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Determining HER2-low status in metastatic breast cancer: The impact of DESTINY-Breast04

A planned exploratory sub-analysis of progression-free survival for ENHERTU® (fam-trastuzumab deruxtecan-nxki) vs. standard of care

Important Safety Information

Indication

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

- 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

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

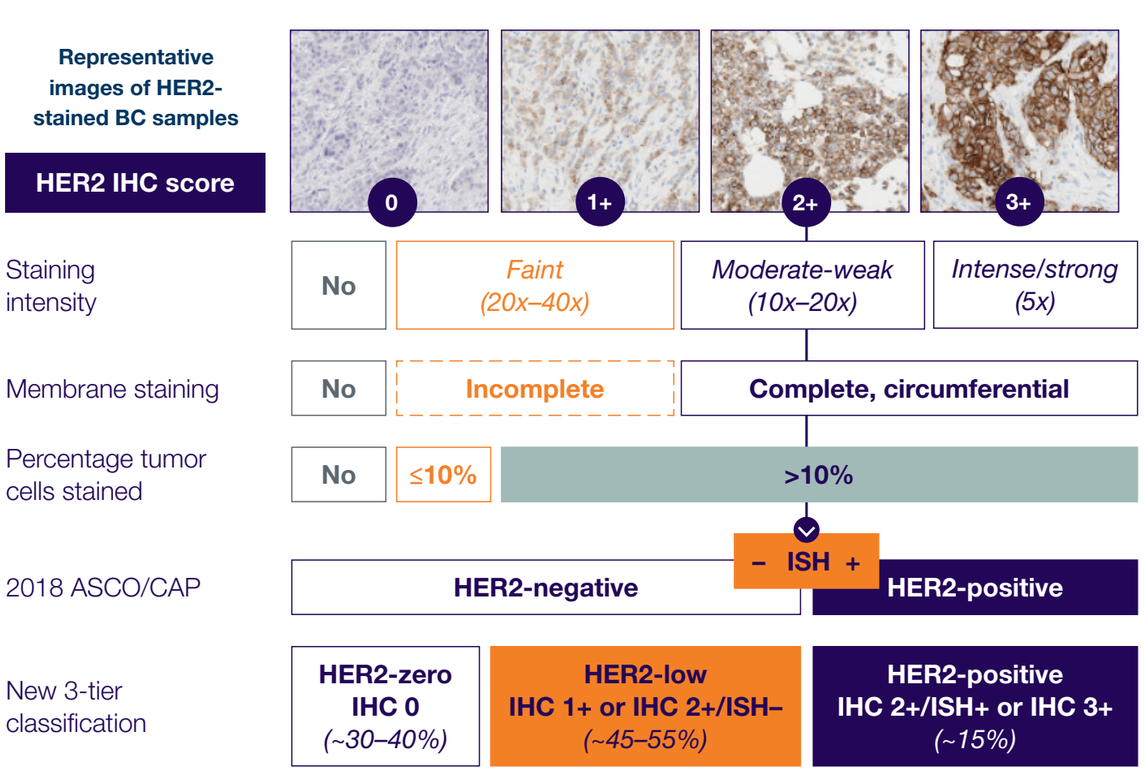
- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 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.

Please see Important Safety Information on page 7 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Certain patients classified as HER2-low may be eligible for targeted treatment

- DESTINY-Breast04, a Phase III, open-label, randomized, multicenter study evaluated the HER2-targeting antibody-drug conjugate (ADC) ENHERTU® (fam-trastuzumab deruxtecan-nxki) vs. treatment of physician's choice (TPC) in previously treated patients with HER2-low (IHC 1+ or IHC 2+/ISH-) metastatic breast cancer (mBC)[1,2]
- This trial was the first to highlight the clinically meaningful benefit of HER2-targeting therapy in HER2-low breast cancer. Accurate identification of patients with HER2-low mBC who may be eligible for ENHERTU may improve certain patient outcomes[1–4]
- Before DESTINY-Breast04, tumors scored as IHC 1+ or IHC 2+/ISH- were classified as HER2-negative and not eligible for HER2-targeting therapy.[1] However, approximately 60% of patients previously classified as HER2-negative may be re-classified as HER2-low and could potentially be eligible for ENHERTU[3,5]
- A 3-tier classification paradigm has been recommended to reflect the results of using HER2-targeting therapies in patients classifed as HER2-low[1–3]

Classification scheme for HER2 staining according to the ASCO/CAP 2018 guidelines and the 3-tier classification[2,5,6]



IHC stained tissue sections (upper row) are evaluated stepwise first by determining intensity of membrane staining using magnification rule, (recommended objective magnifications are stated for each staining intensity) followed by the assessment of circularity and finally the percentage of stained tumor cells. Classification of diagnostic groups is based on these 3 criteria in combination with HER2 ISH data in IHC 2+ cases. Note, the separation between HER2 IHC 0 and IHC 1+ is representative of cases at the HER2 IHC 0 border where staining intensity is similar to HER2 IHC 1+ with incomplete circularity and/or ≤10% stained tumor cells.

