**מאי 2022**

**רופא/ה נכבד/ה**
**רוקח/ת נכבד/ה שלום רב,**

**<u>פרסום עלון לתכשיר: Enhertu – שינוי התוויה</u>**

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון ההתוויה עבור אנהרטו.

**הרכב:**

Trastuzumab Deruxtecan 100 mg.

**התוויה:**

<u>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>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.

**העלון לרופא והעלון לצרכן התעדכנו בעקבות עדכון ההתוויה בהתאם להוראות משרד הבריאות בתאריך מאי 2022.**

<u>העדכונים המהותיים בעלון לרופא הינם:</u>

**2. Therapeutic indications**

**2.1 Metastatic Breast Cancer**

ENHERTU ~~as monotherapy~~ is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received <u>a</u> ~~two or more~~ prior anti-HER2-based regimen<u>s either:</u>~~.~~

- <u>in the metastatic setting, or</u>
- <u>in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.</u>

### 3.2 Recommended Dosage and Schedules

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

### 3.4 Preparation for Administration

….
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 ~~and a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.~~
- 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.

## 6 WARNINGS AND PRECAUTIONS

### 6.1 Interstitial Lung Disease/Pneumonitis

Metastatic Breast Cancer
In clinical studies, of the 491~~234~~ patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in ~~9~~13% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.4~~2.6~~% of patients treated with ENHERTU. Median time to first onset was ~~4.1~~5.5 months (range: 1.1~~1.2~~ to ~~20.8~~8.~~3~~).

### 6.2 Neutropenia

Metastatic Breast Cancer

In clinical studies, of the ~~-~~ 491~~234~~ patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in ~~62~~68% of patients. ~~Sixteen~~ Eighteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was ~~23~~ 22 days (range: 6 to ~~547~~664). Febrile neutropenia was reported in 1.~~7~~2% 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.~~

Metastatic Breast Cancer
In the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, 13 cases (2.6%) of asymptomatic LVEF decrease were reported.

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.

### 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

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%).

*DESTINY-Breast03*

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03 *[see Clinical Studies (14.1)]*. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU and 7 months (range: 0.7 to 25) for patients who received ado-trastuzumab emtansine.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

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

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast03.

**Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast03**

| Adverse Reactions | ENHERTU 5.4 mg/kg N=257 | | Ado-trastuzumab emtansine 3.6 mg/kg N=261 | |
|---|---|---|---|---|
| | All Grades % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 76 | 7 | 30 | 0.4 |
| Vomiting | 49 | 1.6 | 10 | 0.8 |
| Constipation | 34 | 0 | 20 | 0 |

| Adverse Reactions | ENHERTU 5.4 mg/kg N=257 | | Ado-trastuzumab emtansine 3.6 mg/kg N=261 | |
|---|---|---|---|---|
| | All Grades % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| Diarrhea | 29 | 1.2 | 7 | 0.4 |
| Abdominal pain[a] | 21 | 0.8 | 8 | 0.4 |
| Stomatitis[b] | 20 | 0.8 | 5 | 0 |
| Dyspepsia | 11 | 0 | 6 | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue[c] | 49 | 6 | 35 | 0.8 |
| **Blood and Lymphatic System Disorders** | | | | |
| Anemia[d] | 33 | 7 | 17 | 6 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Alopecia[e] | 37 | 0.4 | 3.1 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Musculoskeletal pain[f] | 31 | 1.2 | 25 | 0.4 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 29 | 1.6 | 17 | 0.4 |
| **Investigations** | | | | |
| Weight decreased | 17 | 1.2 | 6 | 0.4 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Respiratory infection[g] | 22 | 0.8 | 12 | 11 |
| Epistaxis | 11 | 0 | 16 | 0.4 |
| Cough | 11 | 0.4 | 10 | 0 |
| Interstitial lung disease[h] | 11 | 0.8 | 1.9 | 0 |
| **Nervous System Disorders** | | | | |
| Headache[i] | 22 | 0.4 | 16 | 0 |
| Peripheral neuropathy[j] | 13 | 0.4 | 14 | 0.4 |
| Dizziness | 13 | 0.4 | 8 | 0 |

Events were graded using NCI CTCAE version 5.0. N = number of patients exposed; PT = preferred term.
a Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain.
b Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.
c Grouped term of fatigue includes PTs of fatigue, asthenia, malaise, and lethargy.
d Grouped term of anemia includes PTs of anemia, decreased hemoglobin, and decreased red blood cell count.
e This Grade 3 event was reported by the investigator. Per NCI CTCAE v.5.0, the highest NCI CTCAE grade for alopecia is Grade 2.
f Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.
g Grouped term of respiratory infection includes PTs of respiratory tract infection, lower and upper respiratory tract infection, pneumonia, influenza, influenza-like illness, viral upper respiratory infection, bronchitis, and respiratory syncytial virus infection.
h Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For ado-trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism.
i Grouped term of headache includes PTs of headache and migraine.
j Grouped term of peripheral neuropathy includes PTs of peripheral neuropathy, peripheral sensory neuropathy, and paresthesia.

