יוני 2026

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

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

Enhertu

Powder for concentrate for solution for infusion

הרכב:

Trastuzumab Deruxtecan 100 mg.

התוויה:

<u>HER2-Positive Metastatic Breast Cancer</u>

- ENHERTU, in combination with pertuzumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer.
- ENHERTU, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) 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 and HER2-Ultralow Metastatic Breast Cancer</u>

ENHERTU, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic

- Hormone receptor (HR)-positive HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, that has progressed on one or more endocrine therapies in the metastatic setting [see Dosage and Administration (3.1)].
- HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

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

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

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

התוויות נגד:

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

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון העלון לרופא והעלון לצרכן בהתאם להוראות משרד הבריאות מתאריך מאי 2025.

2. Therapeutic indications

2.1 HER2-Positive Metastatic Breast Cancer

- ENHERTU, in combination with pertuzumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+~~ positive~~) breast cancer.
- ENHERTU, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received ~~a~~ prior anti-HER2-based regimen either~~:~~
- in the metastatic setting, or,

in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

2.2 HER2-Low and HER2-Ultralow Metastatic Breast Cancer

ENHERTU, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic

- Hormone receptor (HR)-positive HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, that has progressed on one or more endocrine therapies in the metastatic setting [see Dosage and Administration (3.1)].
- HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy *[see Dosage and Administration (3.1)]*.

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

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

2.4 HER2-Positive Locally Advanced or Metastatic Gastric Cancer

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

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

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

3. DOSAGE AND ADMINISTRATION

3.1 Patient Selection

HER2-positive Unresectable Metastatic Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-positive breast cancer with ENHERTU in combination with pertuzumab based on confirmed HER2-positive status or HER2 gene amplification (IHC 3+ or ISH+) *[see Clinical Studies (14.1)]*.

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3.2 Recommended Dosage and Schedules

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Premedication

ENHERTU is 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.

The ~~R~~recommended d~~D~~dosages for ENHERTU as monotherapy and ENHERTU in combination with pertuzumab are presented in Table 1. Administer ENHERTU ~~HER2-Positive HER2-Low, or HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant Unresectable or Metastatic NSCLC, and HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors.~~

~~The recommended dosage of ENHERTU is 5.4 mg/kg given~~ as an intravenous infusion ~~once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.~~[see *Preparation and Administration (3.4)]*

~~Recommended Dosage for HER2-Positive 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.~~

Table 1: Recommended Dosage

Indication	Recommended ENHERTU Dosage	Duration of Therapy
HER2-Positive, HER2-Low, or HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant Unresectable or Metastatic NSCLC, and HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors as monotherapy	ENHERTU 5.4 mg/kg every 3 weeks	Until disease progression or unacceptable toxicity
HER2-Positive Metastatic Breast Cancer in combination with pertuzumab	Cycle 1, Day 1: ENHERTU 5.4 mg/kg, followed by pertuzumab 840 mg[a] Subsequent cycles, Day 1: ENHERTU 5.4 mg/kg, followed by pertuzumab 420 mg every 3 weeks[a]	Until disease progression or unacceptable toxicity
HER2-Positive Locally Advanced or Metastatic Gastric Cancer as monotherapy	ENHERTU 6.4 mg/kg every 3 weeks	Until disease progression or unacceptable toxicity

[a] Administer pertuzumab 30 minutes after ENHERTU.

3.3 Dosage Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described in Tables ~~1~~ 2 and ~~2~~3. Refer to the Prescribing Information for pertuzumab for dose modification recommendations. Pertuzumab is not to be administered as a single agent.

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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 monotherapy or ENHERTU in combination with pertuzumab *[see Adverse Reactions (7.1)]*. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment.

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery *[see Dosage and Administration (3.3)]*. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent)) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD *[see Dosage and Administration (3.3)]*.

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

ENHERTU as Monotherapy

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

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), ILD occurred in 12% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.5% of patients treated with ENHERTU in combination with pertuzumab.

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

6.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU monotherapy or ENHERTU in combination with pertuzumab.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction *[see Dosage and Administration (3.3)]*.

