DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS FOR CONDUCTING CLINICAL TRIALS USING DS-8201A (NSC# 807708)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications for a project using **DS-8201a, a HER2-targeting antibody drug conjugate (ADC)** being developed by CTEP as an anticancer agent in collaboration with Daiichi Sankyo. DS-8201a combines an anti-HER2 antibody linked to a topoisomerase I inhibitor payload (DXd [DX-8951 derivative]) through a "cleavable" linker.

DS-8201a has demonstrated activity in patients with both high and low HER2 expressing tumors in the phase 1 dose escalation/dose expansion trial (NCT02564900). In breast cancer patients, overall response rate (ORR) was 54.5% (54/99) in HER2 positive tumors (*i.e*. IHC 3+ or FISH+) (post T-DM1), and 50.0% (17/34) in those with HER2-low tumors (IHC 1+ or IHC 2+, FISH-) (Iwata *et al.*, 2018a). In HER2 positive gastric cancer (post trastuzumab) the ORR was 43.2% (19/44). Based on the preliminary results of this trial, the FDA granted Breakthrough Therapy designation to DS-8201a in August 2017, for the treatment of HER2-positive locally advanced or metastatic breast cancer in patients who have been treated with trastuzumab and pertuzumab and who have disease progression after T-DM1 treatment.

In preclinical xenograft models, DS-8201a has demonstrated enhanced antitumor activities when combined with anti-PD-1 agents, polyadenosine 5' diphosphoribose (poly [ADP ribose]) polymerase (PARP) inhibitors (PARPi), tubulin targeting chemotherapies and PI3K inhibitors.

The current Daiichi Sankyo clinical development plan is mainly focused on monotherapy in breast and gastric cancers, including phase 2 and phase 3 trials. **See Table 1** for the current listing of all DS-8201a clinical trials.

At the present time, the preliminary CTEP drug development plan is in the following areas (see page 5 for more details):

- **Clinical studies:** DS-8201a monotherapy in additional HER2 expressing tumors, and combination studies with immunotherapy, PARP inhibitors or other agents where supported by preclinical and scientific evidence.
- **Translational studies**: Biomarkers and correlative studies related to the target (HER2) and the payload (Topo 1 inhibitor), with the goal of investigating the mechanisms of resistance, understanding the interactions with partner agents in combination regimens and exploring predictive markers for both monotherapy and combinations.

The project team will include:

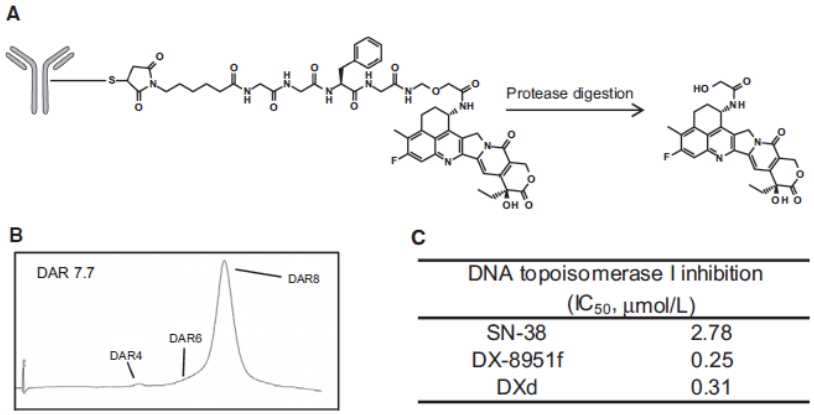
1. **Clinician Scientists** with expertise in early clinical studies and with an interest in relevant tumor settings (fill out **Part A** of the attached Application; Clinician Scientists must belong to a qualifying NCI grant funded institution as defined at the end of this letter);
2. **Translational scientists** with an interest in biomarker development related to HER2 and DNA-damaging/repair pathways, as well as biomarkers potentially related to combination regimens (fill out **Part B** of the attached Application and see the submission instructions at the end of this letter); and
3. **Basic scientists** with expertise in HER2 signaling pathways, DNA repair pathway and resistance mechanisms (fill out **Part C** of the attached Application and see the submission instructions at the end of this letter).

