דצמבר 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלוני התכשיר- תוספת התוויה:</u>

Enhertu

Powder for concentrate for solution for infusion

הרכב:

Trastuzumab Deruxtecan 100 mg.

התוויה:

<u>HER2-Positive Metastatic Breast Cancer</u>
ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH 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.

<u>HER2-Low Metastatic Breast Cancer</u>
ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

<u>HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer</u>
ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an approved test, and who have received a prior systemic therapy.

<u>HER2-Positive Locally Advanced or Metastatic Gastric Cancer</u>
ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

<u>HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors</u>
ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

התוויות נגד:

Hypersensitivity to the active substance or to any of the excipients.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון העלון לרופא והעלון לצרכן בהתאם להוראות משרד הבריאות מתאריך דצמבר 2024.

העדכונים המהותיים בעלון לרופא הינם:

2. Therapeutic indications
2.1 HER2-Positive Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive <u>(IHC 3+ or ISH</u>

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.

2.2 HER2-Low Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy *[see Dosage and Administration (3.1)]*.

2.3 HER2-Mutant Unresectable or Metastatic ~~HER2-Mutant~~ Non-Small Cell Lung Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an approved test, and who have received a prior systemic therapy.

2.4 HER2-Positive Locally Advanced or Metastatic Gastric Cancer

ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

2.5 HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

. DOSAGE AND ADMINISTRATION

3.1 Patient Selection

HER2-Low Unresectable or Metastatic ~~HER2-Low~~ Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer with ENHERTU based on HER2 expression (IHC 1+ or IHC 2+/ISH-) [see Clinical Studies (14.2)].

HER2-Mutant Unresectable or Metastatic ~~HER2-Mutant~~ NSCLC

Select patients for the treatment of unresectable or metastatic HER2-mutant NSCLC with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in tumor or plasma specimens [see Clinical Studies (14.3)]. If no mutation is detected in a plasma specimen, test tumor tissue.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer

Select patients with locally advanced or metastatic HER2-positive gastric cancer based on HER2 protein overexpression or HER2 gene amplification (IHC 3+ or IHC 2+/ISH positive). Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

Select patients for treatment of unresectable or metastatic solid tumors with ENHERTU based on HER2-positive (IHC 3+) specimens ***[see Clinical Studies (14.5)]***.

3.2 Recommended Dosage and Schedules

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Recommended Dosage for HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant Unresectable or Metastatic NSCLC, and HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors.

The recommended dosage of ENHERTU is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Recommended Dosage for ~~Unresectable~~ HER2-Positive Locally Advanced or Metastatic ~~HER2-Mutant NSCLC~~ Gastric Cancer

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The recommended dosage of ENHERTU is ~~5~~6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

~~Recommended Dosage for Locally Advanced or Metastatic Gastric Cancer~~

~~The recommended dosage of ENHERTU is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.~~

3.3 Dosage Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described in Tables 1 and 2.

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

If a planned dose is delayed or missed, administer 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.

Table 1: Dosage Reduction Schedule

Dose Reduction Schedule	Breast Cancer, ~~and~~ NSCLC, and IHC 3+ Soild Tumors	Gastric Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment	Discontinue treatment

6 WARNINGS AND PRECAUTIONS

6.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU *[see Adverse Reactions (7.1)]*. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment.

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 (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery *[see Dosage and Administration (3.3)]*. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent)) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD *[see Dosage and Administration (3.3)]*.

HER2-Positive or HER2-Low Metastatic Breast Cancer, ~~and~~ HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer ~~and~~, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. ~~Median time to first onset was 6 months (range: 0.9 to 32).~~

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

6.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU.

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 *[see Dosage and Administration (3.3)]*.

HER2-Positive or HER2-Low Metastatic Breast Cancer, ~~and~~ HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, ~~and~~ HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in ~~65~~63% of patients. Seventeen~~Sixteen~~ percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in ~~0.9~~1 % of patients.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

6.3 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.

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 less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) *[see Dosage and Administration (3.3)]*.

