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Daiichi-Sankyo

Press Release

TROPION-Lung12 Phase 3 Trial Initiated Evaluating DATROWAY® as Part of Adjuvant Regimen for Patients with Early-Stage Non-Small Cell Lung Cancer at High Risk of Relapse

Tokyo and Basking Ridge, NJ – (January 30, 2025) – The first patient has been dosed in the TROPION-Lung12 phase 3 trial evaluating the efficacy and safety of adjuvant DATROWAY® (datopotamab deruxtecan) plus rilvegostomig or rilvegostomig monotherapy versus standard of care in patients with stage 1 adenocarcinoma non-small cell lung cancer (NSCLC) after complete surgical resection who are ctDNA-positive or have other high risk pathological features.

DATROWAY is a specifically engineered TROP2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca (LSE/STO/Nasdaq: AZN).

Standard treatment for stage 1 NSCLC is tumor resection, but up to 40% of patients may experience disease recurrence.[1,2,3] Tumor resection is typically followed by observation but adjuvant chemotherapy and/or immunotherapy may be offered to patients with stage 1b disease who are identified to be at high risk of relapse.[4] However, novel strategies to identify high risk patients are needed as well as additional treatment options in the adjuvant setting. Research suggests that ctDNA screening may help identify high risk patients who are most likely to benefit from adjuvant therapy.[5,6]

“After surgery for early-stage non-small cell lung cancer, there is no established consensus on adjuvant therapy. As a result, patients may either undergo observation or receive adjuvant chemotherapy and/or immunotherapy if they have stage 1b disease and are determined to be at high risk for disease recurrence,” said Mark Rutstein, MD, Global Head, Oncology Clinical Development, Daiichi Sankyo. “The TROPION-Lung12 trial will help us better understand the role of DATROWAY in combination with immunotherapy in the adjuvant setting as a potential treatment regimen to help prevent disease recurrence in patients with high risk stage 1 adenocarcinoma following surgery.”

“With TROPION-Lung12, we are simultaneously deploying a novel strategy for identifying patients with lung cancer who are at an increased risk of disease recurrence after surgery and evaluating novel

treatment options in the adjuvant setting, including rilvegostomig with and without DATROWAY," said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. "The ambitious approach in this trial underscores our commitment to both enabling more personalized treatment decisions and delivering innovative treatment options to patients with cancer."

About TROPION-Lung12

TROPION-Lung12 is a global, multicenter, three-arm, open-label phase 3 trial where patients will be randomized in a 2:1:2 ratio to evaluate the efficacy and safety of adjuvant DATROWAY (6 mg/kg) in combination with rilvegostomig (750 mg) or rilvegostomig (750 mg) monotherapy versus observation or standard of care adjuvant chemotherapy regimens in those with stage 1 (stage 1a or 1b with tumors < 4 cm) adenocarcinoma NSCLC who are ctDNA-positive (as determined by an investigational ctDNA assay) or have high risk pathological features (as determined by central pathology assessment).

The primary endpoint of TROPION-Lung12 is disease-free survival following complete tumor resection as assessed by blinded independent central review in patients treated with adjuvant DATROWAY and rilvegostomig versus those who undergo observation or receive standard of care. Key secondary endpoints include patient-reported physical functions, patient-reported quality of life outcomes, overall survival and safety.

TROPION-Lung12 will enroll approximately 660 patients in Asia, Europe, North America and South America. For more information visit ClinicalTrials.gov.

Rilvegostomig is AstraZeneca's PD-1/TIGIT bispecific antibody. The TIGIT component of rilvegostomig is derived from the clinical-stage anti-TIGIT antibody, COM902, developed by Compugen Ltd. (Nasdaq/TASE: CGEN).

About Non-Small Cell Lung Cancer

Nearly 2.5 million lung cancer cases were diagnosed globally in 2022.[7] NSCLC is the most common type of lung cancer and adenocarcinoma is the most common subtype of NSCLC, accounting for about 40% of all lung cancer cases.[8]

For patients with stage 1 NSCLC, standard treatment is tumor resection and observation.[4] For patients with stage 1b disease or those otherwise identified as having a high risk of relapse based on clinical or pathological features, tumor resection may be followed by adjuvant chemotherapy and/or

immunotherapy.[4] However, strategies to identify high risk patients are needed as well as more durable and effective treatment options in the adjuvant setting. Research suggests that screening for ctDNA in patients with stage 1 NSCLC may help identify patients most likely to benefit from adjuvant therapy and that combining an immunotherapy with an ADC has the potential to drive deeper and more durable tumor responses.[5,6]

TROP2 is a protein broadly expressed in the majority of NSCLC tumors.[9] There is currently no TROP2 directed ADC approved for the treatment of lung cancer.[10,11]

About DATROWAY

DATROWAY (datopotamab deruxtecan; datopotamab deruxtecan-dlnk in the U.S. only) is a TROP2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, DATROWAY is one of six DXd ADCs in the oncology pipeline of Daiichi Sankyo, and one of the most advanced programs in AstraZeneca's ADC scientific platform. DATROWAY is comprised of a humanized anti-TROP2 IgG1 monoclonal antibody, developed in collaboration with Sapporo Medical University, attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

DATROWAY (6 mg/kg) is approved in Japan and the U.S. for the treatment of adult patients with unresectable or metastatic HR positive, HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease based on the results from the TROPION-Breast01 trial.

