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Press Release

Datopotamab Deruxtecan Showed Promising Responses as Monotherapy and in Combination with Durvalumab in Patients with Metastatic Triple Negative Breast Cancer in Two Early Trials

- Daiichi Sankyo and AstraZeneca's TROP2 directed ADC showed an encouraging objective response rate of 32% and a manageable safety profile in patients with metastatic TNBC in TROPION-PanTumor01 phase 1 trial
- Datopotamab deruxtecan plus durvalumab demonstrated promising updated results with an objective response rate of 73.6% in first-line treatment of patients with metastatic TNBC in BEGONIA phase 1b/2 trial

Tokyo, Munich and Basking Ridge, NJ – (December 9, 2022) – Updated results from the TROPION-PanTumor01 phase 1 trial showed datopotamab deruxtecan (Dato-DXd) continued to demonstrate encouraging responses in patients with heavily pretreated metastatic triple negative breast cancer (TNBC) and disease progression following standard treatment. Results were presented today as a poster presentation (Abstract #P6-10-03) 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 15% of breast cancers are considered triple negative and are associated with higher disease recurrence and worse prognosis compared to other breast cancer subtypes.[1,2] It is estimated that only 12% of patients with metastatic TNBC survive five years after diagnosis and median overall survival is between 12 to 18 months.[1,3]

In the TNBC cohort of TROPION-PanTumor01 (n=44) where patients previously received a median of three lines of treatment for metastatic disease, datopotamab deruxtecan demonstrated an objective response rate (ORR) of 32%, including one complete response (CR), 13 partial responses (PRs) and 18 cases of stable disease (SD) as assessed by blinded independent central review (BICR). In a subgroup of 27 patients who had not been previously treated with topoisomerase I inhibitor-based ADCs, the ORR was 44% including one CR, 11 PRs and 10 cases of SD. The median duration of response (DoR) was 16.8 months (95% confidence interval [CI]: 5.6-NE) across patient groups.

“Triple negative breast cancer is the most aggressive subtype of breast cancer with the average survival rate of less than 18 months for patients with pretreated metastatic disease,” said Aditya Bardia, MD, MPH, Director of Breast Cancer Research Program, Mass General Cancer Center and Associate Professor of Medicine at Harvard Medical School. “The durable tumor response and disease control seen with datopotamab deruxtecan in patients with pretreated triple negative breast cancer are encouraging, particularly in those patients who had not received previous treatment with topoisomerase I inhibitor-based antibody drug conjugate.”

In the overall cohort, datopotamab deruxtecan demonstrated median progression-free survival (PFS) of 4.4 months (95% CI: 3.0-7.3) and median overall survival (OS) of 13.5 months (95% CI: 10.1-16.3). In the subgroup of patients who had not been previously treated with a topoisomerase I inhibitor, median PFS and OS were 7.3 months (95% CI: 3.0-18.0) and 14.3 months (95% CI: 10.5-NE), respectively. The disease control rate (DCR) was consistent across the overall cohort and previously untreated subgroup at 80% and 81%, respectively.

The safety profile of datopotamab deruxtecan was consistent with previously reported data with no new safety signals identified. The most common grade 3 or higher treatment-emergent adverse events (TEAEs) were stomatitis (11%), decreased lymphocyte count (7%), fatigue (7%), vomiting (5%), anemia (2%), decreased neutrophil count (2%) and nausea (2%). Serious TEAEs were reported in nine patients (20.5%). Treatment discontinuations occurred in one patient (2%) due to grade 1 pneumonitis, which was adjudicated as not treatment-related interstitial lung disease (ILD). No cases of ILD were observed. No cases of febrile neutropenia or grade 3 or higher diarrhea were observed.

“Five-year survival rates for previously treated metastatic triple negative breast cancer are significantly lower than other subtypes of breast cancer, underscoring the need for new, durable therapies,” said Mark Rutstein, MD, Global Head, Oncology Clinical Development, Daiichi Sankyo. “We are working with urgency and care to evaluate datopotamab deruxtecan in multiple treatment settings in phase 3 trials, including the TROPION-Breast02 first-line phase 3 trial in patients with locally recurrent inoperable or metastatic triple negative breast cancer not candidates for anti-PD-L1 therapy.”

“The median duration of response of nearly 17 months seen in the TROPION-PanTumor01 trial in these patients reinforces the potential of datopotamab deruxtecan to treat this persistent disease,” said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. “These results, along with the promising clinical response in combination with durvalumab seen in the BEGONIA trial, underscore the potential role of this TROP2 directed antibody drug conjugate for patients with triple negative breast cancer as both a monotherapy and in combinations.”

Patients in the TROPION-PanTumor01 trial were heavily pretreated, receiving a median of three prior regimens in the metastatic setting (range, 1-10). Prior treatments included taxanes (93%), anthracyclines (75%), capecitabine (61%), platinum-based chemotherapy (52%), immunotherapy (45%), topoisomerase I inhibitor-based ADCs (32%) and PARP inhibitors (18%). As of data cut-off on July 22, 2022, three patients remained on study treatment.