Prospective team members may apply for multiple roles using a single application form by completing all the appropriate Parts. The project team will be recruited nationally and will prioritize the research questions regarding DS-8201a monotherapy and combinations, including prioritization of biomarker studies. Although not guaranteed, it is anticipated that most of the clinicians on the drug project team will be tasked with writing the Letters of Intent, based upon the team's recommendations, and that these clinicians will ultimately lead the

clinical studies. It is also anticipated that other extramural members of the drug project team will stay involved in the subsequent design and execution of the proposed trials. It is anticipated that the project team will complete its work in eight weeks or less.

Background/Rationale

DS-8201a is comprised of trastuzumab linked to the topoisomerase I inhibitor (DXd [DX-8951 derivative]) through a maleimide glycine-glycine-phenylalanine-glycine (GGFG) peptide linker (Figure 1A; Ogitani *et al*., 2016a). DS-8201a has a high drug to antibody ratio (DAR) with 8 molecules of DXd conjugated to each anti-HER2 antibody (DAR = 8) compared with a DAR of 2 to 4 for most other ADCs (Figure 1B). The conjugated payload, DXd, is a potent topoisomerase I inhibitor with a half maximum inhibitory concentration (IC_{50}) of 0.31 mcmol/L (Figure 1).



DNA topoisomerase I inhibition (IC_{50}, µmol/L)	
SN-38	2.78
DX-8951f	0.25
DXd	0.31

Figure 1: Structure and characterization of DS-8201a and the topoisomerase I inhibitor payload DXd (Ogitani *et al*., 2016a).

Mechanism of Action

DS-8201a exerts its anti-tumor activity through both topoisomerase I inhibition as well as the antibody component which maintains the mechanisms of action of trastuzumab (Ogitani *et al*., 2016a). The conjugation of DXd to the anti-HER2 antibody does not affect the binding of the antibody to HER2, and DS-8201a is able to induce downregulation of phosphorylated protein kinase B (p-Akt) in SK-BR-3 cells in a dose dependent manner. It also induced ADCC *in vitro* with a maximum cytotoxicity of 48.6% at a half maximum effective concentration (EC_{50}) of 3.8ng/mL.

DS-8201a induces DNA damage and apoptosis through topoisomerase I inhibition by digestion of the peptide linker and release of the DXd payload after HER2 mediated internalization of the ADC (Ogitani *et al*., 2016a). In addition, the released DXd is highly membrane permeable and is able to exert anti-tumor activity on neighboring cells through the ***bystander*** effect; however, this effect does not extend to distant sites, limiting the potential for systemic toxicity (Ogitani *et al*., 2016b). At a concentration of 10mcg/mL, DS-8201a is able to induce the phosphorylation of checkpoint kinase 1 (Chk1) and histone H2AX as well as the cleavage of PARP (Ogitani *et al*., 2016a).

Nonclinical Studies of DS-8201a

Preclinical Efficacy: DS-8201 has demonstrated anti-tumor activity in tumor models with various levels of HER2 expression including those resistant to T-DM1. In patient derived xenograph (PDX) models with weak, moderate to strong HER2 expression, DS-8201a inhibited tumor growth in all of the HER2 expressing lines while T-DM1 was only active in tumors with strong HER2 expressing (KPL-4) (Ogitani *et al*., 2016a). Expression of HER2 was required for activity as neither DS-8201a nor T-DM1 was able to restrict tumor growth in the HER2 negative PDX model (GCIY) (Ogitani *et al*., 2016a). DS8201 was also active in a T-DM1 resistant gastric cancer model (NCI-N87-TDMR) that was derived from the parent cell line (NCI-N87) after exposure to T-DM1 (Takegawa *et al*., 2017).