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

HER2-Positive or HER2-Low Metastatic Breast Cancer, ~~and~~ HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, ~~and~~ HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.~~9~~8% of patients, of which 0.6%~~0.4%~~ were Grade 3.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

7 ADVERSE REACTIONS

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

HER2-Positive and HER2-Low Metastatic Breast Cancer, ~~and~~ HER2-Mutant NSCLC, and Solid tumors (Including IHC 3+) (5.4 mg/kg)

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in ~~1388~~ 1799 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01,

DESTINY- Breast02, DESTINY-Breast03, ~~DESTINY- Breast02,~~ DESTINY-Breast04, ~~and~~ DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, ~~68~~65% were exposed for greater than 6 months and ~~42~~38% were exposed for greater than ~~one year~~12 months. In this pooled safety population, the most common (≥20%)
adverse reactions (including laboratory abnormalities) were nausea (~~75~~73%), decreased white blood cell count (~~71~~70%), decreased hemoglobin (~~67~~66%), decreased neutrophil count (~~65~~63%), decreased lymphocyte count (~~57~~58%), fatigue (56%), decreased platelet count (48%), increased aspartate aminotransferase (~~45~~47%), increased alanine aminotransferase (43%), ~~increased alanine aminotransferase (43%),~~ vomiting (~~42~~40%), increased blood alkaline phosphatase (~~39~~38%), alopecia (~~39~~34%), constipation (~~35~~33%),
decreased appetite (32%), ~~hypokalemia (30%),~~ decreased blood potassium (31%), diarrhea (~~28~~29%), ~~and~~ musculoskeletal pain (~~32~~24%), and abdominal pain (20%).

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
The data described in WARNINGS and PRECAUTIONS reflect exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01
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HER2-positive (IHC3+) Unresectable or Metastatic Solid Tumors
The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who received ENHERTU 5.4 mg/kg in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINYCRC02 [see Clinical Studies (14.1 and 14.5)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8.3 months (range 0.7 to 30.2)..

The median age was 60 years (range 23 to 96); 74% were female; 51% were White, 42% were Asian, 2.9% were Black or African American, 3.5% were of Hispanic or Latino ethnicity; and 40% had an ECOG performance status 0 and 41% had an ECOG performance status of 1.

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.
ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea.
The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection.

Tables 15 and 16 summarize the common adverse reactions and laboratory abnormalities in DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-Breast01, and DESTINY-CRC02.

Table 15: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in HER2-positive (IHC3+) Patients Treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Adverse Reactions	ENHERTU 5.4 mg/kg N= 347	
	All Grades %	Grade 3 or 4 %
Gastrointestinal Disorders		
Nausea	69	7
Vomiting	35	3.5
Diarrhea	31	4.3
Constipation	28	0.6
Stomatitis[a]	20	0.9

Abdominal pain[b]	18	2.0
Dyspepsia	12	0.3
General Disorders and Administration Site Conditions		
Fatigue[c]	59	10
Pyrexia	11	0
Edema[d]	11	0.6
Metabolism and Nutrition Disorders		
Decreased appetite	34	2.6
Skin and Subcutaneous Tissue Disorders		
Alopecia	34	0.3
Rash[d]	13	0.6
Infections and Infestations		
Upper respiratory tract infection[e]	20	0
Pneumonia	6	2.3
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	19	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough[h]	18	0
Interstitial lung disease[i]	16	0.6
Dyspnea[j]	12	1.7
Nervous System Disorders		
Headache[k]	15	0
Investigations		
Decreased weight	10	0.3

[a] Including stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption, tongue ulceration, cheilitis.
[b] Including abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, gastrointestinal pain.
[c] Including fatigue, asthenia, malaise, lethargy.
[d] Including peripheral edema, edema, localized edema, face edema, skin edema, periorbital edema, eyelid edema
[e] Including rash, pustular rash, maculo-papular rash, papular rash, macular rash, pruritic rash dermatitis acneiform, dermatitis, eczema, palmar-plantar erythrodysesthesia syndrome.
[f] Including influenza, influenza-like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis.
[g] Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, limb discomfort.
[h] Including cough, productive cough, upper-airway cough syndrome
[i] Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, organizing pneumonia, respiratory failure, acute respiratory failure, alveolitis, lung opacity, lymphangitis, pneumonia, bacterial pneumonia, pulmonary fibrosis, and radiation pneumonitis. Grade 5 adjudicated drug-induced ILD events were pneumonitis, respiratory failure, acute respiratory failure, lymphangitis, pulmonary fibrosis.
[j] Including dyspnea, exertional dyspnea
[k] Including migraine, headache, sinus headache.

