ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

YOUR ENHERTU RESOURCE GUIDE

- Dosage & Administration
- Recommendations for Adverse Reaction Management

Visit ENHERTUhcp.com for more information

Important Safety Information

Indication

ENHERTU is a 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 two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

ENHERTU efficacy evaluated in DESTINY-Breast01

184 female patients with unresectable and/or metastatic HER2+ breast cancer who had received two or more prior anti-HER2 therapies were studied in a Phase 2, multicenter, single-arm trial[1,2]

- Patients received ENHERTU 5.4 mg/kg administered by IV infusion once every 3 weeks until unacceptable toxicity or disease progression

In DESTINY-Breast01: all trial participants had previously received two or more anti-HER2 therapies[1]

100%	66%	100%
Trastuzumab	Pertuzumab	Ado-trastuzumab emtansine (T-DM1)

- Patients had received a median of 5 (range: 2 to 17) prior cancer regimens in the locally advanced/metastatic setting[1]
- Median age was 55 years (range: 28-96)[1]
- ECOG performance status at baseline was 0 in 55% and 1 in 44% of patients[1]

Primary endpoint[1]	• Confirmed objective response rate (ORR), based on RECIST v1.1[a]
Key secondary endpoints[1,2]	• Overall survival (OS), duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), clinical benefit rate (CBR) and best percent change in the sum of diameters of measurable tumors[b]

Selected exclusion criteria[1]

- History of treated interstitial lung disease (ILD) or ILD at screening
- History of clinically significant cardiac disease
- Active brain metastases[c]
- ECOG performance status >1

Multiple confirmatory Phase 3 studies are underway[3]

[a]ORR defined as CR+PR per RECIST v1.1 in the ITT population as evaluated by ICR. ORR 95% CI calculated using Clopper-Pearson method.[1] [b]DCR=CR+PR+SD; CBR=CR+PR+SD≥6 months.[2]
[c]Patients with brain metastases that were untreated, symptomatic, or required therapy within 2 months of randomization were excluded. A prespecified number of patients with inactive brain metastases were enrolled.[4]
CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; ITT, intent-to-treat; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Important Safety Information

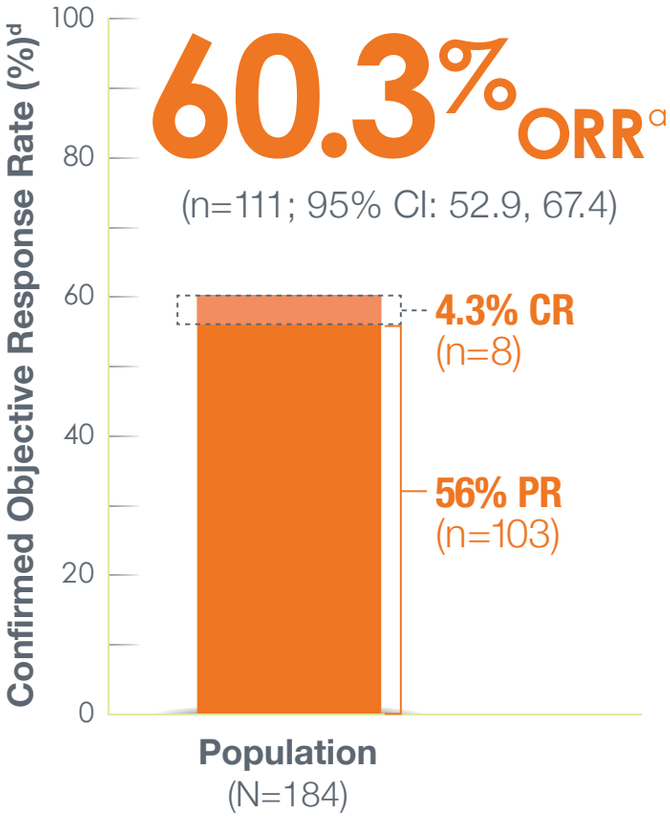
WARNINGS AND PRECAUTIONS

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

ENHERTU monotherapy: efficacy results[1]

Objective response rates (ORR) from the DESTINY-Breast01 Study[1]



ENHERTU anti-tumor activity assessed in these prespecified exploratory patient subgroups[2]

Confirmed ORR by presence of brain metastases[a–c]	
With stable brain metastases	Without brain metastases
58% ORR (n=14/24; 95% CI: 37, 78)	61% ORR (n=98/160; 95% CI: 53, 69)