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

ENHERTU as Monotherapy

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

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), decreased neutrophil count occurred in 79% of patients. Median time to first onset was 22 days (range: 5 to 994). Twenty-nine percent had Grades 3 or 4 decreased neutrophil count. Febrile neutropenia was reported in 2.6% of patients.

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

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

6.3 Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) *[see Dosage and Administration (3.3)]*.

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

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

ENHERTU as Monotherapy

In patients ~~with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors~~ treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 4.6% of patients, of which 0.6%were Grade 3 or 4.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), LVEF decrease was reported in 11% of patients, of which 2.1% were Grade 3 or 4.

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7 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease / Pneumonitis *[see Warnings and Precautions (6.1)]*
- Neutropenia *[see Warnings and Precautions (6.2)]*
- Left Ventricular Dysfunction *[see Warnings and Precautions (6.3)]*

7.1 Clinical Trials Experience

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

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

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY -Breast06, DESTINY -Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for greater than 6 months and 38% were exposed for greater than 12 months. In this pooled safety population, the most common (≥20%) adverse reactions (including laboratory abnormalities) were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (4443%),

increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

ENHERTU in Combination with Pertuzumab

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg in combination with pertuzumab intravenously every 3 weeks in 431 patients in DESTINY-Breast07 (n=50), and DESTINY-Breast09 (n=381). Among these patients, 86% were exposed for greater than 6 months and 73% were exposed for greater than 12 months. In this pooled safety population, the most common (≥20%) adverse reactions (including laboratory abnormalities) were decreased white blood cell count (86%), decreased hemoglobin (80%), decreased neutrophil count (79%), nausea (74%), increased alanine aminotransferase (65%), diarrhea (64%), increased aspartate aminotransferase (63%), decreased lymphocyte count (61%), decreased platelet count (55%), increased blood alkaline phosphatase (54%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (32%), constipation (31%), decreased appetite (31%), decreased weight (28%), musculoskeletal pain (23%), increased blood bilirubin (23%), and abdominal pain (22%).

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

The data described in WARNINGS and PRECAUTIONS reflect exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01.

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast09

The safety of ENHERTU 5.4 mg/kg in combination with pertuzumab was evaluated in DESTINY-Breast09, a randomized, three-arm, multicenter study including 763 patients with HER2-positive (IHC 3+ or ISH+) unresectable or metastatic breast cancer *[see Clinical Studies (14.1)]*. Three hundred eighty-one patients received ENHERTU in combination with pertuzumab and 382 patients received THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab). Among patients who received ENHERTU in combination with pertuzumab, the median duration of treatment was 22 months (range: 0.3 months to 44.5 months).

Serious adverse reactions occurred in 27% of patients receiving ENHERTU in combination with pertuzumab. Serious adverse reactions in >1% of patients were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis.

Fatalities due to adverse reactions occurred in 3.4% of patients including pneumonia (n=3), ILD (n=2), sepsis (n=2), pulmonary embolism, septic shock, acute kidney injury, dyspnea, febrile neutropenia, and intestinal ischemia (one patient each). ENHERTU was discontinued for adverse reactions in 21% of patients. The most frequent adverse reactions (>2%) associated with permanent discontinuation was ILD/pneumonitis (5.8%).

Dose interruptions due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, neutropenia, upper respiratory tract infection, fatigue, anemia, hypokalemia, ILD/pneumonitis, thrombocytopenia, pneumonia, diarrhea, transaminase increased, leukopenia, cough, pyrexia, decreased appetite, and blood bilirubin increased.

Dose reductions occurred in 46% of patients treated with ENHERTU in combination with pertuzumab. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, neutropenia, nausea, diarrhea, ILD/pneumonitis, thrombocytopenia, vomiting, transaminases increased, decreased weight, febrile neutropenia, and hypokalemia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, nausea, increased alanine aminotransferase, diarrhea, increased aspartate aminotransferase decreased lymphocyte count, decreased platelet count, increased blood alkaline phosphatase, decreased blood potassium, fatigue, alopecia, vomiting, upper respiratory tract infection, constipation, decreased appetite, decreased weight, COVID-19, musculoskeletal pain, increased blood bilirubin and abdominal pain.

