אוגוסט 2021

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עלון לתכשיר: Enhertu</u>

הרכב:

Trastuzumab Deruxtecan 100 mg.

התוויה:

<u>Metastatic Breast Cancer</u>
ENHERTU as monotherapy is 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.

<u>Locally Advanced or Metastatic Gastric Cancer</u>
ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal 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 לרופא בהתאם להוראות משרד הבריאות וכן על עלון לצרכן חדש מתאריך אוגוסט 2021.

העדכון העיקרי בעלון לרופא הוא:

2. **Therapeutic indications**

2.<u>2 Locally Advanced or Metastatic Gastric Cancer</u>

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

3. DOSAGE AND ADMINISTRATION

3.1 Patient Selection for Locally Advanced or Metastatic Gastric Cancer

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

3.2 Recommended Dosage and Schedules

Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine.

Recommended Dosage for Metastatic Breast Cancer

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 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 Dose Modifications

Table 1: Dose Reduction Schedule

Dose Reduction Schedule ~~(Starting dose is 5.4 mg/kg.)~~	Breast Cancer~~Dose to be administered~~	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.

Table 2: Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Treatment Modification
Thrombocytopenia	Grade 3 (platelets less than 50 to 25 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.
	Grade 4 (platelets less than 25 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 1 or less. • Reduce dose by one level (see Table 1).

6 WARNINGS AND PRECAUTIONS

6.2 Neutropenia

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

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. 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.

7.1 Clinical Trials Experience

Metastatic Breast Cancer

The most common (>20%) adverse reactions (~~frequency ≥20%)~~ including laboratory abnormalities, were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, ~~neutropenia,~~ diarrhea, hypokalemia, ~~leukopenia, cough~~, and ~~thrombocytopenia~~ cough.

Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Metabolism and Nutrition Disorders		
~~Hypokalemia~~	~~12~~	~~3.4~~
Blood and Lymphatic System Disorders		
~~Neutropenia[g]~~	~~29~~	~~16~~
~~Leukopenia[h]~~	~~22~~	~~6~~
~~Thrombocytopenia[i]~~	~~20~~	~~3.4~~
~~**Investigations**~~		
~~Aspartate aminotransferase increased~~	~~14~~	~~0.9~~
~~Alanine aminotransferase increased~~	~~10~~	~~0.9~~

~~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.~~
jg Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia,

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 *[see Clinical Studies (14.2)]*. Patients intravenously received at least one dose of

either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

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

Tables 5 and 6 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 5: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
Adverse Reactions	**All Grades %**	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Gastrointestinal Disorders				
Nausea	63	4.8	47	1.6
Diarrhea	32	2.4	32	1.6
Vomiting	26	0	8	0
Constipation	24	0	23	0
Abdominal pain[a]	14	0.8	15	3.2
Stomatitis[b]	11	1.6	4.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	60	17	45	13
Dehydration	6	2.4	3.2	1.6
Blood and Lymphatic System Disorders				
Anemia[c]	58	38	31	23
Febrile neutropenia	4.8	4.8	3.2	3.2

Adverse Reactions	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
General Disorders and Administration Site Conditions				
Fatigue[d]	55	9	44	4.8
Pyrexia	24	0	16	0
Edema peripheral	10	0	0	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	22	0	15	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[e]	10	2.4	0	0
Hepatobiliary Disorders				
Hepatic function abnormal	8	3.2	1.6	1.6

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 mucosal blistering.
[c] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased.
[d] Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.
[e] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

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

- *Cardiac Disorders:* asymptomatic left ventricular ejection fraction decrease (8%) *[see Warnings and Precautions (6.3)]*
- *Infections and Infestations:* pneumonia (6%)
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (1.6%)

Table 6: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Hemoglobin decreased	75	38	55	23
White blood cell count decreased	74	29	53	13
Neutrophil count decreased	72	51	45	23
Lymphocyte count decreased	70	28	53	12
Platelet count decreased	68	12	12	5
Chemistry				
Aspartate aminotransferase increased	58	9	32	8

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Blood alkaline phosphatase increased	54	8	34	10
Alanine aminotransferase increased	47	9	17	1.7
Hypokalemia	30	4.8	18	8
Blood bilirubin increased	24	7	5	3.4

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.