Confirmed ORR by HR status[a,b]	
HR+	HR-
58% ORR (n=56/97; 95% CI: 47, 68)	66% ORR (n=55/83; 95% CI: 55, 76)

Confirmed ORR by pertuzumab exposure[a,b]	
Prior pertuzumab	No prior pertuzumab
64% ORR (n=78/121; 95% CI: 55, 73)	54% ORR (n=34/63; 95% CI: 41, 67)

[a]ORR defined as CR+PR per RECIST v1.1 in the ITT population as evaluated by ICR. ORR 95% CI calculated using Clopper-Pearson method.[1]
[b]Data based on cut-off date of August 1, 2019.[2]
[c]Patients with inactive (asymptomatic and previously treated) brain metastases. Brain lesions were non-target lesions.[2]

CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR partial response.

Important Safety Information

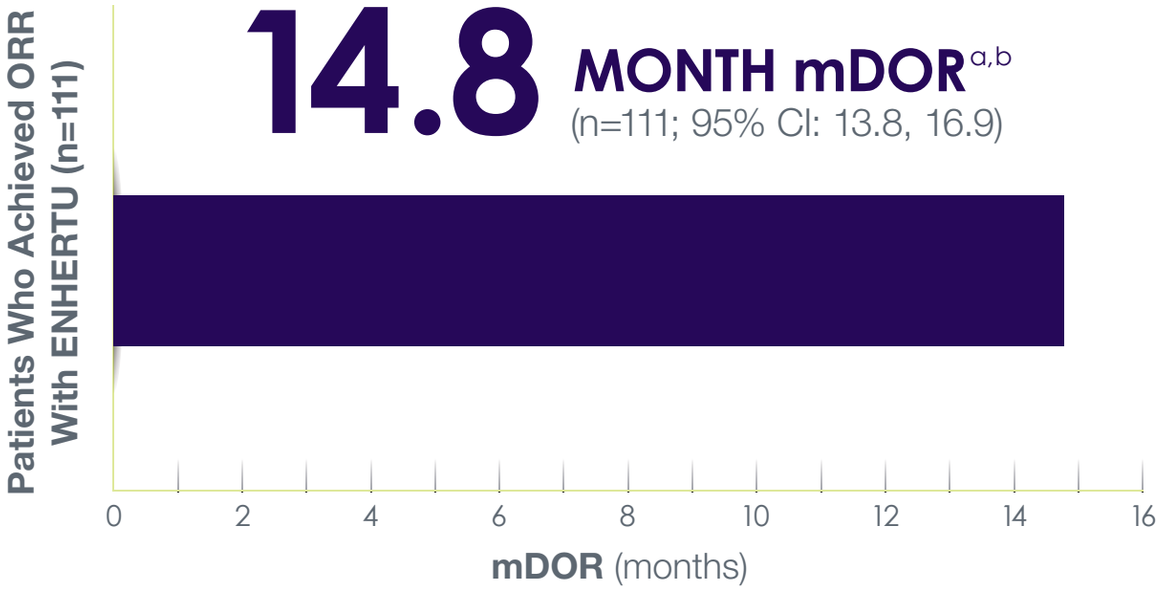
WARNINGS AND PRECAUTIONS

Interstitial Lung Disease / Pneumonitis (continued)

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/ pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level.

ENHERTU monotherapy: efficacy results[1]

Median duration of response (mDOR) from the DESTINY-Breast01 Study[1]



[a]Median DOR based on Kaplan-Meier estimate. 95% CI calculated using Brookmeyer-Crowley method.[1]
[b]DOR based on a median duration of follow-up of 11.1 months.[1]

HR, hormone receptor.

Important Safety Information

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease / Pneumonitis (continued)

Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).