Preclinical Combination Studies

Combination with immunotherapy: In an immune-competent mouse model inoculated with a mouse cancer cell line expressing human HER2 (CT26.WT-hHER2), a single intravenous (IV) dose of DS-8201a (10 mg/kg) induced an increase in the tumor-infiltrating CD86+ dendritic cells, and upregulated PD-L1 and MHC class I. The combination of DS-8201a and anti-PD-1 increased the survival to 80% on Day 38, compared to 20% with either agent alone.

Combination with PAPRi: There are a few lines of support for the combination of DS8201 and PARP inhibitors. First, HER2 expression confer a susceptibility to PARPi veliparib even in the absence of deficiency in homologous recombination (HR) mediated DNA repair in MCF7 breast cancer cells stably overexpressing HER2 (MCF7 HER2). Veliparib significantly delayed tumor growth in the mouse MCF7 HER2 xenograph model but was ineffective in the isogenic control (MCF7 NEO) model (Nowsheen *et al.*, 2012). Furthermore, in the breast cancer model with HER2 expression (BT474), addition of trastuzumab to a PARP inhibitor, Olaparib potentiated the effect by increasing the number of γH2AX foci *in vitro* and decreased the tumor size compared to both agents alone *in vivo* (Garcia-Parra *et al.*, 2014). Secondly, combination of PARP inhibitors and topoisomerase I inhibitors is known to have synergistic antitumor effects, through decrease in the repair of topoisomerase I induced DNA single strand breaks (SSBs).

Additional preclinical data on combinations will be presented at the Project Team discussion.

Clinical Studies of DS-8201a

There are currently eleven ongoing Phase 1, Phase 2, and Phase 3 clinical studies involving DS-8201a. The clinical trials are looking at DS-8201a as a monotherapy, in combination with different chemotherapeutic agents or in comparison to standard of care. The most common indications for the ongoing clinical trials are breast cancer, gastric cancer, and advanced solid tumors.

Table 1: DS-8201a clinical trial listing on ClinicalTrials.gov

NCT	Phase	Agent(s)	Disease/ Indication	Study Start-End	Status/ Sponsor	Planned Accrual	Publications/ Abstracts
NCT02564900	1	DS-8201a	Advanced solid malignant tumors	08/2015 - 09/2019	Active, not recruiting/ Daiichi Sankyo	278	Doi *et al.*, 2017b Tamura *et al*. 2016 Doi *et al.*, 2017a Iwata *et al.*, 2018a Iwasa *et al*., 2018 Modi *et al.*, 2018
NCT03366428	1	DS-8201a	Breast cancer	12/2017 - 04/2019	Active/ Daiichi Sankyo	50	
NCT03383692	1	DS-8201a+ ritonavir or DS8201a+itraconazole	Advanced solid malignant tumors	01/2018 - 04/2019	Active, not recruiting/ Daiichi Sankyo	32	
NCT03368196	1	DS-8201a	Gastric, gastroesophageal junction, or breast cancer	04/2018 - 09/2019	Active, not recruiting/ Daiichi Sankyo	12	
NCT03523572	1	DS-8201a+nivolumab	Breast cancer, or urothelial carcinoma	06/2018 - 09/2020	Active/ Daiichi Sankyo, Bristol-Myers Squibb	99	
NCT03248492	2	DS-8201a	Breast cancer	08/2017 - 02/2020	Active/ Daiichi Sankyo	230	Baselga *et al.*, 2018
NCT03329690	2	DS-8201a *vs.* physician's choice of irinotecan or paclitaxel	Gastric or gastroesophageal junction adenocarcinoma	10/2017 - 12/2019	Active/ Daiichi Sankyo	220	Yamaguchi *et al.*, 2018
NCT03384940	2	DS-8201a	Colorectal adenocarcinoma	02/2018 - 06/2020	Active/ Daiichi Sankyo	90	Yoshino *et al.*, 2018
NCT03505710	2	DS-8201a	Non-small cell lung cancer	05/2018 - 10/2020	Active/ Daiichi Sankyo	80	