Other clinically relevant adverse reactions reported in less than 10% of patients were:
Respiratory, thoracic and mediastinal disorders: epistaxis (9%)

- *Nervous System Disorders:* dizziness (9%) [including dizziness, postural dizziness, and vertigo] and dysgeusia (6%)
- *Skin and Subcutaneous Disorders:* pruritus (5%) and skin hyperpigmentation (4.3%) [including skin hyperpigmentation, skin discoloration, pigmentation disorder]
- *Eye Disorders*; blurred vision (4.0%) [including blurred vision, visual impairment]
- *Metabolism and Nutrition Disorders*: dehydration (3.2%)
- *Gastrointestinal Disorders:* abdominal distension (2.6%), flatulence (1.7%) and gastritis (0.9%)
- *Blood and Lymphatic System Disorders:* febrile neutropenia (1.7%)
- *Injury, Poisoning, and Procedural Complications*: infusion-related reactions (1.4%) [including administration related reaction, anaphylactic reaction, hypersensitivity, infusion-related reaction and infusion-related hypersensitivity reaction]

Table 16: Selected Laboratory Abnormalities in HER2-positive (IHC3+) Patients Treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Laboratory Parameter	ENHERTU 5.4 mg/kg N= 347[a]	
	All Grades	Grades 3 or 4

	%	%
Hematology		
Decreased white blood cell count	75	11
Decreased hemoglobin	67	10
Decreased neutrophil count	66	21
Decreased lymphocyte count	58	21
Decreased platelet count	51	7
Chemistry		
Increased aspartate aminotransferase	45	1.5
Increased alanine aminotransferase	44	1.5
Increased blood alkaline phosphatase	36	1.2
Decreased blood potassium	29	6
Decreased sodium	22	2.9
Increased blood bilirubin	15	0.6
Increased blood creatinine	14	0.6

[a] Percentages were calculated using the number of patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

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8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Of the 1287 patients with HER2-positive or HER2-low breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 3.8% were 75 years or older. No overall differences in efficacy within clinical studies 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 or older (59%) as compared to younger patients (49%).

Of the 101 patients with HER2-mutant unresectable or metastatic ~~HER2-mutant~~ NSCLC treated with ENHERTU 5.4 mg/kg, 40% were 65 years or older and 8% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

Of the 125 patients with HER2-~~mutant~~positive locally advanced or metastatic gastric ~~HER2-positive gastric~~ or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg, in DESTINY-PanTumor02, DESTINY-Lung01 or DESTINY-CRC02, 39% were 65 years or older and 9% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

12 CLINICAL PHARMACOLOGY

Exposure-Response Relationships

Exposure relationship for efficacy has not been fully characterized. Higher systemic exposure to fam-trastuzumab deruxtecan was associated with a higher incidence rate of any grade ILD.

12.3 Pharmacokinetics

The pharmacokinetics of trastuzumab deruxtecan was evaluated in patients with cancer. Following a single dose, exposures (C_{max} and AUC) of trastuzumab deruxtecan and released topoisomerase inhibitor (DXd) increased proportionally over a dose range of 3.2 mg/kg to 8 mg/kg (approximately 0.6 to 1.5 times the recommended dose in breast cancer and NSCLC, and HER2-positive (IHC 3+) solid tumors and 0.5 to 1.25 times the recommended dose in gastric cancer).

~~Metastatic Breast Cancer~~

At the recommended dosage of ENHERTU for patients with metastatic breast cancer, NSCLC, and HER2-positive (IHC 3+) solid tumors, the ~~estimated~~ geometric mean (coefficient of variation [CV]%) $C_{max\ ss}$ of trastuzumab deruxtecan and DXd were ~~133~~ 132 µg/mL (19%) and 4.7 ng/mL (~~43~~48%), respectively, and the ~~corresponding~~ AUC_{ss} of trastuzumab deruxtecan and DXd were ~~780~~ 772 µg day/mL (27%) and 29 ng·day/mL (~~42~~48%), respectively . Accumulation of trastuzumab deruxtecan was approximately 35% at steady state (Cycle 3).

At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the geometric mean $C_{max,ss}$ of fam-trastuzumab deruxtecan and DXd were 126 µg/mL (18%) and 5.2 ng/mL (42%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan and DXd were 743 µg·day/mL (26%) and 33 ng·day/mL (43%), respectively. Accumulation of fam-trastuzumab deruxtecan was approximately 39% at steady-state (Cycle 3).