HER2-low identification in DESTINY-Breast04[1,2]

DESTINY-Breast04 utilized central companion diagnostic (CDx) testing using the PATHWAY HER2 (4B5) assay for the re-assessment of HER2 IHC scores on tumor samples submitted for screening.

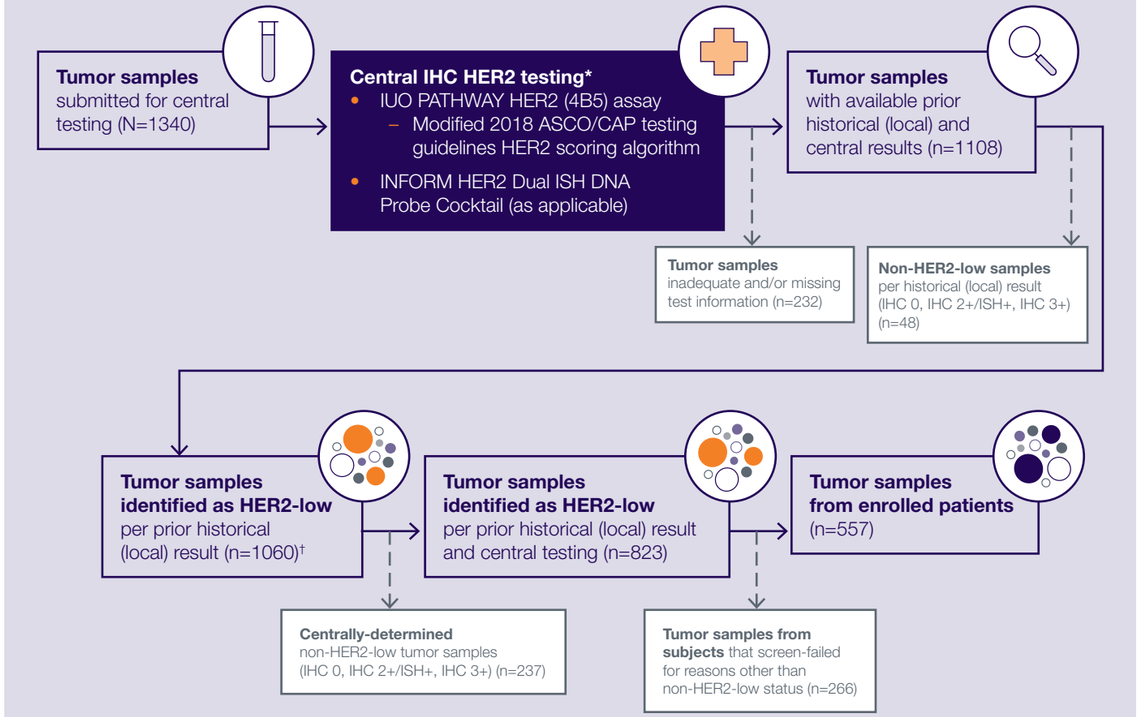
This planned CDx exploratory sub-analysis of DESTINY-Breast04 evaluated the classification of HER2 status, and sought to:

- Describe the tumor sample characteristics from enrolled patients
- Assess concordance between historical and central assessment for HER2 status
- Determine ENHERTU efficacy stratified by the tumor sample characteristics

This was a planned exploratory subgroup analysis and not tested for statistical significance nor analysis powered to show differences between treatment arms or subgroups.

PATHWAY HER2 (4B5) CDx is the only clinically validated and Food and Drug Administration (FDA)-approved diagnostic assay for identifying patients with HER2-low mBC and determining potential eligibility for treatment with ENHERTU[7]

CDx exploratory sub-analysis study design[1]



*Performed on adequate archived or recent tumor biopsy per modified 2018 ASCO/CAP testing HER2 scoring algorithm using the PATHWAY HER2 (4B5) IUO Assay system.

†Some samples submitted for central testing were not HER2-low by local assessment. Subjects confirmed to have prior HER2-positive results or those without a history of HER2-low tumors were excluded from this group. In few instances, prior history of local HER2-low status was confirmed based on a sample different than the one submitted for central testing.