ENHERTU safety evaluated in a pooled analysis[1]

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2+ breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101.[1]

- Median duration of treatment was 7 months (range: 0.7 to 31)[1]
- 94% of patients had visceral disease[1]
- 31% of patients had bone metastases[1]
- 13% of patients had brain metastases[1]
- The majority of adverse reactions were Grade 1 or 2[1]
- In the clinical trials, prophylactic or supportive treatment of ENHERTU induced adverse events was not mandated and was per investigator's discretion and institutional guidelines[4]
- Incidence of alopecia in DESTINY-Breast01 Phase 2 study: Grade 1 (36.4%) and Grade 2 (10.9%)[4]

ENHERTU safety evaluated in a pooled analysis[1] (continued)

Common adverse reactions (≥10% all Grades or ≥2% Grades 3 or 4)[1]

Adverse Reactions		ENHERTU 5.4 mg/kg (N=234)	
		All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal Disorders	Nausea	79	7
	Vomiting	47	3.8
	Constipation	35	0.9
	Diarrhea	29	1.7
	Abdominal pain[a]	19	1.3
	Stomatitis[b]	14	0.9
	Dyspepsia	12	0
General Disorders and Administration Site Conditions	Fatigue[c]	59	6
Skin and Subcutaneous Tissue Disorders	Alopecia	46	0.4[d]
	Rash[e]	10	0
Metabolism and Nutrition Disorders	Decreased appetite	32	1.3
	Hypokalemia	12	3.4
Blood and Lymphatic System Disorders	Anemia[f]	31	7
	Neutropenia[g]	29	16
	Leukopenia[h]	22	6
	Thrombocytopenia[i]	20	3.4
Respiratory, Thoracic, and Mediastinal Disorders	Cough	20	0
	Dyspnea	13	1.3
	Epistaxis	13	0
	Interstitial lung disease[j]	9	2.6[k]
Nervous System Disorders	Headache[l]	19	0
	Dizziness	10	0
Infections and Infestations	Upper respiratory tract infection[m]	15	0
Investigations	Aspartate aminotransferase increased	14	0.9
	Alanine aminotransferase increased	10	0.9
Eye Disorders	Dry eye	11	0.4[n]

Events were graded using NCI-CTCAE version 4.03. N, number of patients exposed; PT, preferred term. Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

[a]Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

[b]Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).

[c]Grouped term of fatigue includes PTs of fatigue and asthenia.

[d]This Grade 3 event was reported by the investigator. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for alopecia is Grade 2.

[e]Grouped term of rash includes PTs of rash, rash pustular, rash maculo-papular

[f]Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.

[g]Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

[h]Grouped term of leukopenia includes PTs of leukopenia, lymphopenia, and white blood cell count decreased.

[i]Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.

[j]Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, alveolitis.

[k]All events had fatal outcomes (n=6).

[l]Grouped term of headache includes PTs of headache, sinus headache, and migraine.

[m]Grouped term of upper respiratory tract infection includes PTs of influenza, influenza like illness, upper respiratory tract infection.

[n]This Grade 4 event was reported by the investigator. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for dry eye is Grade 3.

Selected laboratory abnormalities worsened from baseline reported in patients with HER2+ unresectable or mBC in a pooled analysis of patients treated with ENHERTU (N=234)[1]

Laboratory Parameter		ENHERTU 5.4 mg/kg (N=234)	
		All Grades (%)	Grade 3 or 4 (%)
Hematology	White blood cell count decreased	70	7
	Hemoglobin decreased	70	7
	Neutrophil count decreased	62	16
	Platelet count decreased	37	3.4
Chemistry	Aspartate aminotransferase increased	41	0.9
	Alanine aminotransferase increased	38	0.4
	Hypokalemia	26	3.0

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator. Frequencies were based on NCI-CTCAE v.4.03 grade-derived laboratory abnormalities.

Other clinically relevant adverse reactions reported in <10% of patients were[1]:

- **Injury, Poisoning and Procedural Complications:** infusion-related reactions (2.6%)
- **Blood and Lymphatic System Disorders:** febrile neutropenia (1.7%)

ENHERTU preparation for administration[1]

In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU and not trastuzumab or ado-trastuzumab emtansine.

Reconstitute and further dilute ENHERTU prior to intravenous infusion. Use appropriate aseptic technique.