7.2 Immunogenicity

Treatment-induced anti-trastuzumab deruxtecan antibodies (ADA) developed in ~~0.6% (4/640~~1.7% (14/807)) patients who received ENHERTU across all doses…

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Of the 125 patients with locally advanced or metastatic 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.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Locally Advanced or Metastatic Gastric Cancer

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

Elimination

The median elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer and gastric cancer was approximately 5.7 -5.8 days. Based on population pharmacokinetic analysis, the estimated systemic clearance of trastuzumab deruxtecan was 0.42 L/day.

The median apparent elimination half-life ($t_{1/2}$) of DXd in patients with HER2-positive metastatic breast cancer and gastric cancer was approximately 5.5-5.8 days. Based on population pharmacokinetic analysis, the estimated apparent systemic clearance of DXd was 19.2 6 L/h.

Specific Populations

No clinically significant differences in the pharmacokinetics of trastuzumab deruxtecan or DXd were observed for age (23-96 years), race (Asian [n=291563] and non-Asian [n=221245]), sex, body weight (34.627.3-125.4 kg), mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST, n=215312) hepatic impairment, mild (creatinine clearance [CLcr] ≥60 and <90 mL/min, n=206292) or moderate (CLcr ≥30 and <60 mL/min; n=5854) renal impairment based on population pharmacokinetic analysis.

14 CLINICAL STUDIES

14.2 Locally Advanced or Metastatic Gastric Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Gastric01 (NCT03329690), a multicenter, open-label, randomized trial conducted in Japan and South Korea that enrolled 188 adult patients with HER2-positive (IHC 3+ or IHC 2+/ISH positive), locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. HER2 expression was determined by a central lab on tissue obtained either before or after prior trastuzumab treatment. Patients were excluded for a history of treated or current ILD, a history of clinically significant cardiac disease, active brain metastases, or ECOG performance status >1.

Patients were randomized 2:1 to receive ENHERTU (N=126) 6.4 mg/kg intravenously every 3 weeks or physician's choice of chemotherapy: irinotecan monotherapy (N=55) 150 mg/m^2 intravenously every 2 weeks or paclitaxel monotherapy (N=7) 80 mg/m^2 intravenously weekly. Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH+), ECOG performance status (0 or 1), and region (Japan or South Korea). Tumor imaging assessments were performed at screening and every 6 weeks from the first treatment dose. Treatment was administered until unacceptable toxicity or disease progression. The major efficacy outcomes were ORR assessed by ICR according to RECIST v1.1 and overall survival (OS) in the intent-to-treat population. Additional efficacy outcomes were progression-free survival (PFS) and DOR.

The median age was 66 years (range 28 to 82); 76% were male; and 100% were Asian. All patients received a trastuzumab product. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH+; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; 45% had three or more prior regimens in the locally advanced or metastatic setting. A total of 30% of patients were identified as HER2-positive using tissue obtained following prior treatment with a trastuzumab product.

Efficacy results are summarized in Table 8, and the Kaplan-Meier curve for OS is shown in Figure 1.

