To: CTEP Protocol and Information Office

From: Sarah Shin, MD, MPH, DTC/DCTD/NCI

Date: November 26, 2024

Re: Amendment to Protocol 10346: Pilot Study of DS-8201a Pharmacodynamics in Patients with HER2-expressing Advanced Solid Tumors

---

This amendment is being submitted in response to the CTEP request for rapid amendment dated 11/18/2024. The associated informed consent document has also been updated.

The version date is now November 26, 2024. Thank you for your consideration.

I. Changes from the CTEP Request for Rapid Amendment Dated 11/18/2024:

#	Section	Comments
1.	Cover Page	Updated the protocol version date.
2.	7.3.3	Specific Protocol Revisions to Address Risk Mitigation Plan on pages 59-60: • Inserted updated AE Reporting Tables provided by CTEP.

3.	7.1.1	Revision of the Protocol CAEPR on pages 53-56:
		• The SPEER grades have been updated.
		• Added New Risk:
		  • Likely: Myalgia
		  • Less Likely: Blurred vision; Dysgeusia; GGT increased; Left ventricular systolic dysfunction; Pruritus; Rash maculo-papular; Skin hyperpigmentation
		  • Also Reported on DS-8201a Trials But With Insufficient Evidence for Attribution: Atrial fibrillation; CD4 lymphocytes decreased; Chills; Chronic kidney disease; Colonic obstruction; Death NOS; Edema limbs; Fall; Flatulence; Gallbladder perforation; General disorders and administration site conditions - Other (general physical health deterioration); Hypertension; Hypoalbuminemia; Joint infection; Leukocytosis; Lower gastrointestinal hemorrhage; Lymphedema; Lymphocyte count increased; Non-cardiac chest pain; Pain in extremity; Paresthesia; Peripheral sensory neuropathy; Peritoneal infection; Portal vein thrombosis; Productive cough; Rectal hemorrhage; Rectal obstruction; Rectal ulcer; Scrotal infection; Small intestinal obstruction; Spinal cord compression; Tracheal obstruction

#	Section	Comments

		• Increase in Risk Attribution:
		  • Changed to Likely from Less Likely: White blood cell decreased
		  • Changed to Less Likely from Also Reported on DS-8201a Trials But With Insufficient Evidence for Attribution: Abdominal distension; Alkaline phosphatase increased; Blood bilirubin increased; Hepatobiliary disorders - Other (hepatic function abnormal); Lymphocyte count decreased; Weight loss
		
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  • Added: Cough; Headache; Hypokalemia; Lymphocyte count decreased; Myalgia; Respiratory, thoracic and mediastinal disorders - Other (pneumonitis/interstitial lung disease); Upper respiratory infection; Weight loss; White blood cell decreased
		
		• Provided Further Clarification:
		  • Changed from Hepatobiliary disorders - Other (cholangitis, cholangitis acute) to 'Hepatobiliary disorders - Other (cholangitis)

Pilot Study of DS-8201a Pharmacodynamics in Patients with HER2-expressing Advanced Solid Tumors

Abbreviated Title: Ph I DS-8201a single-agent PD

Corresponding Organization: LAO-NCI / National Cancer Institute LAO
National Cancer Institute
10 Center Drive
Bethesda, Maryland 20892

Principal Investigator:

Sarah Shin, MD, MPH — DCTD
Bldg 31 Room 3A44
Bethesda, MD 20892
Phone: (240) 781-4025
Fax: (240) 541-4515
sarah.shin@nih.gov

Referral Contact: Brooke Augustine, RN — DCTD
Bldg 10 Rm 8D53
Phone: (240) 858-3197
Fax: (301) 451 5625
brooke.augustine@nih.gov

Statistician: Jared Foster, PhD — BRB/DCTD
9609 Medical Center Dr.
Room 5W638
Phone: (240) 276-7385
jared.foster@nih.gov

Participating Organizations:

Limited participation to:

LAO-NCI / National Cancer Institute LAO

LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO

LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO

LAO-PA015 / UPMC Hillman Cancer Center LAO

Study Sponsor: DCTD, NCI

NCI Supplied Agent: DS-8201a (NSC 807708)

IND Number: [redacted]

NCT Number: 04294628

Version Date: November 26, 2024

PRÉCIS

Background:

- DS-8201a is an antibody-drug conjugate (ADC) consisting of the HER2-targeting antibody trastuzumab covalently bound via a lysosomal protease–cleavable linker to the novel topoisomerase I (Top1) inhibitor deruxtecan. Unlike the FDA-approved HER2 ADC T-DM1, which consists of trastuzumab bound to a tubulin-disrupting agent via a non-cleavable linker, DS-8201a is active even in tumors with low HER2 IHC scores of 1+ or 2+.
- The DS-8201a mechanism of action has been shown in cell culture experiments to include both HER2 antibody-dependent cell-mediated cytotoxicity similar to that induced by trastuzumab alone, as well as induction of DNA damage response (DDR) signaling consistent with the deruxtecan payload. However, no preclinical or clinical data have been published to date demonstrating engagement of the Top1 target by the DS-8201a payload.
- The Pharmacodynamic Assay Development and Implementation Section (PADIS) at Frederick National Laboratory for Cancer Research has developed clinically fit-for-purpose Top1 cleavable complex (Top1cc) and total Top1 immunofluorescence microscopy assays (IFAs), which will be used to measure the degree and duration of DS-8201a target engagement.

Primary Objective:

- To assess the effects of DS-8201a on total Top1 levels in biopsy specimens from patients with HER2-expressing advanced solid tumors, at early and late post-treatment time points, thereby establishing the degree and duration of DS-8201 target engagement

Secondary Objectives:

- To assess any associations between serum concentrations of DS-8201a and the effects of DS-8201a on total Top1 levels in tumor biopsy specimens
- To determine the safety and tolerability of DS-8201a administered intravenously every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg
- To determine the overall response rate (CR + PR) for patients administered intravenously with DS-8201a every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg

Exploratory Objectives:

- To evaluate the effects of DS-8201a on CD8+ T cell infiltration and activation in tumor, tumor PD-L1 and HER2 expression, and DDR signaling (for example: γH2AX, RAD51, and pNBS1) in biopsy specimens
- To examine genomic alterations in circulating tumor DNA (ctDNA) that may be associated with DS-8201a response or resistance
- To examine any associations between baseline tumor HER2 amplification or HER2 expression level and response to DS-8201a
- To evaluate the effects of DS-8201a on tumor levels of HER2 and DDR-associated proteins
- To examine any tumor genomic alterations that may be associated with resistance to DS-8201a
- To evaluate anti-drug antibodies following administration of DS-8201a

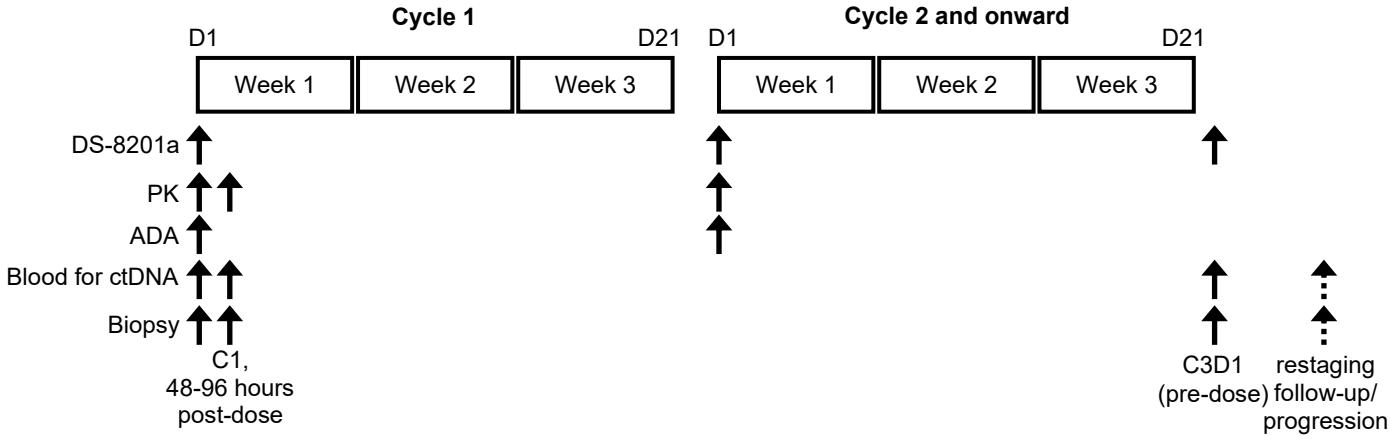
Eligibility:

- Patients ≥ 18 years of age must have histologically documented solid tumors whose disease has progressed on standard therapy or for which there is no available standard therapy
- Patients must have tumors amenable to biopsy and with a HER2 IHC score of 1+ or greater (as determined by CLIA-certified IHC) or *HER2* amplification (as determined by CLIA-certified NGS or ISH)
- Patients must be willing to provide blood and tumor biopsy specimens for research purposes

Study Design:

- DS-8201a will be administered intravenously every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg.
- Mandatory tumor biopsies will be performed at baseline and at 2 post-treatment time points to enable assessments of the early Top1 and DDR responses and the later tumor immune microenvironment responses and analysis of the duration of Top1 inhibition.
- Blood samples will be obtained for pharmacokinetic analysis and to isolate circulating tumor DNA (ctDNA) to examine tumor genomic alterations that may be associated with response or resistance to DS-8201a.

SCHEMA



DS-8201a will be administered intravenously every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg.

Mandatory biopsies will be performed prior to DS-8201a administration on cycle 1 day 1 (up to 7 days prior to DS-8201a administration), cycle 1 48-96 hours post–day 1 dose, and up to 3 days prior to DS-8201a administration on cycle 3 day 1. In addition, an optional biopsy will be performed at time of "restaging follow-up"—i.e., on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles—or at time of disease progression.

Blood samples for PK analysis will be collected on cycle 1 day 1, prior to DS-8201a administration, at end of infusion (up to 30 minutes post-infusion), and at 5 hours (± 30 minutes) post-infusion; at time of the cycle 1 on-treatment biopsy (± 3 hours relative to the biopsy procedure); and on day 1 of cycles 2, 3, and 4 prior to DS-8201a administration and at end of infusion (up to 30 minutes post-infusion).

Blood samples for anti-drug antibody (ADA) analysis will be collected up to 2 days prior to DS-8201a administration on cycle 1 day 1, cycle 2 day 1, and on day 1 of cycle 4 and every 4 cycles thereafter (Cycles 8, 12, 16, etc.); and at the 40-day follow-up appointment (± 7 days).

Blood samples for circulating tumor DNA analysis will be collected prior to DS-8201a administration on cycle 1 day 1 (up to 7 days prior to DS-8201a administration), at the time of the cycle 1 on-treatment biopsy (within 24 hours of the biopsy at this time point), up to 3 days prior to DS-8201a administration on cycle 3 day 1 (unless not clinically indicated), within 24 hours of restaging follow-up biopsy (if applicable), and at the time of disease progression.

TABLE OF CONTENTS

PRÉCIS 3

SCHEMA 5

1 OBJECTIVES 8

2 BACKGROUND 8
2.1 DS-8201a 8
2.2 Rationale 25
2.3 Correlative Studies 26

3 PATIENT SELECTION 31
3.1 Eligibility Criteria 31
3.2 Exclusion Criteria 34
3.3 Inclusion of Women and Minorities 35
3.4 Research Eligibility Evaluation 36

4 REGISTRATION PROCEDURES 37

5 TREATMENT PLAN 42
5.1 Agent Administration 43
5.2 General Concomitant Medication and Supportive Care Guidelines 44
5.3 Duration of Therapy 45
5.4 Duration of Follow Up 45
5.5 Criteria for Removal from Study 46

6 DOSING DELAYS/DOSE MODIFICATIONS 46
6.1 Dose Interruption and Modification/Toxicity Management Guidelines 47

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 52
7.1 Comprehensive Adverse Events and Potential Risks 53
7.2 Adverse Event Characteristics 57
7.3 Expedited Adverse Event Reporting 57
7.4 Routine Adverse Event Reporting 61
7.5 Pregnancy 61
7.6 Secondary Malignancy 61
7.7 Second Malignancy 62
7.8 Overdose 62

8 PHARMACEUTICAL INFORMATION 62
8.1 DS-8201a (NSC 807708) 62
8.2 Agent Ordering 65
8.3 Agent Accountability 65
8.4 Investigator Brochure Availability 65
8.5 Useful Links and Contacts 65

9 CORRELATIVE/SPECIAL STUDIES 66
9.1 Biomarker Plan 66
9.2 Pharmacokinetic Assays 70
9.3 Pharmacodynamic Assays in Tumor Tissue 71
9.4 Blood Collection for ctDNA Analysis 75

9.5 Anti-drug Antibody (ADA) Analysis 77
9.6 Sample Collection and Processing 78
9.7 Privacy Considerations 79
9.8 Management of Genomic Results 80

10 STUDY CALENDAR 80

11 MEASUREMENT OF EFFECT 82
11.1 RECIST v1.1 Criteria for Assessment of Response and Progression 83
11.2 Response Criteria 86
11.3 Evaluation of Target Lesions 86
11.4 Evaluation of Non-Target Lesions 87
11.5 Evaluation of Best Overall Response 87
11.6 Response and Stable Disease Duration (RECIST 1.1) 88

12 DATA REPORTING / REGULATORY REQUIREMENTS 89
12.1 Study Oversight 89
12.2 Data Reporting 89
12.3 Data Quality Portal 91
12.4 Collaborative Agreements Language 92
12.5 Genomic Data Sharing Plan 94
12.6 Study Discontinuation and Closure 94

13 STATISTICAL CONSIDERATIONS 94
13.1 Study Design/Endpoints 95
13.2 Sample Size/Accrual Rate 96
13.3 Analysis of Secondary and Exploratory Endpoints 96

14 HUMAN SUBJECTS PROTECTIONS 97
14.1 Rationale for Subject Selection 97
14.2 Justification for Exclusions 97
14.3 Evaluation of Benefits and Risks/Discomforts 98
14.4 Consent and Assent Process and Documentation 98
14.5 Procedure for Protecting Against or Minimizing Any Potential Risks 99
14.6 Patient Advocate 99

REFERENCES 101

APPENDIX A: Performance Status Criteria 103

APPENDIX B: Procedure for Blood Samples for Pharmacokinetics and ADA Analysis 104

APPENDIX C: Patient Drug Interactions Handout and Wallet Card 108

APPENDIX D: PK/PD Sample Collection Worksheets 109

APPENDIX E: Acceptable Birth Control Methods 116

APPENDIX F: DS-8201a ILD Site Pocket Guide 117

1 OBJECTIVES

Primary Objective:

- To assess the effects of DS-8201a on total Top1 levels in biopsy specimens from patients with HER2-expressing advanced solid tumors, at early and late post-treatment time points, thereby establishing the degree and duration of DS-8201 target engagement

Secondary Objectives:

- To assess any associations between serum concentrations of DS-8201a and the effects of DS-8201a on total Top1 levels in tumor biopsy specimens
- To determine the safety and tolerability of DS-8201a administered intravenously every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg
- To determine the overall response rate (CR + PR) for patients administered intravenously with DS-8201a every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg

Exploratory Objectives:

- To evaluate the effects of DS-8201a on CD8+ T cell infiltration and activation in tumor, tumor PD-L1 and HER2 expression, and DDR signaling (for example: γH2AX, RAD51, and pNBS1) in biopsy specimens
- To examine genomic alterations in circulating tumor DNA (ctDNA) that may be associated with DS-8201a response or resistance
- To examine any associations between baseline tumor HER2 amplification or HER2 expression level and response to DS-8201a
- To evaluate the effects of DS-8201a on tumor levels of HER2 and DDR-associated proteins
- To examine any tumor genomic alterations that may be associated with resistance to DS-8201a
- To evaluate anti-drug antibodies following administration of DS-8201a

2 BACKGROUND

2.1 DS-8201a

2.1.1 Preclinical efficacy and pharmacodynamics

DS-8201a is an antibody-drug conjugate (ADC) consisting of the HER2-targeting antibody trastuzumab covalently bound via a lysosomal protease–cleavable linker to the novel topoisomerase I (Top1) inhibitor deruxtecan (a derivative of exatecan) in a 1:8 antibody: payload ratio **(Figure 1**). Unlike the FDA-approved HER2 ADC T-DM1, which consists of trastuzumab bound to the tubulin-disrupting agent DM1 (mertasine) via a non-cleavable linker, DS-8201a activity is not limited to tumors with high HER2 expression. While T-DM1 has shown efficacy only in preclinical human tumor xenograft models with a HER2 immunohistochemistry (IHC) score of 3+ or *HER2* gene amplification (detected by FISH or next-generation sequencing), DS-8201a is active in these models as well as in those with HER2 IHC scores of 1+ and 2+ [1] (**Figure 2**). Preclinical studies have suggested that this pronounced DS-8201a activity in HER2-low tumors is likely due to the cleavable nature of the linker, which enables bystander killing of HER2-negative cells adjacent to HER2-positive cells via efflux of the cleaved payload from the latter and entry into the former. In an experiment with mixed-tumor xenograft models in which tumors were

comprised of both HER2-positive NCI-N87 and luciferase-expressing, HER2-negative MDA-MB-468 tumor cells, DS-8201a—but not T-DM1 or a DS-8201a-like ADC with a less membrane-permeable analog of the deruxtecan payload ("anti-HER2-DXd (2)")—significantly reduced tumor luciferase activity simultaneously with inducing tumor regression [2], indicating that the cleavable linker and payload membrane permeability of DS-8201a confer the ability to kill non-HER2-expressing tumor cells adjacent to those expressing HER2 (**Figure 3**). Importantly, DS-8201a, like T-DM1 and anti-HER2-DXd (2), had no antitumor activity in xenograft models comprised solely of the luciferase-expressing HER2-negative MDA-MB-468 tumor cells [2].

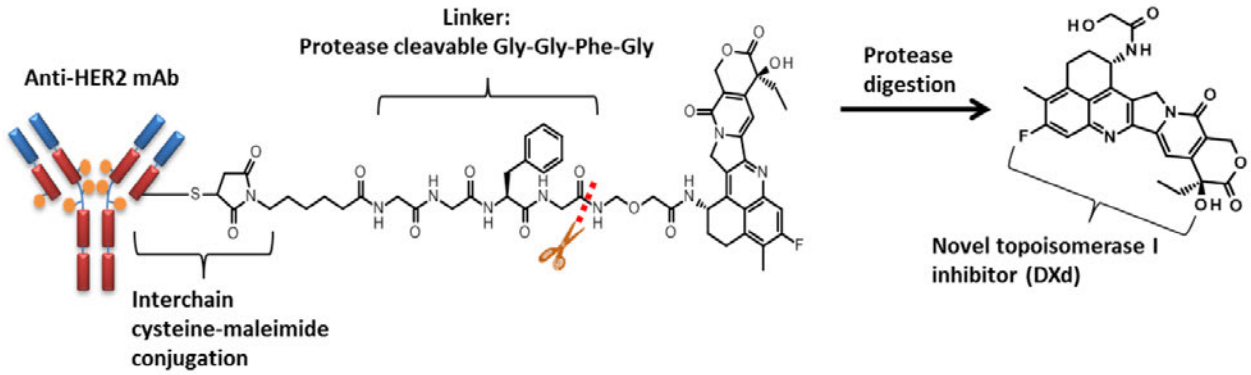


Figure 1. DS-8201a structure. This ADC consists of trastuzumab linked to 8 molecules of deruxtecan. Figure is as shown in [3].

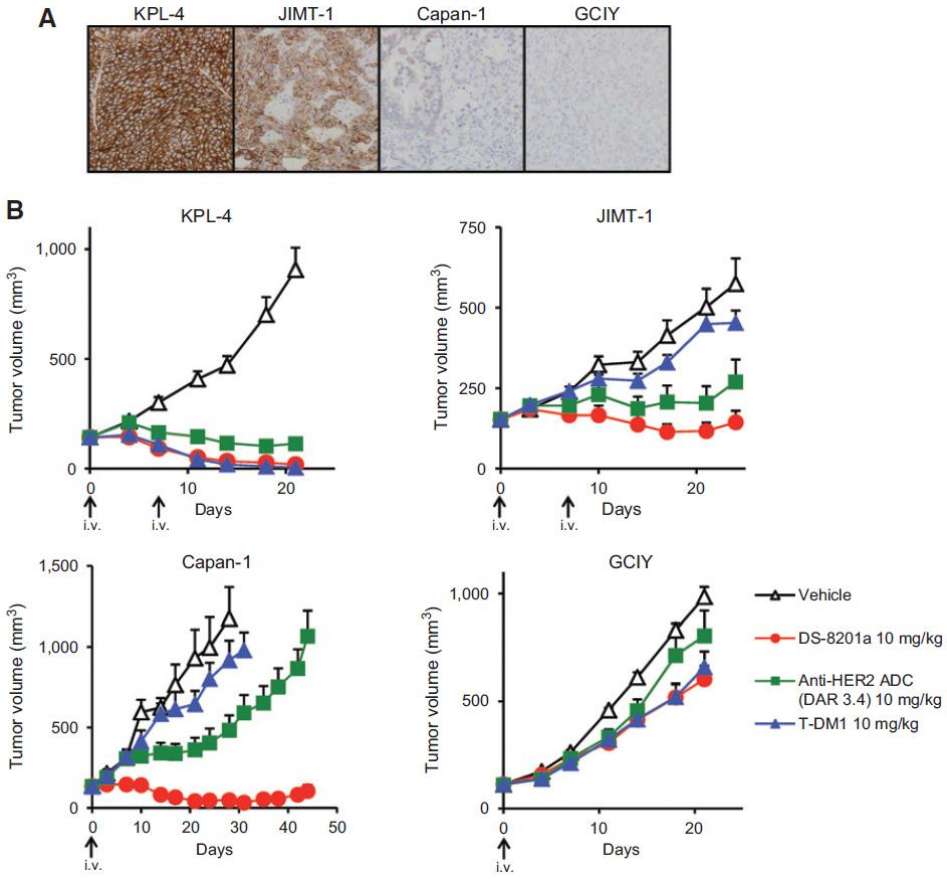


Figure 2. DS-8201a, unlike T-DM1, is active in HER2-low human tumor xenograft models. **A,** Detection of HER2 by IHC in tumor tissue from KPL-4 (breast), JIMT-1 (breast), Capan-1 (pancreatic), and GCIY (gastric) xenograft models. **B,** Antitumor activity of DS-8201a, T-DM1, and the anti-HER2 ADC DAR 3.4 in the xenograft models from (A), administered at the indicated doses. Figure is as shown in [1].