Table 1: DS-8201a clinical trial listing on ClinicalTrials.gov							
NCT	Phase	Agent(s)	Disease/ Indication	Study Start-End	Status/ Sponsor	Planned Accrual	Publications/ Abstracts
NCT03529110	3	DS-8201a *vs.* ado-trastuzumab emtansine (T-DM1)	Breast cancer	07/2018 – 02/2022	Active/ Daiichi Sankyo	500	
NCT03523585	3	DS-8201a *vs.* investigator's choice of trastuzumab+ capecitabine or lapatinib+capecitabine	Breast cancer	08/2018 – 02/2022	Active/ Daiichi Sankyo	600	

Clinical Pharmacokinetics and Toxicology

Based on part 1 of the ongoing dose escalation/dose expansion study, the likely recommended phase 2 dose (RP2D) is 5.4 mg/kg or 6.4 mg/kg IV Q3W (Doi *et al*., 2017b). For the 6 patients treated at 5.4 mg/kg, the maximum serum concentration (C_{max}) was 127 mcg/mL (Standard Deviation [Sd]±17.2), the trough serum concentration (C_{trough}) was 5.09 mcg/mL (Sd±2.19) the half-life ($t_{1/2}$) was 6.03 days (Sd±0.603). The PK profile for the DXd payload was C_{max} = 10.8 ng/mL (Sd±7.56) with C_{trough} of 0.326 ng/mL (Sd±0.0747), and $t_{1/2}$ 6.11 days (Sd±0.811). For the 6 patients treated at 6.4 mg/kg, DS-8201a C_{max} = 181 mcg/mL (Sd±33.1), C_{trough} = 11.4 mcg/mL (Sd±4.46), and $t_{1/2}$ = 7.33 days (Sd±1.64). The PK profile for DXd was C_{max} = 6.80 ng/mL (Sd±1.72), C_{trough} = 0.384 ng/mL (Sd±0.0881), and $t_{1/2}$ = 6.28 days (Sd±1.53). See Figure 2 for the serum concentration over time for DS-8201a and the DXd payload over the first three cycles at the 6.4 mg/kg dose.

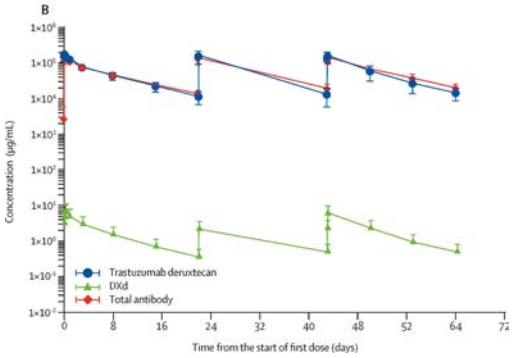


Figure 2: Mean serum concentration versus time for DS-8201a, DXd, and total antibody over cycles 1-3 at a dose of 6.4 mg/kg (from Doi *et al*., 2017b)

There were no dose limiting toxicities (DLT) and the maximum tolerated dose (MTD) was not reached in part 1 of the phase 1 dose escalation trial (Tamura *et al*., 2016, Doi *et al*., 2017b). At the doses of 5.4 mg/kg and 6.4 mg/kg in part 1 and 2 of the trial (N=241), the most common adverse events (AE)s were nausea (68.9%, 2.5% grade ≥3), decreased appetite (55.6%, 3.3% grade ≥3), and vomiting (34.9%, 1.7% grade ≥3). Grade ≥3 hematologic AEs (anemia, platelet count decreased, neutrophil count decreased, and white blood cell count decreased) ranged between 10.4% and 15.4% (Iwata *et al*., 2018a). Five cases of grade 5 interstitial lung disease were reported (Iwata *et al*., 2018a). Updated safety information will be provided at the Project Team discussion.