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%)
- *Skin and Subcutaneous Tissue Disorders:* pruritus (8%) and skin hyperpigmentation (6%) [grouped term includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Nervous System Disorders:* dysgeusia (6%)
- *Metabolism and Nutrition Disorders:* dehydration (4.3%)
- *Eye Disorders:* blurred vision (3.5%)
- *Cardiac Disorders:* asymptomatic left ventricular ejection fraction decrease (2.7%) *[see Warnings and Precautions (6.3)]*
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (2.3%) [grouped term includes PTs of hypersensitivity and infusion-related reactions]
- *Blood and Lymphatic System Disorders:* febrile neutropenia (0.8%)

**Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03**

| Laboratory Parameter | ENHERTU 5.4 mg/kg N=257 | | Ado-trastuzumab emtansine 3.6 mg/kg N=261 | |
|---|---|---|---|---|
| | All Grades % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Hematology** | | | | |
| Decreased white blood cell count | 74 | 8 | 24 | 0.8 |
| Decreased neutrophil count | 70 | 18 | 30 | 2.3 |
| Decreased hemoglobin | 64 | 7 | 38 | 6 |
| Decreased lymphocyte count | 55 | 14 | 23 | 3.9 |
| Decreased platelet count | 52 | 7 | 79 | 24 |
| **Chemistry** | | | | |
| Increased aspartate aminotransferase | 67 | 0.8 | 83 | 5 |
| Increased alanine aminotransferase | 53 | 1.6 | 67 | 6 |
| Increased blood alkaline phosphatase | 49 | 0.8 | 46 | 0.8 |
| Hypokalemia | 35 | 4.7 | 39 | 1.5 |
| Increased blood bilirubin | 20 | 0 | 14 | 0 |
| Increased blood creatinine | 16 | 0.8 | 8 | 0.4 |

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.5.0 grade-derived laboratory abnormalities.

*DESTINY-Breast01 and Study DS8201-A-J101*

…..

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

### 7.2 Immunogenicity

….

Treatment-~~induced~~ emergent anti-trastuzumab deruxtecan antibodies (ADA) developed in ~~1.7~~2.1% (~~14~~27/~~807~~1311) ) patients who received ENHERTU across all doses. The incidence of neutralizing antibodies against trastuzumab deruxtecan

was 0.1% (1/1311). 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. ~~In addition, neutralizing activity of anti-ENHERTU antibodies has not been assessed.~~

## 8 USE IN SPECIFIC POPULATIONS

### 8.5 Geriatric Use

Of the ~~234~~ 491 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ~~26~~22% were 65 years or older and ~~5~~4% 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 (~~53~~60%) as compared to younger patients (~~42~~49%).

### 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. Monitor patients with moderate or severe renal impairment *[see Warnings and Precautions (6.1)]*.

### 12.3 Pharmacokinetics

Metastatic Breast Cancer

At the recommended dosage of ENHERTU for patients with HER2-positive breast cancer, the geometric mean (coefficient of variation [CV]%) $C_{max}$ of trastuzumab deruxtecan and DXd were ~~122~~ 131 µg/mL (20%) and 4.4 ng/mL (~~40~~41%), respectively, and the AUC of trastuzumab deruxtecan and DXd were ~~735~~ 769 µg day/mL (~~31~~28%) and ~~28~~ 27 ng·day/mL (~~38~~40%), respectively, based on population pharmacokinetic analysis. Accumulation of trastuzumab deruxtecan was approximately 35% 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 2.71~~2.78~~ L.

Specific Populations

No clinically significant differences in the pharmacokinetics of trastuzumab deruxtecan or DXd were observed for age (~~23~~20-96 years), race (Asian [n=~~563~~759], White [n=449], Black or African American [n=30] and Other [n=69] ~~non-Asian [n=245]~~), sex, body weight (27.3-125.4 kg), mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST, n=~~312~~385) hepatic impairment, mild (creatinine clearance [CLcr] ≥60 and <90 mL/min, n=~~292~~529) or moderate (CLcr ≥30 and <60 mL/min; n=~~54~~210) renal impairment based on population pharmacokinetic analysis.

## 14 CLINICAL STUDIES

### 14.1 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 were Asian (60%), White (27%) and 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 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%.

