Press Release

Datopotamab Deruxtecan Significantly Extended Progression-Free Survival Versus Chemotherapy in Patients with HR Positive, HER2 Low or Negative Breast Cancer in TROPION-Breast01 Phase 3 Trial

- Daiichi Sankyo and AstraZeneca's datopotamab deruxtecan reduced the risk of disease progression or death by 37%, providing a 2-month median PFS benefit, and was well tolerated in post-endocrine therapy setting

Tokyo and Basking Ridge, NJ – (October 23, 2023) – Positive results from the pivotal TROPION-Breast01 phase 3 trial showed that datopotamab deruxtecan (Dato-DXd) demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to investigator's choice of chemotherapy in patients with inoperable or metastatic hormone receptor (HR) positive, HER2 low or negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer previously treated with endocrine-based therapy and at least one systemic therapy. These data, the first of two positive late-breaking presentations (LBA11) from the datopotamab deruxtecan clinical development program, were featured during Presidential Symposium 3 at the European Society for Medical Oncology (#ESMO23) 2023 Congress.

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).

In the dual primary endpoint analysis, datopotamab deruxtecan reduced the risk of disease progression or death by 37% compared to investigator's choice of chemotherapy (hazard ratio [HR]=0.63; 95% confidence interval [CI]: 0.52-0.76; p<0.0001) in patients with HR positive, HER2 low or negative metastatic breast cancer as assessed by blinded independent central review (BICR). Median PFS was 6.9 months in patients treated with datopotamab deruxtecan compared to 4.9 months in those treated with chemotherapy. A consistent benefit in PFS was observed across subgroups. Results also showed a confirmed objective response rate (ORR) of 36.4% in patients treated with datopotamab deruxtecan compared to an ORR of 22.9% in patients treated with chemotherapy.

For the dual primary endpoint of overall survival (OS), interim results numerically favored datopotamab deruxtecan over chemotherapy (HR=0.84; 95% CI: 0.62-1.14), however, results did not reach statistical significance at the time of this data cut-off. The trial is ongoing to assess OS.

“Despite the initial benefit of endocrine therapy, most patients with HR positive, HER2 low or negative metastatic breast cancer will eventually experience disease progression and require additional treatment with chemotherapy,” said Aditya Bardia, MD, MPH, Director of Breast Cancer Research, Mass General Cancer Center, Associate Professor of Medicine at Harvard Medical School and investigator in the trial. “In the TROPION-Breast01 trial, datopotamab deruxtecan reduced patients’ risk of disease progression or death by more than a third and overall had fewer treatment-related serious adverse events than standard chemotherapy, illustrating its potential to become a new standard of care in a treatment setting where there is a clinical unmet need.”

Datopotamab deruxtecan demonstrated a favorable safety profile over chemotherapy with no new safety concerns identified. Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 21% and 45% of patients in the datopotamab deruxtecan and chemotherapy arms, respectively. The most common grade 3 or higher TRAEs were neutropenia (1% vs. 31%), stomatitis (6% vs. 3%), fatigue (2% vs. 2%) and anemia (1% vs. 2%). In the datopotamab deruxtecan arm, the all-grade interstitial lung disease (ILD) rate was low (3%) and the majority of events were low grade. There was one grade 5 ILD event adjudicated as drug-related by an independent committee. The primary cause of death in this case was attributed to disease progression by the treating investigator.

“These statistically significant and clinically meaningful results from the TROPION-Breast01 trial support datopotamab deruxtecan as a new potential standard of care for patients with advanced HR positive, HER2 low or negative breast cancer in the post-endocrine therapy setting,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “The results further validate the portability of Daiichi Sankyo's DXd antibody drug conjugate technology to additional targets such as TROP2, and we look forward to potentially bringing our second antibody drug conjugate to patients with breast cancer.”

