יולי 2023

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עלון לתכשיר: Enhertu – הוספת שתי התוויות</u>

הרכב:

Trastuzumab Deruxtecan 100 mg.

התוויה:

- HER2-Positive Metastatic Breast Cancer
  Enhertu is 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.
- 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
- 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.
- •Locally Advanced or Metastatic Gastric Cancer
  Enhertu is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or astroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

התווית נגד:

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

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות מתאריך אפריל 2023.

2.1 HER2-Positive Metastatic Breast Cancer

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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 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.

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3. DOSAGE AND ADMINISTRATION

3.1 Patient Selection ~~for Locally Advanced or Metastatic Gastric Cancer~~

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)].

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.

Locally Advanced or Metastatic Gastric Cancer

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3.2 Recommended Dosage and Schedules

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Recommended Dosage for Unresectable or Metastatic HER2-Mutant NSCLC

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.

3.4 Preparation ~~for~~and Administration

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Administration

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- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.

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.

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Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In ~~clinical studies~~, ~~of the 491~~ patients with ~~unresectable or~~ metastatic ~~HER2-positive~~ breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in ~~13~~12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in ~~1.4~~1.0% of patients treated with ENHERTU. Median time to first onset was 5~~.5~~ months (range: ~~1.1~~ 0.9 to ~~20.8~~23).

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

In ~~DESTINY-Gastric01, of the 125~~ 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~~.0~~).

6.2 Neutropenia

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Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In ~~clinical studies, of the 491~~ patients with ~~unresectable or~~ metastatic ~~HER2-positive~~ breast cancer and HER2-mutant NSCLC ~~who received~~treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in ~~68~~65% of patients. ~~Eighteen~~ Sixteen percent had Grade 3 or 4 ~~decrease~~ decreased ~~in~~ neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: ~~6~~ 2 to 664). Febrile neutropenia was reported in 1.~~2~~1% of patients.

~~Locally Advanced or Metastatic Gastric Cancer~~

~~In DESTINY-Gastric01, of the 125 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

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Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In ~~the 491~~ patients with ~~unresectable or~~ metastatic ~~HER2-positive~~ breast cancer and HER2-mutant NSCLC ~~who received~~treated with ENHERTU 5.4 mg/kg, ~~13 cases (2.6%) of asymptomatic~~ LVEF decrease ~~were~~ was reported in 3.6% of patients, of which 0.4% were Grade 3.

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~~Locally Advanced or Metastatic Gastric Cancer~~
~~In DESTINY-Gastric01, of the 125 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.~~

6.4 Embryo-Fetal Toxicity

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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~~ after 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 *[see Use in Specific Populations (8.1, 8.3)]*.

7.1 Clinical Trials Experience

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Metastatic Breast Cancer and HER2-Mutant ~~Solid Tumors~~NSCLC (5.4 mg/kg)

~~The pooled safety population for patients with metastatic breast cancer described in the WARNINGS AND PRECAUTIONS reflects exposure to ENHERTU at 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) in 491 patients in DESTINY-Breast03, DESTINY-Breast01, and Study DS8201-A-J101. Among 491 patients who received ENHERTU, the median duration of treatment was 13 months (range: 0.7 to 37). In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (78%), decreased white blood cell count (74%), decreased hemoglobin (68%), decreased neutrophil count (68%), increased aspartate aminotransferase (58%), fatigue (57%), decreased lymphocyte count (56%), vomiting (50%), decreased platelet count (49%), increased alanine aminotransferase (48%), increased blood alkaline phosphatase (45%), alopecia (41%), constipation (35%), hypokalemia (33%), decreased appetite (32%), diarrhea (31%), musculoskeletal pain (28%), increased transaminases (27%), respiratory infection (24%), headache (21%), and abdominal pain (21%).~~

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and ~~NCT04644237~~DESTINY-Lung02. Among these patients, 65% were exposed for greater than 6
months and 39% were exposed for greater than one year. In this pooled safety population, the most common (≥20%) adverse reactions (including laboratory abnormalities) were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

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.