~~Unresectable or Metastatic HER2-Mutant NSCLC~~

~~At the recommended dosage of ENHERTU for patients with HER2-mutant NSCLC, the estimated geometric mean (CV%) Cmax,ss of fam-trastuzumab deruxtecan-nxki and DXd were 141 µg/mL (21%) and 7.2 ng/mL (44%), respectively, and the corresponding AUCss were 775 µg·day/mL (33%) and 40.9 ng·day/mL (43%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 31% at steady-state.~~

~~Locally Advanced or Metastatic Gastric Cancer~~

~~At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the estimated geometric mean (CV%) $C_{max,ss}$ of trastuzumab deruxtecan and DXd were 126 µg/mL (18%) and 5.2 ng/mL (42%), respectively, and the corresponding AUC_{ss} were 743 µg·day/mL (26%) and 33 ng·day/mL (43%). Accumulation of trastuzumab deruxtecan was approximately 39% at steady-state (Cycle 3).~~

Distribution

~~Based on population pharmacokinetic analysis,~~ T~~t~~he estimated volume of distribution of the central compartment (V_c) of trastuzumab deruxtecan was 2.68 L.

~~For humans,~~ DXd plasma protein binding is approximately 97% and the blood-to-plasma ratio is approximately 0.6, in vitro.

Elimination

The median elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan ~~in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately~~ is 5.4-5.7 days. The estimated systemic clearance of trastuzumab deruxtecan was 0.41 L/day.

The median apparent elimination half-life ($t_{1/2}$) of DXd ~~in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately~~ is 5.4-~~5.7~~6.1 days. The estimated ~~apparent~~ systemic clearance of DXd was 18.3 L/h.

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Specific Populations

No clinically significant differences in the pharmacokinetics of trastuzumab deruxtecan or DXd were observed for age (20-96 years), race (Asian ~~vs Non-Asian [White or Black~~), including White, and Black or African American sex, body weight (27.3-125.4 kg), tumor types; mild hepatic impairment ~~(total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST)~~, mild or moderate renal impairment.

The pharmacokinetics of trastuzumab deruxtecan or DXd in patients with moderate to severe hepatic impairment ~~(total bilirubin >1.5 ULN with any AST)~~ or severe renal impairment ~~(CLcr <30 mL/min)~~ is unknown.

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12.4 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of ENHERTU or of other anti-HER2 products.

~~During the median 11 to 18-month treatment period in patient with HER2-positive breast cancer patients in DESTINY-Breast03 and DESTINY-Breast02 with a median ADA sampling period of 13 to 20 months, the ADA incidence is 2.4% (16/658 patients) with 13% (2/16) patients tested positive for t neutralizing antibodies against fam-trastuzumab deruxtecan-nxki.~~

~~During the median 8-month treatment period in HER2-low breast cancer patients in DESTINY-Breast04 with a median ADA sampling period of 8 months, the ADA incidence is 2.0% (7/357 patients) with 0% (0/7) patients tested positive for neutralizing antibodies against fam-trastuzumab deruxtecan-nxki.~~

~~During the median 3.5-month treatment period in HER2-mutant NSCLC patients in DESTINY-Lung02 with a median ADA sampling period of 2.2 months, the ADA incidence is 0.7% (1/143 patients) with 0% (0/1) patients tested positive for neutralizing antibodies against fam-trastuzumab deruxtecan-nxki.~~

~~During the median 4.6-month treatment period in HER2-positive gastric or GEJ adenocarcinoma patients in DESTINY-Gastric01 with a median ADA sampling period of 4.6 months, the ADA incidence is 7.3%(9/123 of patients) with 0% (0/9) patients tested positive forneutralizing antibodies against fam- trastuzumab deruxtecan-nxki.~~

~~Because of the low occurrence of ADA, the effect of ADAs on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of fam- trastuzumab deruxtecan-nxki is unknown.~~

Among patients who received ENHERTU as a single agent and were tested for ADA over a 6 to 9-month treatment period in 12 clinical trials, trastuzumab deruxtecan antibodies developed in 1.5% (27/1798) of patients who received ENHERTU 5.4 mg/kg every three weeks and in 2.6% (21/793) of patients who received ENHERTU 6.4 mg/kg every three weeks. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, safety, or effectiveness of trastuzumab deruxtecan.