Tables 4 and 5 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast09.

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

Combination with Pertuzumab in DESTINY-Breast09

Adverse Reactions	ENHERTU 5.4 mg/kg + Pertuzumab N= 381		THP* N=382	
	All Grades %	Grade 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	75	5	34	0.3
Diarrhea	64	8	62	6
Vomiting	46	2.4	18	0.5
Constipation	33	0.3	12	0
Abdominal pain[a]	23	0.3	13	0
Stomatitis[b]	16	1.3	17	1.3
Dyspepsia	12	0	6	0
General Disorders and Administration Site Conditions				
Fatigue[c]	53	8	42	2.1
Pyrexia	16	0	18	1.0
Skin and Subcutaneous Tissue Disorders				
Alopecia	48	0	53	0.5
Rash[d]	17	0.3	22	0.3
Pruritus	11	0	11	0.3
Infections and Infestations				
Upper respiratory tract infection[e]	33	1.6	30	0.5
COVID-19	28	0.3	22	0.3
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	18	0.8
Hypoalbuminemia	11	0.3	8	0.3
Investigations				
Decreased weight	30	3.1	11	0.8
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	24	1	33	0.3
Nervous System Disorders				
Headache[g]	19	0.3	14	0

Dysgeusia	13	0	9	0
Dizziness	12	0.3	10	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	17	0.3	13	0
Interstitial lung disease[h]	12	0	1	0
Eye Disorders				
Dry eye	11	0	6	0

[*] THP=taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab
[a] including abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain.
[b] including aphthous ulcer, mouth ulceration, oral mucosal eruption, stomatitis
[c] including asthenia, fatigue, lethargy, malaise.
[d] including rash, rash macular, rash maculo-papular, rash pruritic, rash pustular.
[e] including Influenza, Influenza like illness, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.
[f] including back pain, bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity.
[g] including headache, migraine.
[h] Interstitial lung disease (grouped term) includes PTs of chronic obstructive pulmonary disease (n=1), interstitial lung disease (n=23), pneumonia (n=3), pneumonitis (n=22). These events were adjudicated as ILD and related to use of T-DXd

Other clinically relevant adverse reactions reported in less than 10% of patients treated with ENHERTU in combination with pertuzumab were:

- *Blood and Lymphatic System Disorders:* febrile neutropenia (2.9%)
- *Eye Disorders:* blurred vision (4.2%)
- *Gastrointestinal Disorders:* abdominal distension (6%), gastritis (3.9%), flatulence (2.4%)
- *General Disorders and Administration Site Conditions:* mucosal inflammation (9%)
- *Injury, poisoning, and procedural complications:* infusion related reaction (1.8%) [including hypersensitivity and infusion-related reactions
- *Metabolism and Nutrition Disorders:* dehydration (2.9%)
- *Respiratory, Thoracic, and Mediastinal Disorders:* epistaxis (8%), dyspnea (6%)
- *Skin and Subcutaneous Tissue Disorders:* dry skin (7%), skin hyperpigmentation (6%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]

Table 5: Selected Laboratory Abnormalities in Patients in DESTINY-Breast09

Laboratory Parameter	ENHERTU 5.4 mg/kg + Pertuzumab N= 381		THP* N=382	
	All Grades %	Grade 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	87	11	82	31
Decreased hemoglobin	80	12	86	6
Decreased neutrophil count	78	29	66	40
Decreased lymphocyte count	62	14	58	11
Decreased platelet count	56	8	20	1.9
Chemistry				
Increased alanine aminotransferase	66	3.2	45	1.9
Increased aspartate aminotransferase	62	2.1	41	1.9

Laboratory Parameter	ENHERTU 5.4 mg/kg + Pertuzumab N= 381		THP* N=382	
	All Grades %	Grade 3-4 %	All Grades %	Grades 3-4 %
Increased blood alkaline phosphatase	55	0.3	36	0.3
Decreased blood potassium	54	20	29	6
Increased blood bilirubin	23	0.3	10	0.3
Increased blood creatinine	9	1.8	7	0.3

* THP=taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab]
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.