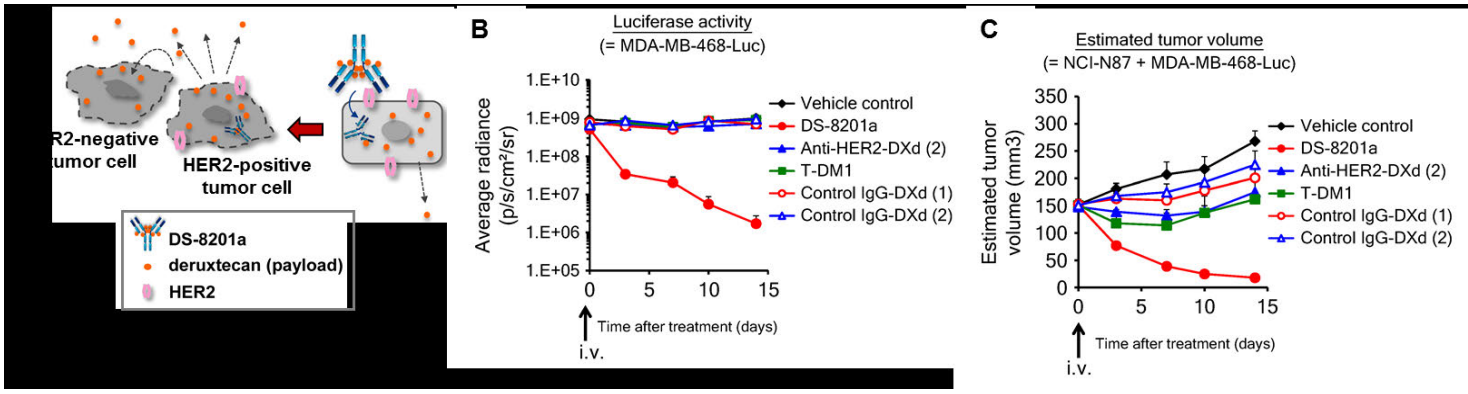


Figure 3. Bystander killing of non-HER2-expressing tumor cells by DS-8201a. **A,** Model of DS-8201a payload efflux from HER2-positive tumor cells to HER2-negative tumor cells following DS-8201a internalization and linker cleavage in HER2-positive cells (figure adapted from Daiichi Sankyo). **B,** Luciferase activity measurements in HER2 ADC-treated xenograft models inoculated with a mixture of HER2-positive NCI-N87 and luciferase-expressing, HER2-negative MDA-MB-468 tumor cells indicate that DS-8201a, but not T-DM1 or anti-HER2-DXd (2), kills HER2-negative cells within the mixed tumors. None of these 3 HER2-targeting ADCs has antitumor activity in human tumor xenograft models of luciferase-expressing MDA-MB-468 cells alone (data not shown) [2]. **C,** DS-8201a, but not T-DM1 or anti-HER2-DXd (2), induces substantial tumor

regression in the mixed HER2-positive/HER2-negative human tumor xenograft models described in B. Panels B and C are as shown in [2].

The DS-8201a mechanism of action has been shown in preclinical cell culture experiments to include both HER2 antibody-dependent cell-mediated cytotoxicity (ADCC) similar to that induced by trastuzumab alone, as well as induction of DNA damage response (DDR) signaling consistent with the deruxtecan payload. DS-8201a binds HER2 with an affinity similar to that of the anti-HER2 antibody portion of the molecule alone and also induces ADCC activity to similar levels in an *in vitro* co-culture system with effector peripheral blood mononuclear cells (PBMC) and SK-BR-3 breast adenocarcinoma target cells (**Figure 4**). In addition, incubation of KPL-4 breast carcinoma cells for 72 hours with DS-8201a or deruxtecan alone induces PARP cleavage (indicative of apoptosis) and phosphorylation of Chk1 and histone H2AX (indicative of DDR signaling); these apoptosis and DDR biomarker responses were not observed upon incubation with the anti-HER2 antibody alone, further demonstrating that these effects are mediated by the deruxtecan payload of DS-8201a (**Figure 4**).

While the downstream DDR effects of DS-8201a have been demonstrated by the aforementioned studies, to date, no preclinical data have been published to demonstrate engagement of the topoisomerase 1 target by the DS-8201a payload.

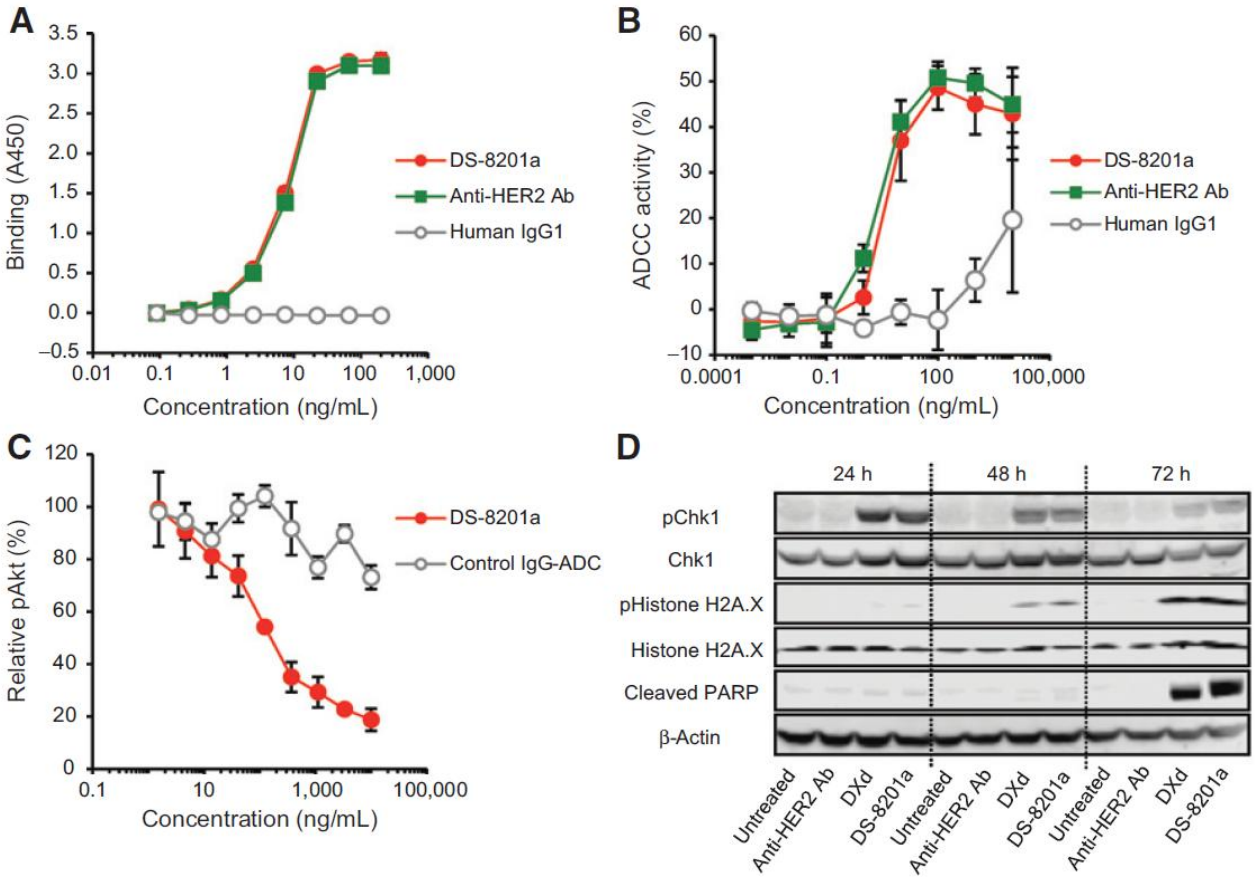


Figure 4. *In vitro* ADCC activity and DDR induction by DS-8201a. **A,** ELISA analysis indicates that the HER2 binding affinity of DS-8201a is similar to that of the unconjugated anti-HER2

antibody. **B,** Co-culture experiments with PBMCs (effector cells) and SK-BR-3 breast adenocarcinoma target cells demonstrate similar ADCC activity for DS-8201a and unconjugated anti-HER2 antibody. **C,** DS-8201a reduces phospho-Akt levels in a concentration-dependent fashion, consistent with ADCC. **D,** Western blotting demonstrates that DS-8201a (10 µg/mL) or deruxtecan alone (Dxd, 10 nM)—but not anti-HER2 antibody alone (10 µg/mL)—induces PARP cleavage and phosphorylation of Chk1 and histone H2AX indicative of apoptosis and DDR activation, respectively, in KPL-4 breast carcinoma cells. Figure panels are as shown in [1].

In addition to the ADCC and DDR effects induced by DS-8201a, this agent also modulates the tumor immune microenvironment, as demonstrated by preclinical studies in immunocompetent syngeneic mouse models (**Figure 5**). Daiichi-Sankyo investigators previously showed that DS-8201a treatment upregulates tumor cell PD-L1 and MHC class I expression in immunocompetent BALB/c mice bearing mouse CT26.WT tumors that express human HER2 [4]. In addition, DS-8201a induces upregulation of CD86 expression on tumor-infiltrating dendritic cells (DCs) in this model. Corroborating the effects of DS-8201a on tumor PD-L1 expression, the combination of this agent with anti-PD-1 therapy yielded a greater-than-single-agent survival benefit in this immunocompetent mouse model (**Figure 5**).

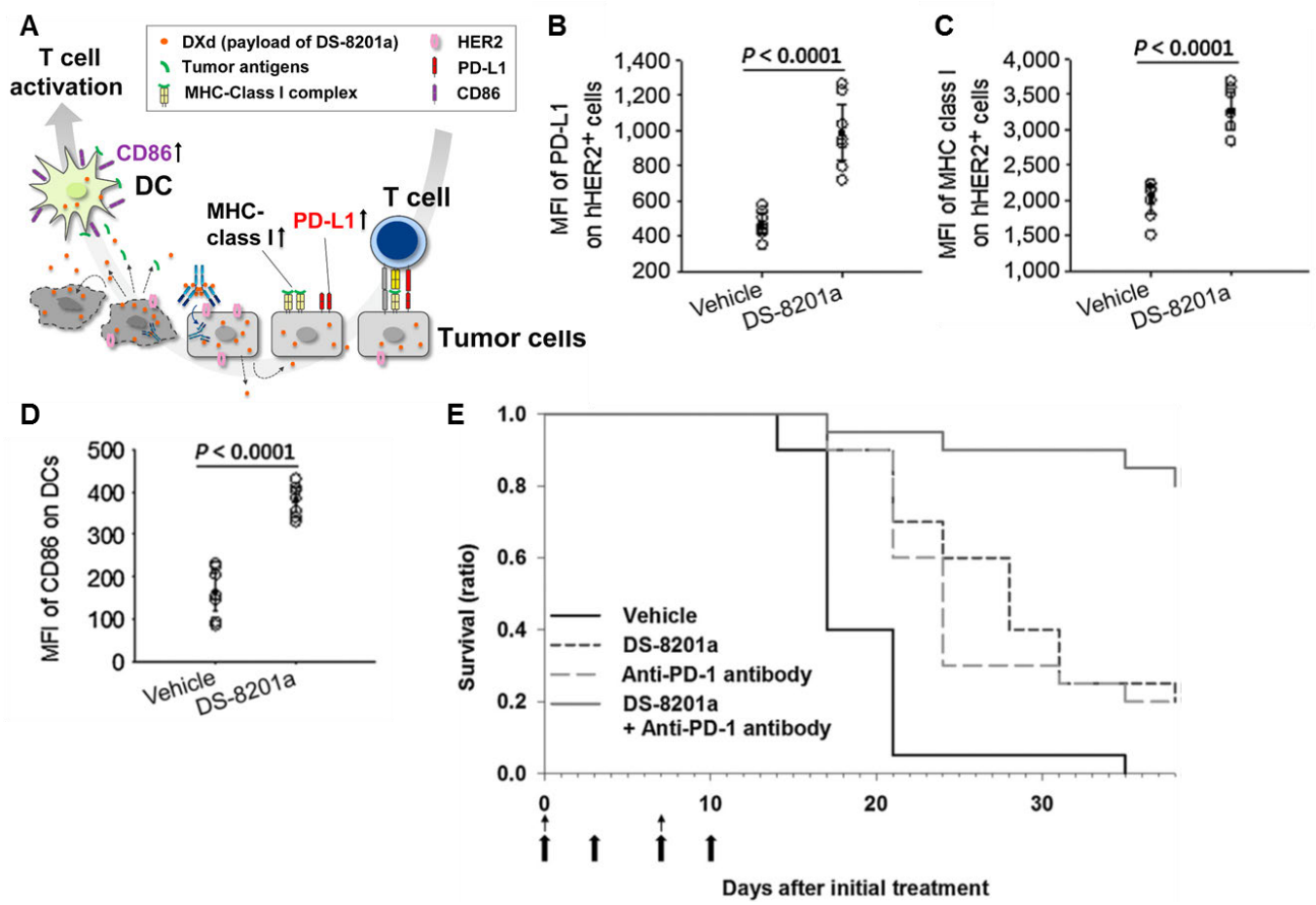


Figure 5. DS-8201a modulates the tumor immune microenvironment in immunocompetent syngeneic mouse models. **A,** Schematic of DS-8201a immune modulatory effects (figure adapted

from Daiichi Sankyo). **B-D,** DS-8201a induces enhances tumor expression of PD-L1 (B) and MHC class I (C) and also increases expression of DC activation marker CD86 in tumor-infiltrating DCs (D) in an immunocompetent mouse model harboring human HER2–expressing CT26.WT-hHER2 tumor cells. **E,** The combination of DS-8201a with anti-PD-1 antibody therapy produces greater-than-single-agent survival benefit in the immunocompetent CT26.WT-hHER2 mouse model. Panels B-E are as shown in [4].

2.1.2 Preclinical pharmacology and toxicology

The following text concerning preclinical pharmacology and toxicology testing results was obtained from the September 2019 Investigator's Brochure and from the clinical protocol from the first-in-human phase 1 study of DS-8201a (DS8201-A-J101; NCT02564900) [3].

2.1.2.1 Safety pharmacology

In telemetered male cynomolgus monkeys treated with single intravenous doses of DS-8201a, no effects on the cardiovascular system, the respiratory system, or the central nervous system were observed at dose levels up to 78.8 mg/kg. In addition, in human ether-a-go-go-related gene (hERG) studies of MAAA-1181, the deruxtecan payload, MAAA-118, did not inhibit the hERG channel current at concentrations of up to 10 μmol/L (approximately 5000 ng/mL).

2.1.2.2 Pharmacokinetics and drug metabolism

In cynomolgus monkeys, the total body clearance (CL) of trastuzumab deruxtecan (0.1 mg/kg to 3 mg/kg) was much lower than that of the hepatic blood flow, and it decreased as the dose increased, suggesting a nonlinear process. The volume of distribution at steady state (Vss) was close to the plasma volume. Both trastuzumab deruxtecan and the total antibody, the sum of conjugated and unconjugated antibody, exhibited similar pharmacokinetic (PK) profiles, indicating that the majority of the administered trastuzumab deruxtecan circulates in the plasma unchanged. The plasma concentrations of MAAA-1181a released from trastuzumab deruxtecan were quite low (molar ratio: approximately 1/400) compared with the levels of trastuzumab deruxtecan and total antibody. No anti-trastuzumab deruxtecan antibodies were detected in any of the animals.

After a single intravenous administration of 6.4 mg/kg of ^{3}H-labeled trastuzumab deruxtecan (in which the antibody portion [MAAL-9001] was ^{3}H-labeled) or ^{14}C-labeled trastuzumab deruxtecan (in which the drug portion [MAAA-1181a] was ^{14}C-labeled) to cynomolgus monkeys, the highest radioactivity was observed in the blood, excluding the contents of the large intestine (a site of excretion), during the study period. The concentrations of radioactivity in all tissues declined in proportion to the decline in the blood concentration, suggesting no retention in specific tissues. The *in vitro* plasma protein binding of MAAA-1181a at concentrations of 10 ng/mL to 100 ng/mL were 90.3% to 92.5% in mice, 94.2% to 96.7% in rats, 86.5% to 89.1% in monkeys, and 96.8% to 98.0% in humans. The *in vitro* blood cell distribution of ^{14}C-labeled MAAA-1181a radioactivity tested at a concentration of 10 ng/mL to 100 ng/mL were 31.6% to 33.8% in mice, 27.8% to 32.7% in rats, 36.4% to 39.7% in monkeys, and 13.0% to 17.7% in humans. The ratio of the concentration of radioactivity in blood to that in plasma was 0.82 to 0.85 in mice, 0.81 to 0.87 in rats, 0.92 to 0.95 in monkeys, and 0.59 to 0.62 in human blood.

The *in vitro* release rates of MAAA-1181a from trastuzumab deruxtecan in mouse, rat, monkey, and human plasma for 3 weeks were 3.9% or less. Cytochrome P450 (CYP) 3A4 was the primary CYP enzyme involved in the metabolism of MAAA-1181a. No human-specific metabolites were detected in cryopreserved hepatocytes *in vitro*.

In rats, the major excretion pathway of radioactivity from administered ^{14}C-MAAA-1181a was the fecal/biliary route. MAAA-1181a was the most abundant component of radioactivity in urine, feces, and bile. In monkeys, radioactivity from administered ^{14}C-trastuzumab deruxtecan was predominantly excreted into feces. MAAA-1181a was the only detectable catabolite in urine and feces.

MAAA-1181a did not exhibit any potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (50% inhibitory concentration [IC50] >50 µmol/L). MAAA-1181a did not exhibit any potential to induce CYP3A4, CYP1A2, and CYP2B6 at concentrations of up to 30 µmol/L. In vitro, MAAA-1181a was a substrate for organic anion transporting polypeptide (OATP) 1B1, OATP1B3, multidrug and toxin extrusion (MATE) 2-K, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP) 1. MAAA-1181a did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, and bile salt export pump (BSEP; IC50 >30 µmol/L [14,804 ng/mL]). MAAA-1181a inhibited OAT1 and OATP1B1 with IC50 values of 12.7 µmol/L (6267 ng/mL) and 14.4 µmol/L (7106 ng/mL), respectively, although the values were much higher than the maximum plasma concentration (C_{max}) of MAAA-1181a in humans (0.0196 µmol/L [9.65 ng/mL] at 8.0 mg/kg of trastuzumab deruxtecan).

The PK in monkeys after single intravenous administration of DS1, the drug substance manufactured using MAAL-9001 produced by CHO-O1, or DS2, the drug substance manufactured using MAAL-9001 produced by CHO-S, at 8 mg/kg was compared. The C_{max} of trastuzumab deruxtecan for DS2 met the bioequivalence criterion, but the area under the plasma concentration-time curve up to 21 days of trastuzumab deruxtecan for DS2 was about 22% lower than that for DS1. No anti-trastuzumab deruxtecan antibodies for either drug substance were detected in any animals.

2.1.2.3 Toxicology

Per the September 2019 Investigator's Brochure, in a study of intermittent intravenous dosing of trastuzumab deruxtecan in rats (q3w dosing for 6 weeks), no deaths or moribund animals were found at dose levels of up to 197 mg/kg, the maximum dose. The major observed findings included testicular and intestinal toxicity at dose levels of 20 mg/kg and greater and lymphatic/hematopoietic, skin, incisor tooth, and renal toxicity at dose levels of 60 mg/kg and greater.