The incidence of neutralizing antibodies against trastuzumab deruxtecan was 0.06% and 0% for the respective dosages. Due to the limited number of patients who developed neutralizing antibodies against trastuzumab deruxtecan, the effect of neutralizing antibodies is unknown.

14 CLINICAL STUDIES

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14.5 HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

The efficacy of ENHERTU was evaluated in 192 adult patients with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three multicenter trials: DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. All three studies excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every three weeks. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The major efficacy outcome measure in all three of the studies was confirmed objective response rate (ORR) and an additional efficacy outcome measure was duration of response (DOR). All outcomes were assessed by independent central review (ICR) based on RECIST v1.1.

DESTINY-PanTumor02

DESTINY-PanTumor02 (NCT04482309) was a multicenter, multicohort, open-label trial that included 111 adult patients with locally advanced, unresectable, or metastatic HER2-positive (IHC 3+ by either local or central assessment) solid tumors that

progressed following at least one prior systemic regimen in the advanced/metastatic setting or that had no satisfactory alternative treatment option.

The median age was 64 years (range 23 to 85); 59% were female; 58% were White, 34% were Asian, and 4% were Black or African American; 3% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of either 0 (49%) or 1 (51%) at baseline. The median number of prior regimens in any treatment setting was 2.

DESTINY-Lung01

DESTINY-Lung01 (NCT03505710) was a multicenter, open-label, 2-cohort trial that included 17 patients with previously treated, unresectable, or metastatic, centrally confirmed HER2-positive (IHC 3+) NSCLC. Patients must have relapsed from or be refractory to standard treatment or have no available standard treatment.

The median age was 59 years (range 31 to 74); 59% were male; 65% were White, 18% were Asian, and 12% were Black or African American. Patients had an ECOG performance status of either 0 (12%) or 1 (88%) at baseline. The median number of prior regimens in any treatment setting was 3.

DESTINY-CRC02

DESTINY-CRC02 (NCT04744831) was a multicenter, randomized, 2-arm trial that included 64 patients with previously treated, unresectable or metastatic centrally confirmed HER2-positive (IHC 3+) colorectal cancer (CRC). Unless contraindicated, patients must have received fluoropyrimidine, oxaliplatin and irinotecan. If clinically indicated, patients must have received anti-EGFR treatment, anti-VEGF treatment and anti-PDL1 therapy.

The median age was 58 years (range 25 to 78); 53% were male; 55% were Asian and 41% were White; 1.6% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of either 0 (58%) or 1 (42%) at baseline. The median number of prior regimens in any treatment setting was 4.

Efficacy results are summarized in Table 23 and Table 24.

Table 23: Efficacy Results in HER2-Positive (IHC 3+) Patients in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Efficacy Parameter	**DESTINY-PanTumor02 N=111**	**DESTINY-Lung01 N=17**	**DESTINY-CRC02 N=64**
Confirmed ORR (95% CI)†‡	51.4% (41.7, 61.0)	52.9% (27.8, 77.0)	46.9% (34.3, 59.8)
Complete Response Rate	2.7%	5.9%	0%
Partial Response Rate	48.6%	47.1%	46.9%
Duration of Response†			
Median§, months (range)	19.4 (1.3, 27.9+)	6.9 (4.0, 11.7+)	5.5 (1.3+, 9.7+)

CI=Confidence interval
†Assessed by independent central review
‡CI is derived based on the Clopper-Pearson method
§Calculated using the Kaplan-Meier technique
+ Denotes ongoing response

Table 24: Efficacy Results in HER2-positive (IHC 3+) Patients by Tumor Type in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Tumor Type	**Patients**	**Confirmed ORR†**	**DOR† Range**