ENHERTU is a cytotoxic drug. Follow applicable special handling and disposal procedures.[5]



Reconstitution

- Reconstitute immediately before dilution
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL
- Swirl the vial gently until completely dissolved. Do not shake
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours from the time of reconstitution, protected from light. Do not freeze
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated

ENHERTU preparation for administration[1] (continued)



Dilution

- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing 100 mL of 5% Dextrose Injection, USP. Do not use sodium chloride solution, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene)
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake
- Cover the infusion bag to protect from light
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours, protected from light. Do not freeze
- Discard any unused portion left in the vial

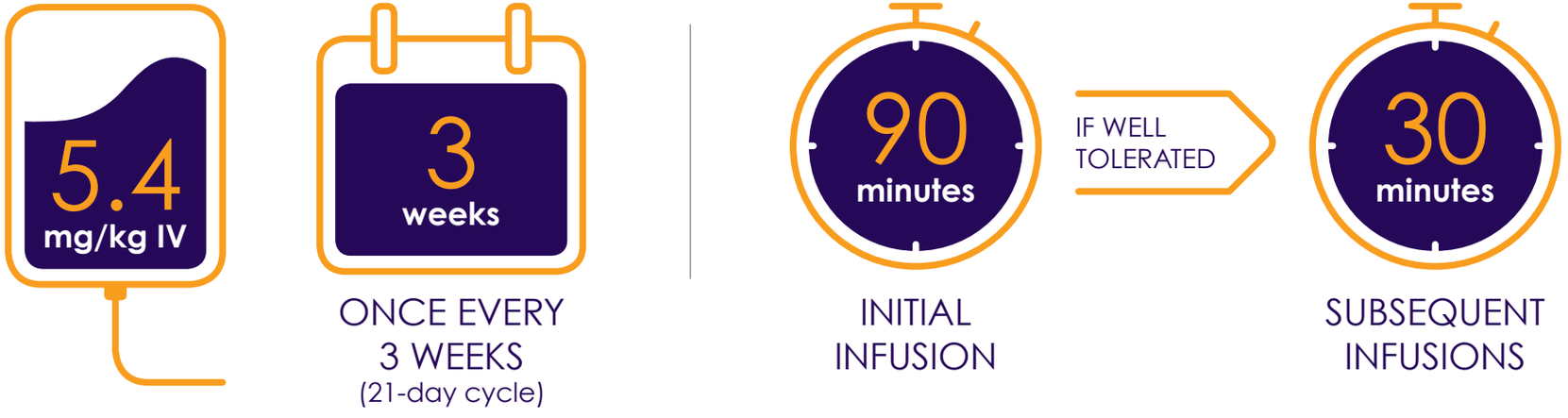


Administration

- If the prepared infusion solution was stored refrigerated (2°C to 8°C [36°F to 46°F]), allow the solution to reach room temperature prior to administration
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene and a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line

ENHERTU dosage and administration

Recommended weight-based dosage and schedule[1]



Until disease progression or unacceptable toxicity[1]

- **Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine**
- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms
- Permanently discontinue ENHERTU in case of severe infusion reactions

Dosage forms and strengths

- For injection: 100 mg of ENHERTU as a white to yellowish-white lyophilized powder in a single-dose vial for reconstitution and further dilution

See Preparation for Administration on pages 8-9.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU per dose modifications provided in the table below.

- Do not re-escalate the ENHERTU dose after a dose reduction is made

If a planned dose is delayed or missed

- ENHERTU should be administered as soon as possible; do not wait until the next planned cycle
- Adjust the schedule of administration to maintain a 3-week interval between doses
- Administer the infusion at the dose and rate the patient tolerated in the most recent infusion

Recommended dose reductions for ENHERTU for adverse reactions[1]

Dose reduction schedule (starting dose is 5.4 mg/kg)	**Dose to be administered**
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment

Most common adverse events in a pooled analysis of patients treated with ENHERTU (N=234)[1]

- Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock

9%
Discontinuation
Due to Adverse Reactions

- The most frequent adverse reaction associated with permanent discontinuation was ILD (6%)
- Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD

33%
Dose Interruptions
Due to Adverse Reactions

- The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD

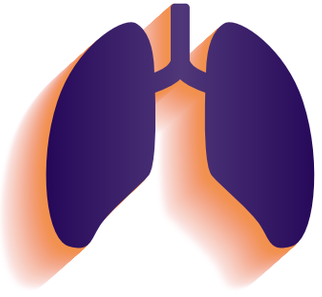
18%
Dose Reductions
Due to Adverse Reactions

- The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia

- The most common adverse reactions (frequency ≥20%) were nausea (79%), fatigue (59%), vomiting (47%), alopecia (46%), constipation (35%), decreased appetite (32%), anemia (31%), neutropenia (29%), diarrhea (29%), leukopenia (22%), cough (20%), and thrombocytopenia (20%)

Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU; monitor patients and initiate management at first sign of ILD[1,a]