In an intermittent intravenous dose toxicity study of trastuzumab deruxtecan in cynomolgus monkeys (q3w for 6 weeks), 1 moribund female was found at 78.8 mg/kg, the highest dose level. The major toxicity findings in this moribund animal were intestinal toxicity, hematopoietic system toxicity, skin toxicity, and renal toxicity. The decline in the condition of this animal was related to

decreased food consumption and body weight secondary to bone marrow and intestinal toxicity. Major findings of toxicity in the surviving animals were observed in the intestine at dose levels of 10 mg/kg and greater and in the lung, testes, and skin at dose levels of 30 mg/kg and greater. In addition, hematopoietic system, renal toxicity, as well as ECG abnormalities (shortened PR interval and QTc prolongation) were found at the dose level of 78.8 mg/kg.

Thus, as described above, the STD10 in a rat intermittent intravenous dose toxicity study with trastuzumab deruxtecan was found to be greater than 197 mg/kg. In an intermittent intravenous dose toxicity study in cynomolgus monkeys, because moribundity caused by a severe worsening of the animal's condition was found at 78.8 mg/kg in 1 animal and evidence of critical pulmonary toxicity (e.g., interstitial inflammation and/or alveolar edema) was found even in the surviving animals, it was concluded that the HNSTD was 30 mg/kg.

In an intermittent intravenous dosing study of trastuzumab deruxtecan (DS2) in cynomolgus monkeys (q3w for 6 weeks), the major findings of toxicity included intestinal toxicity, hematopoietic system toxicity, and skin toxicity, which were also observed in the previous intermittent intravenous dosing study of trastuzumab deruxtecan in cynomolgus monkeys (q3w for 6 weeks). No severe toxicity was observed at up to 30 mg/kg, the highest dose tested. In a 3-month intermittent intravenous dosing study of trastuzumab deruxtecan (DS2) in monkeys, the target organs/tissues affected by trastuzumab deruxtecan were the bone marrow, kidneys, small and large intestines, testes, skin, and lungs. None of the test article-related changes suggested severe toxicity, and the HNSTD of trastuzumab deruxtecan (DS2) was determined to be 30 mg/kg as well as in these studies.

In an intermittent intravenous dose toxicity study with the DS-8201a payload molecule MAAA-1181a (qw dosing for 4 weeks), although lymphatic/hematopoietic system toxicity, intestinal toxicity, and corneal toxicity (single cell necrosis in the corneal epithelium) were observed at 3 mg/kg and greater in rats, no deaths occurred at dose levels of up to 30 mg/kg. Findings similar to those in rats were observed in cynomolgus monkeys at dose levels of 1 mg/kg and greater. In addition, in cynomolgus monkeys, 1 female died and 1 male was found moribund at 12 mg/kg. Although effects on the heart (focal myocardial cell degeneration/necrosis) were found in the moribund male in addition to other toxicities, there were no such cardiomyopathies in the dead female, even though both animals exhibited similar worsening clinical conditions that were associated with sustained decreases in food consumption and with bone marrow and intestinal toxicity. Therefore, these changes were considered the cause of the death and moribundity. Intestinal toxicity and lymphatic/hematopoietic system toxicity were commonly observed in studies of trastuzumab deruxtecan or MAAA-1181a.

In safety pharmacology studies, when male cynomolgus monkeys equipped with a telemetry device received single intravenous doses of trastuzumab deruxtecan, no effects on the cardiovascular system, respiratory system, or central nervous system were found at dose levels of up to 78.8 mg/kg. In addition, in hERG studies of MAAA-1181a, the monohydrate of the drug component, MAAA-1181a, did not inhibit the hERG channel current.

In an *in vitro* 3T3 NRU phototoxicity study, MAAA-1181a was found to be phototoxic to BALB/c 3T3 mouse fibroblasts. However, in a single-dose phototoxicity study of MAAA-1181a in pigmented rats, no phototoxic reaction was noted.

In vitro genotoxicity studies of MAAA-1181a indicated that MAAA-1181a had no potential to induce gene mutation in bacteria but had the potential to induce structural chromosome aberrations in mammalian cultured cells. An *in vivo* micronucleus study in bone marrow of rats indicated that MAAA-1181a had the potential to induce micronuclei.

2.1.3 Clinical status

2.1.3.1 Clinical efficacy

DS-8201a received Breakthrough designation from the FDA in August 2017 for patients with HER2-positive advanced breast cancer who have been treated with trastuzumab (Herceptin) and pertuzumab (Perjeta) and who have progressed on T-DM1. Preliminary efficacy results from all dose cohorts in Part 1 of study DS8201-A-J101 (phase 1 dose escalation and phase 2 tumor specific expansion) demonstrated objective responses in HER2-positive (i.e., FISH positive or IHC 3+) or HER2-low (i.e., IHC 1+ or 2+ without amplification), and in patients with prior anti-HER2 therapies (Investigator's Brochure, September 2019).

As of the February 1, 2019 data cut-off, a total of 289 subjects received trastuzumab deruxtecan in study DS8201-A-J101. The median treatment duration across all tumor types and doses was 7.4 months, and 25.3% of subjects had ≥12 months of treatment. Across tumor types by dose, the median duration of treatment was similar between the 5.4 mg/kg (7.1 months) and 6.4 mg/kg (7.8 months) dose groups. Median duration of treatment was longest in HER2-positive breast cancer (8.5 months in subjects dosed with 5.4 mg/kg and 9.0 months in subjects dosed with 6.4 mg/kg).

- The overall confirmed objective response rate (ORR) in subjects with HER2-positive breast cancer was 52.5% (62/118) (February 1, 2019 data cutoff).
- In 54 HER2-low breast cancer patients, the confirmed ORR was 37.0% (20/54). The disease control rate (DCR) was 87.0%, and the median progression-free survival (PFS) was 11.1 months (February 1, 2019 data cutoff).
- In HER2-positive gastric cancer (post trastuzumab), the ORR was 29.5% (13/44), and confirmed DCR was 84.1% (37/44) (February 1, 2019 data cutoff).

2.1.3.2 Clinical pharmacokinetics

The clinical pharmacology of trastuzumab deruxtecan has been well characterized, with concentrations of all 3 analyte components of the ADC (i.e., intact DS-8201a, total anti-HER2 antibody, and released DXd payload) analyzed in all 5 clinical studies as noted in the September 2019 Investigator's Brochure (Studies DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, and DS8201-A-U201).

PK parameters for DS-8201a and total anti-HER2 antibody were comparable. Serum concentrations of DXd gradually increased and reached peak concentrations with longer median

time to maximum serum concentration (T_{max}; approximately 6 hours) compared to DS-8201a (approximately 2 hours). On a molar basis, the DS-8201a C_{max} and trough concentrations across the 5.4-mg/kg to 7.4-mg/kg doses were approximately 50-fold to 53-fold and 69-fold to 94-fold higher, respectively, than those for DXd, demonstrating *in vivo* stability of the ADC.

The exposure of DS-8201a, total anti-HER2 antibody, and DXd increased in a dose-related manner, with DS-8201a exposure proportional to dose in the 3.2-mg/kg to 8.0-mg/kg dose range. In the 0.8-mg/kg to 8.0-mg/kg dose range, the C_{max} increased proportional to dose, while the area under the serum concentration-time curve (AUC) for DS-8201a and total anti-HER2 antibody increased slightly more than proportional to dose. Exposures (C_{max} and AUC) for DXd increased proportional to dose in the 0.8-mg/kg to 8.0-mg/kg dose range.

Based on the population PK analysis, no dose adjustment is required for subjects with mild or moderate renal impairment and subjects with mild hepatic impairment (based on the NCI Organ Dysfunction Working Group criteria). Limited data preclude a recommendation for subjects with moderate hepatic impairment or with severe renal impairment. DS-8201a was not studied in subjects with severe hepatic impairment.

Results from Study J102 indicated that administration of DS-8201a at 6.4 mg/kg was not associated with a clinically meaningful (defined as change from baseline >10 ms) prolongation of QT interval corrected for heart rate by Fridericia's formula (QTcF).

Results from Study A-A104 showed that concomitant use of the dual OATP1B and CYP3A inhibitor ritonavir or the strong CYP3A inhibitor itraconazole resulted in minimal increases in exposure of DXd, with increases in AUC_{17d} of 22% and 18%, respectively. Concomitant use of ritonavir or itraconazole resulted in minimal increases in exposure of DS-8201a, with increases in AUC_{17d} of 19% and 11%, respectively. The results indicate that concomitant use of ritonavir or itraconazole would not result in clinically meaningful increases in exposures of DS-8201a or DXd. Therefore, strong inhibitors of CYP3A4 and inhibitors of OATP1B, P-gp, and BCRP can be administered without dose adjustment of trastuzumab deruxtecan.

The recommended phase 2 dose (RP2D) of DS-8201a is 5.4 mg/kg IV every three weeks (Q3W).

2.1.3.3 Clinical pharmacodynamics

No clinical PD data are available to date for DS-8201a.

2.1.3.4 Clinical safety summary

As of 08 June 2019, 3 clinical studies (Studies DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104) were completed, and 9 clinical studies (Studies DS8201-A-J101, DS8201-A-U201, DS8201-A-J202, DS8201-A-J203, DS8201-A-U204, DS8201-A-U105, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303) were ongoing, with an estimated 1036 subjects exposed to at least 1 dose of trastuzumab deruxtecan.

Since the ongoing clinical studies (DS8201-A-J101 and DS8201-A-U201) have the longest durations of exposure and largest sample sizes, safety data for the identified risks

has been summarized from these 2 studies individually. As of 01 February 2019, a total of 289 subjects have been treated in the ongoing DS8201-A-J101 study, and as of 21 March 2019, 184 subjects have been evaluated for safety in the ongoing DS8201-A-U201 study.

DS8201-A-J101, is a Phase 1, two part, first-in-human, clinical trial conducted to identify the maximum tolerated dose (MTD) and RP2D (Part 1) and assess safety, tolerability, and efficacy (Part 2) of DS-8201a at the MTD/RP2D (Investigator's Brochure, 2019).

In Part 1, subjects with advanced breast cancer and gastric or gastroesophageal junction (GEJ) adenocarcinoma, received DS-8201a IV on Day 1 of each 21-day cycle escalating dose levels.

A total of 27 subjects received DS-8201a in 3 patient cohorts at 0.8 mg/kg cohort, 1.6 mg/kg, 3.2 mg/kg, and in 6-patient-cohorts of 5.4 mg/kg, 6.4 mg/kg, and 8.0 mg/kg. No dose limiting toxicities (DLTs) were reported. The MTD was not reached. Two doses: 5.4 mg/kg, and 6.4 mg/kg, were chosen for Part 2 (expansion).

Part 2 had multiple expansion cohorts: T-DM1 treated HER2-positive breast cancer (2a); trastuzumab-treated HER2-positive gastric or GEJ adenocarcinoma (2b); HER2 low expressing breast cancer (2c); HER2-expressing solid tumors, other than breast or gastric and/or any tumor with HER2 mutation (2d); and HER2-expressing breast cancer (2e) (Investigator's Brochure, 2018). A total of 244 subjects received DS-8201a at 5.4 mg/kg or 6/4 mg/kg, with a median treatment duration of 7.4 months across all tumor types and doses. Overall, 118 HER2-positive breast cancer subjects received DS-8201a (51 subjects on 5.4 mg/kg and 67 subjects on 6.4 mg/kg). Forty-four HER2-positive gastric/GEJ cancer subjects received the drug (19 subjects on 5.4 mg/kg and 25 subjects on 6.4 mg/kg).

Among 289 subjects enrolled across all parts and cohorts in Study DS8201-A-J101, the most frequent AEs (> 20%) are summarized in the table below (Investigator's Brochure, 2019). Other AEs including pneumonitis are described in **Section 2.1.3.5**, Identified risks of DS-8201a and Adverse Events of Special Interest.

Summary of Treatment-Emergent Adverse Events (TEAEs) (>20%) in Study DS8201-A-J101

	Number (%) of Subjects[a]									
	HER2-Positive Breast Cancer		HER2-Low Breast Cancer		HER2-Positive Gastric/GEJ Cancer		Other Cancers[b]	Total (N = 274)		Total (N = 289)
Preferred Term	5.4 mg/kg (N = 50)	6.4 mg/kg (N = 66)	5.4 mg/kg (N = 21)	6.4 mg/kg (N = 33)	5.4mg/kg (N = 19)	6.4 mg/kg (N = 25)	6.4 mg/kg (N = 59)	5.4 mg/kg (N = 91)	6.4 mg/kg (N = 183)	All Doses
Subjects with any TEAEs	50 (100.0)	66 (100.0)	20 (95.2)	33 (100.0)	19 (100.0)	25 (100.0)	59 (100.0)	90 (98.9)	183 (100.0)	288 (99.7)
Nausea	43 (86.0)	52 (78.8)	15 (71.4)	26 (78.8)	12 (63.2)	19 (76.0)	44 (74.6)	71 (78.0)	141 (77.0)	222 (76.8)
Decreased appetite	23 (46.0)	47 (71.2)	7 (33.3)	20 (60.6)	8 (42.1)	22 (88.0)	35 (59.3)	38 (41.8)	124 (67.8)	168 (58.1)
Vomiting	28 (56.0)	35 (53.0)	10 (47.6)	14 (42.4)	3 (15.8)	8 (32.0)	31 (52.5)	41 (45.1)	88 (48.1)	133 (46.0)
Alopecia	19 (38.0)	45 (68.2)	6 (28.6)	18 (54.5)	4 (21.1)	4 (16.0)	20 (33.9)	29 (31.9)	87 (47.5)	120 (41.5)
Anemia[c]	24 (48.0)	30 (45.5)	7 (33.3)	14 (42.4)	4 (21.1)	14 (56.0)	23 (39.0)	35 (38.5)	81 (44.3)	118 (40.8)
Fatigue	24 (48.0)	32 (48.5)	11 (52.4)	9 (27.3)	4 (21.1)	3 (12.0)	21 (35.6)	39 (42.9)	65 (35.5)	111 (38.4)
Diarrhea	18 (36.0)	28 (42.4)	9 (42.9)	16 (48.5)	3 (15.8)	5 (20.0)	19 (32.2)	30 (33.0)	68 (37.2)	102 (35.3)

Constipation	18 (36.0)	30 (45.5)	7 (33.3)	14 (42.4)	5 (26.3)	7 (28.0)	16 (27.1)	31 (34.1)	67 (36.6)	100 (34.6)
Platelet count decrease[d]	15 (30.0)	24 (36.4)	3 (14.3)	14 (42.4)	5 (26.3)	12 (48.0)	22 (37.3)	24 (26.4)	72 (39.3)	100 (34.6)
Neutrophil count decrease[e]	12 (24.0)	25 (37.9)	3 (14.3)	13 (39.4)	2 (10.5)	12 (48.0)	21 (35.6)	18 (19.8)	71 (38.8)	91 (31.5)
White blood cell count decrease[f]	9 (18.0)	22 (33.3)	4 (19.0)	13 (39.4)	3 (15.8)	11 (44.0)	17 (28.8)	17 (18.7)	63 (34.4)	82 (28.4)
Aspartate aminotransferase increased	9 (18.0)	23 (34.8)	3 (14.3)	10 (30.3)	1 (5.3)	3 (12.0)	12 (20.3)	13 (14.3)	48 (26.2)	63 (21.8)
Malaise	6 (12.0)	19 (28.8)	2 (9.5)	13 (39.4)	3 (15.8)	5 (20.0)	13 (22.0)	11 (12.1)	50 (27.3)	62 (21.5)
Pyrexia	10 (20.0)	18 (27.3)	1 (4.8)	9 (27.3)	3 (15.8)	8 (32.0)	9 (15.3)	14 (15.4)	44 (24.0)	60 (20.8)
Stomatitis[g]	7 (14.0)	18 (27.3)	4 (19.0)	13 (39.4)	1 (5.3)	4 (16.0)	10 (16.9)	12 (13.2)	45 (24.6)	58 (20.1)

GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event

[a] Part 1 and Part 2 subjects are included. Percentage was calculated using the number of subjects in the column heading as the denominator.

[b] Does not include 1 subject with HER2-low gastric cancer who received trastuzumab deruxtecan at 5.4 mg/kg.

[c] Grouped term that includes PTs anemia, hemoglobin count decreased, and red blood cell count decreased.

[d] Grouped term that includes PTs platelet count decreased and thrombocytopenia.

[e] Grouped term that includes PTs neutrophil count decreased and neutropenia.

[f] Grouped term that includes PTs white blood count decreased and leukopenia.

[g] Grouped term that includes PTs stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

Adverse events were coded using MedDRA Version 20.1. Table is presented by decreasing order of preferred terms within the Total (N = 289) All Doses column. Data cutoff date: 01 Feb 2019.

Source: DS8201-A-J101 CSR, Table 10.6.

A total of 139 (48.1%) subjects had TEAEs of Grade ≥3 that the investigator considered to be related to the study drug. The most frequently (≥5% of subjects) reported drug-related TEAEs of Grade ≥3 by PT were anemia (49 [17.0%] subjects), neutrophil count decreased (52 [18.0%] subjects), WBC count decreased (37 [12.8%] subjects), and platelet count decreased (32 [11.1%] subjects).

Across all tumor types, a numerically higher proportion of subjects in the 6.4-mg/kg dose group than in the 5.4-mg/kg group experienced AEs of Grade ≥3 (overall and causally related), SAEs (including causally related), AEs leading to drug withdrawal (overall and causally related), and AEs leading to dose reduction (overall and causally related).

DS8201-A-U201 is a Phase 2 clinical trial assessing the anti-tumor activity, safety, and efficacy of DS-8201a in HER2-positive, unresectable and/or metastatic breast cancer subjects resistant/refractory to T-DM1(Investigator's Brochure, 2019). Part 1 was dose finding and included dose levels 5.4, 6.2, and 7.4 mg/kg, and the **RP2D was determined to be 5.4 mg/kg.**

As of the data cut-off of 21 March 2019, a total of 253 subjects had been treated on this trial (Investigator's Brochure, 2019). The safety evaluation for this study mainly focuses on the 184 subjects who received the recommended dose of trastuzumab deruxtecan at 5.4 mg/kg.

One hundred eighty-three (99.5%) subjects experienced at least 1 TEAE, with the most common events being gastrointestinal or hematological in nature:

- Among the gastrointestinal events, nausea was the most frequently reported TEAE, was mostly Grade 1 or Grade 2, occurred most frequently in the first 2 cycles, and was manageable under routine medical practice without a need for treatment discontinuation.
- Among the hematological events, anemia, neutrophil count decreased, and platelet count decreased were the most frequently reported, were mostly Grade 1 or Grade 2, occurred most frequently in the first 2 cycles, and were manageable under routine clinical practice without a need for treatment discontinuation.

The TEAEs of Grade ≥3 were reported in 94 (51.1%) subjects. The single most common Grade ≥3 TEAE irrespective of causality was neutrophil count decrease (32 [17.4%] subjects), which included 18 (9.8%) subjects with PTs of neutrophil count decreased and 14 (7.6%) subjects with PTs of neutropenia. Other Grade ≥3 TEAEs reported for ≥5% of subjects in the overall 5.4-mg/kg dose cohort were nausea (14 [7.6%] subjects), anemia (12 [6.5%] subjects), and fatigue (10 [5.4%] subjects).

As of the data cutoff date of 21 March 2019, in the overall 5.4-mg/kg dose cohort, 36 (19.6%) subjects had serious TEAEs. The most frequently (>1% of subjects) reported serious TEAEs by PT were vomiting (4 [2.2%] subjects); cellulitis, intestinal obstruction, nausea, and pneumonia (3 [1.7%] subjects each); and abdominal pain, hypokalemia, pleural effusion, pyelonephritis, and urinary tract infection (2 [1.1%] subjects each). Serious TEAEs considered by the investigators to be related to the study drug (16 [8.7%] subjects) included: vomiting (4 [2.2%] subjects), nausea (3 [1.7%] subjects), cellulitis (2 [1.1%] subjects), and lower respiratory tract infection, osteomyelitis, pneumonia, sepsis, hypersensitivity, hypokalemia, cardiac failure congestive, dyspnea, pneumonitis, respiratory failure, and dysphagia (1 [0.5%] subject each).

Ocular toxicities observed to date have all been non-serious and have occurred at low frequencies. In the HER2+ breast cancer cohort (N=234) in subjects dosed at 5.4 mg/kg across two clinical studies (DS8201-A-J101 and DS8201-A-U201) as of August 1st 2019, the following adverse events were reported with a frequency of ≥ 2%: dry eye (27 [11.5%]), vision blurred (8 [3.4%]), conjunctivitis (6 [2.6%]), and keratitis (6 [2.6%]). None of the events in the Eye disorders System Organ Class (SOC) led to study drug discontinuation or dose reduction or were reported as serious adverse events. One event of keratitis (1 [0.4%]) led to study drug interruption.

For further discussion on pneumonitis, refer to **Section 2.1.3.5.**

2.1.3.5 Identified risks of DS-8201a and Adverse Events of Special Interest

As of 08 Jun 2019, based on a cumulative review of the safety data from the clinical studies, including Studies DS8201-A-J101 and DS8201-A-U201, considering the frequency and biological plausibility of the reported AEs, the following have been identified as adverse drug reactions (ADRs). As Studies DS8201-A-J101 and DS8201-A-U201 have the longest durations of exposure and the largest sample sizes, ADRs for all tumor types and doses were selected primarily based on the review of safety data from these 2 studies and are provided in the table below. The safety data from other completed/ongoing studies as well as safety data from nonclinical studies were also reviewed to support the selection of ADRs. These ADRs include both serious and nonserious

TEAEs that the sponsor has assessed as reasonably associated with the use of trastuzumab deruxtecan and classified as identified risks for trastuzumab deruxtecan.