Tumor sample characteristics for assessing HER2 status in the enrolled patient population[1]

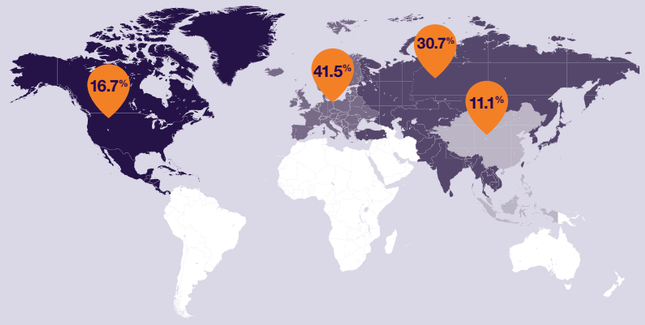
Out of the 557 enrolled patients:

35.2% had samples collected from **primary tumor sites**

64.5% had samples collected from **metastatic sites**

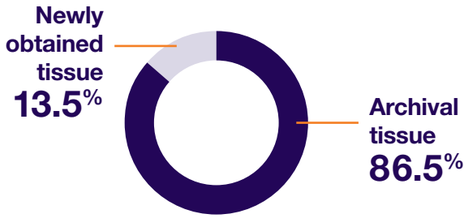
80.4%
were biopsy specimens compared with excision/ resection specimens (19.4%)

Geographical region was categorized into North America, Europe and Israel, Asia and China

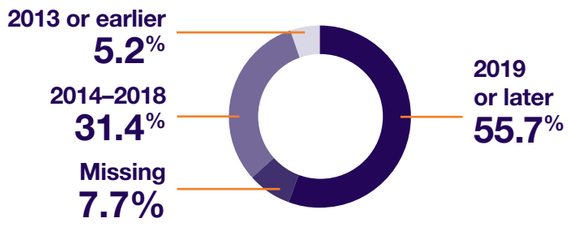


Data represent the percentage of patients enrolled in each region.

Archival tissue was used as the primary source of tissue compared with newly obtained tissue



Collection of patient samples



Concordance between central and historical results for HER2-low status was associated with region and collection date[1]

There was 78% concordance between historical and central HER2 assessment results, despite:

- Lack of a prior clinical utility for HER2-low diagnosis
- Minimum pathologist training for distinguishing HER2 IHC 0 from HER2-low (IHC 1+ or IHC 2+/ISH-)
- Differences in local testing methods
- Differences in key sample characteristics

Among the 22% (237/1060) of discordant samples, 208/237 (88%) were centrally scored as IHC 0, and 29/237 (12%) were scored as IHC 2+/ISH+ or IHC 3+.

Central HER2-low status vs. historical HER2 assessment[1*]

HER2 status by historical result, n

HER2 status by central testing, n	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	Total
IHC 0	18	157	51	2	228
IHC 1+	18	344	126	3	491
IHC 2+/ISH-	5	122	231	0	358
IHC 2+/ISH+	0	9	11	1	21
IHC 3+	1	2	7	0	10
Total	**42**	**634**	**426**	**6**	**1108**

Table includes some samples submitted for central testing that were not classified as HER2-low by local assessment. Subjects confirmed to have prior HER2-positive results or those without a history of HER2-low tumors were excluded from additional screening procedures. In limited instances, prior history of local HER2-low status was confirmed based on a sample different from the one submitted for central testing.

HER2-low identification in DESTINY-Breast04[1]

Factors associated with concordance between historical and central HER2 assessment[1]

Feature	Patients with historical and valid central HER2 results (n=1108) n (%)	Overall percentage agreement (95% CI)
Region of origin		
North America	252 (22.7)	0.85 (0.81–0.90)
Europe and Israel	461 (41.6)	0.70 (0.66–0.74)
Asia, excluding China	287 (25.9)	0.82 (0.77–0.86)
China	108 (9.7)	0.68 (0.59–0.76)
Specimen coliection time (relative to study screening)		
2013 or earlier	94 (8.5)	0.64 (0.54–0.74)
2014–2018	421 (38.0)	0.75 (0.71–0.79)
2019 or later	555 (50.1)	0.79 (0.75–0.82)
Missing	38 (3.4)	0.89 (0.80–0.99)

Assessments completed in North America and Asia (excluding China) had numerically greater concordance than those in Europe or China

The numerically lowest concordance was in those samples collected in or before 2013

*The planned CDx exploratory sub-analysis includes some samples submitted for central testing that were not HER2-low by local assessment. Subjects confirmed to have prior HER2-positive results or those without a history of HER2-low tumors were excluded from additional screening procedures. In few instances, prior history of local HER2-low status were confirmed based on a sample different than the one submitted for central testing.

Correlation between tumor characteristics and PFS[1]

Median PFS among all patients enrolled in DESTINY-Breast04 was 9.9 months (95% CI, 9.0–11.3) for ENHERTU® vs. 5.1 months (95% CI, 4.2–6.8) for TPC. Hazard ratio was 0.50 (95% CI, 0.40–0.63) p<0.001)[2]

Progression-free survival (PFS) following treatment with ENHERTU was not affected by tumor location nor the time at which the tumor sample was collected, if sample collection was within 5 years.