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HER2-Low and HER2-Ultralow Metastatic Breast Cancer

DESTINY-Breast06

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

- *Nervous System Disorders:* dizziness (9%)
- ~~*General Disorders and Administration Site Conditions:* peripheral edema (8%)~~
- *Investigations:* decreased weight (7%)
- *Eye Disorders:* dry eye (7%), and blurred vision (5%)
- *Respiratory, Thoracic, and Mediastinal Disorders:* dyspnea (6%)
- *Gastrointestinal Disorders:* abdominal distension (4.8%), flatulence (2.3%), and gastritis (0.7%)
- ~~*Infections and Infestations:* pneumonia (4.6%)~~
- *Skin and Subcutaneous Tissue Disorders:* pruritus (3.9%), and skin hyperpigmentation (0.9%)
- *Metabolism and Nutrition Disorders:* dehydration (1.6%)
- *Blood and lymphatic system disorders:* febrile neutropenia (1.2%)
- *Injury, Poisoning, and Procedural Complications:* infusion related reaction (1.2%)

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HER2-Mutant Unresectable or Metastatic 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~~ The median duration of treatment was 8 months (range: 0.7 to 28) for patients ~~were exposed for greater than 6 months.~~ who received ENHERTU. The median age was 59 years (range ~~30~~ 31 to ~~83~~84); 64% were female; 23% were White, 64% were Asian, and 14% were other races.

Serious adverse reactions occurred in ~~30~~40% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pleural effusion, thrombocytopenia, dyspnea, nausea, ~~pleural effusion~~, pneumonia, vomiting, myocarditis, pulmonary embolism, and increased troponin I. Fatalities due to adverse reactions ~~Fatality~~ occurred in ~~1 patient with suspected~~ 3% of patients including ILD/pneumonitis ~~(1%)~~, cerebrovascular accident, and pneumococcal sepsis (one patient each).

ENHERTU was permanently discontinued due to an adverse reaction in ~~8~~17% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, ~~diarrhea, decreased~~ pneumonia, blood ~~potassium,~~

~~hypomagnesemia,~~ bilirubin increased, hypokalemia, metastases to meninges, and myocarditis~~, and vomiting~~.

Dose interruptions of ENHERTU due to adverse reactions occurred in ~~23~~50% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia, ~~and~~ COVID-19, ILD/pneumonitis, fatigue, anemia, and pneumonia.

Dose reductions due to an adverse reaction occurred in ~~11~~20% of patients. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, fatigue, and decreased appetite.

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

Tables ~~13~~ 16 and ~~14~~ 17 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Lung02.

Table ~~13~~16: 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~~167	~~3.0~~4
Constipation	~~31~~38	1~~.0~~
Vomiting[a]	~~26~~32	~~2.0~~3
Diarrhea	~~19~~24	1~~.0~~
Stomatitis[b]	~~12~~17	0
Abdominal pain[c]	10	0
General Disorders and Administration Site Conditions		
Fatigue[~~dc~~]	~~32~~48	~~4.0~~48
Metabolism and Nutrition Disorders		
Decreased appetite	~~30~~41	~~1.0~~2
Skin and Subcutaneous Tissue Disorders		
Alopecia	~~21~~22	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[~~ed~~]	~~15~~21	1
Respiratory, Thoracic, and Mediastinal Disorders		
Interstitial lung disease[f]	15	1
Infections and Infestations		
Upper respiratory tract infection[g]	12	0

Events were graded using NCI CTCAE version 5.0.
a Including vomiting and retching
b including mucosal inflammation, ~~and~~ stomatitis and mouth ulceration
c Including abdominal discomfort, abdominal pain, and upper abdominal pain
~~c~~ d Including asthenia, fatigue, and malaise
~~d~~ e Including back pain, bone pain, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, musculoskeletal pain, myalgia, and pain in extremity
fe Interstitial lung disease includes events that were adjudicated as drug-induced ILD for ENHERTU including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure
g Including influenza, influenza-like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, and laryngitis

