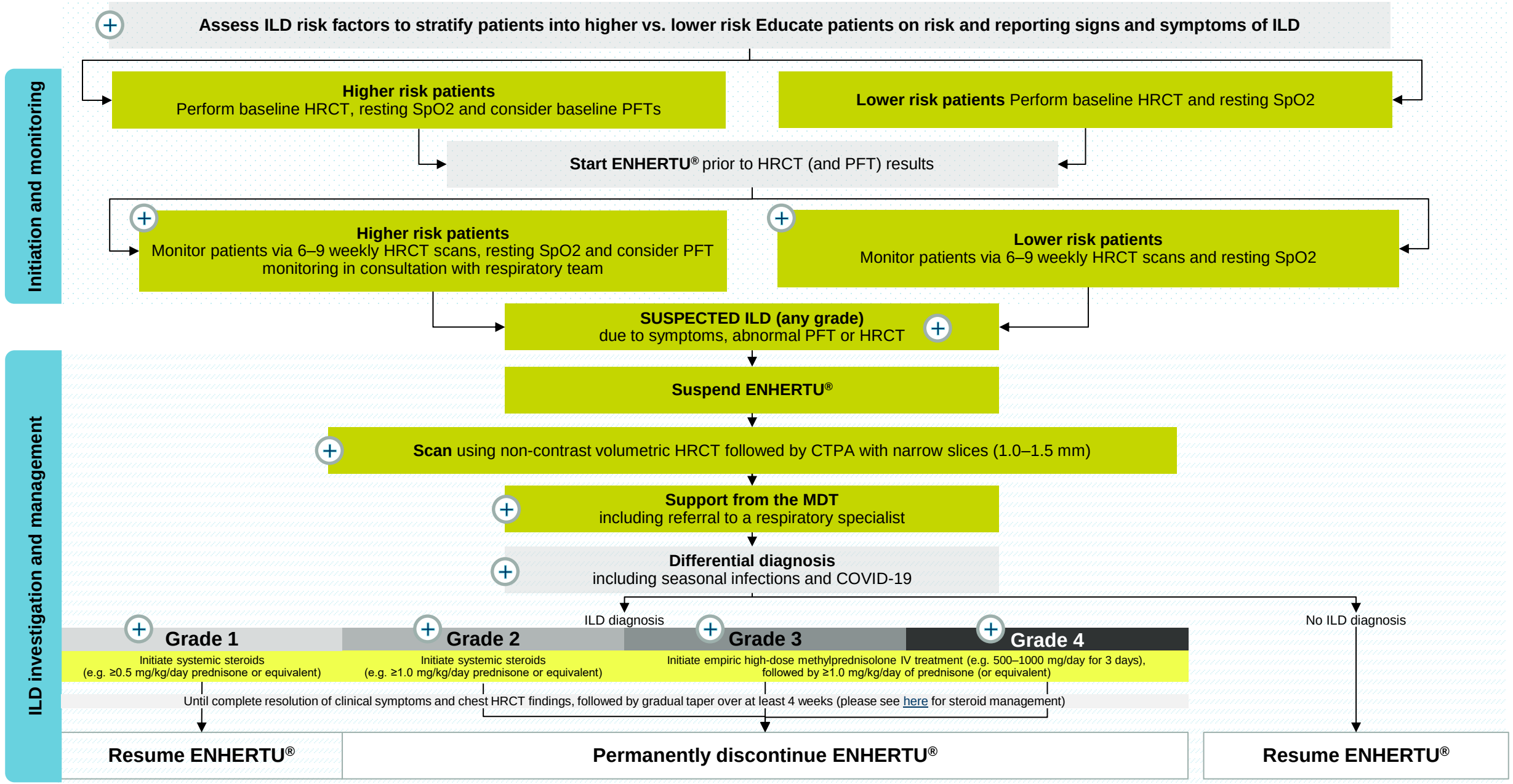


CTPA=computed tomography pulmonary angiogram; HRCT=high-resolution computed tomography; ILD=interstitial lung disease; PFT=pulmonary function test; SpO2=pulse oximetry.

