יולי 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלוני התכשיר:</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 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>Unresectable or Metastatic HER2-Mutant 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>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.

התוות 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 יולי 2024.

העדכונים המהותיים בעלון לרופא הינם:

3. DOSAGE AND ADMINISTRATION

3.2 Recommended Dosage and Schedules

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

Slow or interrupt the infusion rate if the patient develops infusion-related symptoms.
Permanently discontinue ENHERTU in case of severe infusion reactions.

<u>Premedication</u>

ENHERTU is ~~moderately~~ highly emetogenic [see Adverse Reactions (7.1)] which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting.

3.4 Preparation and Administration

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

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

ENHERTU (trastuzumab deruxtecan) is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed *[see Dosage and Administration (3.2)]*.
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- ~~If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.~~
- ~~Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.~~
- ~~If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.~~
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

- Withdraw the calculated amount from the vial(s) using a sterile syringe. .
- ~~Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.~~
-
- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing 100 mL of 5% Dextrose Injection, USP. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene).
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- ~~If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.~~
- Discard any unused portion left in the vials.

Administration

If not used immediately, store the diluted ENHERTU in a refrigerator at 2ºC to 8ºC for up to 24 hours or at room temperature for up to 4 hours including preparation and infusion time.

- ~~If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.~~
- Protect from light. Do not freeze.
- The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours.
- 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.

6 WARNINGS AND PRECAUTIONS

6.1 Interstitial Lung Disease/Pneumonitis

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

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was ~~5~~ 6 months (range: 0.9 to ~~23~~32).

6.2 Neutropenia

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

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. 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 ~~66~~4939). Febrile neutropenia was reported in ~~1.1~~0.9% of patients.

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.

Metastatic Breast Cancer and HER2-Mutant NSCLC (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 ~~984~~ 1388 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY- Breast02, DESTINY-Breast04, and DESTINY-Lung02. Among these patients, ~~65~~68% were exposed for greater than 6
months and ~~39~~42% were exposed for greater than one year. In this pooled safety population, the most common (≥20%) adverse reactions (including laboratory abnormalities) were nausea (~~76~~75%), decreased white blood cell count (71%), decreased hemoglobin (~~66~~67%), decreased neutrophil count (65%), decreased lymphocyte count (~~55~~57%), fatigue (~~54~~56%), decreased platelet count (~~47~~48%), increased aspartate aminotransferase (~~48~~45%), ~~vomiting (44%),~~ increased alanine aminotransferase (~~42~~43%), vomiting (42%), ~~alopecia (39%),~~ increased blood alkaline phosphatase (39%), alopecia (39%), constipation (~~34~~35%),
~~musculoskeletal pain (32%),~~ decreased appetite (32%), hypokalemia (~~28~~30%), diarrhea (28%), and ~~respiratory infection (24%).~~musculoskeletal pain (32%).

DESTINY-Breast02

The safety of ENHERTU was evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02 [see Clinical Studies (14.1)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 11 months (range: 0.7 to 45) for patients who received ENHERTU.

Serious adverse reactions occurred in 26% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were COVID-19, ILD, pneumonia, vomiting, fatigue, and nausea. Fatalities due to adverse reactions occurred in 2.5% of patients including pneumonitis (2 patients), acute myeloid leukemia, brain edema, COVID- 19, hemorrhage, hepatitis B, malignant pleural effusion, pneumonia, and vasogenic cerebral edema (one patient each).

ENHERTU was permanently discontinued in 20% of patients, of which ILD accounted for 9%. Dose interruptions due to adverse reactions occurred in 45% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, COVID-19, anemia, fatigue, leukopenia, upper respiratory tract infection, and thrombocytopenia. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse

reactions (>2%) associated with dose reduction were fatigue, nausea, neutropenia, and vomiting.

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

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast02.