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

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The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count~~, decreased~~, decreased neutrophil count~~, decreased~~, increased aspartate aminotransferase~~, increased~~, decreased hemoglobin~~, decreased~~, decreased lymphocyte count~~ decreased~~, increased alanine aminotransferase~~ increased~~, decreased platelet count~~ decreased~~, fatigue, vomiting, increased blood alkaline phosphatase ~~increased,~~ alopecia, hypokalemia, constipation, ~~anemia,~~ musculoskeletal pain, diarrhea, decreased appetite, headache, respiratory infection abdominal pain, increased blood bilirubin~~ increased~~, and stomatitis.

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HER2-Low Metastatic Breast Cancer
The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast04 [see Clinical Studies (14.2)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4.0% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, constipation, increased blood alkaline phosphatase, decreased appetite, musculoskeletal pain, diarrhea, and hypokalemia. Tables 7 and 8 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast04.

Table 7: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	76	4.6	30	0
Vomiting	40	1.6	13	0
Constipation	34	0.8	22	0
Diarrhea	27	1.3	22	1.7
Abdominal pain[a]	18	0.5	13	0
Stomatitis[b]	13	0.3	12	0.6
General Disorders and Administration Site Conditions				
Fatigue[c]	54	9	48	4.7
Pyrexia	12	0.3	13	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	40	0	33	0

Rash[d]	13	0	23	4.7
Blood and Lymphatic System Disorders				
Anemia[e]	39	10	27	5
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	19	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	32	1.3	31	0.6
Investigations				
Decreased weight	16	0.3	8	0
Vascular Disorders				
Hemorrhage[g]	16	0	3.5	0
Nervous System Disorders				
Headache[h]	15	0.3	6	0
Peripheral neuropathy[i]	13	0	29	5
Dizziness[j]	11	0.5	6	
Infections and Infestations				
Upper respiratory tract infection[k]	14	0.3	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[l]	12	1.3	0.6	0
Dyspnea	10	1.3	9	1.2

Events were graded using NCI CTCAE version 5.0.
a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain
b Including stomatitis, aphthous ulcer, mouth ulceration, and pharyngeal inflammation
c Including fatigue, asthenia, and malaise
d Including rash, pustular rash, pruritic rash, maculo-papular rash, palmar-plantar erythrodysesthesia syndrome, papular rash, macular rash, eczema, erythema multiforme, dermatitis, urticarial dermatitis, drug eruption, and dermatitis bullous
e Including anemia, decreased hemoglobin, and decreased red blood cell count
f Including back pain, myalgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, arthralgia, noncardiac chest pain, musculoskeletal stiffness, arthritis, spinal pain, and neck pain
g Including esophageal varices, hemorrhage, hemorrhoidal hemorrhage, epistaxis, hematuria, conjunctival hemorrhage, vaginal hemorrhage, gingival bleeding, genital hemorrhage, eye hemorrhage, hemoptysis, hemorrhagic cystitis, pharyngeal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, and esophageal hemorrhage
h Including headache and migraine
i Including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia
j Including dizziness, postural dizziness, and vertigo

k Including upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis
l Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

Other clinically relevant adverse reactions reported in less than 10% of patients treated with ENHERTU:
· *Nervous System Disorders:* dysgeusia (10%)
· *Respiratory, Thoracic and Mediastinal Disorders:* cough (10%)
· *Gastrointestinal Disorders:* abdominal distension (5%), gastritis (2.7%), flatulence (2.4%)
· *Eye Disorders:* blurred vision (4.9%) [including blurred vision and visual impairment]
· *Skin and Subcutaneous Tissue Disorders:* pruritus (3.2%) and skin hyperpigmentation (2.7%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
· *Metabolism and Nutrition Disorders:* dehydration (1.9%)
· *Blood and Lymphatic System Disorders:* febrile neutropenia (1.1%)
· *Injury, Poisoning and Procedural Complications:* infusion-related reactions (0.5%) [including injection site reaction and chills]

Table 8: Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased white blood cell count	70	9	78	25
Decreased hemoglobin	64	8	53	6
Decreased neutrophil count	64	14	73	38
Decreased lymphocyte count	55	18	40	11
Decreased platelet count	44	6	21	0.6
Chemistry				
Increased aspartate aminotransferase	38	2.2	38	4.1
Increased alanine aminotransferase	36	0.8	38	4.1
Increased blood alkaline phosphatase	34	0.3	24	0
Hypokalemia	25	3.3	17	1.2
Increased blood bilirubin	16	2.7	15	0.6
Increased blood creatinine	15	1.1	9	0.6

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.5.0 grade-derived laboratory abnormalities.