Serious and Nonserious Adverse Drug Reactions in HER2-Expressing Tumors for All Doses in Studies DS8201-A-J101 and DS8201-A-U201

MedDRA System Organ Class Preferred Term or Grouped Term	Number of Subjects Treated (N = 542)	
	CTCAE Grade	
	Any Grade n (%)[a]	Grade 3-4 n (%)[a]
Blood and lymphatic system disorders		
Anemia[b]	196 (36.2)	83 (15.3)
Neutrophil count decreased[c]	185 (34.1)	106 (19.6)
Platelet count decreased[d]	155 (28.6)	47 (8.7)
White blood cell count decreased[e]	146 (26.9)	55 (10.1)
Febrile neutropenia	13 (2.4)	13 (2.4)
Eye disorders		
Dry eye	48 (8.9)	1 (0.2)
Gastrointestinal disorders		
Nausea	417 (76.9)	29 (5.4)
Vomiting	242 (44.6)	15 (2.8)
Constipation	190 (35.1)	3 (0.6)
Diarrhea	168 (31.0)	8 (1.5)
Stomatitis[f]	100 (18.5)	4 (0.7)
Abdominal pain[g]	76 (14.0)	4 (0.7)
Dyspepsia	51 (9.4)	0 (0.0)
General disorders and administration site conditions		
Fatigue	234 (43.2)	35 (6.5)
Asthenia	37 (6.8)	5 (0.9)
Infections and infestations		
Upper respiratory tract infection	45 (8.3)	0 (0.0)
Injury, poisoning and procedural complications		
IRR[h]	16 (3.0)	0 (0.0)
Investigations		
Aspartate aminotransferase increased	98 (18.1)	13 (2.4)
Alanine aminotransferase increased	72 (13.3)	8 (1.5)
Metabolism and nutrition disorders		
Decreased appetite	248 (45.8)	17 (3.1)
Hypokalemia	71 (13.1)	28 (5.2)
Nervous system disorders		
Headache	79 (14.6)	1 (0.2)
Dizziness	50 (9.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders		
Cough	87 (16.1)	1 (0.2)

MedDRA System Organ Class Preferred Term or Grouped Term	Number of Subjects Treated (N = 542)	
	CTCAE Grade	
	Any Grade n (%)[a]	Grade 3-4 n (%)[a]
ILD[i]	69 (12.7)	16 (3.0)[j]
Epistaxis	56 (10.3)	0 (0.0)
Dyspnea	55 (10.1)	6 (1.1)
Skin and subcutaneous tissue disorders		
Alopecia	244 (45.0)	1 (0.2)

AC = Adjudication Committee; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; IRR = infusion-related reactions; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

[a] Percentages are calculated using the number of subjects in the Safety Analysis Set as the denominator.
[b] The grouped term of anemia includes PTs of anemia, hemoglobin count decreased, and red blood cell count decreased.
[c] The grouped term of neutrophil count decreased includes PTs of neutrophil count decreased and neutropenia.
[d] The grouped term of platelet count decreased includes PTs of platelet count decreased and thrombocytopenia.
[e] The grouped term of white blood cell count decreased includes PTs of white blood cell count decreased and leukopenia.
[f] The grouped term of stomatitis includes PTs of stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.
[g] The grouped term of abdominal pain includes PTs of abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper.
[h] IRR is based on the sponsor case review of the specific PTs.
[i] ILD includes events that were adjudicated as ILD and related to use of trastuzumab deruxtecan (comprises 44 PTs defined in the ILD AC Charter).
[j] Twelve events were Grade 5.
Source: Preliminary data from the clinical database as of the data cutoff dates of 01 Feb 2019 (DS8201-A-J101) and 21 Mar 2019 (DS8201-A-U201).

Adverse events of special interest (AESI) are described in further detail below.

2.1.3.5.1 Pneumonitis/ILD

ILD/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data. Refer to the current IB for a summary of preliminary clinical study data. Daiichi-Sankyo established an external ILD adjudication committee (ILD AC) for the trastuzumab deruxtecan clinical program to adjudicate all events of potential ILD reported by investigators on an ongoing basis.

On Study DS8201-A-J101, as of 01 Feb 2019, 58 (20.1%) subjects had potential ILD events, which were submitted to the ILD AC:

- A total of 49 (17.0%) subjects had events that were adjudicated as ILD:
  - 44 (15.2%) subjects had events that were adjudicated as drug-related ILD.

    Among the 44 (15.2%) subjects who had events that were adjudicated as drug-related ILD, the majority of the ILD events were adjudicated as Grade 1 (14 [4.8%] subjects), Grade 2 (20 [6.9%] subjects), Grade 3 (2 [0.7%] subjects), Grade 4 (2 [0.7%] subjects), and Grade 5 (6 [2.1%] subjects).
  - 5 (1.7%) subjects had events that were adjudicated as not-drug-related ILD.

- 9 (3.1%) subjects had events that were adjudicated as not ILD.

Nine subjects had events of adjudicated ILD associated with a fatal outcome: 8 subjects were determined by the ILD AC to have events as due to drug-related ILD and 1 subject was determined by the ILD AC to have an event as not drug-related ILD. Of the 8 subjects who were adjudicated as having drug-related ILD, 1 subject experienced a Grade 4 drug-related ILD and reportedly died after the data cutoff date, and another subject experienced a Grade 4 drug-related ILD and subsequently died, before the data cutoff date; both died due to ILD and disease progression.

A higher frequency of events adjudicated as drug-related ILD was observed in the following subgroups: subjects treated with 6.4 mg/kg (35/183 [19.1%] subjects) versus 5.4 mg/kg (8/91 [8.8%] subjects) and subjects in Japan (33/178 [18.5%] subjects) versus subjects in United 11/111 [9.9%] subjects).

For Study DS-8201-A-U201, as of 21 March 2019 (across all dose cohorts; N = 253):

- 29 (11.5%) subjects were with potential ILD events:
  - 27 (10.7%) subjects had events that were adjudicated as being ILD:
    - 25 (9.9%) subjects had events that were adjudicated as study drug-related ILD.
    - 2 (0.8%) subjects had events that were adjudicated as not study drug-related ILD
  - 2 (0.8%) subjects had events adjudicated as not ILD

ILD/pneumonitis should be ruled out if a subject develops new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated "Other Non-Laboratory Adverse Events" dose modification in Section 6.1.

If the AE is suspected to be ILD/pneumonitis, study drug should be interrupted pending diagnostic evaluation, which should include high resolution CT and pulmonologist consultation. Other evaluations could include pulmonary function tests such as DLCO and pulse oximetry (SpO_2), arterial blood gases, serum marker testing (*e.g.*, KL-6, SP-D, or others), or other tests as needed. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (refer to drug-induced lung disease guideline [5]).

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification in Section 6.1.

2.1.3.5.2 Left Ventricular Ejection Fraction Decrease

LVEF decrease is considered to be an important potential risk associated with DS-8201a based on the review of available clinical/nonclinical data and literature for the products of the same class.

In Study DS8201-A-J101, among 289 subjects, 7 (2.4%) subjects experienced decreased ejection fraction. Most of these events were Grade 2, with a Grade 3 event reported in 1 (0.3%) subject. With the exception of a dose interruption in 1 subject, dose modification was not required. No notable differences were observed across other subgroups. No association between troponin increase and LVEF decrease was observed. Asymptomatic LVEF decreases have been reported in this study. No events of chronic heart failure or symptomatic LVEF dysfunction were reported. Subjects recovered while continuing on study drug. TEAEs of troponin increased or troponin I increased were reported in 4 subjects. No subject had a TEAE of myocardial infarction.

In Study DS8201-A-U201, among 253 subjects (all dose cohorts), 5 (2.0%) subjects had TEAEs of LVEF decrease: 4 (2.2%) subjects in the 5.4-mg/kg dose cohort and 1 (2.1%) subject in the 6.4-mg/kg dose cohort. One (0.4%) subject (in the 5.4-mg/kg dose cohort) had a baseline Grade 1 cardiac failure reported at Day 1 (LVEF of 52%), which was not considered by the investigator as related to the study drug. One (0.4%) subject (in the 5.4-mg/kg dose cohort) with a history of limb edema had a Grade 2 cardiac failure congestive (LVEF of 63.1% at baseline; LVEF ranged from 66% to 68% while on study drug), which was considered by the investigator as related to the study drug and resolved after medical treatment and study drug discontinuation. Three (1.2%) subjects had ejection fraction decreased (1 [0.4%] subject with Grade 3 [in the 5.4-mg/kg dose cohort] and 2 [0.8%] subjects with Grade 2 [in the 6.4-mg/kg dose cohort]). All 3 events were considered by the investigator as related to the study drug, and all events resolved after interruption of study drug and without the need for additional medical treatment.

LVEF will be measured by either ECHO or MUGA or cardiac MRI scan. All ECHOs/MUGAs/cardiac MRIs will be evaluated by the Investigator or delegated physician for monitoring cardiac function. Troponin will be measured at screening and at the end of treatment, and as needed based on subject reported cardiac signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. Triplicate ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter are to be recorded in the CRF.

2.1.3.5.3 Hepatic Dysfunction

Cases of hepatic toxicity have occurred with T-DM1, lapatinib, and trastuzumab. In subjects receiving T-DM1, hepatic toxicity has manifested mainly as transient asymptomatic liver transaminase elevations, although serious cases of drug-induced liver failure and nodular regenerative hyperplasia have also been reported (Investigator's Brochure, 2019). Lapatinib has also been associated with serious cases of drug-induced liver injury.

As of February and March 2019, respectively, one subject each enrolled in Studies DS8201-A-J101 and DS8201-A-U201 died due to severe abnormal hepatic dysfunction (Investigator's Brochure, 2019). The investigators determined the SAE was related to treatment.

2.1.3.5.4 Diarrhea

Diarrhea and delayed onset diarrhea, which can be severe and lead to dehydration, have been associated with topoisomerase I inhibitors (Investigator's Brochure, 2019).

Among 289 subjects enrolled across all parts and cohorts in DS8201-A-J101 (data cutoff: 01 February 2019), gastrointestinal disorders are the most frequently reported (>20%) TEAEs, including nausea (222 [76.8%]), decreased appetite (168 [58.1%]), vomiting (133 [46%]), diarrhea (102 [35.3%]), and constipation (100 [34.6%]) (Investigator's Brochure, 2019).

2.1.3.5.5 Anemia, Neutrophil Count Decrease (Including Febrile Neutropenia), and Platelet Count Decrease

In the ongoing DS8201-A-J101 clinical study (data cutoff 01 February 2019), a total of 118 (40.8%) subjects experienced an event of anemia, 61 (21.1%) of whom experienced an event of Grade ≥3 in severity. One (0.3%) subject discontinued from the study treatment, 3 (1.0%) subjects had study drug dose reduction, and 7 (2.4%) subjects had study drug interruption due to anemia.

A total of 91 (31.5%) subjects experienced an event of neutrophil count decreased, 53 (18.3%) of whom experienced an event of Grade ≥3 in severity. No SAEs were reported. No subjects were discontinued from the study treatment, 6 (2.1%) subjects had dose reduction, and 38 (13.1%) subjects had study drug interruption due to neutrophil count decreased.

A total of 9 (3.1%) subjects experienced a PT of febrile neutropenia including all tumor types and doses. Febrile neutropenia was reported in 7 (3.8%) subjects who received 6.4 mg/kg compared to 2 (2.2%) subjects who received 5.4 mg/kg, irrespective of the tumor type. All events were Grade 3 except for 1 Grade 5 event. No subject was withdrawn due to febrile neutropenia, dose was reduced in 2 (0.7%) subjects, and drug was interrupted in 2 (0.7%) subjects due to the TEAE.

A total of 100 (34.6%) subjects experienced an event of platelet count decreased, 33 (11.4%) of whom experienced an event of Grade ≥3 in severity. Three (1.0%) subjects were discontinued from the study treatment, 14 (4.8%) subjects experienced dose reduction, and 11 (3.8%) subjects experienced dose interruption.

2.1.3.6 Clinical status of CTEP protocol 10346

As of October 2022 (Amendment F), 36 patients have been enrolled on this study. The best responses documented to date are as follows: 1 withdrew before first assessment, 1 died before first assessment, 9 have not yet been assessed (but are still on study), 7 PD, 11 SD, 4 unconfirmed PR (2 are off study, 2 have recently demonstrated an initial response and are still on treatment, awaiting confirmation), 1 unconfirmed CR (off study due to toxicity), and 2 confirmed PR.

2.2 **Rationale**

Given the lack of data confirming the proposed mechanism of DS-8201a action in patient tumors, we propose this single-agent, PD-driven study of DS-8201a in patients with advanced solid tumors

to demonstrate DS-8201a engagement of the Top1 target via detection of DS-8201–induced reduction in total Top1 levels. In addition to target engagement, this study will also establish the effects of DS-8201a on downstream DDR signaling and the tumor immune microenvironment in patient tumors.

2.3 Correlative Studies

2.3.1 Pharmacodynamic assessments

2.3.1.1 Top1 cleaved complex and DNA damage response

Despite preclinical evidence of DDR signaling in response to the deruxtecan payload of DS-8201a, no preclinical or clinical data have been published to date demonstrating engagement of the topoisomerase 1 target by the DS-8201a payload, which could be accomplished via use of a previously validated antibody to the Top1 cleavable complex (Top1cc) that is stabilized by topoisomerase inhibitors [6]. The Pharmacodynamic Assay Development and Implementation Section (PADIS) at the Frederick National Laboratory for Cancer Research (FNLCR) has recently used this antibody to develop a clinically fit-for-purpose immunofluorescence microscopy assay (IFA) to measure Top1cc (**Figure 6**). For the Top1cc assay, an on-target drug response is defined as ≥ 4% of cells positive for Top1cc (with positivity defined as > 8 Top1cc foci per nucleus) in post-treatment biopsies. For the PADIS DDR3 assay, levels exceeding 4% nuclear area positive (NAP) γH2AX, 4% NAP pNBS1, and 5% cells with ≥5 Rad51 nuclear foci indicate a DNA damage activation response [7].

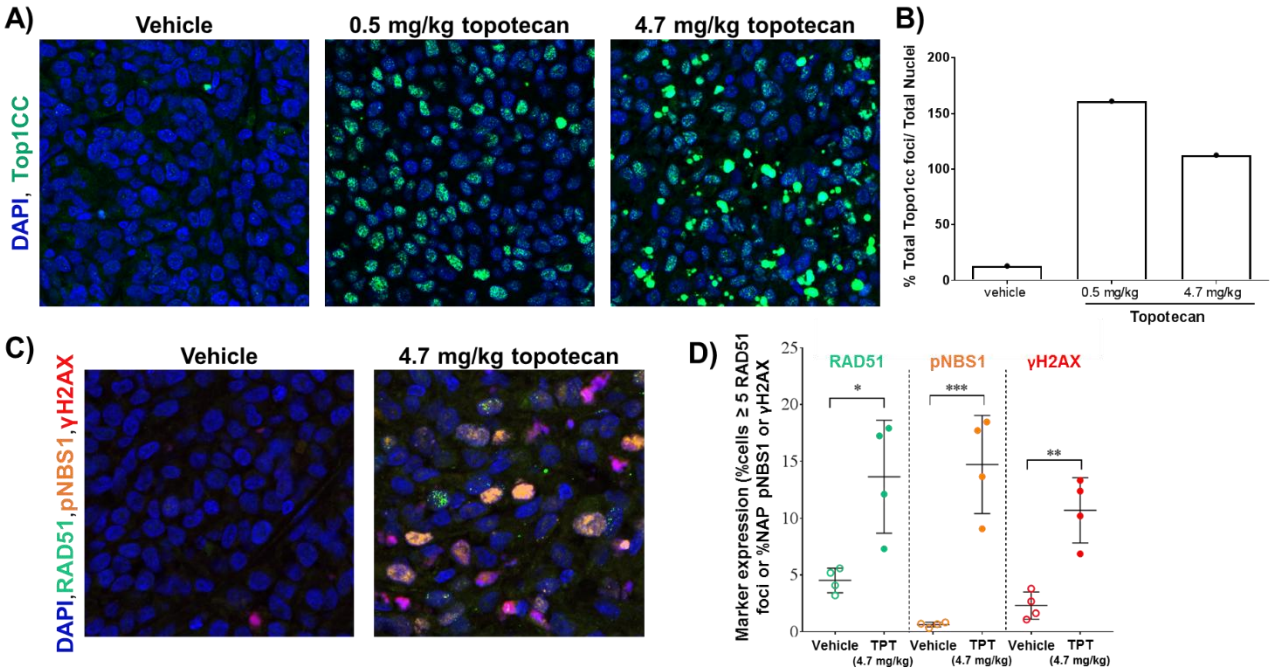


Figure 6. PADIS Top1cc and DDR IFAs measure Top1cc formation and DDR signaling induction, respectively, following topotecan treatment in A375 melanoma xenograft models. Xenograft models were treated with vehicle or the indicated doses of topotecan (TPT), and tumors were harvested for analysis at 4 h post-dose. **A and B,** Induction of Top1cc formation following treatment with a single dose of 0.5 or 4.7 mg/kg topotecan; representative immunofluorescence

images (**A**) and quantitation of Top1cc (% total Top1cc foci/total number of nuclei) (**B**) are shown. **C and D,** DDR signaling induction following treatment with a single dose of 4.7 mg/kg topotecan; representative immunofluorescence images (**C**) and quantitation of each biomarker (% cells with ≥ 5 RAD51 foci; % nuclear area positive [NAP] for pNBS1; or %NAP γH2AX) (**D**) are shown. All data shown are unpublished.

As of Amendment C (June 2021), preclinical time-course data in the HER2-positive MDA-MB-361 and SK-OV-3 xenograft models demonstrate that Top1 cleavable complex (Top1cc) induction following DS-8201a treatment is extremely modest and highly transient, limiting the value of this biomarker for clinical PD studies (**Figure 7a**). In contrast, total Top1 levels were robustly reduced in response to DS-8201a in these models at 48-96 hours post-dose (**Figure 7b**). Given these data, we have revised the biomarker plan for this trial, using total Top1 (rather than Top1cc) as the primary biomarker endpoint and changing the timepoint for the first on-treatment biopsy to cycle 1, 48-96 hours post–day 1 dose.

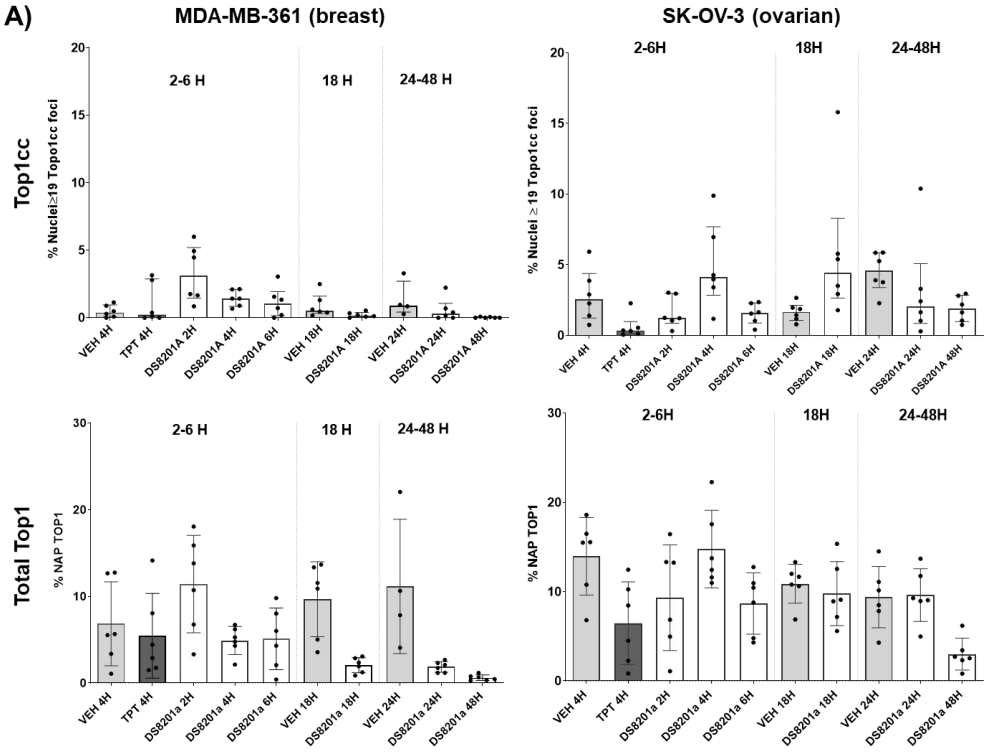


Figure 7 (*legend on following page*). PADIS Top1cc and total Top1 IFA data demonstrate robust modulation of total Top1, but not Top1cc, following DS-8201a treatment in HER2-positive xenograft models.