Table 5: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast02

Adverse Reactions	ENHERTU 5.4 mg/kg N=404		Treatment of Physician's Choice N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	73	7	37	2.6
Vomiting	38	3.7	13	1
Constipation	35	0.3	11	0.5
Diarrhea	27	2.7	54	7
Abdominal pain[a]	22	1	20	2.1
Dyspepsia	12	0	9	0
Stomatitis[b]	12	1	21	1
General Disorders and Administration Site Conditions				
Fatigue[c]	62	9	37	1
Skin and Subcutaneous Tissue Disorders				
Alopecia	37	0.3	4.1	0
Metabolism and Nutrition Disorders				
Decreased appetite	31	1.7	18	0.5
Blood and Lymphatic System Disorders				
Anemia[d]	29	8	14	3.1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[e]	25	0.7	18	0.5
Nervous System Disorders				
Headache[f]	20	0.3	6	0
Investigations				
Decreased weight	18	0.3	3.6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	13	0	10	0
Interstitial lung disease[g]	10	0.7	0.5	0.5

Events were graded using NCI CTCAE version 5.0.

[a] Including abdominal discomfort, abdominal pain, upper abdominal pain, lower abdominal pain, and gastrointestinal pain

[b] Including aphthous ulcer, mouth ulceration, and stomatitis

[c] Including asthenia, fatigue, lethargy, and malaise

[d] Including anemia, decreased hemoglobin, and decreased red blood cell count

[e] Including back pain, bone pain, limb discomfort, musculoskeletal chest pain, musculoskeletal pain, muscle spasms, myalgia, neck pain, and pain in extremity

[f] Including headache and migraine

[g] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, idiopathic interstitial pneumonia, lung disorder, pulmonary toxicity, and pneumonia.

Other clinically relevant adverse reactions reported in less than 10% of patients in the ENHERTU-treated group were:

- Respiratory, Thoracic and Mediastinal Disorders: dyspnea (8%) and epistaxis (8%)
- Skin and Subcutaneous Tissue Disorders: rash (8%) [including rash, pustular rash, maculo-papular rash, and pruritic rash], pruritis (5%), skin hyperpigmentation (5%) [including skin hyperpigmentation and pigmentation disorder]
- Nervous System Disorders: dizziness (8%) and dysgeusia (8%)
- Cardiac Disorders: asymptomatic left ventricular ejection fraction decrease (4.2%) [see Warnings and Precautions (5.3)]
- Eye Disorders: dry eye (6%) and blurred vision [including blurred vision and visual impairment] (3%)
- Metabolism and Nutrition Disorders: dehydration (2.7%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (1.2%)
- Blood and Lymphatic System Disorders: febrile neutropenia (0.3%)

Table 6: Selected Laboratory Abnormalities in Patients in DESTINY-Breast02

Laboratory Parameter	ENHERTU 5.4 mg/kg N=404		Treatment of Physician's Choice N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	70	12	42	3.2
Decreased hemoglobin	67	9	54	3.2
Decreased neutrophil count	64	16	34	4.7
Decreased lymphocyte count	58	17	38	4.7
Decreased platelet count	48	2.7	31	1.6
Chemistry				
Increased alanine aminotransferase	43	1	32	1.6
Increased aspartate aminotransferase	37	0.7	29	2.1
Increased blood alkaline phosphatase	37	0	17	0
Hypokalemia	30	3.7	29	8
Increased blood bilirubin	23	0.3	44	2.1
Increased blood creatinine	7	0.3	13	0

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

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 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, the estimated geometric mean (coefficient of variation [CV]%) $C_{max,ss}$ of trastuzumab deruxtecan and DXd were 133 µg/mL (19%) and 4.7 ng/mL (43%), respectively, and the ~~AUC of trastuzumab deruxtecan and DXd~~ corresponding AUC_{ss} were 780 µg day/mL (27%) and 29 ng·day/mL (42%), ~~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 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 ~~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~~.

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} ~~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).