Unresectable or Metastatic HER2-Mutant NSCLC

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients in DESTINY-Lung02 [see Clinical Studies (14.3)]. Patients received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity. Nineteen percent of patients were exposed for greater than 6 months. The median age was 59 years (range 30 to 83); 64% were female; 23% were White, 64% were Asian, and 14% were other races.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued due to an adverse reaction in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, hypokalemia, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia.

Tables 9 and 10 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Lung02.

Table 9: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	61	3.0
Constipation	31	1.0
Vomiting[a]	26	2.0
Diarrhea	19	1.0
Stomatitis[b]	12	0
Blood and Lymphatic System Disorders		
Anemia	34	10
General Disorders and Administration Site Conditions		
Fatigue[c]	32	4.0
Metabolism and Nutrition Disorders		
Decreased appetite	30	1.0

Skin and Subcutaneous Tissue Disorders		
Alopecia	21	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	15	1.0

Events were graded using NCI CTCAE version 5.0.
a Including vomiting and retching
b including mucosal inflammation and stomatitis
c Including asthenia, fatigue, and malaise
d Including back pain, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, musculoskeletal pain, myalgia, and pain in extremity

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Respiratory, Thoracic and Mediastinal Disorders:* interstitial lung disease (6%) [including interstitial lung disease that was adjudicated as ILD including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure], dyspnea (5%), and epistaxis (3%)
- *Gastrointestinal Disorders:* abdominal pain (9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]
- *Skin and Subcutaneous Disorders:* rash (3%) [including rash and maculo-papular rash]
- *Infections and Infestations:* upper respiratory tract infection (4%) [including upper respiratory tract infection, pharyngitis, and laryngitis]
- *Nervous System Disorders:* headache (4%) [including headache and migraine]

Table 10: Select Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Laboratory Parameter	**ENHERTU 5.4 mg/kg N=101[a]**	
	All Grades[b] %	**Grades 3 or 4[b] %**
Hematology[c]		
Decreased white blood cell count	60	4.0
Decreased hemoglobin	58	10
Decreased neutrophil count	52	12
Decreased lymphocyte count	43	16
Decreased platelet count	40	4.0
Chemistry		
Decreased albumin	39	0
Increased aspartate aminotransferase	35	1.0
Increased alanine aminotransferase	34	2.0
Increased alkaline phosphatase	22	0
Hypokalemia	17	2.0

a 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.
b Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.
c The denominator used to calculate the rate varied from 98 to 99 based on the number of patients with a baseline value and at least one post-treatment value.

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~~7.2 Immunogenicity~~

~~As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of antibodies to ENHERTU in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.~~

~~Treatment-emergent anti-trastuzumab deruxtecan antibodies (ADA) developed in 2.10% (2734/13111668)) of patients who received ENHERTU across all doses and tumor types. The incidence of treatment-emergent neutralizing antibodies against trastuzumab deruxtecan was 0.1% (1/13111668). Due to the limited number of patients who tested positive for ADA, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.~~

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8.3 Females and Males of Reproductive Potential

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Contraception

Females
ENHERTU can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for ~~at least~~ 7 months ~~following~~ after the last dose.

Males
Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for ~~at least~~ 4 months ~~following~~ after the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

~~ENHERTU is not indicated for children and adolescents under 18 years old.~~
Safety and effectiveness of ENHERTU have not been established in pediatric patients

8.5 Geriatric Use

Of the ~~491~~ 883 patients with ~~HER2-positive~~ breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and ~~43~~.6% 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 (60%) as compared to younger patients (~~49~~48%).

Of the 101 patients with 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.

