ENHERTU®
trastuzumab deruxtecan

POWDER FOR CONCENTRATE FOR
SOLUTION FOR INFUSION
I.V

HCP Guide

AstraZeneca

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Health Care Professional Guide

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ENHERTU®

(Trastuzumab deruxtecan)
Important Risk Minimisation Information on ILD/Pneumonitis with Treatment of ENHERTU (Trastuzumab deruxtecan)

WARNING
Risk of confusion between ENHERTU (trastuzumab deruxtecan) and other trastuzumab-containing products include Kadcyla® (trastuzumab emtansine). There are important differences between the products and confusion during prescription, preparation and administration processes can lead to overdose, undertreating and/or toxicity. Healthcare professionals should use both the invented name Enhertu® and the full INN, trastuzumab deruxtecan, when prescribing, preparing the infusion and administering Enhertu® to patients.

This Health Care Professional (HCP) Guide is

- provided for HCPs to read before prescribing and administering ENHERTU.
- an important tool to ensure the early recognition and diagnosis of ILD/pneumonitis, to allow prompt and appropriate treatment and minimise serious outcomes.
- a reminder to distribute a Patient Card to any patient receiving ENHERTU treatment for the first time or if asked for a new copy.

Not all possible side effects are listed in this Guide.
Please read ENHERTU product label for full details including Posology and Warnings and Special Precautions for use.

What is ENHERTU?

ENHERTU is a human epidermal growth factor receptor 2 (HER2)-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with

- unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  # in the metastatic setting, or
  # in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

What is Interstitial Lung Disease (ILD)/Pneumonitis?

ILD is a broad term for a group of diffuse, parenchymal lung disorders , including pneumonitis and idiopathic pulmonary fibrosis (unknown cause), that present as nonspecific cough, fever, and dyspnoea.

Risk of ILD/Pneumonitis with ENHERTU

ILD/pneumonitis, including fatal cases, have been reported with ENHERTU.

Identification and minimisation of ILD/Pneumonitis

Early diagnosis and appropriate management of events of ILD/pneumonitis are essential to minimise serious outcomes. Patients should be monitored closely, and advised to immediately report signs or symptoms of ILD/pneumonitis (e.g. cough, dyspnoea at rest or exertion , fever, fatigue not otherwise explained, decrease in oxygen saturation, and/or any other new or worsening respiratory symptoms.
Promptly hold drug and initiate management at the first suspicion of ILD/pneumonitis.
A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully.

Investigating suspected ILD/Pneumonitis

Any evidence of ILD/pneumonitis should be promptly investigated for Suspected ILD/Pneumonitis[2,3]

- Consider further evaluations, which could include:
  - High-resolution computed tomography (HRCT)[4]
  - Pulmonologist consultation (infectious disease consultation as clinically indicated)
  - Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
  - Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2)
  - Clinical laboratory tests
    > Arterial blood gases, if clinically indicated
    > Blood culture, blood cell count, differential white blood cell count, C-reactive protein, Covid-19 [SARS-CoV-2] test[5]

Instructions for Management of Suspected ENHERTU related ILD/Pneumonitis:

The goal of ILD management is to suppress inflammation and prevent irreversible fibrosis with potential fatal outcome.[6] Corticosteroid treatment is considered to be most effective during the inflammatory phase of ILD.[7] On occasions, ILD can present acutely and progress rapidly. Appropriate management for ILD should be instituted promptly as per management guidelines below when ILD is suspected and adjusted if an alternative aetiology is identified.

<table>
<tr><th>CTCAE Grade</th><th>Description</th><th>Treatment Modification</th></tr>
<tr><td>Grade 1</td><td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td><td>Interrupt ENHERTU until the event resolves to Grade 0 then:
• if resolved in 28 days or less from date of onset, maintain dose.
• if resolved in greater than 28 days from date of onset, reduce dose one level
<table>
<tr><th>Dose Reduction Schedule</th><th>Breast Cancer</th><th>Gastric Cancer</th></tr>
<tr><td>Recommended starting dose</td><td>5.4 mg/kg</td><td>6.4 mg/kg</td></tr>
<tr><td>First dose reduction</td><td>4.4 mg/kg</td><td>5.4 mg/kg</td></tr>
<tr><td>Second dose reduction</td><td>3.2 mg/kg</td><td>4.4 mg/kg</td></tr>
<tr><td>Requirement for further dose reduction</td><td>Discontinue treatment</td><td>Discontinue treatment</td></tr>
</table>
Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g. ≥ 0.5 mg/kg/day prednisolone or equivalent)</td></tr>
<tr><td>Grade 2</td><td>Symptomatic; medical intervention indicated; limiting instrumental activities of daily living</td><td>Permanently discontinue ENHERTU
• Promptly initiate corticosteroid treatment (e.g. ≥1 mg/kg/day prednisolone or equivalent) as soon as ILD/ pneumonitis is suspected for at least 14 days
• Then gradually taper for at least 4 weeks.</td></tr>
<tr><td>Grade 3</td><td>Severe symptoms; limiting self-care activities of daily living; oxygen indicated</td><td rowspan="2">Permanently discontinue ENHERTU
• Promptly initiate corticosteroid treatment (e.g. ≥1 mg/kg/day prednisolone or equivalent) as soon as ILD/ pneumonitis is suspected for at least 14 days
• Then gradually taper for at least 4 weeks.</td></tr>
<tr><td>Grade 4</td><td>Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)</td></tr>
<tr><td>Grade 5</td><td>Death</td><td></td></tr>
</table>

Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[8]

General Risk Factors Linked to ILD/Pneumonitis related to other drugs

The exact mechanisms via which ENHERTU may cause ILD are not yet known.[9] General risk factors for the development of drug-induced ILD vary according to the disease, drug, and population being considered and include the following.[6,7,10]

- **Patient history of ILD or lung disease:** pre-existing lung disease and reduced lung function are important risk factors for drug-induced ILD[6,10,11,12]
- **Poor overall health:** in oncology, poor performance status or metastatic disease may increase the risk for drug- induced ILD[10]
- **Smoking status:** smokers are at an increased risk for drug induced ILD[7]
- **Advanced age:** the elderly, especially those over 60 years old, may have a significantly higher risk for drug-induced ILD[6,7,12]
- **Ethnicity:** Japanese or African American patients may be at an increased risk for drug-induced ILD[6,13]
- **Male sex:** men may be at an increased risk for drug- induced ILD[7,12]
- **Prior treatment**: prior chemotherapy, treatment with multiple chemotherapy regimens, thoracic radiotherapy, and combination therapy with multiple molecular targeted agents with or without cytotoxic agents may increase a patient's risk for drug-induced ILD[6,7,10]

References

2. Kubo K, Azuma A, Kanazawa M, et al; Japanese Respiratory Society Committee. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respir Invest. 2013;51(4):260-77.
3. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610-21.
4. Conte P, Ascierto PA, Patelli G, et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. ESMO Open. 2022; 7(2):100404.
5. A brief introduction to identifying and managing drug-induced interstitial lung disease. Daiichi Sankyo/AstraZeneca. PP-US-8201a-0397. Nov 2019.
6. Schwaiblmair M, Behr W, Haeckel T, et al. Drug induced interstitial lung disease. Open Respir Med J. 2012; 6:63-74.
7. Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. J Clin Med. 2018;7(10):356.
8. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published 27 Nov 2017.
9. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res. 2016;22(20):5097-108.
10. Yonemori K, Hirakawa A, Kawachi A, et al. Drug induced interstitial lung disease in oncology phase I trials. Cancer Sci. 2016;107(12):1830-6.
11. Sakurada T, Kakiuchi S, Tajima S, et al. Characteristics of and risk factors for interstitial lung disease induced by chemotherapy for lung cancer. Ann Pharmacother. 2015;49(4):398-404.
12. Osawa M, Kudoh S, Sakai F, et al. Clinical features and risk factors of panitumumab-induced interstitial lung disease: a postmarketing all-case surveillance study. Int J Clin Oncol. 2015;20(6):1063-71.
13. Vansteenkiste J. Nivolumab for NSCLC in Japanese patients: similar benefits, but beware of pneumonitis. ESMO Open. 2017;2(suppl 1):e000119.

Talking points for Patient's Visit (First or Following)

At the first visit (before prescribing ENHERTU):

- Inform the patient that they may experience serious side effects affecting the lungs. In a few patients these have the potential to be fatal.
- Check whether the patient has a history of ILD/pneumonitis or a history of lung comorbidities, requiring corticosteroids treatment.
- Check for signs and symptoms of lung problems.
- Inform the patient that early diagnosis and appropriate management of events of ILD/pneumonitis are essential to minimise serious outcomes.
- Instruct the patient to contact you immediately if they experience even mild signs or symptoms of ILD as some events can worsen rapidly if not treated. (The patient should seek immediate medical assistance and should show the Patient Alert Card to doctor(s) at other health facility(ies) if the treating oncologist is not available.
- Instruct the patient not to treat their own symptoms.
- Provide the patient with the Patient Card and discuss the therapy with the patient before starting treatment with ENHERTU.
- Fill in the Patient Card and remind the patient to carry it at all times.

At all visits:

- Check for signs and symptoms of lung problems.
- Remind the patient that early diagnosis and appropriate management of lung problems are essential to minimise life-threatening complications.
- Remind the patient to contact you immediately if they experience even mild signs or symptoms of ILD, as some events can worsen rapidly if not treated.
- Remind the patient of the importance of adhering to scheduled appointments.
- Check if patient carries the Patient Alert Card.

Potential questions to ask your patients to help with early identification of ILD/Pneumonitis:

- Have you been coughing recently? Is it a dry cough?
- Have you had any shortness of breath, especially during or after physical activity?
- Have you experienced any new breathing or respiratory problems?
- If you already have respiratory problems, have they become worse?
- Have you had a fever?
- Have you been feeling tired?
- Do you smoke or use e-cigarettes or vape pens?

Reporting suspected adverse drug reactions (ADRs)

Where to find further information
ENHERTU® physician leaflet
You can also contact us on phone number: 073-2226099
To order additional educational materials please call: 073-2226099
Or email to: Safety.Israel@astrazeneca.com

To report suspected adverse reaction
please contact AstraZeneca at:
https://www.contactazmedical.astrazeneca.com
or
Safety.Israel@astrazeneca.com
You can also call us on phone number: 073-2226099
You may also report side effects to the Israeli ministry of health
by using online form: WWW.HEALTH.GOV.IL
or by entering the link: https://sideeffects.health.gov.il

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