Identified risk factors for developing ILD or a poorer outcome following a diagnosis of ILD[1–3]

STEP 1: Assess your patient's risk of developing ENHERTU-related ILD
Consensus is needed regarding stratification and subsequent management for patients at high vs. low risk of developing ILD. Based on risk factors; if any of the below apply to the patient proceed with higher frequency on-treatment screening (this list is based on identified risk factors for ILD and is not necessarily exhaustive)

- ❑ Age ≥65 years
- ❑ History of lung comorbidities* including prior ILD
- ❑ Japanese heritage
- ❑ Baseline SpO2 <95%
- ❑ Decreased baseline renal function
- ❑ History of smoking

STEP 2: HCPs within the oncology team to assess patients using these questions, to evaluate the development of new respiratory symptoms.
These questions can be used in pre-assessment clinics to obtain a baseline and monitor symptoms throughout ENHERTU treatment.
Reinforce the need for patients to immediately report symptoms/ any worsening in symptoms compared to baseline, to their oncologist or another healthcare professional, if their oncologist is unavailable.

- ❑ Have they been coughing recently? If yes, is it a dry cough?
- ❑ Do they feel short of breath, especially during or after physical activity?
- ❑ Have they experienced any new breathing or respiratory problems?
- ❑ Are they feeling unusually tired without obvious cause?
- ❑ Do they currently have or have they had a fever?
- ❑ Have any of their existing respiratory problems become worse recently?

*Includes asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, and radiation pneumonitis.
ILD=interstitial lung disease; SpO2=pulse oximetry.
1. Powell C, et al. *ESMO Open.* 2022;7:1–11; 2. Canellas, A. et al. *Ann Oncol*. 2024;35:S360; 3. Rugo H, et al. *JCO Oncol Pract*. 2023;19:537–546.

Screening recommended for patients at higher-risk of developing ENHERTU®-related ILD[1]

STEP 1: Baseline assessment prior to initiating ENHERTU

- ❑ Baseline HRCT scan
- ❑ Baseline resting SpO2
- ❑ Consider baseline full PFTs (including gas transfer, spirometry*), sit to stand test in consultation with respiratory

STEP 2: On-treatment monitoring

- ❑ **6–9-weekly** HRCT scans
- ❑ Baseline resting SpO2 readings wherever possible
- ❑ **Consider** full PFTs (including gas transfer, spirometry*), sit to stand test and mobilising patient to seek early desaturation compared to baseline SpO2 in consultation with respiratory and local guidelines
- ❑ Consider assessing patients SpO2 pre- and post- mobilisation (e.g. ask patients to walk around waiting room)
- ❑ Regular breathlessness questionnaire completion

Useful resources

- ❑ NHS sit to stand guidance: https://www.rbht.nhs.uk/our-services/heart/pulmonary-hypertension-service/tests

*Note that no evidence exists to support the use of spirometry to detect low-grade ILD.

HRCT=high-resolution computed tomography; ILD=interstitial lung disease; PFT=pulmonary function test; SpO2=pulse oximetry.

1. Recommendations based on discussions between specialist breast oncologists, representing the UKBCG, and national ILD specialists

Screening recommended for patients at lower-risk of developing ENHERTU®-related ILD[1]

STEP 1: Baseline assessment prior to initiating ENHERTU

- ❑ Baseline HRCT scan
- ❑ Baseline resting SpO2

STEP 2: On-treatment monitoring

- ❑ **6–9-weekly** HRCT scans
- ❑ Regular breathlessness questionnaire completion
- ❑ Consider assessing patients SpO2 pre- and post- mobilisation (e.g. ask patients to walk around waiting room)

Useful resources

- ❑ NHS sit to stand guidance: https://www.rbht.nhs.uk/our-services/heart/pulmonary-hypertension-service/tests
- ❑ 6-minute walk test guidance: https://www.cuh.nhs.uk/patient-information/six-minute-walk-test/

*Note that no evidence exists to support the use of spirometry to detect low-grade ILD.
HRCT=high-resolution computed tomography; ILD=interstitial lung disease; SpO2=pulse oximetry.
1. Recommendations based on discussions between specialist breast oncologists, representing the UKBCG, and national ILD specialists

No single clinical factor definitively confirms ILD, but any of the following observations should trigger suspicion

New onset or deterioration of respiratory symptoms

Dry cough, shortness of breath (dyspnoea), particularly on exertion[1–4]

Changes in PFTs compared with baseline and recent patient measurements, reflecting decreased lung volume[1,6]

Abnormal PFTs (such as a drop of 2% from baseline resting SpO2) should prompt referral to an oncology nurse

Radiological findings[1,4]

Chest radiographic abnormalities[5] on HRCT (or equivalent), specifically the COP pattern

Biopsy findings[1,6]

Microscopic patterns of inflammation and fibrosis (on lung biopsies)

Fever[1,2]

Unexplained fatigue[1,4]

COP=cryptogenic organising pneumonia; HRCT=high-resolution computed tomography; ILD=interstitial lung disease; PFT=pulmonary function test; SpO2=pulse oximetry.