Distribution

Based on population pharmacokinetic analysis, the 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 5.4-5.7 days. ~~Based on population pharmacokinetic analysis, T~~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 5.4-5.7 days. ~~Based on population pharmacokinetic analysis, t~~The estimated apparent systemic clearance of DXd was 18.3 L/h.

Specific Populations

No clinically significant differences in the pharmacokinetics of trastuzumab deruxtecan or DXd were observed for age (20-96 years), race (Asian ~~[n=906] vs Non-Asian [n=763], including~~ White ~~[n=619],~~ or Black ~~or African American [n=36] and Other [n=108]~~), sex, body weight (27~~.3~~-125~~.4~~ kg), mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST~~, n=575) hepatic impairment)~~, mild ~~(creatinine clearance [CLcr] ≥60 and <90 mL/min, n=646)~~ or moderate ~~(CLcr ≥30 and <60 mL/min; n=251)~~ renal impairment ~~based on population pharmacokinetic analysis~~.

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~~14~~-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, ~~treatment-emergent~~ the ADA ~~(or anti-fam-trastuzumab deruxtecan-nxki antibodies) developed in 1.6% (4/256) of patients who received ENHERTU. The~~ incidence is 2.4% (16/658 patients) with 13% (2/16) patients tested positive for ~~of treatment-emergen~~t 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~~the ADA ~~developed in~~ incidence is 2.0% (7/357~~) of~~ patients~~) who received ENHERTU. The incidence of treatment-emergent~~ with 0% (0/7) patients tested positive for 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 a median ADA sampling period of 2.2 months, ~~treatment-emergent~~ the ADA ~~developed~~ incidence ~~in~~s 0.7% (1/143~~) of~~ patients~~) who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was~~ with 0% (0/~~249~~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 ~~treatment-emergent~~ ADA incidence is ~~developed in~~ 7.3%
(9/123~~)~~ of patients) with 0% (0/9) patients tested positive for~~who received ENHERTU. The incidence of treatment-emergent~~ neutralizing antibodies against fam- trastuzumab deruxtecan-nxki ~~was 0% (0/123)~~.

~~Due to~~Because of the ~~limited number of patients who tested positive for~~ low occurrence of 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.

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03
The efficacy of ENHERTU was evaluated in study DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids, ILD/pneumonitis at screening, or clinically significant cardiac disease. Patients were also excluded for untreated and symptomatic brain metastases, ECOG performance status >1, or prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting.
Patients were randomized 1:1 to receive either ENHERTU 5.4 mg/kg (N=261) or ado-trastuzumab emtansine 3.6 mg/kg (N=263) by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and visceral versus non-visceral disease. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for all patients at baseline. The major efficacy outcomes were progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and overall survival (OS). Confirmed objective response rate (ORR) was an additional outcome measure.
The median age was 54 years (range: 20-83); 80% were <65 years ~~and~~ 99.6% were female~~. The majority of patients~~ 60% were Asian ~~(60%)~~, 27% were White ~~(27%)~~ and 3.6% Black ~~(~~3.6%~~)~~. ~~Eleven percent (~~11%~~)~~ of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (63%) or 1 (37%) at baseline. Seventy-three percent had visceral disease, 16% had brain metastases at baseline, 52% were hormone receptor positive (HR+) and 48% of patients had received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 10%.
Efficacy results are summarized in Table ~~13~~ 15 and Figures 1 and 2. ~~At the time of the PFS analysis, 16% of patients had died and overall survival (OS) was immature.~~

Table ~~13~~15: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	ENHERTU 5.4 mg/kg	Ado-trastuzumab emtansine 3.6 mg/kg
Progression-Free Survival (PFS) per BICR		
N	261	263
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value‡	p< 0.0001	
Overall Survival (OS)		
N	261	263
Number of events (%)	72 (27.6)	97 (36.9)
Median, months (95% CI)	NR (40.5, NE)	NR (34.0, NE)
Hazard ratio (95% CI)	0.64 (0.47, 0.87)	
p-value§	p=0.0037	
Confirmed Objective Response Rate (ORR) per BICR*		
N	248	241
n (%)	205 (82.7)	87 (36.1)
95% CI	(77.4, 87.2)	(30.0, 42.5)
Complete Response n (%)	39 (15.7)	20 (8.3)
Partial Response n (%)	166 (66.9)	67 (27.8)