- Severe, life-threatening, or fatal ILD, including pneumonitis can occur in patients treated with ENHERTU[1]
- In clinical studies, of the 234 patients with HER2+ unresectable or mBC treated with ENHERTU, ILD and/or pneumonitis occurred in 9% of patients (n=22/234)[1]
  - — Majority of ILD events were Grade 2 (n=12/22)[12]
  - — Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients[1]
- Median time to first onset was 4.1 months (range: 1.2-8.3)[1]



ENHERTU Prescribing Information management recommendations for ILD/pneumonitis, including corticosteroid recommendations, were based on experience in the clinical trials and developed in collaboration with an external ILD expert panel comprised of oncologists, pulmonologists, and radiologists

[a]Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, alveolitis.

Promptly investigate evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist
- Investigation may be prompted by incidental findings on routine scans when checking for progression or symptomatic findings
  - — Diagnosis of ILD requires exclusion of other causes

For asymptomatic ILD (Grade 1)[1]

- Consider corticosteroid treatment (eg, ≥0.5 mg/kg prednisolone or equivalent)
- Interrupt ENHERTU until resolved 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 (see Table on page 11)

For symptomatic ILD (Grade 2 or greater)[1]

- Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg prednisolone or equivalent)
- Upon improvement, follow by gradual taper (eg, 4 weeks)
- Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic ILD

Symptom identification is key to ILD/pneumonitis diagnosis

Monitor patients for signs and symptoms of ILD/pneumonitis: initiate corticosteroid treatment if ILD is suspected[1]

- Cough
- Dyspnea
- Fever
- New or worsening respiratory symptoms

Talk to your patients to raise awareness and help identify symptoms[1]

- Advise patients to contact their healthcare provider immediately for any of the symptoms shown above
- Inform patients of the risks of severe, life-threatening, or fatal ILD
- Advise patients to read the FDA-approved patient labeling (Medication Guide)



Potential questions to ask your patients to help with early identification of ILD[6,7]

- ☐ 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 gotten worse?
- ☐ Have you had a fever?
- ☐ Have you been feeling tired?
- ☐ Have you lost weight?

Talk with your patients about the potential benefits and risks of treatment with ENHERTU

Managing neutropenia with ENHERTU[1]

- Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated
- Based on the severity of neutropenia, manage through treatment interruption or dose reduction
- Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. Febrile neutropenia was reported in 1.7% of patients

Dose modifications for neutropenia[1]

Severity	Treatment Modification
Grade 3 (less than 1.0 to 0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose
Grade 4 (less than 0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 2 or less • Reduce dose by one level (see Dose Modifications for Adverse Reactions on page 11)

Toxicity grades are in accordance with the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

Dose modifications for febrile neutropenia[1]

Severity	Treatment Modification
Absolute neutrophil count of less than 1.0 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of ≥38°C for more than 1 hour	• Interrupt ENHERTU until resolved • Reduce dose by one level (see Dose Modifications for Adverse Reactions on page 11)

Toxicity grades are in accordance with the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

Managing left ventricular dysfunction with ENHERTU[1]

- Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated
- Manage through treatment interruption or discontinuation
- LVEF decrease has been observed with anti-HER2 therapies. In the 234 patients with unresectable or metastatic HER2+ breast cancer who received ENHERTU 5.4 mg/kg, two cases (0.9%) of asymptomatic LVEF decrease were reported

Dose modifications for left ventricular dysfunction[1]

Severity		Treatment Modification
LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with ENHERTU
LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with ENHERTU • Repeat LVEF assessment within 3 weeks
	And absolute decrease from baseline is 10% to 20%	• Interrupt ENHERTU • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU • If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose
LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt ENHERTU • Repeat LVEF assessment within 3 weeks • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU
Symptomatic congestive heart failure (CHF)		• Permanently discontinue ENHERTU

Toxicity grades are in accordance with the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).
LVEF, left ventricular ejection fraction.