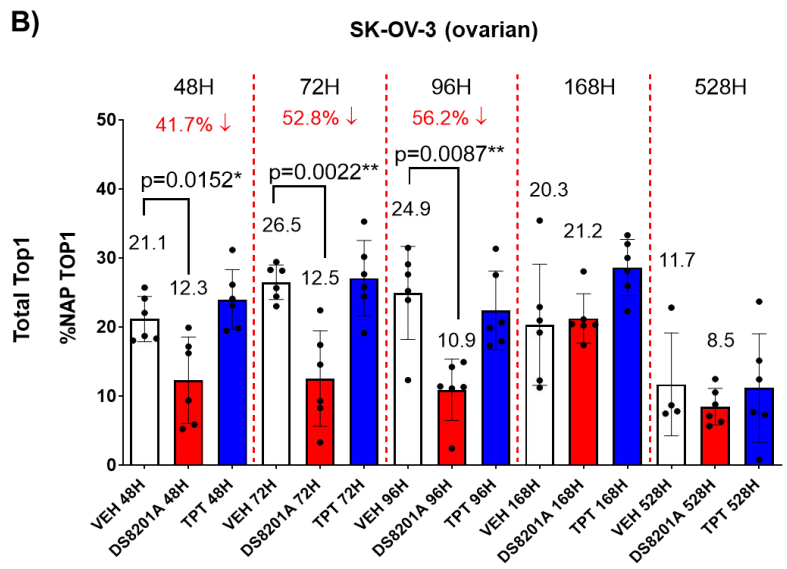


Figure 7 (continued). PADIS Top1cc and total Top1 IFA data demonstrate robust modulation of total Top1, but not Top1cc, following DS-8201a treatment in HER2-positive xenograft models. MDA-MB-361 (breast) and SK-OV-3 (ovarian) HER2-positive xenograft models were treated with a single dose of vehicle, topotecan (TPT, 4.7 mg/kg), or DS-8201a (10 mg/kg), and tumors were harvested for analysis at the indicated post-dose time points. Top1cc and total Top1 were measured at 2-48 hours post-dose (**A**), and a total Top1 was evaluated in a separate, extended time course experiment over 48-528 hours post-dose (**B**). Each data point represents the mean value for an individual animal; columns and error bars indicate mean and standard deviation values, respectively (n = 6 animals per treatment group).

2.3.1.2 ImmunoPD

There are no published data to date demonstrating that the immunomodulatory effects of DS-8201a that have been observed preclinically are also detected in patient specimens. The PADIS lab at FNLCR is also developing clinically fit-for-purpose multiplex IFAs to measure immune-related pharmacodynamic (PD) biomarkers, including PD-L1, CD8, phospho-CD3ζ (p-CD3ζ, indicative of the activating phosphorylation of the T cell receptor [TCR] zeta chain), and phospho-ZAP70 (pZAP70, a biomarker integrating the opposing signals of T cell activation and extrinsic apoptosis pathway activation), together with tumor segmentation using the tumor marker β-catenin to identify whether each immune biomarker signal is localized to tumor. These PADIS immunoPD assays will be used in this biomarker-driven trial of single-agent DS-8201a to measure for the first time tumor immune pharmacodynamic responses to this agent in patients.

Assessing the pharmacodynamic response to immunomodulatory agents such as DS-8201a is challenging, as it requires analysis of both immune cell and cancer cell populations. The PADIS immunoPD multiplex immunofluorescence assays use novel oligo-conjugated antibodies (obtained from Ultivue, Inc.) for simultaneous quantitation of T cell receptor activation (phospho[p]-CD3ζ), immune checkpoint signaling via PD-1 (p-SHP1/p-SHP2), and the net stimulation/inhibition resulting from the integration of these two pathways in CD8 cells (p-ZAP70), while also providing the proximity of CD8 cells to tumor tissue identified by β-catenin. This method has been validated *ex vivo* using CD3+ PBMCs isolated from healthy human donor blood specimens and stimulated

with anti-CD3/CD28 beads (**Figure 8**), as well as clinically using custom tissue microarrays (TMA) containing tumor biopsies from patients with colorectal carcinoma (CRC), non-small cell lung cancer (NSCLC), or breast cancer (**Figure 9**).

Immunomodulation by DS-8201a will be assessed by comparing the distribution (tumor vs. surrounding stroma) and numbers of CD8 T cells in post-treatment vs. baseline biopsy specimens. In addition, reportable endpoints for CD8 T cell activation are still being explored, but one option is to report the extent of T cell activation as defined by the percentage of infiltrating tumor-adjacent CD8 T cells that are positive for p-ZAP70. The p-ZAP70 signal in CD8 T cells will be "thresholded" based on positive and negative T cell controls, allowing patient data to be reported as percent CD8 T cells with net positive or negative p-ZAP70 signal.

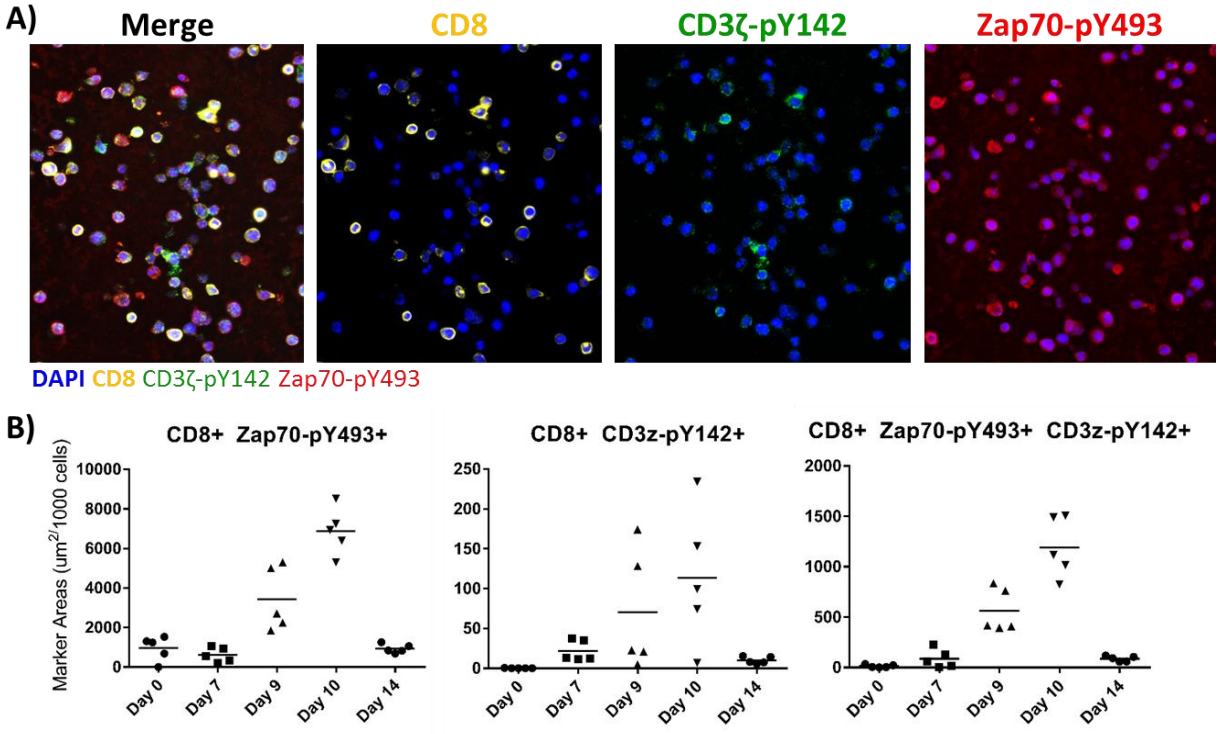


Figure 8. *Ex vivo* validation of the PADIS multiplex immunoPD IFA using CD3 cells stimulated with anti-CD3/CD28 beads. PBMCs were isolated from healthy donor blood specimens using density gradient centrifugation, and CD3+ T cells were isolated from the resulting PBMCs using the Dynabeads Untouched Human T-cell kit (Invitrogen). The isolated CD3+ PBMCs were *ex vivo*–stimulated with Dynabeads Human T-activator CD3/CD28 (Gibco) beads for 14 days; aliquots of cells were collected on the indicated days, fixed, and imaged. **A,** Representative images of CD3+ PBMCs on day 9 of *ex vivo* Dynabead stimulation, showing staining for CD8, phospho (p)-Y142-CD3ζ, and pY493-ZAP70; the merged image allows for identification of CD8+ T cells with activated TCR and/or activated downstream ZAP70 signaling. **B**, Quantitation of CD8+ T cells positive for phospho-Y493-ZAP70, phospho-Y142-CD3ζ, or both at the indicated time points following *ex vivo* Dynabead stimulation. All data shown are unpublished.

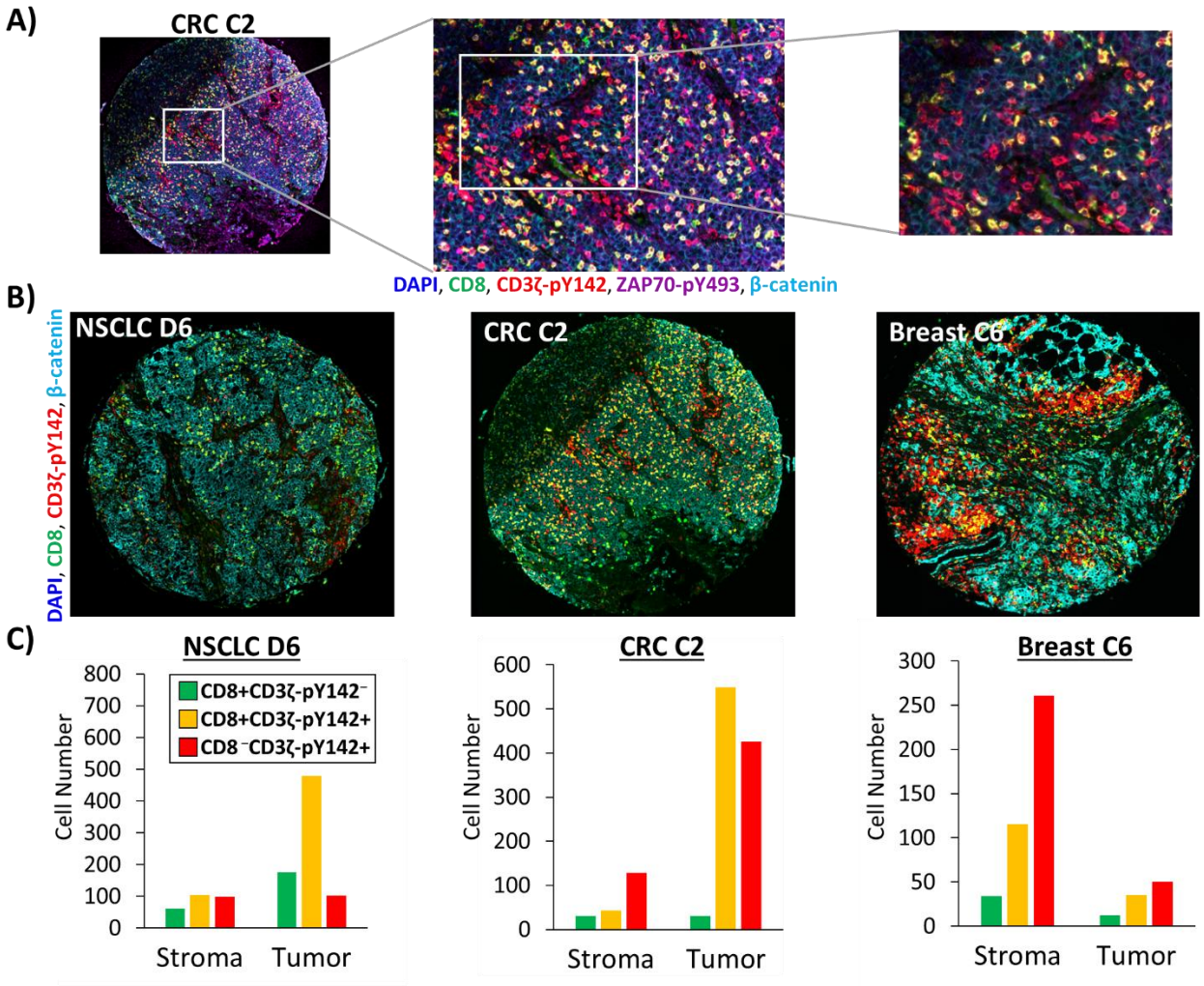


Figure 9. Clinical validation of the PADIS multiplex immunoPD IFA using TMAs consisting of untreated patient CRC, NSCLC, or breast tumors. **A,** immunoPD IFA images of a CRC TMA core ("CRC C2"), showing various magnification images of tumor tissue stained with DAPI and for CD8, pY142-CD3ζ, pY493-ZAP70, and the tumor marker β-catenin (colored as indicated in the center image). **B** and **C,** immunoPD IFA images (**B**) and biomarker quantitation (**C**) from Definiens analysis of example tumor cores from the NSCLC (left), CRC (middle), and breast (right) TMAs, showing staining with DAPI and for CD8, pY142-CD3ζ, and the tumor marker β-catenin. Use of the tumor marker enables determination of biomarker expression in the stroma versus tumor, while the multiplex analysis enables quantitation of CD8-negative cells and CD8-positive that are positive or negative for pY142-CD3ζ. All data shown are unpublished.

2.3.2 Genetic analysis

Blood for circulating tumor DNA (ctDNA) analysis will be collected before treatment, throughout the trial, and at the time of disease progression. Once a patient has come off study, ctDNA from blood samples correlating to clinically informative time points (before treatment, at the time of

each biopsy, and at restaging scans suggesting tumor growth) will be analyzed by MoCha with the TSO500 targeted sequencing assay to quantitatively assess longitudinal changes in ctDNA levels (as a percentage of total circulating, cell-free DNA) and to identify any mutations that may be associated with DS-8201a sensitivity or resistance.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

3.1.2 Patients must have measurable or evaluable disease.

3.1.3 Age ≥18 years of age.

3.1.4 Patients must have HER2-positive or HER2-expressing tumors as defined by CLIA-certified labs. Patients must have either:

- a tumor HER2 IHC score of 1+ or greater (as determined by a CLIA-certified IHC test, per criteria specified in [8]) or
- a tumor with *HER2* amplification (as determined by CLIA-certified ISH or a CLIA-certified next-generation sequencing assay).

Patients with *HER2* mutations are eligible, as are patients with HER2-positive breast cancer.

3.1.5 Patients must have ECOG performance status ≤ 1 (Karnofsky ≥70%; see Appendix A).

3.1.6 Patients must have normal organ and marrow function within 8 days of enrollment, as defined below:

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– leukocytes	≥3,000/mcL
– hemoglobin	≥9 g/dL (≥8.0 g/dL for gastric cancer **[GC] only**)
– serum albumin	≥2.5 g/dL **(GC Only)**
– total bilirubin	≤1.5 X institutional upper limit of normal (≤3 × upper limit of normal in the presence of documented Gilbert's syndrome or liver metastases at baseline)
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal OR ≤5 X institutional upper limit of normal for

patients with liver metastases at baseline

- creatinine ≤1.5X institutional upper limit of normal

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above 1.5X institutional normal

- No transfusions with red blood cells or platelets are allowed within 1 week prior to screening assessment.
- No administration of G-CSF is allowed within 1 week prior to screening assessment.
- International normalized ratio (INR)/Prothrombin time (PT) and either partial thromboplastin or activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.1.8 Willingness to provide blood samples for research purposes.

3.1.9 Patients must have a lesion or lesions amenable to biopsy and must be willing to undergo 3 core needle biopsy procedures for research purposes.

3.1.10 Patients must have left ventricular ejection fraction (LVEF) ≥ 50% by either an echocardiogram (ECHO), multigated acquisition (MUGA), or cardiac MRI scan within 28 days prior to enrollment.

3.1.11 Patients receiving standard of care androgen deprivation treatment (surgical castration versus LHRH agonist or antagonist treatment) are eligible to participate in the trial. Patients receiving LHRH agonist or antagonist may continue treatment throughout the duration of this study.

3.1.12 Patients who are Human Immunodeficiency Virus (HIV) positive may participate IF they meet the following eligibility requirements:

1. They must be stable on their anti-retroviral regimen, and they must be healthy from an HIV perspective.
2. They must have a CD4 count of greater than 250 cells/mcL over the past 6 months on this same anti-retroviral regimen and must not have had a CD4 count <200 cells/µl over the past 2 years, unless it was deemed related to the **cancer and/or immunotherapy-induced** bone marrow suppression.
   - For patients who have received chemotherapy in the past 6 months, a CD4 count <250 cells/µl during chemotherapy is permitted as long as viral loads were undetectable during this same chemotherapy.
3. They must have an undetectable viral load and a CD4 count ≥250 cells/µL within 8 days of enrolment.
4. They must not be currently receiving prophylactic therapy for an opportunistic infection and must not have had an opportunistic infection within the past 6 months.

HIV-infected patients should be monitored every 12 weeks for viral load and CD4 counts.

3.1.13 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.14 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.15 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression for ≥1 month after treatment of the brain metastases.

3.1.16 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.17 The effects of DS-8201a on the developing human fetus are unknown. For this reason and because HER2 antibodies conjugated to topoisomerase 1 inhibitor agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence; see Appendix E) prior to study entry and for the duration of study participation and for at least 7 months after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of DS-8201a administration. For methods considered as highly effective methods of contraception please refer to Appendix E.

3.1.18 Women of non-child-bearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<147 pmol/L] is confirmatory) are eligible. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for women of child-bearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

3.1.19 Subjects must not freeze, donate, or retrieve for their own use ova or sperm starting at screening, throughout the study period, and for at least 4.5 months after the final study drug administration. Preservation of sperm or ova should be considered prior to enrollment in this study.

3.1.20 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with DS-8201a, breastfeeding should be discontinued if the mother is treated with DS-8201a.

3.2 Exclusion Criteria

3.2.1 Patients who have had:

- Chemotherapy (including antibody drug therapy, retinoid therapy, hormonal therapy for cancer—with the exception of standard of care androgen deprivation treatment, as noted in section 3.1.11) within:
    - 4 weeks or five half-lives, whichever is shorter, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel *or*
    - 6 weeks for nitrosoureas or mitomycin C *or*
- Immunotherapy, including monoclonal antibody therapy, within 4 weeks.

3.2.2 Patients with any of the following pulmonary-related illnesses:

- A history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, current ILD/pneumonitis, or for whom suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within three months of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease (COPD) grade 3-4 per GOLD criteria, restrictive lung disease, pleural effusion, etc.), and any autoimmune, connective tissue, or inflammatory disorders with potential pulmonary involvement (i.e., Rheumatoid arthritis, Sjogren's, sarcoidosis, etc.), or prior pneumonectomy.

3.2.3 Patients who have had radiation therapy within 4 weeks (or palliative stereotactic radiation therapy within 2 weeks).

3.2.4 Patients who have had a major surgery within 4 weeks.

3.2.5 Patients who are receiving any other investigational agents.

3.2.6 Patients with a medical history of myocardial infarction within 6 months before enrollment, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV), or with troponin levels consistent with myocardial infarction (as defined according to the assay manufacturer) 28 days prior to

enrollment.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to DS-8201a (e.g., other topoisomerase I inhibitors) or the inactive ingredients in the drug product.

3.2.8 Patients who have a history of severe hypersensitivity reactions to other monoclonal antibodies.

3.2.9 Patients with a Fridericia's formula–corrected QT interval (QTcF) prolongation to >470 ms (females) or >450 ms (males) based on average of the screening triplicate 12-lead ECG.

3.2.10 Patients with spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.

3.2.11 Patients with an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

3.2.12 Patients with unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities (e.g., Grade 2 chemotherapy-induced neuropathy) may be eligible per the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee. Subjects should no longer be symptomatic nor require treatment with corticosteroids or anticonvulsants and must have recovered from the acute toxic effect of radiotherapy

3.2.13 Patients with substance abuse or any other medical conditions that would increase the safety risk to the subject or interfere with participation of the subject or evaluation of the clinical study in the opinion of the Investigator.

3.2.14 Patients with uncontrolled intercurrent illness.

3.2.15 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.16 Pregnant women are excluded from this study because DS-8201a is a HER2 antibody conjugated to a topoisomerase 1 inhibitor agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with DS-8201a, breastfeeding should be discontinued if the mother is treated with DS-8201a.

3.2.17 Patients are not allowed to receive chloroquine/hydroxychloroquine. Patients receiving chloroquine/hydroxychloroquine require a washout of > 14 days.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Research Eligibility Evaluation

Patient eligibility screening tests will be performed as described below. Eligibility history, physical examination, laboratory evaluations, urinalysis, and ECG are to be conducted within 8 days prior to enrollment. As noted in Section 5, if protocol therapy is started within 8 days of these eligibility screening evaluations, values from the screening evaluations may be used as baseline measurements; if >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, urinalysis, and ECG must be repeated prior to starting protocol therapy. Eligibility and baseline imaging scans, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments must be done within 28 days prior to enrollment and prior to the start of protocol therapy, respectively.