	N	% (95% CI)‡	(months)
Colorectal Cancer	64	46.9 (34.3, 59.8)	(1.3+, 9.7+)
Bladder Cancer	27	37.0 (19.4, 57.6)	(2.8, 19.7+)
Biliary Tract Cancer	22	45.5 (24.4, 67.8)	(2.1, 22.0+)
NSCLC	17	52.9 (27.8, 77.0)	(4.0, 11.7+)
Endometrial Cancer	16	56.3 (29.9, 80.2)	(5.8, 23.7+)
Ovarian Cancer	15	66.7 (38.4, 88.2)	(1.3, 27.9+)
Cervical Cancer	10	70.0 (34.8, 93.3)	(7.2+, 25.0+)
Salivary Gland Cancer	9	66.7 (29.9,92.5)	(5.6, 20.1)
Pancreatic Cancer	5	0 (0, 52.2)	NA
Oropharyngeal Neoplasm	1	PR	15.3
Vulvar Cancer	1	PR	2.6
Extramammary Paget's Disease	1	PR	19.4
Lacrimal Gland Cancer	1	PR	19.8+
Lip and/or Oral Cavity Cancer	1	SD	NA
Esophageal Adenocarcinoma	1	PR	2.8
Esophageal Squamous Cell Carcinoma	1	PD	NA

CI=Confidence interval, NA=Not applicable, PD=Progressive disease, PR=Partial response, SD=Stable disease
†Assessed by independent central review
‡CI is derived based on the Clopper-Pearson method
+ Denotes ongoing response

העדכונים המהותיים בעלון לצרכן הינם:

1. למה מיועדת התרופה?

- **סרטן שד גרורתי מסוג HER2-חיובי**

אנהרטו מיועד לטיפול במטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג HER2-חיובי (IHC 3+ or ISH positive), אשר קיבלו טיפול קודם כנגד HER2 עבור:

- מחלתם בשלב הגרורתי

או

- מחלתם בשלב המוקדם כטיפול טרום-ניתוחי או משלים, ואשר מחלתם נשנתה במהלך 6 חודשים מסיום הטיפול עבור מחלתם המוקדמת

- **סרטן שד גרורתי מסוג HER2-נמוך**

אנהרטו מיועד לטיפול במטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג HER2-נמוך (IHC 1+ or IHC 2+/ISH-), אשר קיבלו טיפול כימותרפי קודם בשלב הגרורתי או שמחלתם נשנתה במהלך 6 חודשים מסיום הטיפול הכימותרפי המשלים.

- **סרטן ריאות לא נתיח או גרורתי מסוג תאים לא קטנים (Non-Small Cell Lung Cancer – NSCLC) עם מוטציית HER2 ~~לא נתיח או גרורתי~~**

אנהרטו מיועד לטיפול במטופלים מבוגרים עם סרטן ריאות מסוג תאים לא קטנים (NSCLC) לא נתיח או גרורתי, אשר לגידולים שלהם יש מוטציות מפעילות HER2 (ERBB2), כפי שזוהו בבדיקה מאושרת, ואשר קיבלו טיפול סיסטמי קודם

- **סרטן קיבה ~~מקומי~~מתקדם מקומית או גרורתי מסוג HER2-חיובי**

אנהרטו מיועד לטיפול במבוגרים עם אדנוקרצינומה של הקיבה או מעבר ושט קיבה, עבור מחלה מתקדמת או גרורתית מסוג HER2-חיובי (IHC 3+ or IHC 2+/ISH positive), אשר טופלו בעברם עם טראסטוזומאב

- **גידולים מוצקים שאינם נתיחים או גרורתיים מסוג HER2-חיובי (IHC 3+)**

אנהרטו מיועד לטיפול במבוגרים עם גידולים מוצקים שאינם נתיחים או גרורתיים, מסוג HER2-חיובי (IHC 3+), אשר קיבלו טיפול סיסטמי קודם ואין להם אפשרויות טיפול חלופיות מספקות

4. תופעות לוואי

תופעות הלוואי השכיחות ביותר בעת נטילת אנהרטו לטיפול בסרטן שד גרורתי וסרטן ריאות מסוג תאים לא קטנים (Non-Small Cell Lung Cancer – NSCLC) עם מוטציית HER2, וגידולים מוצקים אחרים מסוג HER2-חיובי, כוללות:

- בחילה
- ספירה נמוכה של תאי דם לבנים
- ספירה נמוכה של תאי דם אדומים
- תחושת עייפות
- הקאות
- נשירת שיער
- עלייה בתפקודי כבד בבדיקות דם
- ספירת טסיות נמוכה
- עצירות
- ירידה בתאבון
- שלשול
- רמה נמוכה של אשלגן בדם
- כאב בשרירים או בעצמות
- כאב באזור הבטן

מקרא לעדכונים המסומנים:

תוספות או מחיקות טקסט מסומנות בצבע.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

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