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study

Incidence of nausea in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1	41.3%
Grade 2	28.3%
Grade 3	7.6%
Grade 4	0%

- Incidence by Cycle[4]
  - Cycle 1 = 65.2% of patients
  - Cycle 2 = 28% of patients
  - Rates decreased in subsequent cycles
    - No conclusions may be drawn on whether the decreased rates are due to increased tolerance, prophylaxis use, patient discontinuations, dose modifications, etc.
- Prophylaxis and Treatment[4]
  - 70.1% of patients received an antiemetic and/or antinauseant as prophylaxis or for treatment of nausea
  - Available data did not allow for differentiation between prophylaxis use and treatment of nausea
- The median duration of the first event of nausea was 8.0 days (range: 1-323)[4]
- 34.8% of patients had 1 event of nausea, 13.6% had 2 events, and 28.8% had >2 events[4]
- No patients discontinued treatment due to nausea; dose interruption was required in 1.6% of patients and 2.7% required dose reduction[4]

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study (continued)

Incidence of vomiting in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1	27.2%
Grade 2	14.1%
Grade 3	3.8%
Grade 4	0%

- Incidence by Cycle[4]
  - Cycle 1 = 27.2% of patients
  - Cycle 2 = 14.8% of patients
  - Rates decreased in subsequent cycles
    - No conclusions may be drawn on whether the decreased rates are due to increased tolerance, prophylaxis use, patient discontinuations, dose modifications, etc.
- Prophylaxis and Treatment[4]
  - 70.1% of patients received an antiemetic and/or antinauseant as prophylaxis or for treatment of vomiting
  - Available data did not allow for differentiation between prophylaxis use and treatment of vomiting
- The median duration of the first event of vomiting was 3.0 days (range: 1-215)[4]
- 23.4% of patients had 1 event of vomiting, 7.1% had 2 events, and 14.7% had >2 events[4]
- No patients discontinued treatment due to vomiting; dose interruption was required in 1.1% of patients and 1.6% required dose reduction[4]

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study (continued)

Incidence of fatigue in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1	22.3%
Grade 2	20.1%
Grade 3	5.4%
Grade 4	0%

- Incidence by Cycle[4]
  - Cycle 1 = 29.3% of patients
  - Cycle 2 = 11.5% of patients
  - Rates decreased in subsequent cycles
    - No conclusions may be drawn on whether the decreased rates are due to increased tolerance, patient discontinuations, dose modifications, etc.
- The median duration of the first event of fatigue was 15.0 days (range: 1-207)[4]
- 32.1% of patients had 1 event of fatigue, 7.6% had 2 events, and 8.2% had >2 events[4]
- No patients discontinued treatment due to fatigue; dose interruption was required in 1.6% of patients and 3.3% required dose reduction[4]

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study (continued)

Incidence of alopecia in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1[a]	36.4%
Grade 2[b]	10.9%[c]

[a] Grade 1: Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage.[10]
[b] Grade 2: Hair loss of ≥50% of normal that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact.[10]
[c] 0.4% grade 3 alopecia was reported by investigators. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for alopecia was Grade 2.[4]

- Alopecia was most commonly reported in the first 4 cycles[4]

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study (continued)

Incidence of constipation in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1	26.6%
Grade 2	7.1%
Grade 3	0.5%
Grade 4	0%

- Incidence by Cycle[4]
  - Cycle 1 = 15.8% of patients
  - Cycle 2 = 8.2% of patients
  - Rates decreased in subsequent cycles
    - No conclusions may be drawn on whether the decreased rates are due to increased tolerance, prophylaxis use, patient discontinuations, dose modifications, etc.
- Prophylaxis and Treatment[4]
  - 39.7% of patients received medication for constipation
  - Available data did not allow for differentiation between prophylaxis use and treatment of constipation
- The median duration of the first event of constipation was 15.0 days (range: 1-180)[4]
- 25.5% of patients had 1 event of constipation, 5.4% had 2 events, and 3.3% had >2 events[4]
- No patients discontinued treatment due to constipation; No patients required dose interruption or dose reduction[4]

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study (continued)

Incidence of diarrhea in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1	16.8%
Grade 2	8.2%
Grade 3	1.6%
Grade 4	0%

- Incidence by Cycle[4]
  - Cycle 1 = 10.9% of patients
  - Cycle 2 = 7.1% of patients
  - Rates decreased in subsequent cycles
    - No conclusions may be drawn on whether the decreased rates are due to increased tolerance, prophylaxis use, patient discontinuations, dose modifications, etc.
- Prophylaxis and Treatment[4]
  - 19.6% of patients received medication for the treatment of diarrhea
  - Available data did not allow for differentiation between prophylaxis use and treatment of diarrhea
- The median duration of the first event of diarrhea was 4.0 days (range: 1-99)[4]
- 17.4% of patients had 1 event of diarrhea, 7.1% had 2 events, and 2.2% had >2 events[4]
- No patients discontinued treatment due to diarrhea; dose interruption was required in 1.1% of patients and 0.5% required dose reduction[4]