3.4.1 HER2 expression or *HER2* amplification status (as determined by CLIA-certified IHC or ISH/NGS) must be available prior to enrollment.

3.4.2 A complete history and physical examination (including height, weight, vital signs, and performance score) will be conducted within 8 days prior to both enrollment and protocol therapy. This will include evaluation of measurable disease and triplicate 12-lead ECG (taken in close succession [i.e., within approximately 2-5 minutes apart] while in a supine/semi-recumbent position).

3.4.3 Diagnostic imaging studies and ECHO (or MUGA or cardiac MRI) evaluation must be performed within 28 days prior to both enrollment and start of protocol therapy.

3.4.4 Laboratory Evaluation: baseline laboratory data are to be obtained within 8 days prior to both enrollment and start of protocol therapy:

- Hematological Profile: CBC with differential, hemoglobin, platelets.
- Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH
- Troponin-I
- Serum or urine pregnancy test for female participants of childbearing potential
- Urinalysis

3.4.5 Ophthalmologic assessments—including visual acuity testing, slit lamp examination, and fundoscopy—will be performed, only as clinically indicated, within 28 days prior to both enrollment and start of protocol therapy.

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR): MD, DO, or international equivalent,
- Non Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- Associate Plus (AP): clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,

- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status,
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster,
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number,

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and

Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org),
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *LAO-NCI*, and protocol number *10346*,

Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in

the Help Topics button in the DTL application and describes DTL task assignments, CI signature, and CTEP registration requirements, as well as including a Master Task List.

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of individuals is assigned to the task and have met the training requirements.

4.2.3 Checking Site Registration Status

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 **Patient Registration**

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study. Slots can be reserved for a maximum of 14 calendar days.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Following registration, patients should begin protocol treatment within 8 days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

4.3.2 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 **General Guidelines**

Following registration, patients should begin protocol treatment within 8 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not

receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5 TREATMENT PLAN

This is an open-label, pharmacodynamics-driven pilot trial of DS-8201a in patients with HER2-expressing refractory solid tumors whose disease has progressed on standard therapy that is known to be associated with a survival advantage or have disease for which there is no known standard therapy.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, laboratory evaluations, and triplicate ECG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and triplicate ECG must be repeated prior to starting protocol therapy. Baseline tumor imaging, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments must be performed within 28 days prior to start of protocol therapy. If protocol therapy is started within 28 days of the eligibility screening tumor imaging, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments, these screening evaluation results may be used as baseline measurements; if > 28 days have passed since the screening evaluation tumor imaging, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments, the imaging and ECHO (or MUGA or cardiac MRI) must be repeated prior to starting protocol therapy.

History and physical exam will be performed at baseline (within 8 days of the start of protocol therapy), during weeks 1 and 2 of cycle 1, and at the start of every cycle thereafter (+/- 1 day during the cycle and up to 3 days before start of a new cycle).

Labs (CBC with differential; serum chemistries, platelets) will be performed at baseline (within 8 days of the start of protocol therapy), during weeks 1 and 2 of cycle 1, and at the start (+/- 1 day during the cycle and up to 3 days before start of a new cycle) and during week 1 of every cycle thereafter.

For women of childbearing potential, a serum or urine pregnancy test will be conducted within 72 hours prior to DS-8201a administration at baseline, within 72 hours before the beginning of each cycle, and at end of treatment. A positive urine pregnancy test result must immediately be confirmed using a serum test.

ECHO (or MUGA or cardiac MRI) scan assessments (note: the same test must be used for the subject throughout the study) will be performed at baseline (within 28 days prior to the start of protocol therapy), within 7 days prior to infusion on Day 1 of Cycle 5, and then every 4 cycles (±7 days) thereafter: e.g., Cycle, 9, 13, 17, and so on.

Ophthalmologic assessments—including visual acuity testing, slit lamp examination, and fundoscopy—will be performed, only as clinically indicated, at baseline (within 28 days prior to the start of protocol therapy), at the end of treatment (for patients that return to clinic for the end-of-study visit), and as clinically indicated.

Troponin-I will be assessed at baseline, end of treatment, and as clinically indicated.

Triplicate ECG (taken in close succession [i.e., within approximately 2-5 minutes apart] while in a supine/semi-recumbent position) will be performed at baseline (within 8 days of the start of protocol therapy) and as clinically indicated.

Blood samples for correlative PD and PK studies, and for analysis of ADA, will be collected from all patients as described in Section 9.

CT scans will be performed at baseline (within 28 days of the start of protocol therapy); repeat-imaging scans will be performed every 3 cycles for disease restaging (every 4 cycles for patients on study for more than one year).

5.1 Agent Administration

DS-8201a will be administered intravenously at a dose of 5.4 mg/kg every 3 weeks (Q3W), in 21-day cycles, in an outpatient setting. DS-8201a dose rounding will be allowed as per institutional guidelines. Each subject's weight at screening (baseline) will be used to calculate the initial dose; if a subject's weight changes by ≥ ±10% of the baseline weight, the dose will be recalculated.

See Section 8.1 for detailed instructions on the preparation and dispensing of DS-8201a Solution for Infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. DS-8201a should be administered through central or peripheral venous access. When DS-8201a is administered via a peripheral vein, an alternate arm should be used for all PD and PK/ADA blood draws. If this is not possible, then the PD or PK/ADA draw should be as distal to the DS-8201a infusion site as possible. The site of the PK/ADA draws should be documented.

For the initial dose of DS-8201a on Cycle 1 Day 1, the entire contents of the DS-8201a IV bag will be infused at a constant rate over 90 minutes (± 5 minutes). The start and end time of IV infusion should be recorded accurately, particularly in Cycle 1 when PK assessments are performed. The infusion line may be flushed with 5% Dextrose in Water, USP only, immediately after administration as per institutional guidelines. The volume of 5% Dextrose in Water, USP only, solution used for line flushing is not considered part of the volume of the DS-8201a IV bag to be documented. The subject's weight at screening (baseline) will be used to calculate the initial dose. If the subject's weight changes by ± 10% of the baseline weight, the dose will be recalculated.

If there is no infusion related reaction after initial dose, all subsequent doses of DS-8201a will be infused intravenously into each subject over 30 minutes (± 5 minutes).

The infusion may be slowed or stopped and restarted for any associated infusion reactions. All

infusion times must be recorded. DS-8201a should be infused immediately after infusion solution preparation if possible, but the prepared infusion solution may be stored at room temperature for up to 4 hours in total. This 4 hour period is from dilution start time until the start of infusion.

Patients must be monitored for adverse reactions after drug infusions during cycle 1; if no fusion-related adverse reactions occur during cycle 1, infusion monitoring may be discontinued for cycle 2 and beyond. Vital signs monitoring will be performed +/- 5 minutes from the following time points during cycle 1: prior to the start of infusion, 30 minutes after start of infusion, at completion of infusion, and 90 minutes after completion of infusion). For patients that exhibit infusion-related adverse reactions during cycle 1, vital signs monitoring for cycle 2 and beyond will be performed +/- 5 minutes from the following time points: prior to the start of infusion, 30 minutes after start of infusion, every 30 minutes thereafter until completion of infusion (if infusion time is ≥ 60 minutes), and 30 minutes after completion of infusion. Reported adverse events and potential risks are described in Section 7; patients will be encouraged to report all adverse events.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of DS-8201a with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions (see list of guidelines, below). The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Drug Interactions Handout and Wallet Card) should be provided to patients if available.

The following medications, treatment and procedures will be prohibited during the treatment period with DS-8201a:

1. Other anticancer therapy; including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anti-cancer hormonal treatment (with the exception of standard of care androgen deprivation treatment; see section 3.1.11).
2. Other investigational therapeutic agents.
3. Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in Section 6).
4. Radiotherapy to the thorax.
5. Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing adverse events; (Inhaled steroids or intra articular steroid injections are permitted in this study.)
   - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.

The following are other protocol restrictions:

1. Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the investigator.
2. Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged, but not prohibited.
3. Prophylactic or supportive treatment of study-drug induced adverse events will be otherwise as per investigator's discretion and institutional guidelines.
4. Consideration should be given to avoid concomitant use of strong inhibitors of MATE2-K, P-gp, BCRP, or MRP1.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Significant toxicity occurs despite 2 dose reductions or no lower dose level exists
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgement of the investigator
- Clinical progression
- Patient non-compliance
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up

Patients will be followed for 40 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The evaluation of toxicities at follow-up will consist of a phone call between Days 37-40 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drug that have not resolved or

stabilized by Day 40 post-treatment will be followed until stabilization or resolution via phone calls as clinically indicated. In addition to the follow-up telephone evaluation of toxicities, patients will be requested to return for a 40-day follow-up clinic visit (± 7 days) for end-of-treatment eye exams and for collection of blood samples for exploratory ADA analysis.

5.5 Criteria for Removal from Study

Patients will be removed from the study for one of the following reasons:

- Completion of 40-day post treatment follow-up period
- Toxicities are unresolved but stabilized
- Patient enrolls on another protocol
- Patient receives standard of care
- Pregnancy
- Death

The reason for study removal and the date the patient was removed must be documented in the medical record.

6 DOSING DELAYS/DOSE MODIFICATIONS

All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity (CTCAE version as specified in Section 7.1). Appropriate clinical experts should be consulted as deemed necessary.

Doses of DS-8201a will be held or modified for adverse events that are felt to be at least possibly related to study drug or if a patient has serious medical condition regardless of attribution to drug. A dose can be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a subject is assessed as requiring a dose delay of longer than 28 days, the subject will be withdrawn from the study. Treatment cycles for a subject for whom DS-8201a dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last trastuzumab deruxtecan dose.

Patients will be allowed 2 dose reductions, to 4.4 mg/kg and then 3.2 mg/kg IV every 3 weeks, in 21-day cycles, based on the original phase 1 dose escalation trial of DS-8201a [3] (see table below). Patients who require a dose reduction will not have the dose re-escalated. More than 2 dose reductions are not allowed, and the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

Dose Reduction Schema (21-day cycles)	
Dose level	**DS-8201a (mg/kg IV every 3 weeks)**
-2	3.2
-1	4.4
1 (starting)	5.4

6.1 Dose Interruption and Modification/Toxicity Management Guidelines

A dose can be delayed for up to 28 days from the planned date of administration. If a subject is assessed as requiring a dose delay of longer than 28 days, the subject will be withdrawn from the protocol therapy.

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the CTEP Medical Monitor.

For studies using NCI-CTCAE version 5.0:

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
No toxicity	Maintain dose and schedule
Infusion-Related Reaction	
Grade 1 (Mild transient reaction, infusion interruption not indicated, intervention not indicated)	• If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (*e.g.,* antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs)	• Administration of DS-8201a should be interrupted and symptomatic treatment started (*e.g.* antihistamines, NSAIDs, narcotics, IV fluids). • If the event resolves or improves to grade 1, infusion can be re-started at a 50% reduced infusion rate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	• Administration of DS-8201a should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation *etc.,* should be administered.
Hematologic Toxicity	
Neutrophil Count Decrease and/or White Blood Cell Count Decrease	
Grade 3	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 3 white blood cell count decrease in the presence of Grade 3-4 neutropenia for ≥ 5 days	Delay dose until resolved to ≤ Grade 2, Reduce dose 1 level
Grade 4	Delay dose until resolved to ≤ Grade 2, Reduce dose 1 level
Febrile Neutropenia (absolute neutrophil count <1 x 10^9/L, fever >38.3°C or a sustained temperature of ≥38 °C for more than one hour)	Delay dose until resolved, Reduce dose by 1 level

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (<0.2 x 10^9/L)	Delay dose until resolved to ≤Grade 2: - If resolved in ≤14 days from day of onset, maintain dose - If resolved in >14 days from day of onset, reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin (Hb) <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (platelets <50 – 25 x 10^9/L)	Delay dose until resolved to ≤ Grade 1: - If resolved in ≤7 days from day of onset, maintain dose - If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (platelets < 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic LVEF decrease or congestive heart failure (CHF)	Discontinue subject from study treatment
Decrease in Left ventricle ejection fraction (LVEF) 10-20% (absolute value), but LVEF >45%	Continue treatment with DS-8201a
LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	Continue treatment with DS-8201a Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤45% and decrease is ≥10% (absolute value) from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, discontinue subject from study treatment
LVEF <40% or >20% (absolute value) drop from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment
QTc Prolongation	
Grade 3 (Average QTc >500 ms or >60 ms change from baseline)	Delay dose until resolved to ≤ Grade 1 (QTc ≤480 ms), determine if another medication the subject was taking may be responsible and can be adjusted, then if attributed to DS-8201a, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment
Pulmonary Toxicity	<u>Guidelines for workup and management</u> If a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
	other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD/pneumonitis. (If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below). If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • high resolution CT • pulmonologist consultation (Infectious Disease consultation as clinically indicated) • blood culture and CBC. Other blood tests could be considered as needed. • consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • pulmonary function tests and pulse oximetry (SpO_2) • arterial blood gases if clinically indicated • one blood sample collection for PK and exploratory biomarkers analysis as soon as ILD is suspected, if feasible. • other tests could be considered, as needed. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. The administration of trastuzumab deruxtecan must be interrupted for any ILD events regardless of grade.
Grade 1	• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (e.g., at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* Delay dose until resolved to Grade 0, then: - If resolved in ≤28 days from day of onset, maintain dose - If resolved in >28 days from day of onset, reduce dose 1 level

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
	However, if the event grade 1 ILD/pneumonitis occurs beyond day 22 of any cycle and has not resolved within 49 days from the last infusion, the drug should be discontinued. * If patient is asymptomatic, then patient should still be considered as Grade 1 even if steroid treatment is given. For further management, see guidance above.
Grade 2	• Permanently discontinue subject from study treatment. • Promptly start systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks. • Monitor symptoms closely. Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent), and administration may be switched to intravenous (e.g., methylprednisolone). • Re-consider additional work-up for alternative etiologies as described above. • Escalate care as clinically indicated. For further management, see guidance above.
Grade 3 or 4	• Permanently discontinue subject from study treatment. • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, o Re-consider additional work-up for alternative etiologies as described above. o Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Renal Toxicity (serum creatinine)	
Grade 3 (>3.0 to 6.0 × upper limit of normal [ULN])	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose 1 level
Grade 4 (>6.0 × ULN)	Discontinue subject from study treatment
Hepatic Toxicity	
Aspartate transaminase (AST) or alanine transaminase (ALT) with simultaneous Total bilirubin (TBL)	
AST/ALT ≥3.0 × ULN with simultaneous TBL >2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out.

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
	• If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. • If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. • Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.
Aspartate transaminase (AST) or alanine transaminase (ALT)	
Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1, then: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 3 (>8.0 - 20.0 × ULN if baseline was normal; >8.0 - 20.0 × baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was > 3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Total Bilirubin	
Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: - If resolved in ≤7 days from day of onset, maintain dose - If resolved in >7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (>3.0 - 10.0 × ULN if baseline was normal; >3.0 - 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1: - If resolved in ≤7 days from day of onset, reduce dose 1 level - If resolved in >7 days from day of onset, discontinue DS-8201a If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 2: - If resolved in ≤7 days from day of onset, reduce dose 1 level - If resolved in >7 days from day of onset, discontinue DS-8201a
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Alkaline Phosphatase Increased	
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) or Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤3 days from day of onset, maintain dose If resolved in >3 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other Non-Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

All dose modifications should be based on the worst preceding toxicity.
CTCAE: Common Terminology Criteria for Adverse Events.

In addition, Investigators may consider dose reductions or discontinuations of the study drug according to the subject's condition and after discussion with the CTEP Medical Monitor.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following sub-sections will determine whether the event requires expedited reporting (via Rave-CTEP-AERS integration) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks

The Comprehensive Adverse Event and Potential Risks (CAEPR) list provides a single, complete list of reported and/or potential AEs associated with an agent, using a uniform presentation of events by body system.

7.1.1 CAEPR for DS-8201a

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
DS-8201a (NSC 807708)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1703 patients.* Below is the CAEPR for DS-8201a.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, September 18, 2024[1]

Adverse Events with Possible Relationship to DS-8201a (CTCAE 5.0 Term) [n= 1703]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
		Febrile neutropenia	
CARDIAC DISORDERS			
	Left ventricular systolic dysfunction		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
GASTROINTESTINAL DISORDERS			
	Abdominal distension Abdominal pain		
Constipation			***Constipation (Gr 2)***

Adverse Events with Possible Relationship to DS-8201a (CTCAE 5.0 Term) [n= 1703]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Diarrhea			*Diarrhea (Gr 2)*
	Dyspepsia		
	Mucositis oral		*Mucositis oral (Gr 2)*
Nausea			*Nausea (Gr 2)*
Vomiting			*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			*Fatigue (Gr 2)*
	Fever		*Fever (Gr 2)*
	Malaise		*Malaise (Gr 2)*
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatic function abnormal)		
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		*Upper respiratory infection (Gr 2)*
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		*Aspartate aminotransferase increased (Gr 2)*
	Blood bilirubin increased		
	Ejection fraction decreased[2]		
	GGT increased		
	Lymphocyte count decreased		*Lymphocyte count decreased (Gr 2)*
Neutrophil count decreased			*Neutrophil count decreased (Gr 3)*
Platelet count decreased			*Platelet count decreased (Gr 4)*
	Weight loss		*Weight loss (Gr 2)*
White blood cell decreased			*White blood cell decreased (Gr 4)*
METABOLISM AND NUTRITION DISORDERS			
Anorexia			*Anorexia (Gr 2)*
	Hypokalemia		*Hypokalemia (Gr 2)*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			

Adverse Events with Possible Relationship to DS-8201a (CTCAE 5.0 Term) [n= 1703]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Epistaxis		
	Respiratory, thoracic and mediastinal disorders - Other (pneumonitis/interstitial lung disease)[3]		***Respiratory, thoracic and mediastinal disorders - Other (pneumonitis/interstitial lung disease)[3] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Pruritus		
	Rash maculo-papular		
	Skin hyperpigmentation		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The frequencies of infusion related reaction and ejection fraction decreased are <3%.

[3]Pneumonitis/interstitial lung disease is considered an important identified risk and can, in rare instances, be life-threatening or fatal.

Adverse events reported on DS-8201a trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that DS-8201a caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Pericardial effusion; Pulmonary valve disease; Restrictive cardiomyopathy
GASTROINTESTINAL DISORDERS - Anal stenosis; Ascites; Colitis; Colonic obstruction; Colonic perforation; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastric stenosis; Gastritis; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (gastrointestinal mucosa hyperemia); Gastrointestinal disorders - Other (gastrointestinal obstruction);

Gastrointestinal disorders - Other (gastrointestinal ulcer); Gastrointestinal disorders - Other (inguinal hernia); Gastrointestinal disorders - Other (intra-abdominal hematoma); Ileus; Lower gastrointestinal hemorrhage; Obstruction gastric; Pancreatitis; Rectal hemorrhage; Rectal obstruction; Rectal ulcer; Small intestinal obstruction; Small intestinal perforation; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Disease progression; Edema limbs; Flu like symptoms; General disorders and administration site conditions - Other (general physical health deterioration); Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis; Cholecystitis; Gallbladder perforation; Hepatic failure; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (cholangitis); Hepatobiliary disorders - Other (jaundice cholestatic); Portal vein thrombosis
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Abdominal infection; Anorectal infection; Bacteremia; Biliary tract infection; Bone infection; Device related infection; Enterocolitis infectious; Fungemia; Hepatitis viral; Infections and infestations - Other (cholangitis infective); Infections and infestations - Other (diverticulitis); Infections and infestations - Other (lower respiratory tract infection); Infections and infestations - Other (lymphangitis); Infections and infestations - Other (parotitis); Joint infection; Kidney infection; Lung infection; Peritoneal infection; Pleural infection; Scrotal infection; Sepsis; Skin infection; Soft tissue infection; Urinary tract infection; Wound infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture; Injury, poisoning and procedural complications - Other (gastrointestinal stoma complication); Injury, poisoning and procedural complications - Other (radiation necrosis); Tracheal obstruction
INVESTIGATIONS - CD4 lymphocytes decreased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Flank pain; Generalized muscle weakness; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (pericarditis malignant); Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Meningismus; Nervous system disorders - Other (central nervous system lesion); Nervous system disorders - Other (hemiplegia); Nervous system disorders - Other (peroneal nerve palsy); Paresthesia; Peripheral sensory neuropathy; Presyncope; Seizure; Spinal cord compression; Transient ischemic attacks
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (genital hemorrhage)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Hypoxia; Pleural effusion; Pneumothorax; Productive cough; Pulmonary edema; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (angioedema)
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Lymphedema; Thromboembolic event; Vascular disorders - Other (aneurysm ruptured); Vascular disorders - Other (shock haemorrhagic)

Note: DS-8201a in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously

associated with either agent.

7.2 Adverse Event Characteristics

7.2.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1) should be reported through Rave-CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*, and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during

trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL</u> <u>SAEs</u> that meet the above criteria **<u>MUST</u>** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via Rave-CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4).