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8.6 Renal Impairment

No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance (CLcr) ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment *[see Clinical Pharmacology (12.3)]*. ~~No data are available in patients with severe renal impairment.~~ A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment [see Warning and Precautions (6.1)]. Monitor patients with moderate ~~or severe~~ renal

impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment *[see Warnings and Precautions (6.1)] (CLcr<30 mL/min) [see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment of ENHERTU is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd *[see Dosage and Administration (3.3)]*. No data are available in The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

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 brest cancer and NSCLC 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 HER2-positivemetastatic breast cancer, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 131 133 µg/mL (2019%) and 4.44.7 ng/mL (4143%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 769 780 µg day/mL (2827%) and 27 29 ng·day/mL (4042%), respectively, based on population pharmacokinetic analysis. Accumulation of trastuzumab deruxtecan was approximately 35% at steady state (Cycle 3).

Unresectable or Metastatic HER2-Mutant NSCLC
At the recommended dosage of ENHERTU for patients with HER2-mutant NSCLC, the 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 AUCss of fam-trastuzumab deruxtecan-nxki and DXd 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 based on population pharmacokinetic analysis.

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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 14-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast03 with a median ADA sampling period of 13 months, treatment-emergent ADA (or anti-fam-trastuzumab deruxtecan-nxki antibodies) developed in 1.6% (4/256) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0.4% (1/256).

During the median 7-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast01 with a median ADA sampling period of 9 months, treatment-emergent ADA developed in 1.2% (3/249) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/249).

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, treatment-emergent ADA developed in 2.0% (7/357) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/357).

During the median 3.5-month treatment period in HER2-mutant NSCLC patients in DESTINY-Lung02 with median ADA sampling period of 2.2 months, treatment-emergent ADA developed in 0.7% (1/143) of patients who received

ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/249).

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, treatment-emergent ADA developed in 7.3%
(9/123) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/123).

Due to the limited number of patients who tested positive for ADA, the effect of treatment-emergent ADAs and treatment-emergent neutralizing antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of fam-trastuzumab deruxtecan-nxki is unknown.

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14.2 HER2-Low Metastatic Breast Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Breast04 (NCT03734029), a randomized, multicenter, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor-positive (HR+) patients and 63 hormone receptor-negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined at a central laboratory using Ventana's PATHWAY Anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay.. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=373) by intravenous infusion every 3 weeks or physician's choice of chemotherapy (N=184, eribulin, capecitabine, gemcitabine, nab paclitaxel, or paclitaxel). Randomization was stratified by HER2 IHC status of tumor samples (IHC 1+ or
~~i~~ IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.44 The study 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 untreated or symptomatic brain metastases or ECOG performance status >1.

The major efficacy outcome measure was PFS in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Additional efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomized HR+ and HR- patients), OS in HR+ patients, and OS in the overall population.

The median age was 57 years (range: 28 to 81); 24% were age 65 or older; 99.6% were female ; 48% were White, 40% were Asian, and 2% were Black or African American 3.8% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (55%) or 1 (45%) at baseline; 58% were IHC 1+, 42% were IHC 2+/ISH-; 70% had liver metastases, 33% had lung metastases, and 6% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 58% having 1 and 41% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6i treatment.