Clinical efficacy

All clinical efficacy data to date are derived from the phase 1 dose escalation/dose expansion trial (NCT02564900), in which DS-8201a has demonstrated activity in both high or low HER2 expressing tumors (Doi *et al*., 2017b). The updated results from this study presented at the American Society of Clinical Oncology Annual Meeting in 2018, showed the overall confirmed response rate of 49.3% with durable responses for subjects who received one of the recommended doses for expansion (5.4 or 6.4 mg/kg) across all tumor types. In breast cancer patients, ORR was 54.5% (54/99) in HER2 positive tumors (*i.e*. IHC 3+ or FISH+) (post T-DM1), and 50.0% (17/34) in those with HER2-low tumors (IHC 1+ or IHC 2+, FISH-) (Iwata

et al., 2018a). In HER2 positive gastric cancer (post trastuzumab) the ORR was 43.2% (19/44) (Iwata *et al.*, 2018a).

CTEP's Plans for DS-8201a Development

Pending discussion with the Project Team, CTEP is considering development in the following areas:

1. Clinical Trials:
   - Studies of DS-8201a as a monotherapy in HER2 expressing tumors in expanded indications. This may be pursued in an umbrella/basket trial or single-histology trials as appropriate
   - Studies of DS-8201a in combination with immunotherapy, including check point inhibitors
   - Studies of DS-8201a in combination with PARP inhibitors or other DNA repair agents
   - Pending preclinical data, additional combination studies may be considered

2. Correlative Studies would include but are not limited to the following objectives:
   - HER2 based assays for patient selection and mechanistic studies
   - Topoisomerase I related biomarkers for exploration of the mechanisms of actions and the molecular basis of resistance
   - Immune monitoring to assess the impact of this ADC on the tumor microenvironment
   - Biomarkers related to combination regimens to be studies

DS-8201a Project Team Selection, Composition, and Tasks

The DS-8201a drug project team will meet regularly by WebEx to review available evidence and formulate the overall development plans as well as specific clinical and translational studies. The project team will be composed of intramural and extramural members. The extramural members will include

- **Clinician Scientists** with expertise in early clinical studies and with an interest in relevant tumor settings (e.g. GU and GI cancer or other tumors of interest). Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of accrual to early phase studies in relevant indications.
- **Translational scientists** with an interest in biomarker development related to HER2 and DNA-damaging/repair pathways, as well as biomarkers potentially related to combination regimens (fill out **Part B** of the attached Application and see the submission instructions at the end of this letter); and
- **Basic scientists** with expertise in HER2 signaling pathways, DNA repair pathway and resistance mechanisms (fill out **Part C** of the attached Application and see the submission instructions at the end of this letter).

Questions regarding this request for applications may be addressed to Helen Chen, M.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: helen.chen@nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical cancer research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors to participate as Project Team members and to develop Career Development Letters of Intent (CrDLs) after conclusion of Project Team activities.

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the DS-8201a Project Team (clinician scientist, translational scientist or basic scientist). The PTMA should also be accompanied by an NIH Biosketch containing a personal statement customized to this project. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern**

Time (ET), October 3, 2018. The most recent version of the PTMA form, which has been distributed with this communication, must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: CTEPPTMASubmissions@mail.nih.gov

Please note that Clinician Scientists may only participate through association with the ETCTN, an NCTN Group, or a consortium (see below), and will need to submit the PTMA through their ETCTN LAO's Coordinating Center or the Group/Consortium Operations office, as applicable. That organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. Please allow sufficient time for your organization's review. Qualifying clinical institutions include:

- ETCTN Participating Institution (under UM1 grant)
- NCTN Group member institution (under U10 grant; Alliance, COG, ECOG-ACRIN, NRG Oncology, or SWOG)
- Institutional affiliation with the Pediatric Brain Tumor Consortium (PBTC), Adult Brain Tumor Consortium (ABTC), or Cancer Immunotherapy Trials Network (CITN)

Basic and **Translational Scientists** who belong to a participating ETCTN institution (Lead Academic Organization [LAO] or Affiliated Organization [AO]) **must** submit applications through your LAO's Coordinating Center. Please allow sufficient time for your organization's review. Basic and Translational Scientists from non-ETCTN-affiliated institutions may submit their applications directly to PIO.