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 drug-induced ILD including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure],~~ dyspnea (~~5~~7%), and epistaxis (~~3~~5%)
- *Nervous System Disorders:* headache (7%) [including headache and migraine]
- ~~*Gastrointestinal Disorders:* abdominal pain (9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]~~

- *Skin and Subcutaneous Disorders:* rash (~~3~~6%) [including rash and rash 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 ~~14~~17: 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~~hemoglobin	~~60~~68	4~~1~~2
Decreased white blood cell count~~hemoglobin~~	~~58~~66	~~10~~7
Decreased neutrophil count	~~52~~59	~~12~~19
Decreased lymphocyte count	~~43~~56	~~16~~26
Decreased platelet count	~~40~~49	~~4~~5
Chemistry		
~~Decreased albumin~~Increased aspartate aminotransferase	~~39~~51	~~0~~1
~~Increased aspartate aminotransferase~~ Decreased albumin	~~35~~50	~~1~~0
Increased alanine aminotransferase	~~34~~41	2
Increased alkaline phosphatase	~~22~~37	0
Decreased blood potassium	~~17~~29	~~2~~5

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~~ 100 to ~~99~~ 101 based on the number of patients with a baseline value and at least one post-treatment value.

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8.5 Geriatric Use

ENHERTU as Monotherapy

Of the ~~1741~~ 2355 patients with HER2-positive or HER2-low, or HER2-ultralow breast cancer treated with ENHERTU 5.4 mg/kg, ~~24~~23% were 65 years or older and 4.9% 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 (~~61~~55%) as compared to younger patients (~~52~~50%).

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

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

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

ENHERTU in Combination with Pertuzumab

In patients with HER2-positive unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), 17% were 65 years or older and 3% 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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12.2 Pharmacodynamics

Exposure-Response Relationships

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

Cardiac Electrophysiology

~~The administration of multiple doses~~ At the dosage of ENHERTU (6.4 mg/kg every 3 weeks ~~did not show~~ a ~~large~~ mean ~~effect (i.e. >20 ms)~~ increase in on the QTc interval ~~in an open-label, single-arm study in 51 patients with metastatic HER2-positive cancer~~>20 ms was not observed..

12.3 Pharmacokinetics

The pharmacokinetics of trastuzumab deruxtecan ~~was~~ and its payload DXd were evaluated in patients with cancer. ~~Following a single dose, exposures (C_{max} and AUC)~~ and are presented as mean (% coefficient of variation), unless otherwise specified. At the dosage of 5.4 mg/kg, the maximum concentration (C_{max}) 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,NSCLC, and HER2-positive (IHC 3+) solid tumors and 0.5 to 1.25 times the recommended dose in gastric cancer).~~

~~At the recommended dosage of ENHERTU for patients with metastatic breast cancer, NSCLC, and HER2-positive (IHC 3+) solid tumors, the geometric mean (coefficient of variation [CV]%) $C_{max,ss}$~~ is 132 µg/mL (20%) and of DXd is 4.7 ng/mL (48%) and the AUC of trastuzumab deruxtecan ~~and DXd were 132 µg/mL (20%) and 4.7 ng/mL (48%), respectively, and the AUC of trastuzumab deruxtecan and DXd were~~ is 772 µg day/mL (27%) and of DXd is 29 ng·day/mL (48%~~), respectively . Accumulation of trastuzumab deruxtecan was approximately 35% at steady state (Cycle 3).~~

At the ~~recommended~~ dosage of ~~ENHERTU for patients with HER2-positive gastric cancer, the geometric mean~~ 6.4 mg/kg $C_{max,ss}$ of fam-trastuzumab deruxtecan ~~and DXd were~~ is 126 μg/mL (18%) and of DXd is 5.2 ng/mL (42%), ~~respectively,~~ and the AUC_{ss} of fam-trastuzumab deruxtecan and DXd ~~were~~ is 743 μg·day/mL (26%) and of DXd is 33 ng·day/mL (43%), respectively.