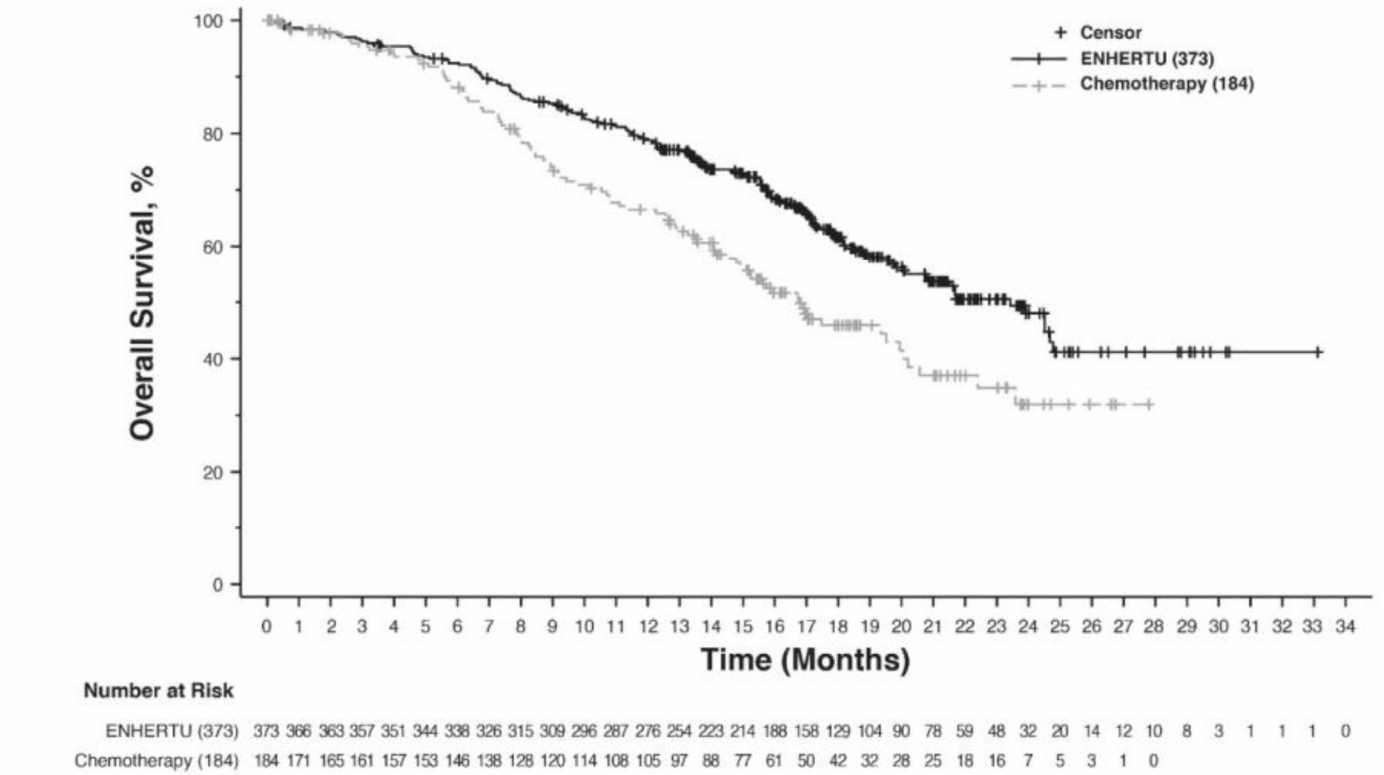
Efficacy results are summarized in Table 13 and Figures 2 and 3.

Table 13: Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Overall Survival				
Number of events (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)		0.64 (0.49, 0.84)	
p-value	0.0028		0.001	
Progression-Free Survival per BICR				
Number of events (%)	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)		0.50 (0.40, 0.63)	
p-value	<0.0001		<0.0001	
Confirmed Objective Response Rate per BICR*				
n (%)	175 (52.69)	27 (16.36)	195 (52.3)	30 (16.3)
95% CI	47.03, 58.04	11.02, 22.823.2	47.1, 57.4	11.3, 22.5
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.25)	26 (15.76.0)	183 (49.1)	28 (15.2)
Duration of Response per BICR*				
Median, months (95% CI)	10.7 (8.5, 13.7)	6.8 (6.5, 9.9)	10.7 (8.5 13.2)	6.8 (6.0, 9.9)