1. Tarantino P, et al. *JAMA Oncol.* 2021;7:1873–1881; 2. Yonemori K, et al. *Cancer Sci.* 2016;107:1830–1836; 3. Antoine M and Mlika M. *StatPearls Publishing*. 2023; 4. Kahlmann V, et al. *Chest.* 2020;158:2026–2033; 5. Nishino M, et al. *JCO Precis Oncol.* 2023;7:e2300391; 6. Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378.

Scan using non-contrast volumetric HRCT followed by CTPA with narrow slices

STEP 1: Perform scans without contrast first

- ❑ Non-contrast volumetric HRCT scan (to diagnose ILD)

STEP 2: Perform scans with contrast second

- ❑ CTPA with narrow slices (to exclude PE)

Considerations

- Specify non-contrast volumetric HRCT followed by CTPA with narrow slices (1.0–1.5 mm) in scan request (HRCT and CTPA can be performed in one sitting with 2 single breath holds [1 per scan])
- Contrast interferes with the images required for ILD diagnosis; ground glass opacities caused by contrast displacing the air, cannot be discerned from physiological ground glass opacities due to disease
- Refer to a respiratory specialist if scans are unclear

CTPA=computed tomography pulmonary angiogram; HRCT=high-resolution computed tomography; ILD=interstitial lung disease; PE=pulmonary embolism.

1. Recommendations based on discussions between specialist breast oncologists, representing the UKBCG, and national ILD specialists

Support MDT and educate patients to communicate signs and symptoms of ILD

STEP 1: Support patients

- ❑ Emphasise the importance of carrying alert cards
- ❑ Recommend the use of an alert wristband
- ❑ Educate patients on the signs and symptoms of ILD

STEP 2: Support front-line HCPs (e.g., GPs and Acute Services)

- ❑ Ensure patients are educated on the importance of presenting wrist bands, alert cards and are aware of the signs and symptoms of ILD
- ❑ Reiterate to patients the importance of immediately reporting these symptoms and flagging to HCPs that these could be associated with ENHERTU treatment

STEP 3: Support nurses

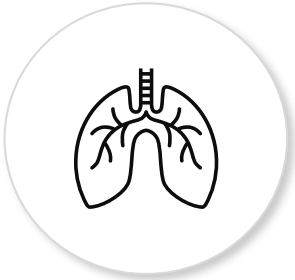
- ❑ Educate nurses on the signs and symptoms of ILD and the appropriation escalation pathways

STEP 4: Support MDT collaboration in suspected cases

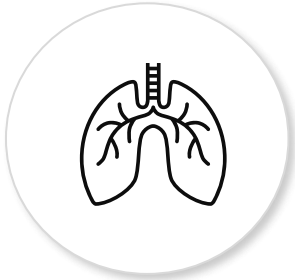
- ❑ Identify local referral pathways to respiratory specialists
- ❑ Collaborate with other disciplines e.g. radiology and respiratory to facilitate fast diagnosis

GP=General Practitioner; HCP=healthcare professional; ILD=interstitial lung disease; MDT=multidisciplinary team.