Median PFS analyzed by tumor sample characteristics[1]

	Number of events		Median PFS, months (95% CI)		Hazard ratio (95% CI)
Subgroup (n)	**ENHERTU**	**TPC**	**ENHERTU**	**TPC**	
Tumor location					
Primary (196)	96/136	43/60	9.6 (7.1–11.3)	4.2 (1.6–6.4)	0.47 (0.32–0.70)
Metastases (359)	145/235	84/124	10.9 (9.5–12.3)	5.4 (4.3–7.1)	0.50 (0.38–0.66)
Specimen type					
Biopsy (448)	189/299	103/149	10.9 (9.6–12.0)	5.3 (4.2–6.9)	0.46 (0.35–0.59)
Excision/resection (108)	53/73	24/35	7.5 (5.7–9.9)	3.0 (1.4–11.0)	0.57 (0.33–1.0)
Collection type					
Archival tissue (482)	203/324	109/158	10.3 (8.6-12.0)	5.3 (4.2-7.0)	0.48 (0.37–0.61)
Newly obtained tissue (75)	40/49	18/26	9.7 (5.6–10.9)	4.8 (2.8–6.9)	0.57 (0.30–1.1)
Tumor specimen collection date					
2013 and earlier (29)	11/19	9/10	7.0 (2.8–NE)	6.8 (1.4–11.1)	0.78 (0.24–2.54)
2014–2018 (175)	76/126	33/49	11.4 (9.5–15.1)	4.3 (1.6–7.0)	0.44 (0.28–0.70)
2019 or later (310)	137/203	75/107	9.8 (8.4–11.3)	5.1 (4.1–7.1)	0.49 (0.37–0.66)
Missing (43)	19/25	10/18	6.6 (2.8–10.8)	2.8 (1.2–8.3)	0.54 (0.20–1.4)

Conclusions

- Concordance of HER2-low status between historical and centrally assessed samples was 78%, which is comparable to previously reported concordance data for HER2-positive samples[1,8,9]
- Concordance may be affected by geographical region or older archival samples (>5 years). Discordance was primarily observed when distinguishing between IHC 0 and IHC 1+[1]
- Results from this planned DESTINY-Breast04 CDx exploratory sub-analysis illustrate that the median PFS for ENHERTU and TPC were largely consistent regardless of tumor sample characteristics used for HER2-low identification, including those utilized for metastatic tumor samples. However, the exploratory sub-analysis was not tested for statistical significance nor analysis powered to show differences between treatment arms or subgroups[1]
- These data suggest that regardless of the breast tumor sample type used, classification of HER2 expression according to the methodology described in DESTINY-Breast04 is effective in identifying patients with HER2-low mBC who are potentially eligible for ENHERTU treatment.[1–3] The PATHWAY HER2 (4B5) assay is approved in the US as the first CDx test to identify patients with HER2-low mBC[7]

Important Safety Information

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Indication

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

- 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

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.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)

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

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 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/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.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)

In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Important Safety Information Continued

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.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)

In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

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 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

Adverse Reactions

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and another clinical trial. Among these patients 65% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

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 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

ENHERTU®
trastuzumab deruxtecan

Important Safety Information Continued

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 hypokalemia (25%).

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 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.6% 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 (60%) as compared to younger patients (48%).

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. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times upper limits of normal and any aspartate aminotransferase.

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.

Abbreviations

ADC=antibody-drug conjugate; **ANC**=absolute neutrophil count; **ASCO**=American Society of Clinical Oncology; **(m) mBC=metastatic breast cancer**; **CAP**=College of American Pathologists; **CDx**=companion diagnostic; **CI**=confidence interval; **HER2**=human epidermal growth factor receptor 2; **IHC**=immunohistochemistry; **ILD**=interstitial lung disease; **ISH**=*in situ* hybridization; **LVEF**=left ventricular ejection fraction; **PFS**=progression-free survival; **TPC**=treatment of physician's choice.

References

1. Prat A, et al. San Antonio Breast Cancer Symposium 2022; December 6–10; San Antonio, TX. Presentation HER2-18. **2.** Modi S, et al. *N Engl J Med*. 2022;387(1):9–20. **3.** ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing Information. November 2022. **4.** Viale G, et al. San Antonio Breast Cancer Symposium 2022; December 6–10; San Antonio, TX. Presentation HER2-15. **5.** Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951–1962. **6.** Wolff AC, et al. *J Clin Oncol*. 2018;36:2105–2122. **7.** Roche. Press Release. Available at: https://diagnostics.roche.com/global/en/news-listing/2022/roche-receives-fda-approval-for-first-companion-diagnostic-to-id.html. (Accessed March 2023); **8.** Roche PC, et al. *J Natl Cancer Inst*. 2002;94(11):855–857. **9.** Perez EA, et al. *J Clin Oncol*. 2006;24(19):3032–3038.

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