About the DATROWAY Clinical Development Program

A comprehensive global clinical development program is underway with more than 20 trials evaluating the efficacy and safety of DATROWAY across multiple cancers, including NSCLC, triple negative breast cancer and HR positive, HER2 negative breast cancer. The program includes eight phase 3 trials in lung cancer and five phase 3 trials in breast cancer evaluating DATROWAY as a monotherapy and in combination with other anticancer treatments in various settings.

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 seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADC portfolio currently consists of ENHERTU, a HER2 directed ADC, and DATROWAY, a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc, Rahway, NJ, USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

DATROWAY U.S. Important Safety Information

Indication

DATROWAY® is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic, hormone receptor (HR)-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH−) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease/Pneumonitis

DATROWAY can cause severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis.

In TROPION-Breast01, ILD/pneumonitis occurred in 4.2% of patients treated with DATROWAY, including 0.5% of patients with Grade 3-4 ILD/pneumonitis, and 0.3% with fatal ILD/pneumonitis. Six patients (1.7%) permanently discontinued DATROWAY due to ILD/pneumonitis. The median time to onset of ILD/pneumonitis was 3.5 months (range: 1.2 months to 10.8 months). Patients were excluded from TROPION-Breast01 for a history of ILD/pneumonitis requiring treatment with steroids or for ongoing ILD/pneumonitis.

Monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever) during treatment with DATROWAY. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Withhold DATROWAY in patients with suspected ILD/pneumonitis and permanently discontinue DATROWAY if Grade ≥2 ILD/pneumonitis is confirmed.

Ocular Adverse Reactions
DATROWAY can cause ocular adverse reactions including dry eye, keratitis, blepharitis, meibomian gland dysfunction, increased lacrimation, conjunctivitis, and blurred vision.

In TROPION-Breast01, ocular adverse reactions occurred in 51% of patients treated with DATROWAY. Seven patients (1.9%) experienced Grade 3 ocular adverse reactions, including dry eye, keratitis, and blurred vision. The most common (≥5%) ocular adverse reactions were dry eye (27%), keratitis (24%), blepharitis and increased lacrimation (8% each), and meibomian gland dysfunction (7%). Patients with clinically significant corneal disease were excluded from TROPION-Breast01.

The median time to onset for ocular adverse reactions was 2.1 months (range: 0.03 months to 23.2 months). Of the patients who experienced ocular adverse reactions, 45% had complete resolution; 9% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade at last follow up). Ocular adverse reactions led to permanent discontinuation of DATROWAY in 0.8% of patients.

Advise patients to use preservative-free lubricant eye drops several times daily for prophylaxis. Advise patients to avoid use of contact lenses unless directed by an eye care professional.

Refer patients to an eye care professional for an ophthalmic exam including visual acuity testing, slit lamp examination (with fluorescein staining), intraocular pressure, and fundoscopy at treatment initiation, annually while on treatment, at end of treatment, and as clinically indicated.

Promptly refer patients to an eye care professional for any new or worsening ocular adverse reactions. Monitor patients for ocular adverse reactions during treatment with DATROWAY, and if diagnosis is confirmed, dose delay, dose reduce, or permanently discontinue DATROWAY based on severity.

Stomatitis
DATROWAY can cause stomatitis, including mouth ulcers and oral mucositis.

In the TROPION-Breast01 study, stomatitis occurred in 59% of patients treated with DATROWAY, including 7% of patients with Grade 3-4 events. Median time to first onset was 0.7 months (range: 0.03

months to 8.8 months). Stomatitis led to interruption of DATROWAY in 1.9%, dosage reductions in 13%, and permanent discontinuation in 0.3% of patients.

In patients who received DATROWAY, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis/oral mucositis at any time during the treatment.

Advise patients to use a steroid-containing mouthwash for prophylaxis and treatment of stomatitis. Instruct the patient to hold ice chips or ice water in the mouth throughout the infusion of DATROWAY.

Monitor patients for signs and symptoms of stomatitis. If stomatitis occurs, increase the frequency of mouthwash and administer other topical treatments as clinically indicated. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue DATROWAY.

Embryo-Fetal Toxicity
Based on its mechanism of action, DATROWAY can cause embryo-fetal harm when administered to a pregnant woman because the topoisomerase inhibitor component of DATROWAY, DXd, is genotoxic and affects actively dividing cells.