Incidence of select adverse reactions in the Phase 2 DESTINY-Breast01 study (continued)

Incidence of decreased appetite in patients who received ENHERTU 5.4 mg/kg (N=184)[1,4]

Grade	Incidence
Grade 1	20.1%
Grade 2	7.1%
Grade 3	1.6%
Grade 4	0%

- Incidence by Cycle[4]
  - Cycle 1 = 17.4% of patients
  - Cycle 2 = 4.9% of patients
  - Rates decreased in subsequent cycles
    - No conclusions may be drawn on whether the decreased rates are due to increased tolerance, prophylaxis use, patient discontinuations, dose modifications, etc.
- Prophylaxis and Treatment[4]
  - 1.6% of patients received appetite stimulants
  - Available data did not allow for differentiation between prophylaxis use and treatment of decreased appetite
- The median duration of the first event of decreased appetite was 16.0 days (range: 2-288)[4]
- 20.7% of patients had 1 event of decreased appetite, 4.3% had 2 events, and 3.8% had >2 events[4]
- No patients discontinued treatment due to decreased appetite; dose interruption was required in 0% of patients and 1.1% required dose reduction[4]

ENHERTU 4U provides access and financial support resources for patients prescribed ENHERTU

Access 	• Support options are available to help your patients access ENHERTU. Enroll today for help with benefit verifications, understanding prior authorization requirements, and more
Affordability Options 	• We have multiple options to help your patients afford their treatment. Visit ENHERTU4U.com for programs and enrollment information
Nursing Support 	• ENHERTU4U has nurses available to speak to your patients and answer questions about their treatment with ENHERTU. Your patients may call 1-833-ENHERTU (1-833-364-3788) to speak to a nurse

ENHERTU4U does not guarantee access or cost savings for patients prescribed ENHERTU. Restrictions apply.

To enroll your patients visit ENHERTU4U.com or call 1-833-ENHERTU (1-833-364-3788).

Important Safety Information

Indication

ENHERTU is a 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 two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Contraindications

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. Median time to first onset was 1.4 months (range: 0.3 to 18.2). Febrile neutropenia was reported in 1.7% of patients.

Important Safety Information (continued)

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less. Reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3ºC or a sustained temperature of ≥38ºC for more than 1 hour), interrupt ENHERTU until resolved. Reduce dose by one level.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of <40% or absolute decrease from baseline of >20% is confirmed. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

Adverse Reactions

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

Important Safety Information (continued)

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common adverse reactions (frequency ≥20%) were nausea (79%), fatigue (59%), vomiting (47%), alopecia (46%), constipation (35%), decreased appetite (32%), anemia (31%), neutropenia (29%), diarrhea (29%), leukopenia (22%), cough (20%), and thrombocytopenia (20%).

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (53%) as compared to younger patients (42%).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc, at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

ENHERTU®

fam-trastuzumab deruxtecan-nxki

20 mg/mL INJECTION FOR INTRAVENOUS USE

Visit ENHERTUhcp.com for more information

Please see Important Safety Information throughout as well as on pages 25 to 27, and click here for full Prescribing Information, including Boxed WARNING, and click here for Medication Guide.

References: 1. ENHERTU [prescribing information]. Daiichi Sankyo, Inc., Basking Ridge, NJ and AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2019. **2.** Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med.* 2019; doi:10.1056/NEJMoa1914510. Accessed December 11, 2019. **3.** FDA filing Letter DS8201. August 29, 2019. Daiichi Sankyo, Inc. **4.** Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. **5.** OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html. **6.** 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 Investig.* 2013;51(4):260-277. **7.** Ripley BA, Kelil T, Gill RR. Deciphering drug-induced interstitial lung disease. A mechanistic approach. *Appl Radiol.* 2016;45(4):9-18. **8.** Cummings KM, Dresler CM, Field JK, et al. E-cigarettes and cancer patients. *J Thorac Onc.* 2014;9(4):438-441. **9.** Schwaiblmair M, Behr W, Haeckel T, et al. Drug induced interstitial lung disease. *Open Respir Med J.* 2012;6:63-74. **10.** National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. NIH publication 09-5410. Published May 28, 2009; Revised June 14, 2010.

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