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Daiichi-Sankyo

Press Release

Two Phase 3 Trials of Datopotamab Deruxtecan Plus Durvalumab Initiated in Patients Across Two Breast Cancer Subtypes

- TROPION-Breast04 is evaluating Daiichi Sankyo and AstraZeneca's datopotamab deruxtecan plus durvalumab as neoadjuvant treatment for early-stage triple negative and HR low, HER2 low or negative breast cancers
- TROPION-Breast05 is evaluating datopotamab deruxtecan alone and in combination with durvalumab in patients with advanced or metastatic triple negative breast cancer whose tumors express PD-L1

Tokyo and Basking Ridge, NJ – December 18, 2023 – The first patient has been dosed in two global, randomized phase 3 trials evaluating the efficacy and safety of Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) datopotamab deruxtecan (Dato-DXd) in combination with durvalumab, AstraZeneca's anti-PD-L1 therapy, in two types of breast cancer.

Datopotamab deruxtecan is a specifically engineered TROP2 directed DXd antibody drug conjugate (ADC) being jointly developed by Daiichi Sankyo and AstraZeneca.

TROPION-Breast04 is evaluating neoadjuvant datopotamab deruxtecan plus durvalumab followed by adjuvant durvalumab with or without chemotherapy in patients with stage II-III triple negative breast cancer (TNBC) or hormone receptor (HR) low, HER2 low or negative breast cancer. TROPION-Breast05 is evaluating datopotamab deruxtecan alone and in combination with durvalumab in patients with locally recurrent inoperable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10).

Approximately 300,000 people worldwide are diagnosed annually with TNBC, accounting for approximately 15% of all breast cancer diagnoses.[1,2] TNBC is characterized by its aggressive nature and high likelihood of recurrence and progression regardless of stage.[3] Standard treatment for patients with early-stage disease (stage II-III) is typically chemotherapy alone or in combination with immunotherapy prior to tumor resection.[6] For patients with metastatic disease, standard first-line treatment can include chemotherapy alone or in combination with immunotherapy.[2,3,4]

In addition to patients with TNBC, TROPION-Breast04 will enroll patients with HR low, HER2 low or negative breast cancer whose tumors express low levels of hormone receptors (estrogen and/or progesterone receptor levels 1% to < 10%). Patients with HR low, HER2 low or negative disease have historically been excluded from TNBC research as their tumors are not triple negative. However, these patients tend to have

worse outcomes relative to those with hormone receptor-strongly positive tumors (estrogen and/or progesterone receptor levels ≥ 10%) on standard endocrine therapies.[5]

"While the addition of immune checkpoint inhibitors to chemotherapy has led to survival improvements for patients with triple negative breast cancer, the overall prognosis for these patients remains poor," said Mark Rutstein, MD, Global Head, Oncology Clinical Development, Daiichi Sankyo. "These two phase 3 trials will evaluate whether combining datopotamab deruxtecan, a TROP2 directed antibody drug conjugate, with durvalumab may offer a more effective option for patients across different settings of breast cancer."

"In an early phase trial, the datopotamab deruxtecan and durvalumab combination has shown robust and durable tumor responses and a manageable safety profile in patients with previously untreated advanced triple negative breast cancer," said Cristian Massacesi, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. "The initiation of the TROPION-Breast04 and TROPION-Breast05 phase 3 trials underscores our confidence in this promising combination and our commitment to researching its potential across multiple settings of triple negative breast cancer and in HR low disease."

Daiichi Sankyo and AstraZeneca have two additional ongoing phase 3 trials evaluating datopotamab deruxtecan in TNBC. TROPION-Breast02 is evaluating datopotamab deruxtecan versus chemotherapy in patients with previously untreated locally recurrent inoperable or metastatic TNBC who are not candidates for anti-PD-1/PD-L1 therapy. TROPION-Breast03 is evaluating datopotamab deruxtecan with and without durvalumab versus investigator's choice of therapy in patients with stage I to III TNBC with residual disease after neoadjuvant therapy.

About TROPION-Breast04

TROPION-Breast04 is a global, randomized, open-label, double-arm, phase 3 trial evaluating the efficacy and safety of neoadjuvant datopotamab deruxtecan plus durvalumab followed by adjuvant durvalumab with or without chemotherapy compared to neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab with or without chemotherapy in patients with previously untreated stage II or III TNBC or HR low, HER2 low or negative breast cancer.