Bibliography

Baselga, J., K. Tamura, T. Yamashita, *et al*. (2018). A phase 2, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with T-DM1. *J Clin Oncol*. 36(15_suppl):epub ahead of print.

Doi, T., H. Iwata, J. Tsurutani, *et al*. (2017a). Single agent activity of DS-8201a, a HER2-targeting antibody-drug conjugate, in heavily pretreated HER2 expressing solid tumors. *J Clin Oncol*. 35(15_suppl):108.

Doi, T., K. Shitara, Y. Naito, *et al*. (2017b). Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol*. 18(11):1512-1522.

Garcia-Parra, J., A. Dalmases, B. Morancho, *et al*. (2014). Poly (ADP-ribose) polymerase inhibition enhances trastuzumab antitumor activity in HER2 overexpressing breast cancer. *Eur J Cancer*. 50(15):2725-2734.

Iwasa, S., K. Shitara, S. Takahashi, *et al*. (2018). Updated results of phase 1 study of DS-8201a in subjects with HER2-expressing gastric cancer. *J Clin Oncol*. 34(4_suppl):118.

Iwata, H., K. Tamura, T. Doi, *et al.* (2018a). Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: Long-term results of a large phase 1 study with multiple expansion cohorts. *J Clin Oncol.* 36(15_suppl):2501.

Iwata, T.N., C. Ishii, S. Ishida, *et al*. (2018b). A HER2-targeting antibody-drug conjugate, trastuzumab deruxtecan (DS-8201a), enhances antitumor immunity in a mouse model. *Mol Cancer Ther*. 17(7):1494-1503.

Modi, S., J. Tsurutani, S. Takahashi, *et al*. (2018). Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2 expressing breast cancers. *Cancer Res*. 78(4 Suppl):Abstract nr PD3-07.

Murai, J., Y. Zhang, J. Morris, *et al*. (2014). Rationale for Poly(ADP-ribose) polymerase (PARP) inhibitors in combination therapy with camptothecins or temozolomide based on PARP trapping versus catalytic inhibition. *J Pharmacol Exp Ther*. 349:408-416.

Nowsheen, S., T. Cooper, J.A. Bonner, *et al*. (2012). HER2 overexpression renders human breast cancers sensitive to PARP inhibition independently of any defect in homologous recombination DNA repair. *Cancer Res*. 72(18):4796-4806.

Ogitani, Y., T. Aida, K. Hagihara, *et al*. (2016a). DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. *Clin Cancer Res*. 22(20):5097-5108.

Ogitani, Y., K. Hagihara, M. Oitate, *et al.* (2016b). Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci*. 107(7):1039-1046

Takegawa, N., Y. Nonagase, K. Yonesaka, *et al*. (2017). DS-8201a, a new HER2-targeting antibody-drug conjugate incorporating a novel DNA topoisomerase I inhibitor, overcomes HER2-positive gastric cancer T-DM1 resistance. *Int J Cancer*. 141(8):1682-1689.

Tamura, K., K. Shitara, Y. Naito, *et al*. (2016). Single agent activity of DS-8201a, a HER2-targeting antibody drug conjugate, in breast cancer patients previously treated with T-DM1: Phase 1 dose escalation. *Ann Oncol*. 27(suppl_6):LBA17.

Yamaguchi, K., Y-J. Bang, D. Sakai, *et al*. (2018). A randomized phase 2, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressin gastric cancer. *J Clin Oncol*. 36(15_suppl):epub ahead of print.

Yoshino, T., S. Siena, R. Dalal, *et al*. (2018). P-295: A multicenter, multicohort, phase 2 study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing metastatic colorectal cancer – Trial in progress. *Ann Oncol*. 29(suppl_5):mdy151.924.