Advise patients of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with DATROWAY and for 7 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with DATROWAY and for 4 months after the last dose.

Adverse Reactions
The safety of DATROWAY was evaluated in 360 patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH−) breast cancer who received at least one dose of DATROWAY 6 mg/kg in TROPION-Breast01. DATROWAY was administered by intravenous infusion once every three weeks. The median duration of treatment was 6.7 months (range: 0.7 months to 16.1 months) for patients who received DATROWAY.

Serious adverse reactions occurred in 15% of patients who received DATROWAY. Serious adverse reactions in >0.5% of patients who received DATROWAY were urinary tract infection (1.9%), COVID-19 infection (1.7%), ILD/pneumonitis (1.1%), acute kidney injury, pulmonary embolism, vomiting, diarrhea, hemiparesis, and anemia (0.6% each). Fatal adverse reactions occurred in 0.3% of patients who received DATROWAY and were due to ILD/pneumonitis.

Permanent discontinuation of DATROWAY due to an adverse reaction occurred in 3.1% of patients. Adverse reactions which resulted in permanent discontinuation of DATROWAY in >0.5% of patients included ILD/pneumonitis (1.7%) and fatigue (0.6%). Dosage interruptions of DATROWAY due to an adverse reaction occurred in 22% of patients. Adverse reactions which required dosage interruption in >1% of patients included COVID-19 (3.3%), infusion-related reaction (1.4%), ILD/pneumonitis (1.9%), stomatitis (1.9%), fatigue (1.7%), keratitis (1.4%), acute kidney injury (1.1%), and pneumonia (1.1%). Dose reductions of DATROWAY due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dose reduction in >1% of patients included stomatitis (13%), fatigue (3.1%), nausea (2.5%), and weight decrease (1.9%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, were stomatitis (59%), nausea (56%), fatigue (44%), decreased leukocytes (41%), decreased calcium (39%), alopecia (38%), decreased lymphocytes (36%), decreased hemoglobin (35%), constipation (34%), decreased neutrophils (30%), dry eye (27%), vomiting (24%), increased ALT (24%), keratitis (24%), increased AST (23%), and increased alkaline phosphatase (23%).

Clinically relevant adverse reactions occurring in <10% of patients who received DATROWAY included infusion-related reactions (including bronchospasm), ILD/pneumonitis, headache, pruritus, dry skin, dry mouth, conjunctivitis, blepharitis, meibomian gland dysfunction, blurred vision, increased lacrimation, photophobia, visual impairment, skin hyperpigmentation, and madarosis.

Use in Specific Populations

- **Pregnancy:** Based on its mechanism of action, DATROWAY can cause embryo-fetal harm when administered to a pregnant woman because the topoisomerase inhibitor component of DATROWAY, DXd, is genotoxic and affects actively dividing cells. There are no available data on the use of DATROWAY in pregnant women to inform a drug-associated risk. Advise patients of the potential risks to a fetus.
- **Lactation:** There are no data regarding the presence of datopotamab deruxtecan-dlnk or its metabolites 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 DATROWAY and for 1 month after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy Testing: Verify pregnancy status of females of reproductive potential prior to initiation of DATROWAY. Contraception: *Females:* Advise females of reproductive potential to use effective contraception during treatment with DATROWAY and for 7 months after the last dose. *Males:* Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with DATROWAY and for 4 months after the last dose. Infertility: Based on findings in animal toxicity studies, DATROWAY may impair male and female reproductive function and fertility. The effects on reproductive organs in animals were irreversible.
- **Pediatric Use:** Safety and effectiveness of DATROWAY have not been established in pediatric patients.
- **Geriatric Use:** Of the 365 patients in TROPION-Breast01 treated with DATROWAY 6 mg/kg, 25% were ≥65 years of age and 5% were ≥75 years of age. Grade ≥3 and serious adverse reactions were more common in patients ≥65 years (42% and 25%, respectively) compared to patients <65 years (33% and 15%, respectively). In TROPION-Breast01, no other meaningful differences in safety or efficacy were observed between patients ≥65 years of age versus younger patients.
- **Renal Impairment:** A higher incidence of ILD/pneumonitis has been observed in patients with mild and moderate renal impairment (creatinine clearance [CLcr] 30 to <90 mL/min). Monitor patients with renal impairment for increased adverse reactions, including respiratory reactions. No dosage adjustment is recommended in patients with mild to moderate renal impairment. The effect of severe renal impairment (CLcr <30 mL/min) on the pharmacokinetics of datopotamab deruxtecan-dlnk or DXd is unknown.
- **Hepatic Impairment:** No dosage adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST). Limited data are available in patients with moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST). Monitor patients with moderate hepatic impairment for increased adverse reactions. The recommended dosage of DATROWAY 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 the Medication Guide.

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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