Embargoed for Release: 7 a.m. CT, Dec. 11, 2019

To interview Ian Krop, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Krop, click here.

New HER2 Antibody-drug Conjugate Yielded Promising Clinical Responses in Breast Cancer Patients Pretreated with T-DM1

SAN ANTONIO — The investigational HER2-targeted antibody-drug conjugate [Fam-] trastuzumab deruxtecan (T-DXd) demonstrated durable objective responses in patients with HER2-positive breast cancer who were heavily pretreated, including with T-DM1 (Kadcyla) and other HER2-targeted treatments, according to results from the phase II clinical trial DESTINY-Breast01 presented at the San Antonio Breast Cancer Symposium, held Dec. 10-14.

Data from this study are being published simultaneously in the *New England Journal of Medicine.*

"Although HER-2 directed therapies such as trastuzumab (Herceptin), pertuzumab (Perjeta), and T-DM1 have led to improved outcomes for patients with HER2-positive advanced breast cancer, resistance to these drugs develops almost inevitably and we do not have a clear standard of care for these patients once resistance occurs," said Ian Krop MD, PhD, associate chief of the Division of Breast Oncology at Dana-Farber Cancer Institute. "Thus, there clearly is an unmet medical need for new and improved therapies for such patients."

Similar to T-DM1, T-DXd has a monoclonal antibody targeted toward HER2, but unlike T-DM1, which has a microtubule inhibitor as the cytotoxic payload, T-DXd has a topoisomerase 1 inhibitor as the payload. T-DXd has eight molecules of the payload, which is twice as many as T-DM1, Krop explained.

Data published from a prior phase I study showed T-DXd yielded an objective response rate of 59 percent in patients with advanced HER-2 positive breast cancer previously treated with T-DM1. The U.S. Food and Drug Administration granted priority review to T-DXd in October.

In the phase II study, Krop and colleagues enrolled 253 patients with metastatic HER2-positive breast cancer previously treated with T-DM1. The trial had three parts, I, IIa, and IIb, and overall, 184 patients received the recommended phase II dose (RP2D) of 5.4 mg/kg T-DXd. The patients had received a median of six prior treatments for advanced disease, including HER2-targeted therapeutics.

The overall response rate in the 184 patients who received the RP2D was 60.9 percent, with 6 percent complete responses (CR) and 54.9 percent partial responses (PR). The median progression free survival was 16.4 months.

"Both of these measures of efficacy are substantially higher than that seen in any other study of patients with pretreated HER2-positive metastatic breast cancer," Krop said.

The disease control rate in the 184 patients was 97 percent. “This suggests that the vast majority of cancers in this population seem to have at least some sensitivity to this agent,” Krop noted. “Consistent with this, the objective response rate to T-DXd appeared largely independent of tumor hormone receptor status, prior exposure to pertuzumab, and prior history of brain metastases.”

Ninety-nine percent of the patients had treatment-emergent adverse events (TEAEs), with 57 percent experiencing TEAEs of grade 3 or higher, including decreased neutrophil count, nausea, anemia, decreased lymphocyte count, and fatigue; 15 percent of patients discontinued treatment because of TEAEs.

Interstitial lung disease (ILD) was observed in 25 patients. “ILD is a serious concern in patients treated with T-DXd,” said Krop. “While these events were primarily grade 1 or 2, there were unfortunately four grade 5 ILD-related deaths (2.2 percent) on the study. Because of this potential toxicity, close monitoring for signs and symptoms of ILD is recommended for early detection. If ILD is suspected, evaluations should include high-resolution CT, pulmonologist consultation, pulmonary function tests, and other tests. Although data on treatment for T-DXd-induced ILD are limited, if diagnosed, interruption of treatment and prompt intervention with glucocorticoids is recommended.”

Krop added, “The high rate of durable responses observed with trastuzumab deruxtecan in patients whose cancers had progressed on T-DM1 and other therapies suggests this agent could provide a new treatment option for this patient population.”