CI = confidence interval

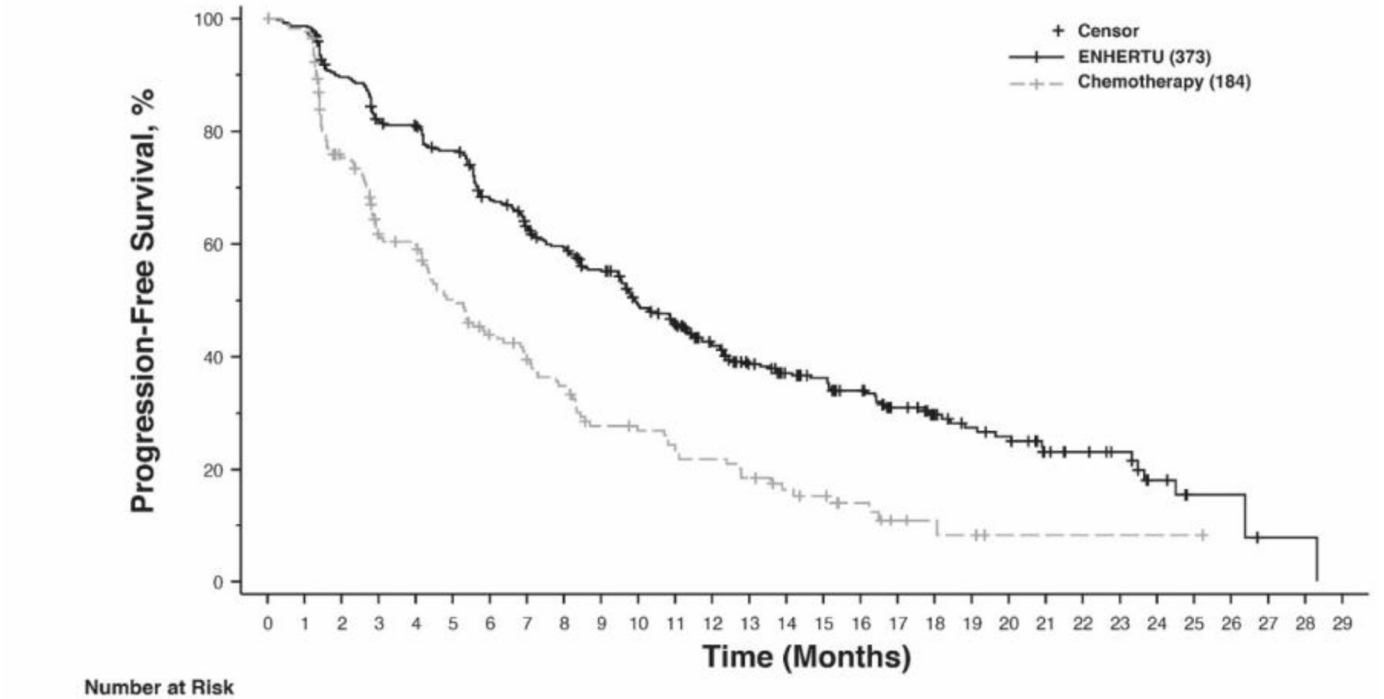
Figure 2: Kaplan-Meier Plot of Overall Survival (Overall Population)



Number at Risk

ENHERTU (373)	373	366	363	357	351	344	338	326	315	309	296	287	276	254	223	214	188	158	129	104	90	78	59	48	32	20	14	12	10	8	3	1	1	1	0
Chemotherapy (184)	184	171	165	161	157	153	146	138	128	120	114	108	105	97	88	77	61	50	42	32	28	25	18	16	7	5	3	1	0						

Figure 3: Kaplan-Meier Plot of Progression-Free Survival (Overall Population)



Number at Risk

ENHERTU (373)	373	365	325	295	290	272	238	217	201	183	156	142	118	100	88	81	71	53	42	35	32	21	18	15	8	4	4	1	1	0	
Chemotherapy (184)	184	166	119	93	90	73	60	51	45	34	32	29	26	22	15	13	9	5	4	3	1	1	1	1	1	1	0				

14.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU was evaluated in DESTINY-Lung01 (NCT03505710) and at two dose levels in DESTINY-Lung02 (NCT04644237). Patients were prospectively selected for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations by local testing using tissue. Samples from DESTINY-Lung01 were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation, Tissue-test) and Guardant360® CDx test (Guardant Health Inc., Plasma test). Demographic and baseline disease characteristics were similar for patients in DESTINY-Lung01 and DESTINY-Lung02, except for race (34% Asian vs 79% Asian, respectively). Response rates were consistent across dose levels. Increased rates of ILD/pneumonitis were observed at the higher dose. The approved recommended dose of 5.4 mg/kg intravenously every 3 weeks in the DESTINY-Lung02 study is described below *[see Adverse Reactions (6.1)]*.