CTCAE SOC	Adverse Event	Grade	≥24 h Hospitalization[a]
Investigations	lymphocyte count decreased	any	regardless
Skin and subcutaneous tissue disorders	alopecia	any	regardless
Investigations	Activated partial thromboplastin time prolonged, without bleeding	1-3	regardless

CTCAE SOC	Adverse Event	Grade	≥24 h Hospitalization[a]
Metabolism and nutrition disorders	hypercalcemia, hypocalcemia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypernatremia, hyponatremia, hyperphosphatemia, hypophosphatemia	1-3	no

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through Rave-CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **Rave-CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via Rave-CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.8 Overdose

Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either a serious adverse event, a non-serious adverse event, or no adverse event occurs and is considered by the investigator as clinically relevant, i.e., poses an actual or potential risk to the subject.

Details of any occurrence of overdose, including DS-8201a dose administered, clinical course, associated AEs, seriousness, and outcome must be captured in the eCRF. In the event of an overdose, an additional blood sample for PK analysis will be collected. Dosing errors in the absence of adverse events will be reported as protocol deviations.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational administered in this study can be found in Section 7.

8.1 DS-8201a (NSC 807708)

Chemical Name or Amino Acid Sequence: N-[6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-[(2-{[(1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12Hbenzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl]amino}-2-oxoethoxy)methyl]glycinamide

Other Names: Trastuzumab deruxtecan, Enhertu®, T-DXd, fam-trastuzumab deruxtecan-nxki

Classification: DS-8201a is a human epidermal growth factor receptor 2 (HER2)-targeted antibody and topoisomerase I inhibitor conjugate.

Molecular Formula: $C_{52}H_{56}FN_9O_{13}$ **M.W.:** 150 kDa

Description: DS-820a is composed of a recombinant humanized antihuman epidermal growth factor receptor 2 (anti-HER2) immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that has the same amino acid sequence of trastuzumab, covalently conjugated to a drug-linker, deruxtecan (DXd).

Mode of Action: DS-8201a exhibits antitumor activity through the released drug, DXd, inducing deoxyribonucleic acid (DNA) damage and apoptosis by topoisomerase I inhibition. T-DXd also exhibits antibody-dependent cellular cytotoxic (ADCC) activity and HER2-mediated Akt phosphorylation inhibition.

How Supplied: DS-8201a is supplied by Daiichi Sankyo and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as a white to yellowish-white sterile lyophilized powder dosage form in a single-use amber borosilicate (Type I) glass vial. Each vial contains 100 mg of DS-8201a with L-histidine, L-histidine hydrochloride monohydrate, sucrose, and polysorbate 80. Each vial is packaged in a single vial carton.

Preparation: Each 100 mg vial of DS-8201a lyophilized powder is to be reconstituted with 5 mL of water for injection to 20 mg/mL. Gently swirl the solution until all solids are dissolved. Do not vigorously agitate the vial. The reconstituted solution should appear clear and colorless to light yellow. Visually inspect the solution to ensure that the entire content of the lyophilized cake is completely reconstituted. DS-8201a is further diluted with 5% Dextrose in Water, USP to a concentration between 1 mg/mL and 6.7 mg/mL. Immediately following reconstitution, add the calculated volume of DS-8201a solution to a 100 mL or 250 mL bag of 5% Dextrose in Water, USP. Invert the bag gently to thoroughly mix the contents, **do not shake the bag**. Cover the infusion bag with a light protection cover.

Note: It is recommended to use the prepared infusion immediately. If not used immediately, the storage period must not be longer than 24 hours at 2°C to 8ºC with protection from light. This 24-hour period is from vial reconstitution start time until the start of infusion.

Note: It is recommended that the infusion solution be allowed to reach room temperature prior to administration, to ensure that the infusion is comfortable for the patient. The prepared infusion solution may be stored at room temperature for up to 4 hours in total. This 4-hour period is from vial reconstitution start time until the start of infusion.

Note: The patient's weight at screening (baseline) will be used to initially calculate the dose. If the patient's weight changed by $\geq \pm$ 10% of the baseline weight, the dose will be recalculated.

Storage: Store vials of DS-8201a at 2°C to 8°C in their cartons (protected from light) until the time of preparation.

If a storage temperature excursion is identified, promptly return DS-8201a to 2°C to 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of

temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

> *CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. The reconstituted product must be diluted in 5% Dextrose in Water, USP immediately following reconstitution. Any unused product is to be destroyed per institutional policy.*

Route of Administration: intravenous (IV) infusion

Method of Administration: The initial IV infusion is administered over 90 minutes. If there are no infusion related reactions, subsequent infusions are administered over at least 30 minutes. Flush tubing with 5% Dextrose in Water, USP only. A 0.2 or 0.22 micron filter is mandatory for administration.

Potential Drug Interactions: DXd (released drug from DS-8201a) is primarily metabolized by CYP3A4. DXd did not show any potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. DXd did not show any potential to induce CYP3A4, CYP1A2, and CYP2B6 at clinically relevant concentrations.

In vitro DXd is a substrate for OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP1. DXd did not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, and BSEP in nonclinical PK studies.

Study DS8201-A-A104 suggested that strong CYP3A4 inhibitors (eg, boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, telaprevir, telithromycin, and voriconazole) or OATP1B inhibitors (eg, lopinavir/ritonavir, cyclosporine, and rifampicin) can be administered without dose adjustment.

Incompatibilities: DS-8201a is compatible with syringes, infusion bags, and administration sets made of the following materials: polypropylene, polyolefin, polyvinyl chloride (PVC), polysulfone, polyurethane, polyether sulfone, polytetrafluoroethylene, polyethylene terephthalate, polycarbonate, polyisoprene and polyacetal.

DS-8201a is not compatible with saline solutions.

Patient Care Implications: Female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months after the last dose of study drug. Do not breastfeed during treatment with DS-8201a and for 7 months after the last dose. Males involved with women of childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4 months after the last dose of study drug.

Assess LVEF prior to initiation of DS-8201a and at regular intervals during treatment. Permanently discontinue DS-8201a in patients with symptomatic congestive heart failure.

8.2 Agent Ordering

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.3 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9 CORRELATIVE/SPECIAL STUDIES

We plan to evaluate the pharmacodynamic effects of DS-8201a by examining tumor tissue from mandatory biopsies, with the primary endpoint of demonstrating engagement of the topoisomerase 1 target by the DS-8201a payload, using our assay for Top1 cleavable complex. We will also collect mandatory blood samples for PK analysis to examine associations between serum DS-8201a levels and tumor PD response. In addition, we will examine in an exploratory fashion levels of total Top1, DNA damage response markers (RAD51, pNBS1, γH2AX, and/or other markers of DDR), CD8+ T cell infiltration and activation (phospho-CD3ζ, and phospho-ZAP70), PD-L1, and HER2 (confirmatory testing using the Ventana IHC assay). We will also examine in an exploratory fashion the emergence and persistence of any anti-drug antibodies (ADA). Finally, we will perform exploratory targeted sequencing (Oncomine version 3) for confirmatory *HER2* amplification testing and to explore the molecular mechanisms of response and resistance to DS-8201a; we will also perform targeted sequencing analysis of blood specimens for circulating tumor DNA assessments.

9.1 Biomarker Plan

The following tables outline the aforementioned biomarker assays and respective tissue requirements. Mandatory biopsies will be performed up to 7 days prior to DS-8201a administration on cycle 1 day 1, cycle 1 48-96 hours post–day 1 dose, and up to 3 days prior to DS-8201a administration on cycle 3 day 1 (unless not feasible for safety reasons). In addition, an optional biopsy will be performed at time of disease progression or at "restaging follow-up"—i.e., on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles.

Table 1. Blood-based biomarker analyses.

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	PK	Ligand binding assay (DS8201-a and total antibody) and LC-MS/MS (deruxtecan) [12]	Integrated, To examine any associations between the magnitude of PD responses and serum concentrations of the ADC, free antibody, and free payload	M	C1D1 prior to DS-8201a administration, at end of infusion (up to 30 minutes post-infusion), and at 5 hours (± 30 minutes) post-infusion; at time of the cycle 1 on-treatment biopsy (± 3 hours); D1 of C2, C3, and C4 prior to DS-8201a administration and at end of infusion (up to 30 minutes post-infusion)	Peripheral whole blood	4 mL blood per time point, in a serum separation (gold-top) tube	Daiichi-Sankyo
2	ADA Analysis	Anti-drug antibody assay	Exploratory, To evaluate any anti-drug antibodies to DS-8201a	O	Up to 2 days prior to DS-8201a administration on cycle 1 day 1, cycle 2 day 1, and day 1 of cycle 4 and every 4 cycles thereafter; and at 40-day follow-up (± 7 days)	Peripheral whole blood	4 mL blood per time point, in a serum separation (gold-top) tube	Daiichi-Sankyo
3	Gene variants found in cell-free, circulating tumor DNA	Illumina TSO 500	Exploratory, Hypothesis generation: to evaluate DNA alterations found in cell-free, circulating tumor DNA and their potential correlation with response to DS-8201a	O	Baseline, at time of the cycle 1 on-treatment biopsy (± 24 hours), C3D1, progression/ restaging follow-up	Peripheral whole blood	7.5 mL blood per time point, in a 10-mL Streck tube	MoCha, FNCLR

Table 2. Tumor tissue-based biomarker analyses.

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	Total Top1	Top1 IFA CLIA: N No Review Required	Integrated, Proof-of-mechanism	M (Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1↓), O (progression/ restaging follow-up)	Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1↓, progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	PADIS, FNLCR
2†**	HER2	Ventana HER2 IHC CLIA: N No Review Required	Integrated (Baseline), Exploratory (progression/restaging follow-up) Proof-of-mechanism and to evaluate the effects of DS-8201a on tumor levels of HER2	M (Baseline) O (progression/ restaging follow-up)	Baseline, progression/ restaging follow-up**	tumor biopsy (FFPE‡)	three 4-µm tissue sections	NCLN laboratory, MD Anderson Cancer Center
3	Top1 cleavable complex	Top1cc IFA CLIA: N No Review Required	Exploratory, To be used together with total Top1 measurements to determine the fraction of Top1 inhibited by DS-8201a	O	Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1↓, progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	PADIS, FNLCR
4	DDR signaling (including biomarkers such as: γH2AX, RAD51, and pNbs1)	PADIS DDR3 and other DDR IFA panels CLIA: N No Review Required	Exploratory, To examine the effects of DS-8201a on DDR pathway activation	O	Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1↓, progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	PADIS, FNLCR or NCLN PD Assay Laboratory at MD Anderson
5	CD8+ T cell infiltration	PADIS immunoPD multiplex IFA CLIA: N No Review Required	Exploratory, To examine the effects of DS-8201a on the tumor immune microenvironment	O	Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1↓, progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	PADIS, FNLCR

6	CD8+ T cell activation (pZAP70 and pCD3ζ)	PADIS immunoPD multiplex IFA CLIA: N No Review Required	Exploratory, To examine the effects of DS-8201a on tumor-infiltrating T cell activation	O	Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1[ɻ], progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	PADIS, FNLCR
7	PD-L1	PADIS immunoPD multiplex IFA CLIA: N No Review Required	Exploratory, To examine the effects of DS-8201a on tumor PD-L1 expression	O	Baseline, Cycle 1 48-96 h post-day 1 dose, C3D1[ɻ], progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	PADIS, FNLCR
8	*HER2* amplification and other variants in the Oncomine version 3 panel	Oncomine version 3 CLIA: N No Review Required	Exploratory, To evaluate any associations between *HER2* amplification (and other genomic alterations) and response to DS-8201a	O, if remaining tissue is available after the above analyses are completed	Baseline, progression/ restaging follow-up	tumor biopsy (flash-frozen)	2-5*	MoCha, FNLCR

[ɻ]Mandatory biopsy at C3D1 can be canceled by PI if collection is not deemed medically justifiable (e.g.: to ensure patient safety).

[†]HER2 IHC (FFPE) will be the second-priority assay at baseline and first priority for optional progression/restaging follow-up biopsies. The first two cores at baseline should be flash-frozen, the third formalin fixed, and remaining cores flash frozen wherever possible.

*All PADIS assays **combined** will require 2-5 18-gauge, flash-frozen cores per time point; all of these cores will be embedded in the same tissue block, and no additional methods of core processing are required.

**For biopsies collected at time of progression or restaging follow-up, HER2 IHC will be the top-priority assay; the first biopsy core obtained will be formalin fixed and paraffin embedded for HER2 IHC, and any additional cores will be flash-frozen and used for PD analyses.

[‡]Under circumstances in which no FFPE core is available, exploratory HER2 IHC analysis may be performed on flash-frozen cores thawed into formalin.

9.2 Pharmacokinetic Assays

Blood samples for PK analysis will be collected for analysis of the full DS-8201a ADC, as well as the trastuzumab antibody component and the deruxtecan payload. PK measurements will be used for correlation with pharmacodynamic effects measured in tumor biopsy specimens and will therefore be collected at the time of each biopsy. All PK analyses for this study will be performed by Daiichi-Sankyo.

One 4-mL serum separation (gold-top) tube will be obtained for each of the time points, and the actual time of collection will be noted for each sample. **See Appendix B for reagents, procedures, and shipping instructions for PK studies**.

Blood will be collected at the following times:

- Cycle 1 day 1, prior to DS-8201a administration, at end of infusion (up to 30 minutes post-infusion), and at 5 hours (± 30 minutes) post-infusion
- At time of the cycle 1 on-treatment biopsy (± 3 hours relative to the biopsy procedure)
- On day 1 of cycles 2, 3, and 4: prior to DS-8201a administration and at end of infusion (up to 30 minutes post-infusion)

In addition, for patients experiencing interstitial lung disease, one optional blood sample collection for PK and exploratory biomarkers analysis may be collected as soon as ILD is suspected, if feasible.

Based upon the results of the initial measurements, sampling times may be adjusted but neither the total number of samples nor the total amount of blood will be increased.

9.3 Pharmacodynamic Assays in Tumor Tissue

9.3.1 Timing of Tumor Biopsies

Mandatory paired biopsies will be collected from all patients at the following time points:

- baseline (pre-treatment; up to 7 days prior to DS-8201a administration)
- cycle 1, 48-96 hours post-day 1 dose
- cycle 3 day 1, up to 3 days prior to DS-8201a administration (unless not feasible for safety reasons).
- optionally, at time of disease progression or "restaging follow-up"—i.e., on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles

9.3.2 Biopsy Procedure

Serial tumor biopsies will be obtained by the Interventional Radiology team. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology team, an attempt for biopsy will be made. Because approximately 20% of tumor biopsies collected on research trials are not usable due to the presence of stroma or normal and/or necrotic tissue and paired biopsies are necessary for analysis, up to 5 core biopsies ≥18-gauge in diameter and ≥1 cm in length will be obtained during each procedure to try and ensure adequate tumor content and quality. Cores from different areas of the tumor are preferred when feasible.

Acceptable biopsy procedures are:

- Percutaneous biopsy with local anesthetic.

- Excisional cutaneous biopsy with local anesthetic
- Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications < 2%

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and Interventional Radiology.

Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed.

9.3.3 Biopsy Processing

A webinar training session with PADIS staff will be held with each participating site prior to their first biopsy collection to review proper procedure. Each site should contact NCI_PD_Support@mail.nih.gov to initiate training and clarify shipping procedures.

For baseline mandatory biopsies:
Up to five tissue cores will be collected; **one baseline biopsy core is to be formalin fixed, while all remaining cores will be flash-frozen**. Priority should be given to flash-frozen tissue at baseline.

- **Flash-frozen cores (First 2 cores and cores 4 and 5 if available)** will be transferred into a 1.5-mL pre-chilled cryovial and then flash-frozen in liquid nitrogen per DCTD SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). In accordance with SOP340507, biopsy specimens are collected into pre-chilled 1.5-mL Sarstedt, O-ring screw cap tubes (VWR, Cat#: 83009-010) and then flash-frozen in liquid nitrogen or a dry ice/ethanol bath. It is ***imperative*** that biopsies are flash frozen *within 2 minutes of collection* in order to preserve key pharmacodynamic biomarkers. Samples will be submitted to the PADIS laboratory for evaluation of the aforementioned markers, as well as H&E pathology evaluation. The frozen biopsy specimens are transferred to PADIS on dry ice, where the core biopsy samples are stored at -80°C and subsequently processed within 7-10 days for analysis. Biopsy samples will be analyzed for PD biomarkers as described above; any additional cores will be flash-frozen and kept

for future analysis. The sample shipping manifest and batch record are included in SOP340507.

- **Formalin-fixed core (1 per patient, third core collected)** will be collected into jars filled with neutral buffered formalin (pre-filled 30 mL) pre-labeled with the participant ID, biopsy date, protocol number, and site of tissue biopsy. Formalin-fixed cores will be shipped on the day of collection via overnight courier at ambient temperature to Dr. Mickey Williams' laboratory (MoCha) at the Frederick National Laboratory for Cancer Research (FNLCR) as defined in Section 9.3.4.

For cycle 1 and cycle 3 mandatory biopsies:
Up to five tissue cores will be collected; all will be flash-frozen. The cores will be transferred into a 1.5-mL pre-chilled cryovial and then flash-frozen in liquid nitrogen per DCTD SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). Samples will be submitted to the PADIS laboratory for evaluation of the aforementioned markers, as well as H&E pathology evaluation. The frozen biopsy specimens are transferred to PADIS on dry ice, where the core biopsy samples are stored at -80°C and subsequently processed within 7-10 days for analysis. Biopsy samples will be analyzed for PD biomarkers as described above; any additional cores will be flash-frozen and kept for future analysis. The sample shipping manifest and batch record are included in SOP340507.

For optional restaging follow-up or progression biopsies:
The first biopsy core will be formalin fixed for HER2 IHC analysis and shipped via overnight courier at ambient temperature to the MoCha laboratory at FNLCR. Any remaining cores will be flash-frozen and transferred to PADIS as described above.

9.3.4 Biopsy Specimen Shipping

9.3.4.1 **Biopsy shipping for participating sites only**

Flash-frozen biopsy cores for PD analysis:
Biopsies for PD analyses will be shipped on dry ice to the PADIS laboratory after the specimens for all biopsy timepoints have been collected. Store all frozen biopsies at -80ºC or lower until shipment.

Sites are required to create a FedEx shipping label to accommodate the variable dry ice weight of the shipment package. Use only FedEx Priority Overnight Shipping. NCI-F PD Support will provide a FedEx account number to cover the cost of the shipment. By linking the NCI-F FedEx account number provided to the biopsy shipment, NCI-F PD Support can closely monitor the shipment and cover all shipping costs.

Frozen biopsy samples from participating sites are shipped and delivered to FNLCR PD Central Receiving using the following delivery address:

Attention: Leroy Smith NCI-F/FNLCR
Natural Products and Tumor Repositories | Charles River
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21702
Phone: 301-846-5748

Please Note: Do not ship frozen biopsy specimens on Fridays or one day prior to any Federal holiday as FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. This prevents the risk of dry ice sublimation and loss of sample integrity.

Email the NCI-F PADIS group at NCI_PD_Support@mail.nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the primary tumor, tracking information, and site information. PADIS needs to be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s), and these must be noted on the sample shipping manifest and batch record, both of which are included in SOP340507. One batch record is completed per patient's biopsy specimens, with all required information noted. If shipping multiple patient biopsies, one shipping manifest can be completed, including all patient specimens within the shipment.

Please contact Amy Pantella (office: 301.846.6747, cell: 301.401.8070) or Rachel Andrews (office: 301.846.1951, cell: 240.344.5697) (email: NCI_PD_Support@mail.nih.gov **to obtain the PADIS FedEx account number** or to ask any questions regarding storage or shipment of these specimens.

Formalin-fixed cores for HER2 IHC (baseline and optional restaging follow-up/progression biopsies only) will be shipped at ambient temperature via overnight courier, and flash-frozen biopsy cores for genomic analysis (optional restaging follow-up or progression biopsies only) will be shipped on dry ice, to:
Attn: Lindsay Dutko
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room 107
Frederick, MD 21702
MoChaSampleReceiving@nih.gov

Email the MoCha Histology group at MoChaSampleReceiving@nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the primary tumor, tracking information, and site information. MoCha

should be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s).

Specimens should be shipped on dry ice. **Do not ship frozen biopsy specimens on Fridays or one day prior to any Federal holiday** as FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. This prevents the risk of dry ice sublimation and loss of sample integrity.

Please contact Maria Saeed at 301.846.7035 (email: MoChaSampleReceiving@nih.gov) **to obtain the MoCha FedEx account number** or to ask any questions regarding storage or shipment of the restaging or progression biopsy specimens.
The MoCha sample shipping manifest which can be found in Appendix H, should be completed and included with the shipment.

9.3.4.2 Biopsy shipping for NCI only

Flash-frozen biopsy cores for PD analysis will be shipped on dry ice to:
Attn: PADIS IQC Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 425, Room 105
Frederick, MD 21702
Phone: 301-846-7292
NCI_PD_Support@mail.nih.gov

Formalin-fixed cores for HER2 IHC (baseline and optional restaging follow-up/progression biopsies only) will be shipped at ambient temperature via overnight courier, and flash-frozen biopsy cores for genomic analysis (optional restaging follow-up or progression biopsies only) will be shipped on dry ice, to:
Attn: Lindsay Dutko
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room 107
Frederick, MD 21702
MoChaSampleReceiving@nih.gov

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893

9.4 Blood Collection for ctDNA Analysis

Plasma, derived from whole blood collected from all patients who consent to genomic analyses, will undergo ctDNA assessment by the TSO500 panel to quantitatively assess

longitudinal changes in ctDNA levels (as a percentage of total circulating, cell-free DNA) and to identify any tumor genomic alterations that may be associated with response or resistance to DS-8201a; the results of these studies will not be returned to patients. Once a patient has come off study, ctDNA from blood samples correlating to clinically informative time points (minimally, before treatment and at restaging scans suggesting tumor growth) will be analyzed.

