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Press Release

Datopotamab Deruxtecan Showed Encouraging and Durable Efficacy in Patients with Heavily Pretreated HR Positive, HER2 Low or Negative Metastatic Breast Cancer

- First results for Daiichi Sankyo and AstraZeneca's TROP2 directed ADC in this setting reported from TROPION-PanTumor01 phase 1 trial
- Pivotal TROPION-Breast01 phase 3 trial is ongoing, evaluating datopotamab deruxtecan in these patients in earlier lines of treatment

Tokyo, Munich and Basking Ridge, NJ – (December 8, 2022) – Initial results from the TROPION-PanTumor01 phase 1 trial of datopotamab deruxtecan (Dato-DXd) showed encouraging and durable efficacy in patients with heavily pretreated hormone receptor (HR) positive, HER2 low (immunohistochemistry [IHC] 1+ or IHC 2+/in-situ hybridization [ISH]-) or HER2 negative (IHC 0) unresectable or metastatic breast cancer. Safety data were consistent with previous trials of datopotamab deruxtecan. Results were presented today as a Spotlight Poster Discussion (Abstract #PD13-08) at the 2022 San Antonio Breast Cancer Symposium (#SABCS22).

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

Approximately 70% of breast cancer tumors are considered HR positive and HER2 low or negative.[1] For patients with HR positive, HER2 low or negative metastatic breast cancer that progress on or are not suitable candidates for endocrine therapy, the current standard of care is single-agent chemotherapy.[2]

In this cohort of TROPION-PanTumor01 (n=41) where patients previously received a median of five lines of treatment for metastatic disease, datopotamab deruxtecan demonstrated an objective response rate (ORR) of 27% as assessed by blinded independent central review (BICR). All responses were partial (n=11) and 56% of patients achieved stable disease (n=23). The disease control rate (DCR) was 85% and median progression-free survival (PFS) was 8.3 months (95% confidence interval [CI]: 5.5-11.1). With median follow-up of 13.7 months (range, 9-16), the median duration of response (DoR; 95% CI: 4.4-NE) and the median overall survival (OS) had not been reached with 59% of patients alive for more than one year.

"Patients with HR positive, HER2 low or negative metastatic breast cancer who are not eligible for endocrine therapy or have exhausted treatment options have a poor prognosis," said presenting author Funda

Meric-Bernstam, MD, Chair of the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center. “These preliminary results with datopotamab deruxtecan in patients with heavily pretreated HR positive, HER2 low or negative metastatic breast cancer are encouraging and warrant further evaluation in this setting.”

The safety profile of datopotamab deruxtecan was consistent with previous data with no new safety signals identified. The most common grade 3 or higher treatment-emergent adverse events (TEAEs) were decreased lymphocyte count (15%), stomatitis (10%), anemia (7%), dyspnea (2%) and fatigue (2%). Serious TEAEs were observed in six (15%) patients, including one death due to dyspnea that was not considered treatment-related. Treatment discontinuations due to an adverse event occurred in five (12%) patients. No cases of grade 3 or higher diarrhea or febrile neutropenia were observed. One case of grade 3 interstitial lung disease was adjudicated as treatment-related.

“These results add to the growing body of data demonstrating the potential of datopotamab deruxtecan to treat certain types of metastatic breast cancer,” said Mark Rutstein, MD, Global Head, Oncology Clinical Development, Daiichi Sankyo. “We look forward to the continued evaluation of our TROP2 directed antibody drug conjugate, including comparisons to standard therapy in earlier lines of treatment for HR positive, HER2 low or negative metastatic breast cancer through our ongoing TROPION-Breast01 phase 3 trial.”

“Many of these patients with metastatic breast cancer in TROPION-PanTumor01 had exhausted most of their available treatment options, having received a striking median of five prior regimens, including a CDK4/6 inhibitor for nearly all patients,” said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. “These promising results with datopotamab deruxtecan in such a heavily pretreated patient population support our strong belief that this TROP2 directed antibody drug conjugate has the potential to improve outcomes for patients with HR positive, HER2 low or negative breast cancer in this, and possibly earlier settings.”