The primary endpoints of TROPION-Breast04 are pathological complete response and event-free survival. The key secondary endpoint is overall survival (OS) and additional secondary endpoints include distant disease-free survival, pharmacokinetics, immunogenicity, safety and tolerability.

TROPION-Breast04 will enroll approximately 1,700 patients with previously untreated TNBC or HR low, HER2 low or negative breast cancer at study sites in Asia, Europe, North America, Oceania and South America. For more information, visit ClinicalTrials.gov.

About TROPION-Breast05

TROPION-Breast05 is a global, randomized, open-label, three-arm phase 3 trial evaluating the efficacy and safety of datopotamab deruxtecan alone and in combination with durvalumab versus investigator's choice of chemotherapy plus pembrolizumab in participants with locally recurrent inoperable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10). Patients must have completed treatment for stage I to III breast cancer, if indicated, and ≥ 6 months have elapsed between completion of treatment with curative intent and the first documented recurrence.

The primary endpoint of TROPION-Breast05 is progression-free survival (PFS) as assessed by blinded independent central review. The key secondary endpoint is OS and additional secondary endpoints include PFS as assessed by investigator, objective response rate, duration of response, pharmacokinetics, immunogenicity, safety and tolerability.

TROPION-Breast05 will enroll 625 patients with TNBC at study sites across Asia, Europe, North America and Oceania. For more information, visit ClinicalTrials.gov.

About Triple Negative Breast Cancer

Breast cancer is the most common cancer in the world and leading cause of cancer-related death.[1] More than two million breast cancer cases were diagnosed in 2020 with nearly 685,000 deaths globally.[1]

While some breast cancers test positively for estrogen receptors, progesterone receptors or an overexpression of human epidermal growth factor receptor 2 (HER2), TNBC tests negative for all three.[2] Approximately 15% of breast cancer tumors or 300,000 cases annually are considered triple negative.[1,2] Standard treatment for patients with early stage disease (stage II-III) is typically chemotherapy alone or in combination with immunotherapy prior to tumor resection.[6] For patients with metastatic disease, standard first-line treatment can include chemotherapy alone or in combination with immunotherapy.[2,3,4] The median OS of patients living with metastatic TNBC is 12 to 18 months, with only about 12% of patients living five years following diagnosis.[7,8]

TNBC is characterized by its aggressive nature and high likelihood of progression and recurrence regardless of stage.[4] There is a great need for innovative therapeutic options across disease stages and treatment settings.

TROP2 is a protein broadly expressed in several solid tumors, including TNBC.[9] TROP2 is associated with increased tumor progression and poor survival in patients with breast cancer.[10]

About Hormone Receptor Low, HER2 Low or Negative Breast Cancer

HR low, HER2 low or negative breast cancers test positively for hormone receptors but at low levels (estrogen and/or progesterone receptor levels 1% to < 10%) and low or negatively for HER2 (immunohistochemistry [IHC] scores of 0 or 1+ or IHC 2+/ISH-).[11,12] HR low breast cancer occurs in approximately 2 to 3% of patients with HR positive disease and continues to represent a clinical challenge as limited data are available regarding optimal treatment for these patients.[11]

HR expression is a key prognostic and predictive biomarker in breast cancer. While HR positive tumors (estrogen and/or progesterone receptor levels 1% to ≥ 10%) are likely to derive clinical benefit from standard endocrine therapies, HR low tumors do not.[11] Patients with HR low tumors have also historically been excluded from TNBC research given their tumors are not triple negative. However, early research suggests HR low tumors may be more similar to TNBC than HR positive tumors, supporting the inclusion of these patients in TNBC clinical trials.[11]

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 datopotamab deruxtecan 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 datopotamab deruxtecan.

About Datopotamab Deruxtecan (Dato-DXd)

Datopotamab deruxtecan (Dato-DXd) is an investigational TROP2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC technology, datopotamab deruxtecan is one of six ADCs in the oncology pipeline of Daiichi Sankyo, and one of the most advanced programs in AstraZeneca's ADC scientific platform. Datopotamab deruxtecan 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.

A comprehensive development program called TROPION is underway globally with more than 14 trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple tumors, including non-small cell lung cancer, TNBC, HR low, HER2 low or negative breast cancer and HR positive, HER2 low or

negative breast cancer. Beyond the TROPION program, datopotamab deruxtecan also is being evaluated in novel combinations in several ongoing trials.

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan, a TROP2 directed ADC, 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, N.J., USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

Designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, 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.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan and DS-3939 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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