A limitation of the study is that this was a single-arm trial and therefore it is not possible to determine whether T-DXd is more effective than other therapies from these data.

The study was sponsored by Daiichi Sankyo Inc. and AstraZeneca. Krop received grant support and research support from Genentech/Roche and Pfizer; personal fees from Daiichi Sankyo, Macrogenics, AstraZeneca, and Genentech/Roche.

ABSTRACT

Publication Number: GS1-03

[Fam-] trastuzumab deruxtecan (T-DXd; DS-8201a) in subjects with HER2-positive metastatic breast cancer previously treated with T-DM1: A phase 2, multicenter, open-label study (DESTINY-Breast01)

Ian E Krop[1], Cristina Saura[2], Toshinari Yamashita[3], Yeon Hee Park[4], Sung-Bae Kim[5], Kenji Tamura[6], Fabrice Andre[7], Hiroji Iwata[8], Yoshinori Ito[9], Junji Tsurutani[10], Joohyuk Sohn[11], Neelima Denduluri[12], Christophe Perrin[13], Kenjiro Aogi[14], Eriko Tokunaga[15], Seock-Ah Im[16], Keun Seok Lee[17], Sara Hurvitz[18], Javier Cortes[19], Caleb Lee[20], Shuquan Chen[20], Lin Zhang[20], Javad Shahidi[20], Antoine Yver[20] and Shanu Modi[21]. [1]Dana-Farber Cancer Institute, Boston, MA;[2]Vall Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain[3]Kanagawa Cancer Center, Yokohama, Japan[4]Samsung Medical Center, Seoul, Korea, Republic of[5]Asan Medical Center, Seoul, Korea, Republic of[6]National Cancer Center Hospital, Tokyo, Japan[7]Gustave Roussy, Universite Paris Sud, Villejuif, France[8]Aichi Cancer Center Hospital, Nagoya, Japan[9]The Cancer Institute Hospital of JFCR, Tokyo, Japan[10]Kindai University Faculty of Medicine, Osaka and Advanced Cancer Translational Research Institute, Showa University, Tokyo, Japan[11]Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea, Republic of[12]The US Oncology Network, Virginia Cancer Specialists, Arlington, VA;[13]Centre Eugene Marquis, Rennes, France[14]NHO Shikoku Cancer Center, Matsuyama, Japan[15]National

Hospital Organization Kyushu Cancer Center, Fukuoka, Japan16Seoul National University Hospital, Seoul, Korea, Republic of17National Cancer Center Korea, Goyang, Korea, Republic of18University of California Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA;19IOB Institute of Oncology, Quiron Group, Madrid & Barcelona and Vall d?Hebron Institute of Oncology (VHIO), Barcelona, Spain20Daiichi Sankyo, Inc., Basking Ridge, NJ;21Memorial Sloan Kettering Cancer Center, New York, NY