Following a single dose, C_{max} and AUC of fam-trastuzumab deruxtecan-nxki and DXd increase in a dose proportional

manner over a dose range of 3.2 mg/kg to 8 mg/kg (approximately 0.5 to 1.25 times the highest approved dose). Accumulation of fam-trastuzumab deruxtecan was approximately ~~39%~~ 1.4-fold at steady-state (Cycle 3).

Distribution

The estimated volume of distribution of the central compartment (V_c) of trastuzumab deruxtecan ~~was~~ is 2.~~68~~ 7 L.

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 is 5.4 to ~~-~~5.7 days. The estimated systemic clearance of trastuzumab deruxtecan ~~was~~ is 0.~~41~~ 4 L/day.

The median elimination half-life ($t_{1/2}$) of DXd is 5.4-6.1 days. The estimated systemic clearance of DXd ~~was~~ is 18.3 L/h.

Metabolism
The ~~humanized HER2 IgG1~~ monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways ~~in the same manner as endogenous IgG~~.

~~In vitro,~~ DXd is primarily metabolized by CYP3A4.

Specific Populations

No clinically significant differences in the pharmacokinetics of trastuzumab deruxtecan or DXd were observed for age (20-96 years), race (Asian [48%] vs Non-Asian [52%]), including White (43%), and Black or African American (1.9%); sex, body weight (27.138~~3 125.4~~ kg), tumor types; mild hepatic impairment, and mild or moderate renal impairment.

The pharmacokinetics of trastuzumab deruxtecan or DXd in patients with moderate to severe hepatic impairment or severe renal impairment is unknown.

Drug Interaction Studies

Clinical Studies

~~*Effect of CYP3A Inhibitors on DXd:* Coadministration of itraconazole, a strong CYP3A inhibitor, with multiple doses of ENHERTU increased steady state $AUC_{0\text{-}17\ days}$~~ No clinically significant differences in pharmacokinetics of trastuzumab deruxtecan ~~by 11% and~~ or DXd were observed when used concomitantly with itraconazole (strong CYP3A Inhibitor) and ~~by 18%. The impact of these changes is not clinically meaningful.~~

~~*Effect of OATP Inhibitors on DXd:* Coadministration of~~ ritonavir~~, a dual~~ (strong CYP3A inhibitor and OATP inhibitor~~ of OATP1B/CYP3A, with multiple doses of ENHERTU increased steady state $AUC_{0\text{-}17\ days}$ of trastuzumab deruxtecan by 19% and DXd by 22%. The impact of these changes is not clinically meaningful.~~

In Vitro Studies

~~*Effects of DXd on* *CYP Enzymes:*~~ DXd does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A nor induce CYP1A2, CYP2B6, or CYP3A.

UGT Enzymes: DXd is not a substrate of UGT.

~~*Effects of DXd on* *Transporters:* At clinically relevant concentrations (steady-state C_{max} of ~0.2 µmol/L),~~ *Systems:* DXd ~~has a low potential to inhibit~~ is not an inhibitor OAT1 ~~(IC_{50} value of 12.7 µmol/L)~~, OAT3, OCT1, OCT2, OATP1B1 ~~(IC_{50} value of 14.4 µmol/L)~~, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP ~~transporters~~.

~~*Effects of Other Drugs on DXd:*~~ DXd is a substrate of OATP1B1, OATP1B3, MATE2-K, P-gp, MRP1 and BCRP.

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 trastuzumab deruxtecan or of other trastuzumab deruxtecan products.

Among patients who received ENHERTU as a single agent and were tested for ADA over a 6 to 9-month treatment period in 13 clinical trials, anti-trastuzumab deruxtecan antibodies developed in 2.2% (49/2,231) of patients who received ENHERTU 5.4 mg/kg every three weeks and in 2.6% (21/793) of patients who received ENHERTU 6.4 mg/kg every three weeks. ~~There was no identified clinically significant effect of ADAs on pharmacokinetics, or safety, of trastuzumab deruxtecan. Because of the low occurrence of ADA, the effect of ADAs on the effectiveness of trastuzumab deruxtecan is unknown.~~Among patients who received ENHERTU (5.4 mg/kg every three weeks) in combination with pertuzumab for a median of 16 months in 2 clinical trials, anti-fam-trastuzumab deruxtecan-nxki antibodies developed in 7.7% (33/426) of patients.

