146TiP A multicenter, multicohort, phase II study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing metastatic colorectal cancer

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Background: Approximately 1% to 5% of metastatic colorectal cancers (mCRC) are HER2-overexpressing. HER2 is potentially an important target for mCRC, however no HER2-targeted therapies are approved for mCRC. Trastuzumab deruxtecan (DS-8201a) is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a cleavable peptide-based linker (deruxtecan), and with a high drug-to-antibody ratio of 7 to 8. In the ongoing phase 1 DS8201-A-J101 trial, DS-8201a provided durable antitumor activity with a manageable safety profile in subjects with HER2-expressing solid tumors, including subjects with mCRC (preliminary objective response rate [ORR] of 20.0% in mCRC) (Tsurutani et al, ESMO 2017).

Trial design: This multicenter, open-label, 3-cohort, phase 2 study (ClinicalTrial.gov: NCT03384940) will assess the efficacy and safety of DS-8201a in subjects with HER2-expressing mCRC. Cohort A will include approximately 50 subjects with HER2-positive (IHC 3+ or IHC 2+/ISH+) mCRC. At the start of the study, only cohort A will be active. Depending on the risk/benefit assessment after at least 20 subjects in cohort A complete tumor assessments at week 12, cohort B (IHC 2+/ISH-) and cohort C (IHC 1+) will open to enroll approximately 20 subjects each. All enrolled subjects will receive a 6.4 mg/kg dose of DS-8201a once every 3 weeks; study treatment will be continued until disease progression, unacceptable toxicity, or other treatment discontinuation criteria are met. The anticipated duration of the study is at least 24 months. The primary endpoint is ORR (complete response or partial response), as assessed by an independent central review committee, in cohort A. Secondary efficacy endpoints include progression-free survival, duration of response, disease control rate, and overall survival. Safety assessments include serious and treatment-emergent AEs, physical examination findings, and vital sign measurements. The study will enroll subjects in Japan, the US, and Europe. Recruitment began in December 2017.

Editorial acknowledgement: Editorial support was provided by Stefan Kolata, PhD, of AlphaBioCom, LLC, King of Prussia, PA, USA.

Clinical trial identification: NCT03384940; release date December 28, 2017.

Legal entity responsible for the study: Daiichi Sankyo Co., Ltd.

Funding: Daiichi Sankyo Co., Ltd.

Disclosure: T. Yoshino: Grants: MSD KK, Sumitomo Dainippon Pharma Co, GSK KK, Nippon Boehringer Ingelheim Co; Grants, personal fees: Sanofi KK, Chugai Pharmaceutical Co; Personal fees: Eli Lilly Japan KK, Merck Serono Co. R. Dalal: Employee: Daiichi Sankyo, Inc.,; Holds stock: Daiichi Sankyo, Inc., Eli Lilly. Y. Okuda, E. Yamamoto: Employee: Daiichi Sankyo Co., Ltd. A. Grothey: Non-financial support: Daiichi Sankyo provided to the Mayo Clinic; Grants and non-financial support: Genentech, Bayer, Array, Boston Biomedical provided to the Mayo Clinic. All other authors have declared no conflicts of interest.