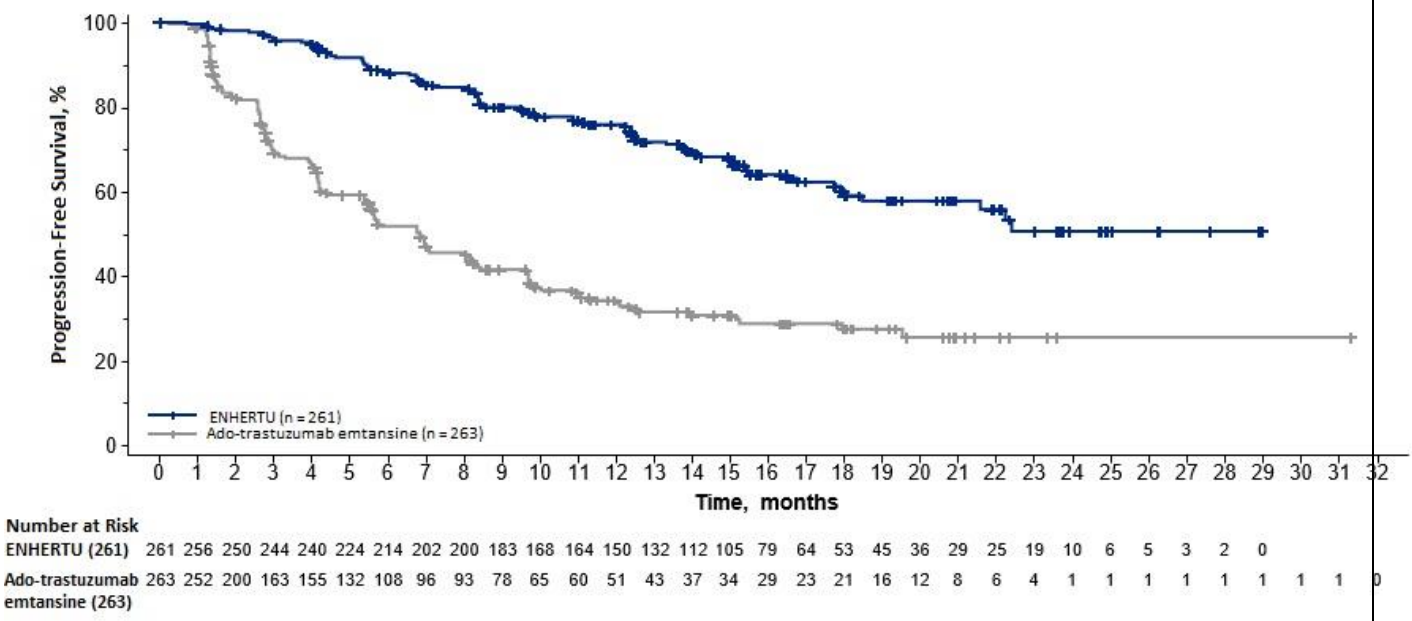
Efficacy results are summarized in Table 9 and Figure 1. At the time of the PFS analysis, 16% of patients had died and overall survival (OS) was immature.

**Table 9: 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< 0.000001* | |
| **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) |

CI = confidence interval; NR = not reached; NE=not estimable
*Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.

**Figure 1: Kaplan-Meier Plot of Progression-Free Survival per BICR (Intent-to-Treat Analysis Set)**




העדכונים המהותיים בעלון לצרכן הינם:

## 1. למה מיועדת התרופה?

אנהרטו ~~כטיפול מונותרפי~~ מיועד כטיפול עבור מטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג HER2-חיובי, אשר קיבלו ~~שני~~ טיפול~~ים~~ קוד~~מים~~ ~~לפחות~~ 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

## 3. כיצד תשתמש בתרופה?

לפני מתן העירוי, הרופא המטפל יתן לך תרופות כדי לסייע במניעת בחילות והקאות.

ייתכן כי איש הצוות הרפואי יאט או יפסיק את העירוי באופן זמני אם אתה מפתח תופעות לוואי הקשורות לעירוי. ייתכן כי הטיפול יופסק לצמיתות, אם אתה מפתח תופעות לוואי חמורות במהלך העירוי.

## 4. תופעות לוואי

**תופעות הלוואי השכיחות ביותר בעת נטילת אנהרטו לטיפול בסרטן שד כוללות:**

- בחילה
- ספירה נמוכה של תאי דם לבנים
- ספירה נמוכה של תאי דם אדומים
- תחושת עייפות
- הקאות
- נשירת שיער
- עלייה בבדיקות לתפקודי כבד
- ספירת טסיות נמוכה

- עצירות
- ירידה בתאבון
- שלשול
- רמה נמוכה של אשלגן בדם
- ~~שיעול~~זיהומים בדרכי הנשימה
- כאב בשרירים ובעצמות
- כאבי ראש
- כאב באזור הבטן

מקרא לעדכונים המסומנים:

תוספת טקסט מהותי מסומנת בצבע אדום.

מחיקת טקסט מסומנת בקו חוצה בצבע כחול.

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