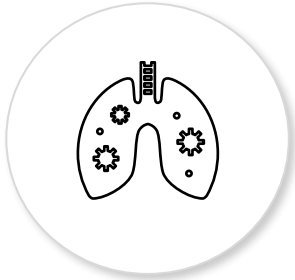
There are many common differential diagnoses and comorbidities of ILD that need to be considered:



Pneumonia (CAP vs. atypical vs. fungal vs. viral)

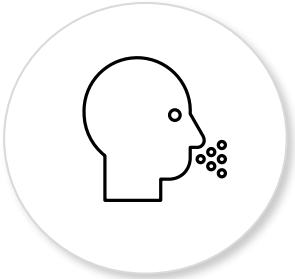


Alveolar haemorrhage

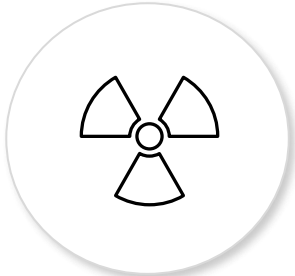


Metastatic involvement of the lung

Systolic or diastolic heart failure



Aspiration pneumonia



Radiation induced lung injury

Pulmonary embolism

COVID-19 and other seasonal infections

Ruling out opportunistic infections, such as pneumocystis pneumonia* (PCP), is essential towards establishing a diagnosis of ENHERTU®-induced ILD
Refer to local Trust Guidelines for the management of patients receiving long-term high-dose steroids for the treatment of PCP

*Caused by pneumocystis jirovecii.

CAP=community-acquired pneumonia; ILD=interstitial lung disease; PCP=pneumocystis pneumonia.

Grade 1: Once ILD is diagnosed, initiate steroids

HCPs should manage ENHERTU-related ILD in collaboration with an MDT; a pulmonologist should be involved early to benefit from their expertise

	Grade 1
Toxicity management[1–4]	• Monitor and closely **follow-up in 2–7 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** (e.g. at least **0.5 mg/kg/day** prednisone or equivalent) until improvement, followed by **gradual taper over at least 4 weeks**, especially for cases with extensive lung involvement or in patients at increased risk for progression of ILD/pneumonitis • If **diagnostic observations continue to worsen** despite initiation of corticosteroids, then **follow Grade 2 guidelines***

T–DXd dose modification[1–4]	• Withhold ENHERTU until recovery (resolved to Grade 0)
	  • 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 ILD/pneumonitis occurs beyond Day 22 and has not resolved within 49 days from the last infusion, discontinue ENHERTU

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

CT=computed tomography; HCP=healthcare professional; ILD=interstitial lung disease; IV=intravenous; MDT=multidisciplinary team; PI=Prescribing Information; SmPC=Summary of Product Characteristics.

1. Supplement to: Cortes J, et al. *N Engl J Med* 2022;386:1143–1154; 2. Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378; 3. Daiichi Sankyo, Inc. ENHERTU PI. April 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf. Accessed November 2024; 4. Daiichi Sankyo UK Ltd. ENHERTU SmPC. April 2024. Available from: https://www.medicines.org.uk/emc/product/12135. Accessed November 2024.

Grade 2: Once ILD is diagnosed, initiate steroids

HCPs should manage ENHERTU-related ILD in collaboration with an MDT; a pulmonologist should be involved early to benefit from their expertise

	Grade 2

Toxicity management[1–4]	• Promptly **treat with systemic steroids** (e.g. at least **1.0 mg/kg/day** prednisone or equivalent) until complete resolution of clinical symptoms and chest CT findings, then followed by a **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** (e.g. 2.0 mg/kg/day prednisone or equivalent) and administration may be switched to IV (e.g. methylprednisolone) followed by a **gradual taper over at least 4 weeks**
	  • **Re-consider additional work-up for alternative aetiologies** as described above
	  • **Escalate care** as clinically indicated

T–DXd dose modification[1–4]	• Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic (≥Grade 2) ILD/pneumonitis

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

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Grade 3/4: Once ILD is diagnosed, initiate steroids

HCPs should manage ENHERTU-related ILD in collaboration with an MDT; a pulmonologist should be involved early to benefit from their expertise

	Grade 3/4

Toxicity management[1–4]	• **Hospitalisation required**
	• Promptly **initiate empiric high-dose methylprednisolone IV treatment** (e.g. 500–1000 mg/day for 3 days), followed by at least **1.0 mg/kg/day** of prednisone (or equivalent) **for at least 14 days** or until complete resolution of clinical symptoms and chest CT findings, then followed by a **gradual taper over at least 4 weeks**
	• **Re-image as clinically indicated**
	• If still no improvement within 3 to 5 days:
	  • **Re-consider additional work-up for alternative aetiologies** as described above
	  • **Consider other immuno-suppressants** and/or treat as per local practice

T–DXd dose modification[1–4]	• Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic (≥Grade 2) ILD/pneumonitis

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

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