NEWS RELEASE

ENHERTU® (fam-trastuzumab deruxtecan-nxki) approved in the US as first tumor-agnostic HER2-directed therapy for previously treated patients with metastatic HER2-positive solid tumors

4/5/2024

Based on three Phase II trials of AstraZeneca and Daiichi Sankyo's ENHERTU which showed clinically meaningful responses across a broad range of tumors

ENHERTU now has five approved indications with the latest in HER2-expressing (IHC 3+) metastatic cancers

WILMINGTON, Del.--(BUSINESS WIRE)-- AstraZeneca and Daiichi Sankyo's ENHERTU® (fam-trastuzumab deruxtecan-nxki) has been approved in the US 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.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DoR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU is a specifically engineered HER2-directed antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed and commercialized by AstraZeneca and Daiichi Sankyo.

The first tumor-agnostic approval of a HER2-directed therapy and ADC by the Food and Drug Administration (FDA) was based on results from the subgroup of patients with HER2-positive IHC 3+ tumors in each of the **DESTINY-PanTumor02**, **DESTINY-Lung01** and **DESTINY-CRC02** Phase II trials.

Funda Meric-Bernstam, MD, Chair of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center, US, said: "Until the approval of fam-trastuzumab deruxtecan-nxki, patients with metastatic HER2-positive solid tumors have had limited treatment options. Based on the clinically meaningful response rates seen across clinical trials, this tumor-agnostic approval means that patients may now be treated with a HER2-directed medicine."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca, said: "As the first antibody drug conjugate to be granted a tumor-agnostic indication, ENHERTU is truly delivering on its potential across metastatic HER2-targetable tumors. The approval also elevates the importance of testing for biomarkers, including HER2, across a broad range of tumors to ensure these patients with advanced cancer who have few options know whether a targeted medicine might be right for them."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc., said: "This fifth indication in the US is a significant milestone as eligible patients with previously treated metastatic HER2-positive solid tumors may now be treated with ENHERTU. The accelerated approval by the FDA for this tumor-agnostic indication is based on the clinically meaningful efficacy seen with ENHERTU across numerous types of metastatic cancers."

In the DESTINY-PanTumor02 Phase II trial, patients with centrally or locally assessed HER2-positive (IHC 3+) solid tumors including either biliary tract, bladder, cervical, endometrial, ovarian, pancreatic or other tumors treated with ENHERTU showed a confirmed ORR of 51.4% (95% confidence interval [CI]: 41.7-61.0) and a median DoR range of 19.4 months (range: 1.3-27.9+ [+ denotes ongoing responses at data cutoff]). In DESTINY-Lung01, patients with centrally confirmed HER2-positive (IHC 3+) non-small cell lung cancer (NSCLC) treated with ENHERTU showed a confirmed ORR of 52.9% (95% CI: 27.8-77.0) and median DoR range of 6.9 months (range: 4.0-11.7+). A confirmed ORR of 46.9% (95% CI: 34.3-59.8) and median DoR range of 5.5 months (range: 1.3+-9.7+) was seen in patients with centrally confirmed HER2-positive (IHC 3+) colorectal cancer in the DESTINY-CRC02 trial.

The safety of ENHERTU was evaluated in 347 patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors in the DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 trials. The safety profile observed across the trials was consistent with previous clinical trials of ENHERTU with no new safety concerns identified.

Based on these results, fam-trastuzumab deruxtecan-nxki (ENHERTU) has been included in the NCCN Clinical

Practice Guidelines in Oncology (NCCN Guidelines®) as a treatment option for multiple metastatic tumors. See NCCN Guidelines® for detailed recommendations.1

This approval was granted under the FDA's Real-Time Oncology Review program after securing **Priority Review** and Breakthrough Therapy Designation for ENHERTU in the US in this setting.

The US regulatory submission was reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. As part of Project Orbis, ENHERTU is also under regulatory review for the same indication by regulatory authorities in Australia, Brazil and Singapore.

Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive (IHC 3+ or ISH 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

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

This indication is approved under accelerated approval based on objective response rate and duration of

response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- 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
- Unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. 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 ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days

from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (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.

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

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 1.0% of patients treated with ENHERTU.

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).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 109/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 109/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 109/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

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

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 63% of patients. Seventeen 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% 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.

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. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

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

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 3.8% of patients, of which 0.6% were Grade 3.

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, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU.