Background [Fam-] trastuzumab deruxtecan (T-DXd; formerly DS-8201a) is an antibody-drug conjugate with a HER2 antibody, peptide-based cleavable linker, and a novel topoisomerase I inhibitor payload. In a phase 1 trial, the objective response rate (ORR) was 59.5% (66/111) and median progression-free survival (PFS) was 22.1 mo in subjects with HER2-positive metastatic breast cancer (BC) previously treated with T-DM1 (Tamura, *Lancet Oncol*, 2019). DESTINY-Breast01 (NCT03248492) is an open-label, international, multicenter, phase 2 registration study of T-DXd in subjects with centrally confirmed HER2-positive metastatic BC.
Methods Part 1 of this 2-part study was performed in 2 stages (pharmacokinetics and dose finding; T-DXd 5.4, 6.4, 7.4 mg/kg) and served to identify the recommended Part 2 dose (RP2D). In Part 2, subjects were treated at the RP2D. Subjects in Parts 1 and 2a were required to have metastatic BC that progressed on or after T-DM1. Subjects in a small additional cohort (Part 2b) had discontinued T-DM1 for reasons other than progression. The primary endpoint was ORR (complete response [CR] + partial response [PR]) per independent central review (ICR). Additional endpoints included disease control rate (DCR; CR + PR + stable disease [SD]), duration of response (DOR), and PFS. Abstract results represent 6 mo of follow-up from the date the last subject enrolled in the study.
Results As of data cutoff (March 21, 2019), 253 subjects were enrolled and 184 received the RP2D (5.4 mg/kg), 4 of which were enrolled in Part 2b. All subjects were female, 55% were white, and 38% were Asian. Median age was 55 y (range, 28-96 y; ≥ 65 y, 24%); 53% were hormone receptor (HR) positive and 45% were HR negative. Median number of prior treatment regimens was 6 (range, 2-27), including trastuzumab (100%), T-DM1 (100%), pertuzumab (66%), and other HER2-targeted regimens (54%). The reported best response to T-DM1 before enrollment was 22% CR or PR, 21% SD, and 36% progressive disease (PD); 21% were not evaluable. At data cutoff, 60% of subjects remained on T-DXd treatment; primary reasons for discontinuation were PD (21%) and treatment-related adverse events (TEAEs, 8%).
The confirmed ORR by ICR in subjects treated at the RP2D in Parts 1, 2a, and 2b was 60% (111/184 [95% CI, 53%-68%]). ORRs were consistent across subgroups, including those with prior pertuzumab (64%) and those with ≥ 3 prior regimens (59%). The DCR was 97% (95% CI, 94%-99%); only 5 of 184 subjects did not have SD or better at the time of first postbaseline scan. As of the data cutoff, median DOR and PFS had not been reached; median duration of follow up was 7.2 mo (range, 0.7-17.2 mo).
In the 184 subjects, the median treatment duration was 6.9 mo (range, 0.7-16 mo); 70% had > 6 mo of treatment. TEAEs occurred in 99% of subjects (grade ≥ 3, 51%); the most common any-grade TEAEs were gastrointestinal (nausea [77%], vomiting [45%], constipation [34%], decreased appetite [29%], and diarrhea [27%]), alopecia (48%), fatigue (48%), and hematologic (decreased neutrophil count [31%] and anemia [26%]). Most common grade ≥ 3 AEs were decreased neutrophil count (17%), nausea (7.6%), anemia (6.5%), decreased lymphocyte count (5.4%), and fatigue (5.4%). 15 subjects (8.2%) had interstitial lung disease (ILD) adjudicated as ILD related to T-DXd by an independent adjudication committee; ILD was primarily grade 1 or 2 (6.0%; no grade 3 or 4; 2.2% grade 5).
[Additional follow up and first DOR/PFS data will be presented at the meeting.]
Conclusion Overall, T-DXd treatment demonstrated clinically meaningful and durable activity in a heavily pretreated patient population with HER2-positive metastatic BC. T-DXd had a generally manageable safety profile, with ILD identified as a risk warranting proactive awareness and management.

# # #

Follow the meeting on Twitter: @SABCSSanAntonio and #SABCS19

About SABCS®
Since 1977 the San Antonio Breast Cancer Symposium® (SABCS®) has been the leading scientific conference for basic scientists, physician-scientists, clinical investigators and breast care providers, and advocates seeking an exchange of new information in experimental biology, etiology, prevention, diagnosis, and therapy of premalignant breast disease and breast cancer. Founded, owned, and operated by UT Health San Antonio, the symposium has grown to a five-day event attended by an international audience of academic investigators and private physicians

from over 80 countries to attain information through abstract presentations, panel discussions, research findings, and state-of-the-art educational sessions. UT Health San Antonio, the American Association for Cancer Research (AACR), and Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine support SABCS, which provides education and accessibility to the latest information regarding the prevention, diagnosis, and treatment of premalignant breast cancer and breast disease. For more information about the symposium, please visit www.sabcs.org.