These anti-drug antibodies have no clinically significant effect on the pharmacokinetics or safety of fam-trastuzumab deruxtecan-nxki. Because of the low occurrence of anti-drug antibodies, the effect of antibodies on the effectiveness of fam-trastuzumab deruxtecan-nxki products is unknown.

Among patients with anti-drug antibodies, neutralizing ~~N~~neutralizing antibodies against trastuzumab deruxtecan. were detected in 6% (4/70) of patients who w~~ere ADA-positive. Due to the limited number of patients who developed neutralizing antibodies against trastuzumab deruxtecan, the effect of neutralizing antibodies is unknown.~~ received ENHERTU as a single agent (5.4 mg/kg or 6.4 mg/kg every 3 weeks) and in 18% (6/33) of patients who received ENHERTU (5.4 mg/kg every 3 weeks) in combination with pertuzumab.

…

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

DESTINY-Breast09

The efficacy of ENHERTU in combination with pertuzumab was evaluated in DESTINY-Breast09 (NCT04784715), a randomized, three-arm, multicenter, global study that enrolled 1157 adult patients with HER2-positive advanced, or metastatic breast cancer who had not received prior chemotherapy or HER2-targeted therapy or had received neoadjuvant or adjuvant HER2-targeted therapy more than 6 months before the diagnosis of advanced or metastatic disease. A single line of prior endocrine therapy was permitted for advanced or metastatic breast cancer. HER2 expression was confirmed at a central laboratory using PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody and HER2 Dual ISH DNA Probe Cocktail with HER2 positivity defined as HER2 IHC 3+ or ISH positive.

Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with symptomatic brain metastases, or ECOG performance status >1, and patients with a history of clinically significant cardiac disease.

Patients were randomized 1:1:1 to receive either, ENHERTU 5.4 mg/kg plus pertuzumab (N=383), THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab) (N=387), or an investigational therapy (N=387) by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Patients with hormone receptor (HR) positive disease (N=416) were allowed to receive concurrent endocrine therapy after 6 cycles of ENHERTU or after discontinuation of the taxane in the THP arm; this occurred in 13.5% of patients in the ENHERTU in the combination with pertuzumab arm and in 38.3% of patients in the THP arm. Randomization was stratified by prior treatment status (de novo vs recurrent), hormone receptor status, and PIK3CA mutation status.

The major efficacy outcome was progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall survival (OS) and confirmed objective response rate (ORR) assessed by BICR.

The median age was 54 years (range: 20-88); 82% were <65 years; 100% were female; 50% of the patients were Asian, 37% were White, 2% were American Indian or Alaska Native, and 3% were Black or African American; 14% were Hispanic or Latino; 8% other or race unknown; 52% had de novo disease and 48% had recurrent disease; 53% were HR-positive and 47% HR-negative; and 31% of patients had a PIK3CA mutation.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to ENHERTU in combination with pertuzumab compared to THP. Efficacy results are summarized in Table 22 and Figure 1. At the time of the PFS analysis, OS data was not mature with 126 (16%) of patients who died across both study arms in the overall population.

Table 22: Efficacy Results in DESTINY-Breast09

Efficacy Parameter	ENHERTU 5.4 mg/kg + Pertuzumab N = 383	THP§ N = 387
Progression-Free Survival (PFS) per BICR		
Number of events (%)	118 (31)	172 (44)
Median, months (95% CI)	40.7 (36.5, NE)	26.9 (21.8, NE)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
p-value¶	< 0.0001	
Confirmed Objective Response Rate (ORR) per BICR		
Patients with Measurable Disease at Baseline, N	374	371
ORR (95% CI)‡	87 (83, 90)	81 (77, 85)
Complete Response, %	15	8
Partial Response, %	72	73

CI = confidence interval; NE = not estimable, N = number
¶ The stratified log-rank test p-value is compared with the allocated alpha of 0.00043 for this interim analysis (with 73% of the planned number of events for final analysis).
‡ 95% CI was based on Clopper-Pearson method.
§ THP = taxane (docetaxel or paclitaxel), trastuzumab,and pertuzumab

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

…

~~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 final analysis occurred after all responders had been followed for at least 6 months from the date of initial response or until disease progression or death, whichever came first.