Additional Dose Modifications

Thrombocytopenia

For Grade 3 thrombocytopenia (platelets <50 to 25 x 109/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 109/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

Adverse Reactions

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

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 1799 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 65% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (73%), decreased white blood cell count (70%), decreased hemoglobin (66%), decreased neutrophil count (63%), decreased lymphocyte count (58%), fatigue (56%), decreased platelet count (48%), increased aspartate aminotransferase (47%), increased alanine aminotransferase (43%), vomiting (40%), increased blood alkaline phosphatase (38%), alopecia (34%), constipation (33%), decreased appetite (32%), decreased blood potassium (31%), diarrhea (29%), musculoskeletal pain (24%), and abdominal pain (20%).

HER2-Positive Metastatic Breast Cancer

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 intravenously once every three weeks in DESTINY-Breast03.

The median duration of treatment was 14 months (range: 0.7 to 30).

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 (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), decreased blood potassium (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), headache (22%), respiratory infection (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and decreased blood potassium (25%).

HER2-Mutant Unresectable or Metastatic NSCLC (5.4 mg/kg)

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 with HER2-mutant unresectable or metastatic NSCLC who received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. Nineteen percent of patients were exposed for >6 months.

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

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (61%), decreased white blood cell count (60%), decreased hemoglobin (58%), decreased neutrophil count (52%), decreased lymphocyte count (43%), decreased platelet count (40%), decreased albumin (39%), increased aspartate

aminotransferase (35%), increased alanine aminotransferase (34%), fatigue (32%), constipation (31%), decreased appetite (30%), vomiting (26%), increased alkaline phosphatase (22%), and alopecia (21%).

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

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m2 biweekly or paclitaxel (N=7) 80 mg/m2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

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

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), decreased blood potassium (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

HER2-Positive (IHC3+) Unresectable or Metastatic Solid Tumors

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. The median duration of treatment was 8.3 months (range 0.7

to 30.2).

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (20%).

Use in Specific Populations

- Pregnancy: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- Lactation: There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- Females and Males of Reproductive Potential: Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with

ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.

- Pediatric Use: Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- Geriatric Use: Of the 1287 patients with HER2-positive or HER2-low breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.8% were ≥75 years. 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 (59%) as compared to younger patients (49%). Of the 101 patients with HER2-mutant unresectable or metastatic NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥65 years and 8% were ≥75 years. 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 and 14% were ≥75 years. 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.
- 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 renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- Hepatic Impairment: In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see accompanying full **Prescribing Information** , including Boxed WARNINGS, and **Medication Guide.**

Notes

Financial considerations

Sales of ENHERTU in the US are recognized by Daiichi Sankyo. AstraZeneca reports its share of gross profit margin

from ENHERTU sales in the US as alliance revenue in the Company's financial statements.

Further details on the financial arrangements were set out in the **March 2019 announcement** of the collaboration.

HER2 expression in solid tumors

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of various tissue cells throughout the body and is involved in normal cell growth.2,3 In some cancers, HER2 expression is amplified or the cells have activating mutations.2,4 HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease and poor prognosis.5

HER2-directed therapies have been used to treat breast, gastric, lung and colorectal cancers for a number of years.3,6,7 Although HER2 is expressed in solid tumor types including biliary tract, bladder, cervical, endometrial, ovarian and pancreatic cancers, testing is not routinely performed in these additional tumor types and as a result, available literature is limited.4 In these solid tumors, HER2-positive expression, classified as immunohistochemistry (IHC) 3+, has been observed at rates from 1% to 28%.8,9 Approximately 1% to 5% of patients with NSCLC have tumors with HER2 overexpression (IHC 3+), however, the levels of protein expression reported vary in the literature.8,10 Approximately 1% to 4% of patients with metastatic colorectal cancer have tumors which are HER2 overexpressing (IHC 3+).8,11,12

DESTINY-PanTumor02

DESTINY-PanTumor02 is a global, multicenter, multi-cohort, open-label Phase II trial evaluating the efficacy and safety of ENHERTU (5.4mg/kg) for the treatment of previously treated HER2-expressing tumors, including biliary tract cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer or other tumors.

The primary efficacy endpoint of DESTINY-PanTumor02 is confirmed ORR as assessed by investigator. Secondary endpoints include DoR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, tolerability and pharmacokinetics.