DESTINY-Breast02

The efficacy of ENHERTU was evaluated in study DESTINY-Breast02 (NCT03523585), a multicenter, open-label, randomized study that enrolled 608 patients with HER2-positive, unresectable and/or metastatic breast cancer who were previously treated with ado-trastuzumab emtansine. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=406) by intravenous infusion every 3 weeks or treatment of physician's choice (TPC) (N=202, trastuzumab plus capecitabine or lapatinib plus capecitabine) until unacceptable toxicity or disease progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and visceral versus non-visceral disease. The major efficacy outcomes were PFS as assessed by BICR based on RECIST v1.1 and OS.

The median age was 54 years (range: 22 to 88); 80% were <65 years; 99% were female; 63% were White, 29% were Asian, and 3% were Black or African American; 11% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (57%) or 1 (42%) at baseline. Seventy-eight percent had visceral disease, 18% had brain metastases at baseline, 59% were hormone receptor positive (HR+), and 5% of patients had received one line of prior systemic therapy in the metastatic setting.

Efficacy results are summarized in Table 16 and Figures 3 and 4.

Table 16: Efficacy Results in DESTINY-Breast02

Efficacy Parameter	ENHERTU N=406	Treatment of Physician's Choice N=202
PFS per BICR		
Number of events (%)	200 (49.3)	125 (61.9)
Median, months (95% CI)	17.8 (14.3, 20.8)	6.9 (5.5, 8.4)
Hazard ratio (95% CI)	0.36 (0.28, 0.45)	
p-value	p<0.0001	
Overall Survival (OS)		
Number of events (%)	143 (35.2)	86 (42.6)
Median, months (95% CI)	39.2 (32.7, NE)	26.5 (21.0, NE)
Hazard ratio (95% CI)	0.66 (0.50, 0.86)	
p-value[a]	p=0.0021	
Confirmed Objective Response Rate (ORR) per BICR		
n (%)	283 (69.7)	59 (29.2)
95% CI	(65.0, 74.1)	(23.0, 36.0)
Complete Response n (%)	57 (14.0)	10 (5.0)
Partial Response n (%)	226 (55.7)	49 (24.3)
Duration of Response per BICR		
Median, months (95% CI)	19.6 (15.9, NE)	8.3 (5.8, 9.5)

CI = confidence interval; NE=not estimable

[a] The stratified log-rank test p-value is compared with the allocated alpha of 0.004 for this interim analysis (with 53% of the planned number of events for final analysis)

העדכונים המהותיים בעלון לצרכן הינם:

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 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
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- רמה נמוכה של אשלגן בדם
- ~~זיהומים בדרכי הנשימה~~

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העדכונים המהותיים בחלק ההוראות לצוות הרפואי:

The following information is intended for healthcare professionals only:

Reconstitution

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

Dilution

- Withdraw the calculated amount from the vial(s) using a sterile syringe
- ~~Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.~~
- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing 100 mL of 5% Dextrose Injection, USP. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene).
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- ~~If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.~~
- Discard any unused portion left in the vials.

Administration

- ~~If not used immediately, store~~ the ~~diluted~~ ENHERTU in a refrigerator at 2ºC to 8ºC for up to 24 hours or ~~at room temperature for up to 4 hours including preparation and infusion~~ time.~~, or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.~~
- ~~Protect from light. Do not freeze.~~

- The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours.
- 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:

תוספות או מחיקות טקסט מסומנות בצבע.

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

טלפון 073-2226099 פקס 09-7406527