“With these TROPION-Breast01 results, datopotamab deruxtecan has the potential to meaningfully improve treatment expectations for patients with HR positive, HER2 low or negative metastatic breast cancer by offering an effective and better tolerated treatment option after endocrine therapy and only one line of chemotherapy,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “We look forward to continuing discussions with regulatory authorities with the goal of bringing this TROP2 directed antibody drug conjugate to eligible patients as soon as possible.”

After endocrine therapy, the most common prior treatments for patients in the datopotamab deruxtecan and chemotherapy arms, respectively, included one (63% vs. 61%) to two (37% vs. 38%) lines of chemotherapy and CDK4/6 inhibitors (82% vs. 78%). At the July 17, 2023 data cut-off, 93 patients remained on treatment with datopotamab deruxtecan and 39 remained on chemotherapy.

Summary of TROPION-Breast01 Efficacy Results

	Datopotamab Deruxtecan (n=365)	Investigator's Choice Chemotherapy (n=367)
PFS as assessed by BICR		
Median PFS (months, 95% CI)	6.9 months (5.7-7.4)	4.9 months (4.2-5.5)
Hazard Ratio (95% CI)	0.63 (0.52-0.76)	
p-value	p<0.0001	
PFS as assessed by investigator		
Median PFS (months)	6.9 months	4.5 months
Hazard Ratio (95% CI)	0.64 (0.53-0.76)	
OS		
Hazard Ratio (95% CI)[i]	0.84 (0.62-1.14)	
ORR (confirmed), %[ii,iii]	36.4%	22.9%
CR rate, %	0.5%	0%
PR rate, %	35.9%	22.9%

CI, confidence interval; CR, complete response; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; PR, partial response
[i] with median follow-up of 9.7 months, OS data were not mature
[ii] as assessed by BICR
[iii] ORR is (complete response + partial response)

Daiichi Sankyo and AstraZeneca have two phase 3 trials evaluating datopotamab deruxtecan in triple negative breast cancer (TNBC). TROPION-Breast02 is comparing datopotamab deruxtecan to 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 1 to 3 TNBC with residual disease after neoadjuvant therapy.

About TROPION-Breast01

TROPION-Breast01 is a global, randomized, multicenter, open-label phase 3 trial evaluating the safety and efficacy of datopotamab deruxtecan versus investigator's choice of single-agent chemotherapy (eribulin, capecitabine, vinorelbine or gemcitabine) in patients with inoperable or metastatic HR positive, HER2 low or negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have previously progressed on or are not suitable for endocrine therapy per investigator assessment and have received at least one systemic therapy.

The dual primary endpoints of TROPION-Breast01 are PFS as assessed by BICR and OS. Key secondary endpoints include ORR, duration of response, investigator-assessed PFS, disease control rate and time to first subsequent therapy.

TROPION-Breast01 enrolled more than 700 patients at sites in Asia, Europe, North America, South America and Africa. For more information visit ClinicalTrials.gov.

About HR Positive, HER2 Low or Negative Breast Cancer

Breast cancer is the most common cancer in the world and a 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]

Breast cancer is considered HR positive, HER2 low or negative when tumors test positive for estrogen and/or progesterone hormone receptors and low or negative for HER2 (measured as HER2 score of IHC 0, IHC 1+ or IHC 2+/ISH-).[2,3] HR positive, HER2 low or negative breast cancer is the most common subtype, accounting for more than 65% of diagnosed cases.[2]

Standard initial treatment for this subtype of breast cancer is endocrine therapy but most patients with advanced disease will develop resistance, underscoring the need for additional options.[4,5] Approximately 30% of patients diagnosed with HR positive, HER2 low or negative breast cancer are expected to live five years after their diagnosis.[2]

TROP2 is a protein broadly expressed in several solid tumors, including HR positive, HER2 low or negative breast cancer.[6] TROP2 expression is associated with increased tumor progression and poor survival in patients with breast cancer.[6,7]

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 12 trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple tumors, including non-small cell lung cancer, TNBC 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 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 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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