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Daiichi-Sankyo

Press Release

ENHERTU® Approved in Japan as First Tumor Agnostic HER2 Directed Medicine for Previously Treated Patients with HER2 Positive Metastatic Solid Tumors

- Based on four phase 2 trials where ENHERTU demonstrated clinically meaningful responses across a broad range of tumors
- ENHERTU is now approved for six indications in Japan

Tokyo – (March 23, 2026) – ENHERTU® (trastuzumab deruxtecan) has been approved in Japan for the treatment of adult patients with HER2 positive (*HER2* [*ERBB2*] gene amplification or immunohistochemistry [IHC] 3+) advanced or recurrent solid cancers refractory or intolerant to standard treatments.

ENHERTU is a specifically engineered HER2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being developed and commercialized by Daiichi Sankyo in Japan.

The approval by Japan's Ministry of Health, Labour and Welfare (MHLW) is based on results from four phase 2 trials, including HERALD, an investigator-initiated trial conducted in Japan, DESTINY-PanTumor02, DESTINY-CRC02 and DESTINY-Lung01 where ENHERTU demonstrated clinically meaningful responses across a broad range of tumors. A companion diagnostic (CDx) to test liquid biopsy for HER2 amplification is approved for this new tumor agnostic indication of ENHERTU in Japan. A separate CDx submission to test tumor tissue for HER2 expression (IHC 3+) is planned.

In HERALD, ENHERTU demonstrated a confirmed objective response rate (ORR) of 56.5% (95% confidence interval [CI]: 43.3-69.0) as assessed by investigator in patients (n=62) with unresectable, advanced or recurrent HER2 positive solid cancers refractory or intolerant to standard treatments, including biliary tract, cervical, colorectal, endometrial, esophageal, gastric, melanoma, non-small cell lung (NSCLC), ovarian, pancreatic, prostate, salivary gland, small intestine, urothelial cancer or other tumors.

In DESTINY-PanTumor02, ENHERTU demonstrated a confirmed ORR of 61.3% (95% CI: 49.4-72.4) as assessed by investigator in a subgroup of previously treated patients (n=75) with HER2 positive unresectable advanced or recurrent solid tumors, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic or other tumors. In DESTINY-Lung01, ENHERTU demonstrated a confirmed ORR of 52.9% (95% CI: 27.8-77.0) in a subgroup of patients (n=17) with HER2 positive unresectable or metastatic NSCLC. In DESTINY-

CRC02, ENHERTU demonstrated a confirmed ORR of 46.9% (95% CI: 34.3-59.8) in a subgroup of patients (n=64) with HER2 positive locally advanced, unresectable or metastatic colorectal cancer.

“This is the first tumor agnostic approval for a HER2 directed medicine and antibody drug conjugate in Japan and marks the sixth approved indication for ENHERTU,” said Yuki Abe, PhD, Head of R&D Division in Japan and Head of Research, Daiichi Sankyo. “Based on the clinically meaningful efficacy seen with ENHERTU across numerous types of metastatic cancer, this milestone validates the importance of testing for HER2 across a broad range of tumors.”

In HERALD, adverse reactions occurred in 59 patients (95.2%) treated with ENHERTU. The most common adverse reactions were nausea (58.1%), decreased appetite (53.2%), fatigue (46.8%), anemia (38.7%), decreased neutrophil count (32.3%), decreased white blood cell count (32.3%), decreased platelet count (24.2%) and stomatitis (22.6%). In DESTINY-PanTumor02, adverse reactions occurred in 65 patients (86.7%) treated with ENHERTU. The most common adverse reactions were fatigue (50.7%), nausea (46.7%), decreased neutrophil count (45.3%), diarrhea (33.3%), anemia (28.0%) and decreased appetite (21.3%). In DESTINY-Lung01, adverse reactions occurred in 17 patients (100%), including two Japanese patients, treated with ENHERTU. The most common adverse reactions were nausea (82.4%), fatigue (52.9%), decreased appetite (35.3%), vomiting (23.5%), diarrhea (23.5%) and anemia (23.5%). In DESTINY-CRC02, adverse reactions occurred in 61 patients (93.8%) treated with ENHERTU. The most common adverse reactions were nausea (56.9%), fatigue (43.1%), decreased neutrophil count (30.8%), diarrhea (23.1%), decreased appetite (23.1%), alopecia (23.1%) and vomiting (20.0%).

ENHERTU is approved in Japan with a Warning in its prescribing information for interstitial lung disease (ILD). ILD occurred in 262 patients (11.6%) treated with ENHERTU across multiple clinical trials. As cases of ILD, including fatal cases, have occurred in ENHERTU-treated patients, ENHERTU is to be used in close collaboration with a respiratory disease expert. Patients should be closely observed during therapy by monitoring for early signs or symptoms of ILD (such as dyspnea, cough or fever) and performing regular peripheral artery oxygen saturation (SpO_2) tests, chest X-ray scans and chest CT scans. If abnormalities are observed, discontinue administration of ENHERTU and take appropriate measures, such as corticosteroid administration. Prior to initiation of ENHERTU therapy, a chest CT scan should be performed and medical history taken to confirm the absence of any comorbidity or history of ILD with the patient and carefully consider the eligibility of the patient for ENHERTU therapy.