Summary of TROPION-PanTumor01 Results in Metastatic TNBC

Efficacy Measure	**All TNBC Patients [n=44 (6 mg/kg, n=42; 8 mg/kg, n=2)]**	**Patients Without Prior Topoisomerase I Inhibitor-Based ADC [n=27 (6 mg/kg, n=25; 8 mg/kg, n=2)]**
Confirmed ORR, %[i,ii]	32% (n=14)	44% (n=12)
CR, %	2% (n=1)	4% (n=1)
PR, %	30% (n=13)	41% (n=11)
SD, %	41% (n=18)	37% (n=10)
Non-CR/non-PD, %	7% (n=3)	0
PD, %	18% (n=8)	15% (n=4)
NE, %	2% (n=1)	4% (n=1)
DCR, %[i,iii]	80% (n=35)	81% (n=22)
Median DoR (months) (95% CI)[i]	16.8 months (5.6-NE)	16.8 months (5.6-NE)
Median PFS (months) (95% CI)[i]	4.4 months (3.0-7.3)	7.3 months (3.0-18.0)
Median OS (months) (95% CI)	13.5 months (10.1-16.3)	14.3 months (10.5-NE)

CI, confidence interval; CR, complete 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)

BEGONIA Arm 7 Updated Results

Updated results from the BEGONIA phase 1b/2 trial (n=61) showed datopotamab deruxtecan in combination with durvalumab, AstraZeneca's immune checkpoint inhibitor, demonstrated an ORR of 73.6% (95% CI: 59.7-84.7) in patients with previously untreated unresectable, locally advanced or metastatic TNBC as assessed by investigator. Among the 53 evaluable patients, there were four CRs and 35 PRs. Responses were observed regardless of PD-L1 expression (low and high tumors) with 82% of patients continuing to respond at the time of data cut-off on July 22, 2022. These data were presented as a Spotlight Poster Discussion (abstract #PD11-09) at SABCS on December 8.

The safety profile of datopotamab deruxtecan in combination with durvalumab was consistent with the known safety profiles of both agents. The most common all-grade TEAEs occurring in 20% or more of

patients were nausea (57.4%), stomatitis (55.7%), alopecia (45.9%), fatigue (39.3%), constipation (39.3%), rash (27.9%) and vomiting (21.3%). Serious TEAEs were observed in 10 (16.4%) patients. Treatment discontinuations due to an adverse event occurred in four patients (6.6%). Two (3.3%) cases were adjudicated as treatment-related grade 1 ILD.

Twenty-five patients (41.0%) had not received prior treatment for metastatic TNBC. Prior treatments for patients with disease progression following treatment for early-stage disease included radiotherapy (49.2%), anthracyclines (45.9%), taxanes (41.0%), platinum-based chemotherapy (14.8%), hormonal therapy (14.8%) and targeted therapy (4.9%). Seven (11.5%) patients had high PD-L1 expression (tumor area positivity [TAP]≥10%) and 53 patients (86.9%) had low PD-L1 expression (TAP<10%). At data cut-off, 45 patients remained on study treatment.

Daiichi Sankyo and AstraZeneca have a broad clinical development program for datopotamab deruxtecan in TNBC, including the recently initiated global TROPION-Breast03 phase 3 trial evaluating datopotamab deruxtecan with and without durvalumab in patients with stage 1 to 3 TNBC with residual disease after neoadjuvant therapy. The first patients were enrolled in November 2022 and are expected to be dosed in December 2022. SWOG Cancer Research Network Clinical Trials Partnerships (SWOG CTP) is the lead academic group for the trial and a key collaborator in its protocol development, US site selection and planned recruitment and analysis.

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, 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 BEGONIA

BEGONIA is an open-label, two-part, multicenter phase 1b/2 trial evaluating durvalumab in combination with oncology therapies with or without paclitaxel for the first-line treatment of metastatic TNBC. Arm 7 of the trial is evaluating the safety, tolerability and preliminary efficacy of datopotamab deruxtecan in combination with durvalumab in patients with previously untreated, unresectable locally advanced or metastatic TNBC.

The primary endpoints are safety and tolerability. The secondary endpoints include investigator-assessed ORR, PFS, DoR and OS.

About Triple Negative Breast Cancer

Breast cancer is the most common cancer and one of the leading causes of cancer-related deaths worldwide.[4] More than two million breast cancer cases were diagnosed in 2020 with nearly 685,000 deaths globally.[4]

Approximately 15% of breast cancers are considered triple negative, which is defined by tumors that test negative for estrogen and progesterone hormone receptors (HRs) and low or negative for human epidermal growth factor 2 receptor (HER2), as determined by an immunohistochemistry (IHC) test and/or an in-situ hybridization (ISH) test.[1] Tumors with HER2 expression measured as IHC 0 are considered HER2 negative and tumors with HER2 expression measured as IHC 1+ or IHC 2+/ISH- are considered HER2 low.[1,5] TNBC is considered the most aggressive subtype of breast cancer.[1,2] Compared to patients with other breast cancer subtypes, the prognosis for patients with metastatic TNBC is generally worse with a five-year survival rate estimated at 12% and a median overall survival rate of 12 to 18 months.[1,3]

TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is broadly expressed in several types of solid tumors, including approximately 80% of patients with TNBC.[6,7,8] TROP2 expression is an unfavorable prognostic factor for overall survival in all types of breast cancer.[6]

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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