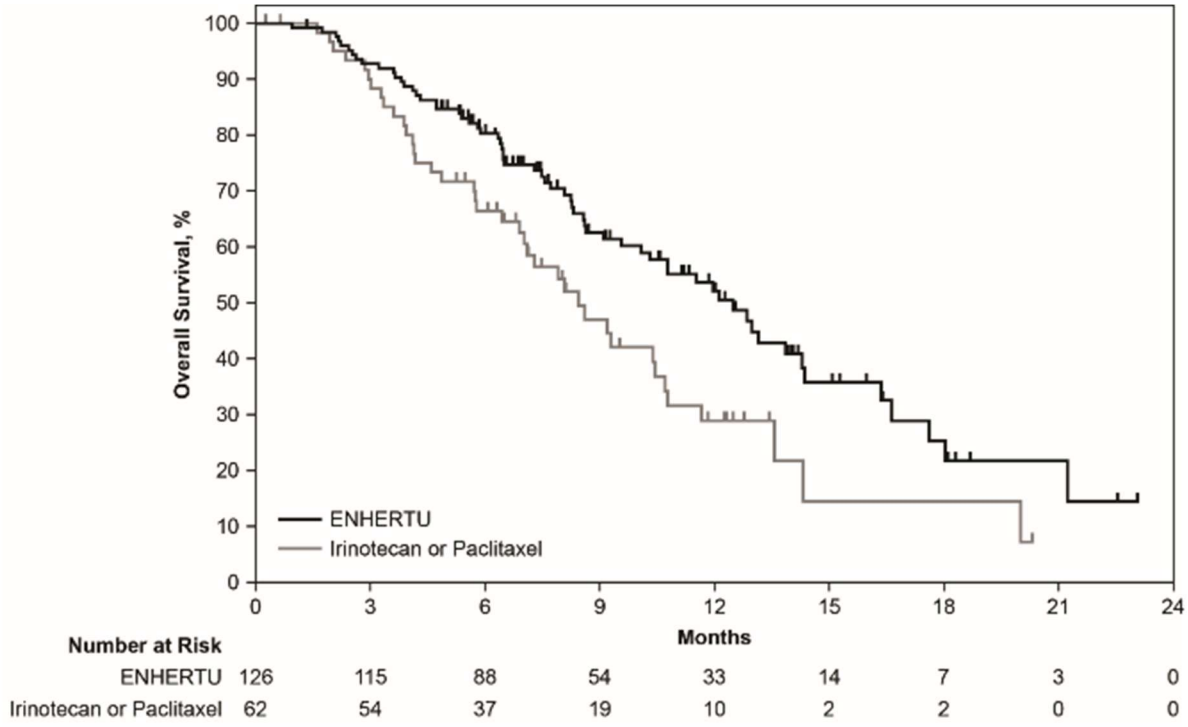
Table 8: Efficacy Results in DESTINY-Gastric01

Efficacy Parameter	**ENHERTU N=126**	**Irinotecan or Paclitaxel N=62**
Overall Survival (OS)*		
Median, months (95% CI)†	12.5 (9.6, 14.3)	8.4 (6.9,10.7)
Hazard ratio (95% CI)‡	0.59 (0.39, 0.88)	
p-value¥	0.0097	
Progression-Free Survival (PFS)§		
Median, months (95% CI)†	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)‡	0.47 (0.31, 0.71)	
Confirmed Objective Response Rate (ORR)§		

Efficacy Parameter	ENHERTU N=126	Irinotecan or Paclitaxel N=62
n (%)	51 (40.5)	7 (11.3)
95% CI¶	(31.8, 49.6)	(4.7, 21.9)
p-value#	<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Duration of Response (DOR)§		
Median, months (95% CI)†	11.3 (5.6, NR)	3.9 (3.0, 4.9)

CI = confidence interval; NR = not reached
*OS was evaluated following a statistically significant outcome of ORR.
†Median based on Kaplan-Meier estimate; 95% CI for median calculated using Brookmeyer-Crowley method
‡Based on the stratified Cox proportional hazards regression model (stratified by region)
¥Based on the stratified log-rank test (stratified by region)
§Assessed by independent central review
¶95% exact binomial confidence interval
#Based on the stratified Cochran-Mantel-Haenszel test (stratified by region)

Figure 1: Kaplan-Meier Plot of Overall Survival



תוספות לעלון מסומנות בקו תחתון וטקסט שנמחק מסומן בקו חוצה.

העלון מפורסם במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

בכבוד רב,

קארין קנבל דובסון

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