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 (IC50) of 0.31 mcemol/L (Figure 1).

**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 (EC50) 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-8201 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 PARPi 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.

<p>| Table 1: DS-8201a clinical trial listing on ClinicalTrials.gov |
|----------------------------------|------------------|------------------|-------------------|----------------|-------------------|</p>
<table>
<thead>
<tr>
<th>NCT</th>
<th>Phase</th>
<th>Agent(s)</th>
<th>Disease/Indication</th>
<th>Study Start-End</th>
<th>Status/Sponsor</th>
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<td>NCT02564900</td>
<td>1</td>
<td>DS-8201a</td>
<td>Advanced solid malignant tumors</td>
<td>08/2015 - 09/2019</td>
<td>Active, not recruiting/ Daiichi Sankyo</td>
<td>278</td>
<td>Doi et al., 2017b Tamura et al. 2016 Doi et al., 2017a Iwata et al., 2018a Iwasa et al., 2018 Modi et al., 2018</td>
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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 ($C_{\text{max}}$) was 127 mcg/mL (Standard Deviation [Sd]=17.2), the trough serum concentration ($C_{\text{trough}}$) 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 $C_{\text{max}} = 10.8$ ng/mL (Sd=7.56) with $C_{\text{trough}}$ 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 $C_{\text{max}} = 181$ mcg/mL (Sd=33.1), $C_{\text{trough}} = 11.4$ mcg/mL (Sd=4.46), and $t_{1/2} = 7.33$ days (Sd=1.64). The PK profile for DXd was $C_{\text{max}} = 6.80$ ng/mL (Sd=1.72), $C_{\text{trough}} = 0.384$ 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](image_url)

**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 (AEs) 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.

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**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**