DESTINY-PanTumor02 has enrolled 267 patients, including 111 HER2-positive (IHC 3+) adult patients, at multiple sites in Asia, Europe and North America, and is to be expanded to recruit more patients with metastatic HER2-postive IHC 1+, IHC 2+ and IHC 3+ tumors. For more information about the trial, visit **ClinicalTrials.gov**.

DESTINY-Lung01

DESTINY-Lung01 is a global Phase II, open-label, two-cohort trial evaluating the efficacy and safety of ENHERTU (5.4mg/kg or 6.4mg/kg) in patients with HER2-mutant (cohort 2, n=91) or HER2-overexpressing (defined as IHC 3+ or IHC 2+) [cohort 1 and 1a, n=90]) unresectable or metastatic non-squamous NSCLC who had progressed after one or more systemic therapies.

The primary endpoint is confirmed ORR by independent central review. Key secondary endpoints include DoR, DCR, PFS, OS and safety.

DESTINY-Lung01 enrolled 181 patients, including 17 HER2-postive (IHC 3+) adult patients, at multiple sites, including Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov**.

DESTINY-CRC02

DESTINY-CRC02 is a global, randomized, two arm, parallel, multicenter Phase II trial evaluating the efficacy and safety of two doses (5.4mg/kg or 6.4mg/kg) of ENHERTU in patients with locally advanced, unresectable or metastatic HER2-positive colorectal cancer of BRAF wild-type, RAS wild-type or RAS mutant tumor types previously treated with standard therapy.

The trial was conducted in two stages. In the first stage, patients (n=80) were randomized 1:1 to receive either 5.4mg/kg or 6.4mg/kg of ENHERTU. In the second stage, additional patients (n=42) were enrolled in the 5.4mg/kg arm.

The primary endpoint is confirmed ORR as assessed by blinded independent central review. Secondary endpoints include DoR, DCR, investigator-assessed confirmed ORR, clinical benefit ratio, PFS, OS and safety.

DESTINY-CRC02 enrolled 122 patients, including 64 HER2-positive (IHC 3+) adult patients, at multiple sites in Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov**.

DESTINY-Breast01

DESTINY-Breast01 is a global, single-arm, open-label, two-part multicenter Phase II trial evaluating the safety and efficacy of ENHERTU in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine (T-DM1).

The primary endpoint of the trial is ORR, as determined by independent central review. Secondary objectives include DoR, DCR, clinical benefit rate, PFS and OS.

DESTINY-Breast01 enrolled 253 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov**.

ENHERTU

ENHERTU is a HER2-directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC technology, ENHERTU is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced program in AstraZeneca's ADC scientific platform. ENHERTU consists of a HER2 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads, (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

ENHERTU (5.4mg/kg) is approved in more than 60 countries for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or in-situ hybridization [ISH]+) breast cancer who have received a (or one or more) 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 based on the results from the DESTINY-Breast03 trial.

ENHERTU (5.4mg/kg) is approved in more than 55 countries 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 systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on the results from the DESTINY-Breast04 trial.

ENHERTU (5.4mg/kg) is approved in more than 35 countries worldwide for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer whose tumors have activating HER2 (ERBB2) mutations, as detected by a locally or regionally-approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 trial. Continued approval in the US for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4mg/kg) is approved in more than 45 countries for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 trial and/or DESTINY-Gastric02 trial.

ENHERTU (5.4 mg/kg) is approved in the US 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 based on the results from the DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 trials. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU development program

A comprehensive clinical development program is underway globally, evaluating the efficacy and safety of ENHERTU monotherapy across multiple HER2-targetable cancers. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

Daiichi Sankyo collaboration

Daiichi Sankyo Company, Limited (TSE: 4568) [referred to as Daiichi Sankyo] and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU (a HER2-directed ADC) in **March 2019**, and datopotamab deruxtecan (DS-1062; a TROP2-directed ADC) in **July 2020**, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and datopotamab deruxtecan.

AstraZeneca in oncology

AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyze changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines in Oncology, Rare Diseases and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries, and its innovative medicines are used by millions of patients worldwide. For more information, please visit **www.astrazeneca-us.com** and follow us on social media **@AstraZeneca**.

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1. Referenced with permission from the NCCN Guidelines. © National Comprehensive Cancer Network 2024. All rights reserved. Accessed March 2024. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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PP-US-EN-2483

04/24

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Source: AstraZeneca