The efficacy of ENHERTU was evaluated in DESTINY-Lung02, a multicenter, multi-cohort, randomized, blinded, dose-optimization trial. Eligible patients were required to have unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after one prior systemic therapy. Patients with a history of steroid dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status >1 were excluded. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with stable brain metastases at baseline.

Results from an interim efficacy analysis in a pre-specified patient cohort are described below. The major efficacy outcomes were confirmed ORR as assessed by BICR using RECIST v1.1 and DOR.

The median age was 58 years (range 30 to 78); 69% were female; 79% were Asian, 12% were White, and 10% were other races; 29% had an ECOG performance status of 0 and 71% had 1; 33% had stable brain metastases; 94% had a mutation in the ERBB2 kinase domain and 6% had a mutation in the extracellular domain. The median number of prior regimens was 2 (range: 1 to 12); 100% of patients received prior platinum therapy, 71% received prior immunotherapy, and 44% received both in combination. Fifty percent of patients were never-smokers and 50% were former smokers; 96% of patients had adenocarcinoma histology.

Efficacy results are provided in Table 16.

Table 16: Efficacy Results for DESTINY-Lung02*

Efficacy Parameter	**DESTINY-Lung02 N=52**
Confirmed Objective Response Rate (95% CI)	57.7% (43.2, 71.3)
Complete Response	1.9%
Partial Response	55.8%
Duration of Response Median, months (95% CI)†	8.7 (7.1, NE)

ORR 95% CI calculated using Clopper-Pearson method
NE=not estimable
*Data cut-off: 22 June 2022
†Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method

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Revised in ~~May~~April ~~2022~~ 2023 according to MOHs guidelines

העדכונים המהותיים בעלון לצרכן הינם:

1. למה מיועדת התרופה?

- סרטן שד גרורתי מסוג HER2-חיובי

אנהרטו מיועד לטיפול בטמטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג HER2-חיובי, 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 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 או גרורתי

אנהרטו מיועד לטיפול במבוגרים עם אדנוקרצינומה של הקיבה או מעבר ושט קיבה, עבור מחלה מתקדמת או גרורתית מסוג HER2-חיובי, אשר טופלו בעברם עם טראסטוזומאב

4. תופעות לוואי

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- 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 כוללות:

- בחילה
- ספירה נמוכה של תאי דם לבנים
- ספירה נמוכה של תאי דם אדומים
- תחושת עייפות
- הקאות
- נשירת שיער
- עלייה בבדיקות לתפקודי כבד בבדיקות דם
- ספירת טסיות נמוכה
- עצירות
- ירידה בתאבון
- שלשול
- רמה נמוכה של אשלגן בדם
- זיהומים בדרכי הנשימה
- כאב בשרירים או בעצמות
- ~~כאבי ראש~~
- ~~כאב באזור הבטן~~
- שיעול

תופעות הלוואי השכיחות ביותר בעת נטילת אנהרטו לטיפול ~~בסרטן קיבה~~באדנוקרצינומה של הקיבה או מעבר ושט קיבה מסוג HER2-חיובי, כוללות:

...

6. מידע נוסף

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נערך ~~במאי~~ באפריל ~~2022~~ 2023 בהתאם להנחיות משרד הבריאות.

The following information is intended for healthcare professionals only:

Preparation ~~for~~ and Administration

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Administration

- If the prepared infusion solution was stored refrigerated (2ºC to 8ºC), allow the solution to reach room temperature prior to administration. Cover the infusion bag to protect from light.
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene
- Administer ENHERTU with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.
- Do NOT administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light during administration.
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.

מקרא לעדכונים המסומנים:

תוספת טקסט מהותי מסומנת בצבע כלשהו עם קו תחתון.

מחיקת טקסט מסומנת ~~בקו חוצה בצבע כלשהו~~.

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

בכבוד רב,

קארין קנבל דובסון רוקחת ממונה

אסטרהזניקה (ישראל) בע"מ

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1, כפר סבא 4464301

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