Of the 102 patients randomized to receive ENHERTU 5.4 mg/kg, the median age was ~~58~~ 59 years (range ~~30~~ 31 to ~~78~~84); ~~69~~64% were female; ~~79~~64% were Asian, ~~12~~23% were White, and ~~10~~14% were other races; ~~29~~28% had an ECOG performance status of 0 and ~~71~~72% had 1; ~~33~~34% had stable brain metastases; ~~94~~97% had a mutation in the ERBB2 kinase domain and ~~6~~3% 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~~74% received prior immunotherapy, and ~~44~~50% received both in combination. Fifty-four percent of patients were never-smokers and ~~50~~46% were former smokers; ~~96~~98% of patients had adenocarcinoma histology.

Efficacy results are provided in Table ~~24~~28.

Table ~~24~~28: Efficacy Results for DESTINY-Lung02*

Efficacy Parameter	DESTINY-Lung02 N=~~52~~102
Confirmed Objective Response Rate (95% CI)	50.0% (39.9, 60.1)~~57.7% (43.2, 71.3)~~
Complete Response	~~1~~2.9%
Partial Response	~~55.8%~~47.1%
Duration of Response Median, months (95% CI)†	~~8.7~~12.6 (~~7.1~~6.4, 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

העדכונים המהותיים בעלון לצרכן הינם:

1. למה מיועדת התרופה?

- **סרטן שד גרורתי מסוג HER2-חיובי**
  - אנהרטו בשילוב עם פרטוזומאב, מיועד לטיפול קו ראשון במטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג HER2-חיובי (IHC 3+ or ISH+) .
  - אנהרטו, כטיפול תרופתי יחיד (מונותרפי), מיועד לטיפול במטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג HER2-חיובי (IHC 3+ or ISH ~~positive~~ +) אשר קיבלו טיפול קודם כנגד HER2 עבור:
    - מחלתם בשלב הגרורתי

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

- **סרטן שד גרורתי מסוג HER2-נמוך ואולטרה נמוך**

אנהרטו, כטיפול תרופתי יחיד (מונותרפי), מיועד לטיפול במטופלים מבוגרים עם סרטן שד לא-נתיח או גרורתי מסוג

  - HER2-נמוך (IHC 1+ or IHC 2+/ISH-) או HER2-אולטרה נמוך (IHC 0 עם צביעה ממברנלית), חיובי לקולטנים הורמונליים, אשר מחלתם התקדמה במהלך טיפול אנדוקריני אחד או יותר עבור מחלתם בשלב הגרורתי

  - HER2-נמוך (IHC 1+ or IHC 2+/ISH-), אשר קיבלו טיפול כימותרפי קודם בשלב הגרורתי או שמחלתם נשנתה במהלך 6 חודשים מסיום הטיפול הכימותרפי המשלים.

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

אנהרטו, כטיפול תרופתי יחיד (מונותרפי), 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 מתקדם מקומית או גרורתי מסוג HER2-חיובי**

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

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

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

...

4. תופעות לוואי

תופעות הלוואי השכיחות ביותר בעת נטילת אנהרטו בשילוב עם פרטוזומאב, לטיפול בסרטן שד מסוג HER2-חיובי כוללות:

- ספירה נמוכה של תאי דם לבנים
- ספירה נמוכה של תאי דם אדומים
- בחילה
- עלייה בתפקודי כבד בבדיקות דם
- שלשול
- ספירת טסיות נמוכה
- רמה נמוכה של אשלגן בדם
- תחושת עייפות
- נשירת שיער

- הקאות
- זיהום בדרכי הנשימה העליונות
- עצירות
- ירידה בתיאבון
- ירידה במשקל
- מחלת קורונה (COVID-19)
- כאב בשרירים או בעצמות
- כאב בטן

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
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