About HERALD

HERALD is a multicenter, open-label, single-arm, investigator-initiated, phase 2 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) in patients with unresectable, advanced or recurrent solid tumors

refractory or intolerant to standard treatments and have *HER2* gene amplification in circulating tumor DNA, including biliary tract, cervical, colorectal, endometrial, esophageal, gastric, melanoma, NSCLC, ovarian, pancreatic, prostate, salivary gland, small intestine, urothelial cancer or other tumors.

The primary endpoint of HERALD is confirmed ORR as assessed by investigator. Secondary endpoints include duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), time to treatment failure, overall survival (OS), ORR by independent central review and safety. Results from HERALD were published in the *Journal of Clinical Oncology*.

HERALD enrolled 62 patients at seven sites in Japan. For more information about the trial, visit Japan's Registry of Clinical Trials.

About DESTINY-PanTumor02

DESTINY-PanTumor02 is a global, multicenter, multi-cohort, open-label, phase 2 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) for the treatment of previously treated HER2 expressing tumors, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic cancer or other tumors.

The primary endpoint of DESTINY-PanTumor02 is confirmed ORR as assessed by investigator. Secondary endpoints include DOR, DCR, PFS, OS, safety, tolerability and pharmacokinetics. Results from DESTINY-PanTumor02 were published in the *Journal of Clinical Oncology*.

DESTINY-PanTumor02 enrolled 267 patients, including 75 HER2 positive (IHC 3+) adult patients at multiple sites in Asia, Europe, North America, South America and Oceania. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Lung01

DESTINY-Lung01 is a global, open-label, two-cohort, phase 2 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg or 6.4 mg/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 NSCLC who had progressed after one or more systemic therapies.

The primary endpoint of DESTINY-Lung01 is confirmed ORR by independent central review. Key secondary endpoints include DOR, DCR, PFS, OS and safety. Results from the *HER2* mutant cohort were published in *The New England Journal of Medicine* and results from the HER2 overexpressing cohort were published in *The Lancet Oncology*.

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

About DESTINY-CRC02

DESTINY-CRC02 is a global, randomized, two arm, parallel, multicenter, phase 2 trial evaluating the efficacy and safety of two doses (5.4 mg/kg or 6.4 mg/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 5.4 mg/kg or 6.4 mg/kg of ENHERTU. In the second stage, additional patients (n=42) were enrolled in the 5.4 mg/kg arm.

The primary endpoint in DESTINY-CRC02 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. Results from DESTINY-CRC02 were published in *The Lancet Oncology*.

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

About HER2 Expression and Amplification 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.[1] In some cancers, the *HER2* gene is amplified or the cells have activating mutations.[2] HER2 protein overexpression and *HER2* gene amplification may be associated with aggressive disease and poor prognosis in some cancers.[3]

HER2 directed therapies have been used to treat breast, colorectal, gastric, lung and salivary gland cancers.[1,4,5,6] Although HER2 is expressed or amplified 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.[2,7]

About ENHERTU

ENHERTU (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) 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 (5.4 mg/kg) in combination with pertuzumab is approved in the U.S. as a first-line treatment for adult patients with unresectable or metastatic HER2 positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test, based on the results from the DESTINY-Breast09 trial.

ENHERTU (5.4 mg/kg) is approved in more than 90 countries/regions worldwide 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 based on the results from the DESTINY-Breast03 trial.

ENHERTU (5.4 mg/kg) is approved in more than 90 countries/regions worldwide 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 (5.4 mg/kg) is approved in more than 60 countries/regions worldwide 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, as determined by a locally or regionally approved test, that have progressed on one or more endocrine therapies in the metastatic setting based on the results from the DESTINY-Breast06 trial.

ENHERTU (5.4 mg/kg) is approved in more than 70 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic NSCLC 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 and/or DESTINY-Lung05 trials. Continued approval in China and the U.S. for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in more than 80 countries/regions worldwide 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, DESTINY-Gastric02 and/or DESTINY-Gastric04 trials.

ENHERTU (5.4 mg/kg) is approved in more than 15 countries/regions worldwide 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 efficacy results from the

DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-CRC02 and/or HERALD trials. Continued approval in the U.S. for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

About the ENHERTU Clinical Development Program

A comprehensive global clinical development program is underway evaluating the efficacy and safety of ENHERTU as a monotherapy or in combination or sequentially with other cancer medicines across multiple HER2 targetable cancers.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in March 2019 and DATROWAY® in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and DATROWAY.

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of eight ADCs in clinical development crafted from ADC technology discovered in-house by Daiichi Sankyo.

The DXd ADC Technology platform of Daiichi Sankyo consists of seven ADCs in clinical development where each ADC is comprised of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADCs include ENHERTU and DATROWAY, which are being jointly developed and commercialized globally with AstraZeneca, and ifinatamab deruxtecan (I-DXd), raludotatug deruxtecan (R-DXd) and patritumab deruxtecan (HER3-DXd), which are being jointly developed and commercialized globally with Merck & Co., Inc, Rahway, NJ, USA. DS-3939 and DS3790 are being developed by Daiichi Sankyo.

An additional ADC being developed by Daiichi Sankyo is DS3610, which consists of an antibody attached to a novel payload that acts as an agonist of STING.

Ifinatamab deruxtecan, raludotatug deruxtecan, patritumab deruxtecan, DS-3939, DS3610 and DS3790 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical need. For more information, please visit www.daiichisankyo.com.

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