Patients in this cohort were heavily pretreated, receiving a median of five prior lines of treatment in the metastatic setting (range, 3-10). Prior treatments included CDK4/6 inhibitors (95%), capecitabine (83%), taxanes (59%), anthracyclines (54%), neoadjuvant chemotherapy (37%), mTOR inhibitors (29%) and PI3KCA inhibitors (20%). As of data cut-off on July 22, 2022, five patients remained on study treatment.

Summary of Results

Efficacy Measure	Datopotamab Deruxtecan (6 mg/kg) n=41
Confirmed ORR, %[i,ii]	27% (n=11)
PR, %	27% (n=11)
SD, %	56% (n=23)
Non-CR/non-PD, %	2% (n=1)
PD, %	12% (n=5)
NE, %	2% (n=1)
DCR, %[i,iii]	85% (n=35)
Median DoR (months) (95% CI)[i]	NE (4.4-NE)
Median PFS (months) (95% CI)[i]	8.3 months (5.5-11.1)
Median OS (months)	Not reached

CI, confidence interval; CR, clinical response; DCR, disease control rate; DoR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease
[i] As assessed by BICR
[ii] ORR is (CR + PR)
[iii] DCR is (CR + PR + SD + non-CR/non-PD)

Daiichi Sankyo and AstraZeneca have a broad clinical development program for datopotamab deruxtecan in breast cancer, including the ongoing pivotal TROPION-Breast01 phase 3 trial evaluating datopotamab deruxtecan in patients with HR positive, HER2 low or negative, inoperable or metastatic breast cancer previously treated with chemotherapy.

About TROPION-PanTumor01

TROPION-PanTumor01 is a first-in-human, open-label, two-part, multicenter phase 1 trial evaluating the safety and preliminary efficacy of datopotamab deruxtecan in patients with advanced solid tumors that have relapsed or are refractory to standard treatment or for which no standard treatment is available. The dose escalation portion of the trial enrolled patients with non-small cell lung cancer (NSCLC) to assess the safety and efficacy of datopotamab deruxtecan to determine the recommended dose for expansion (6 mg/kg). The dose expansion part of TROPION-PanTumor01 is enrolling several different cohorts including patients with NSCLC, triple negative breast cancer (TNBC), HR positive, HER2 low or negative breast cancer, small cell lung cancer, urothelial, gastric, pancreatic, castration-resistant prostate and esophageal cancer.

Safety endpoints include dose-limiting toxicities and serious adverse events. Efficacy endpoints include ORR, DoR, time to response, PFS and OS. Pharmacokinetic, biomarker and immunogenicity endpoints also are being evaluated.

About HR Positive, HER2 Low or Negative Breast Cancer

Breast cancer is the most common cancer and one of the leading causes of cancer-related deaths worldwide.[3] More than two million breast cancer cases were diagnosed in 2020 with nearly 685,000 deaths globally.[3]

Breast cancer is considered HR positive, HER2 low or negative when the tumors test positive for estrogen and/or progesterone hormone receptors and low for HER2 (measured as a HER2 score of IHC 1+ or IHC 2+/ISH-) or negative for HER2 (measured as IHC 0).[1,4] This subtype accounts for approximately 70% of diagnosed breast cancer cases and is associated with lower survival rates with 30% of patients anticipated to live beyond five years after diagnosis.[1] Current standard of care treatment for patients with HR positive, HER2 low or negative metastatic breast cancer that progress on hormone therapy-based regimens is sequential single-agent chemotherapy, which is associated with a low median PFS of less than 10 months and OS of less than two years, underscoring the need for additional treatment options.[2,5,6,7]

TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is broadly expressed in several types of solid tumors, including HR positive, HER2 low or negative breast cancer.[8,9] TROP2 expression is an unfavorable prognostic factor for overall survival in all types of breast cancer.[8]

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 the three lead 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, via tetrapeptide-based cleavable linkers.

A comprehensive development program called TROPION is underway globally with more than 10 trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple TROP2 targetable tumors, including NSCLC, TNBC and HR positive, HER2 low or negative breast cancer. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize datopotamab deruxtecan in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for the manufacturing and supply of datopotamab deruxtecan.

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases

with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit: www.daiichisankyo.com.

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