Blood should be collected in 10-mL Streck tubes and gently inverted 8-10 times to ensure the blood is thoroughly mixed with the Streck reagent. Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as a first choice collection method. If a Streck cfDNA tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck cfDNA tube is recommended.

Two whole blood samples of at least 7.5 mL each will be collected into two 10-mL Streck tubes at each of the following time points and shipped to MoCha within 3 days for ctDNA analysis:

- cycle 1 day 1 pre-treatment (baseline; up to 7 days prior to DS-8201a administration),
- cycle 1 on-treatment biopsy (within 24 hours of the biopsy at this time point)
- cycle 3 day 1 (pre-dose; up to 3 days prior to DS-8201a administration)
- within 24 hours of the optional restaging follow-up biopsy (if applicable)
- at time of disease progression

9.4.1 Blood Specimen Shipping for ctDNA Analysis

Labeling:

Blood specimens should be labeled with:

- Sample type (e.g., whole blood)
- Time point (e.g., C1D1 pre-dose)
- Collection date and time
- Sample ID, containing:
    - CTEP protocol number
    - Unique patient ID (**Do NOT include patient name, medical record number, or initials**)
    - Consecutive 800-series sample collection number as specified in Appendix D (i.e., 800, 801, 802)
        - The 2 tubes for each time point should be designated using "A" and "B" (e.g., the two pretreatment specimens should be labeled 800A and 800B).

For example, the sample ID for the C1D1 pre-dose ctDNA blood sample collected on Study 10346 for NCI DTC patient #004 should be: 10346_NCIDTC_004_800.

The sample shipping manifest, which can be found in Appendix G, should be completed and included with the shipment.

Ship blood specimens at ambient temperature via FedEx (using MoCha account number) to:
Attn: Lindsay Dutko
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room 107
Frederick, MD 21702
MoChaSampleReceiving@nih.gov

Blood samples should be shipped at ambient temperature to the MoCha Laboratory at FNLCR via FedEx First Overnight or FedEx Priority Overnight. The MoCha Lab will provide a FedEx account number to cover the cost of the shipment. The sample shipping manifest, which can be found in Appendix G, should be completed and included with the shipment.

Please contact Alyssa Chapman at 301.846.1718 (email: MoChaSampleReceiving@nih.gov) **to obtain the MoCha FedEx account number** or to ask any questions regarding storage or shipment of these specimens.

Email the MoCha Histology group at MoChaSampleReceiving@nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the primary tumor, tracking information, and site information. MoCha should be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s).

Samples should **arrive at MoCha within 2 days of collection when possible; arrival within 3 days of collection is permissible when necessary**. Note that FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. **Therefore, these blood samples for ctDNA analysis should not be collected on a Friday, or the day before a Federal holiday.**

For NIH Clinical Center specimens only: Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893. Non-NIH sites should not contact this number; please contact the MoCha Lab as described above.

9.5 Anti-drug Antibody (ADA) Analysis

Blood samples will be collected for ADA analysis, which will be performed by Daiichi-Sankyo. The ADA testing will be performed using a validated ADA assay following tiered assay steps including screening, confirmatory, and titer determination testing. Samples

confirmed positive will be banked until availability of the neutralizing ADA assay, and sample storage time will not exceed 15 years.

One 4-mL serum separation (gold-top) tube will be obtained for each of the time points, and the actual time of collection will be noted for each sample. **See Appendix B for reagents, procedures, and shipping information for the ADA studies**.

Blood for ADA analysis will be collected at the following times:

- Cycle 1 Day 1, up to 2 days prior to DS-8201a administration
- Cycle 2 Day 1, up to 2 days prior to DS-8201a administration
- Up to 2 days prior to DS-8201a administration on Day 1 of Cycle 4 and every 4 cycles thereafter (Cycles 8, 12, 16, etc.)
- At time of the 40-day follow up appointment (± 7 days).

Based upon the results of the initial measurements, sampling times may be adjusted but neither the total number of samples nor the total amount of blood will be increased.

9.6 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality (analyte preservation) and patient confidentiality pursuant to informed consent provisions. Information about each specimen (e.g., blood, tumor biopsy, per specific protocol) will be recorded on a PK/PD collection worksheet.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
200 series: blood for PK
500 series: tumor biopsies
700 series: blood for ADA
800 series: blood for research

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

NCI patients participating in treatment protocols are often also enrolled on the NCI DTC longitudinal protocol, 17-C-0156, which enables transfer of a patient's research data and specimens longitudinally across multiple trials in which the patient has been enrolled. For NCI patients on the DS-8201a study who are also enrolled on this longitudinal protocol, any frozen biopsy samples collected on this trial that are not needed to be used as the "baseline" tissue sample to determine the eligibility of the patient for a subsequent treatment-intent protocol (i.e., for which there is the possibility of direct benefit), can at the discretion of the PI be used for additional pharmacodynamic analysis to address questions about tumor responses to treatment. This affords us the opportunity to measure dynamic drug-specific target effects (e.g., changes in epithelial-mesenchymal transition, DNA damage response, or immune cell infiltration) in patients on consecutive clinical trials at the Developmental Therapeutics Clinic; there is tremendous value in being able to evaluate molecular changes before and during disease progression to understand why the tumors initially responded but then became resistant to treatment.

Patients on this study will not be consented to new use of their research tissue samples or informed of the results of these studies because (i) broad consent was obtained under the longitudinal protocol and (ii) there will be no direct benefit or added risk to the patient. No new samples will be collected on this study beyond those specified in the current protocol to meet the primary and secondary objectives. No information beyond that associated with the patient's longitudinal protocol registration ID will be shared with investigators performing the pharmacodynamic studies.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.7 **Privacy Considerations**

As patient clinical response data (both for this study and, potentially, after a patient is off-study) will be required for comparison to sequencing results, de-identifying the samples is not feasible. A Certificate of Confidentiality has been obtained to help protect the privacy of all study participants. The informed consent document for this protocol contains language informing patients about the performance of genetic studies, and patients will have the option to choose whether they wish to take part in these studies.

9.8 Management of Genomic Results

Results from the non-CLIA OCAv3 targeted sequencing assay will not be returned to the patient and cannot be used for clinical decision making.

10 STUDY CALENDAR

Baseline history, physical examination, laboratory evaluations, and triplicate ECG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and triplicate ECG must be repeated prior to starting protocol therapy. Baseline tumor imaging, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments must be performed within 28 days prior to start of protocol therapy. If protocol therapy is started within 28 days of the eligibility screening tumor imaging, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments, these screening evaluation results may be used as baseline measurements; if > 28 days have passed since the screening evaluation tumor imaging, ECHO (or MUGA or cardiac MRI), and any clinically indicated ophthalmologic assessments, the imaging and ECHO (or MUGA or cardiac MRI) must be repeated prior to starting protocol therapy.

Start of next cycle may be delayed for up to 8 days to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle. The research team may perform additional safety/monitoring tests as clinically indicated.

	Pre-Study Eligibility Screening	Baseline Clinical Evaluation	Cycle 1			Cycle 2			Cycle 3 onwards
			Wk1	Wk2	Wk3	Wk1	Wk2	Wk3	
DS-8201a[a]			X			X			X
Informed consent	X								
Demographics	X								
Med. History	X	X[l]				X			prior to treatment
Physical exam[b]	X	X[l]	X	X		X			prior to treatment
ECG[b]	X	X[l]							
ECHO or MUGA or cardiac MRI[c]	X	X[l]	ECHO/MUGA/cardiac MRI will be conducted as noted in Section 5.						
Troponin-I[d]	X	X[l]							X
Urinalysis	X								
Height and Weight	X	X[l]				X			X
Performance Status	X	X[l]	X	X		X			X
CBC w/diff, plts[e]	X	X[l]	X	X		X			X
Serum chemistry[e]	X	X[l]	X	X		X			X
Blood coagulation[f]	X								
Tumor Measurement[g]	X	X[l]							X
Radiologic evaluation[g]	X	X[l]							X
B-HCG[h]	X	X	X			X			X
PK blood[i]			X						X
Blood for ADA[i]			X			X			X
Blood samples for ctDNA[j]			X						X
Biopsies[k]			Biopsies will be performed as noted in Section 9.3.1..						
Ophthalmologic assessments[m]	X	X[l]	Ophthalmalogic assessments will be conducted as noted in Section 5.						
Adverse event evaluation			X……..…X						

a. DS-8201a will be administered intravenously at a dose of 5.4 mg/kg every 3 weeks, in 21-day cycles; the start of each cycle may be delayed for up to 8 days for scheduling reasons (e.g., weekends, holidays, or patient convenience).

b. A physical examination including vital signs will be conducted pre-study, during weeks 1 and 2 of cycle 1, and then at the start of every cycle thereafter (+/- 1 day during the cycle and up to 3 days before start of a new cycle). Triplicate ECG (taken in close succession [i.e., within approximately 2-5 minutes apart] while in a supine/semi-recumbent position) will be performed at baseline and as clinically indicated.

c. ECHO or MUGA or cardiac MRI assessments (note: the same test must be used for the subject throughout the study) must be performed within 28 days prior to both enrollment and start of protocol therapy, within 7 days prior to infusion on Day 1 of Cycle 5, and then every 4 cycles (±7 days) thereafter: e.g., Cycle, 9, 13, 17, and so on.

d. Troponin-I will be assessed at screening, end of treatment, and as clinically indicated.

e. Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH) and CBC with differential and platelets will be performed pre-study, during weeks 1 and 2 of cycle 1, and then at the start of every cycle thereafter (+/- 1 day during the cycle and up to 3 days before start of a new cycle). *Additional samples may be drawn in week 2 as clinically indicated to ensure patient safety.*

f. Blood coagulation laboratory evaluations (INR/PT and partial thromboplastin or aPTT) will be assessed at eligibility screening.

g. Radiologic examination will be performed at baseline and then every 3 cycles (i.e., end of cycle 3, 6, 9 etc.). Patients on study for > 1 year will undergo radiologic examination every 4 cycles.

h. Serum or urine pregnancy test (for women of childbearing potential) will be conducted within 72 hours prior to DS-8201a administration at baseline, within 72 hours before the beginning of each cycle, and at end of treatment. A positive urine pregnancy test result must immediately be confirmed using a serum test.

i. Blood for PK and ADA analyses will be obtained from all patients as specified in Section 9.2 and Section 9.5, respectively.

j. Blood samples for ctDNA analysis will be collected from patients as specified in Section 9.4.

k. Biopsies will be collected from all patients as specified in Section 9.3.1.

l. Values from eligibility screening tests may be used as baseline evaluation values if the test was performed within 8 days of start of protocol therapy (or, for radiologic evaluation and tumor measurement, within 28 days of start of protocol therapy). See Section 3.4 and Section 5.

m. Ophthalmologic assessments—including visual acuity testing, slit lamp examination, and fundoscopy—will be performed, only as clinically indicated, at screening and baseline (within 28 days prior to both enrollment and the start of protocol therapy, respectively), at the end of treatment (for patients that return to clinic for the end-of-study visit), and as clinically indicated.

Note: For suspected ILD/pneumonitis, study drug should be interrupted pending evaluation, which should include: high-resolution CT and pulmonary consultation. Other evaluations could include: pulmonary tests including diffusing capacity of the lungs for carbon monoxide (DLCO), pulse oximetry (SpO2); arterial blood gases and serum markers testing (e.g., KL-6, SP-D, or others).

11 MEASUREMENT OF EFFECT

Patients should be re-evaluated for response at the end of cycle 3 (before cycle 4), and at the end of every 3 cycles thereafter (i.e., at the end of cycles 6, 9, 12, etc.). Restaging scans may be performed less frequently for patients on study for more than 1 year (every 4 cycles). Confirmatory scans should also be obtained ≥4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [13]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1 RECIST v1.1 Criteria for Assessment of Response and Progression

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. All patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of response to treatment. These patients will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which

greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.2 Response Criteria

11.3 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as

evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Patients that are clinically well may continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria. In this situation, patients do not have unequivocal progression until immune response criteria are met (see Section 11.2).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.4 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.6 Response and Stable Disease Duration (RECIST 1.1)

Response duration will be measured from the time measurement criteria for CR/PR are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of registration/randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

The Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems. Upon occurrence of any grade 5 event other than disease progression, accrual will be held pending review of the grade 5 incident and available cumulative safety data by the Protocol Principal Investigator and the CTEP Medical Officer.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR), and

    - Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

12.2.1 Method

CTMS Comprehensive Monitoring:

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

It is the responsibility of the PI at the site to ensure that all investigators understand the procedures for data submission for each protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS are reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 **Data Quality Portal**

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

12.4 **Collaborative Agreements Language**

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any

manuscript, abstract and/or press release/ media presentation should be sent to: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 **Genomic Data Sharing Plan**

The NIH Genomic Data Sharing (GDS) Policy does not apply to this protocol due to the limited number of samples collected for genetic analysis; therefore, a GDS plan is not warranted.

12.6 **Study Discontinuation and Closure**

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Determination that the primary endpoint has been met
- Determination of futility

The Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or Food and Drug Administration (FDA).

13 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to assess the effects of DS-8201a (5.4 mg/kg administered intravenously every 3 weeks, in 21-day cycles) on total Top1 levels in biopsy specimens from patients with HER2-expressing advanced solid tumors, at early and late post-treatment time points, thereby establishing the degree and duration of DS-8201 target engagement.

Secondary objectives are to assess any associations between serum concentrations of DS-8201a and total Top1 levels formation in tumor biopsy specimens; to determine the safety and tolerability of DS-8201a administered intravenously every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg; and to determine the overall response rate (CR + PR) for patients administered intravenously with DS-8201a every 3 weeks, in 21-day cycles, at a dose of 5.4 mg/kg. Exploratory objectives include evaluating the effects of DS-8201a on CD8+ T cell infiltration and activation in tumor, tumor PD-L1 and HER2 expression, and DDR signaling (for example: γH2AX, RAD51, and pNBS1) in biopsy specimens, examining genomic alterations in tumor tissue or in circulating tumor DNA

(ctDNA) that may be associated with DS-8201a response or resistance, examining any associations between baseline tumor HER2 amplification or HER2 expression level and response to DS-8201a, evaluating the effects of DS-8201a on tumor levels of HER2 and DDR-associated proteins, and evaluating the emergence and persistence of anti-drug antibodies following administration of DS-8201a. Details concerning the PK and PD assays are provided in Section 9.

13.1 **Study Design/Endpoints**

Mandatory biopsies will be collected for PD analysis from up to 45 patients at 3 time points, including baseline. With a 70% evaluability rate on individual biopsies, there will be 89% likelihood of at least 12 patients with 3 evaluable biopsies. The primary endpoints will be early Top1/DDR response (baseline vs. C1 48-96 hours post–day 1 dose) and later tumor immune microenvironment response (baseline vs. C3D1). For either endpoint, if we observe at least 2 out of the 12 patients with evaluable biopsy sets demonstrating response, we will declare the agent promising with respect to that endpoint. This design will give us 91% power to detect a true 30% PD response rate, across patients, for either endpoint, with less than .065 probability of a false positive in the event that the agent has no effect on that endpoint, and the true likelihood of a false positive PD response, for an individual patient, is less than 3.5%. Accrual will stop once 12 patients are accrued with sufficient tissue quality for each of the 2 timepoint pairs: 1) the baseline-early timepoint pair and 2) the baseline-late timepoint pair (i.e., 12 sufficient-quality biopsy pairs are needed for the baseline vs. C1 48-96 hours post–day 1 dose comparisons, and 12 sufficient-quality pairs are needed for the baseline vs. C3D1 comparisons).

For the total Top1 assay, an on-target drug response is defined as a decrease in total Top1 protein as measured by %nuclear area positive (%NAP) in post-treatment biopsies compared to baseline biopsies using a quantitative immunofluorescence assay. For the PADIS DDR3 assay, levels exceeding 4% nuclear area positive (NAP) γH2AX, 4% NAP pNBS1, and 5% cells with ≥5 Rad51 nuclear foci indicate a DNA damage activation response [7]. Immunomodulation by DS-8201a will be assessed by comparing the distribution (tumor vs. surrounding stroma) and numbers of CD8 T cells in post-treatment vs. baseline biopsy specimens. In addition, reportable endpoints for CD8 T cell activation are still being explored, but one option is to report the extent of T cell activation as defined by the percentage of infiltrating tumor-adjacent CD8 T cells that are positive for p-ZAP70. The p-ZAP70 signal in CD8 T cells will be "thresholded" based on positive and negative T cell controls, allowing patient data to be reported as percent CD8 T cells with net positive or negative p-ZAP70 signal.

With Amendment C (6/1/21), the timing of the early on-treatment biopsy was changed from C1D7 to Cycle 1 48-96 hours post-dose in light of preclinical longitudinal PD data demonstrating that no significant changes in the primary endpoint (Top1 levels) could be detected in DS-8201a–treated vs. vehicle-treated xenograft models at the C1D7 (168 h) timepoint (see Section 2.3.1.1). Prior to approval of Amendment C, sufficient-quality paired baseline/C1D7 biopsies were obtained from total of 5 patients. Based on the corresponding preclinical data, appreciable Top1 modulation in the patient biopsy specimens collected at the C1D7 timepoint is not anticipated, and PD results

from these biopsy pairs will not be combined with those from pairs collected at the revised (C1 48-96 h post-dose) timepoint for statistical analyses of study endpoints.

13.2 Sample Size/Accrual Rate

We anticipate enrolling a minimum of 12 patients and a maximum of 45 patients. To allow for a small number of patients who may not be evaluable, the accrual ceiling for this trial is set at 55 patients. It is anticipated that 1-2 patients may be enrolled per month onto this study. It is expected that 18 months will be required to accrue the number of patients necessary to complete the trial.

To replace 8 pairs of unanalyzable tumor biopsies, 8 additional patients will be enrolled, raising the maximum accrual ceiling to 63 patients. Enrollment will be stopped once 12 patients are accrued with sufficient tissue quality for each of the 2 timepoints, as specified in Section 13.1.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	8	3	0	0	**11**
Native Hawaiian or Other Pacific Islander	1	1	0	0	**2**
Black or African American	5	3	0	0	**8**
White	21	6	6	3	**36**
More Than One Race	2	1	2	1	**6**
Total	**37**	**14**	**8**	**4**	**63**

Planned enrollment demographics are based on the patient demographics for prior studies at the study institutions.

13.3 Analysis of Secondary and Exploratory Endpoints

The association between serum concentrations of DS-8201a and Top1cc formation will be assessed by computing the sample correlation between the area under the DS-8201a serum concentration curve (AUC) and the initial change in Top1cc (from baseline to Cycle 1 48-96 h post-day 1 dose). We will also compute the sample correlation between the maximum serum concentration of DS-8201a and the initial change in Top1cc (from baseline to Cycle 1 48-96 h post-day 1 dose). These relationships will also be summarized graphically using scatterplots and overlaid LOWESS curves.

Additional secondary and exploratory evaluations will be performed on the PD and PK parameters outlined above, with results of these tests reported with appropriate caveats about the exploratory

nature of the analysis, and without formal adjustment for multiple comparisons. With biopsy sets from 12 patients, there will be 90% power to detect treatment-related changes in a biomarker, equivalent to 1.4 standard deviations associated with the normal between-patient variation of the markers, at the 2-sided .05 significance level.

In addition to the PD and PK parameter evaluations described above, safety and efficacy evaluations will be performed. To assess safety, descriptive analyses of CTCAE data will be performed, as will analysis of anti-drug antibodies. To assess efficacy, we will estimate the overall response rate (CR + PR) among eligible patients who have received at least one dose of DS-8201a. A 95% confidence interval for this response rate will also be computed. For this analysis, response classifications will follow RECIST v1.1 guidelines.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Rationale for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, pregnant women and children are excluded from this study. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). Participants should realize that there is no guarantee of benefit to them from participation in this trial. The results of this trial may benefit future cancer patients. To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

14.1.1 Inclusion of Women and Minorities

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met.

14.2 Justification for Exclusions

Because the effects of DS-8201a on the developing human fetus are unknown, pregnant women will be excluded from this trial. Nursing women are also excluded, as there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with study medications.

Participants with unstable or serious medical conditions (ongoing or active infection, symptomatic congestive heart failure [AHA Class II or worse], unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements) are excluded due to the possibility that the underlying condition may obscure the attribution of effect and adverse events with respect to study drugs and may limit study compliance.

14.2.1 Participation of Children

Because no clinical dosing or adverse event data are currently available on the use of DS-8201a in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

14.3 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 5 and Section 6. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations. A Certificate of Confidentiality has been obtained to help protect the privacy of all study participants.

14.4 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided IRB-approved consent(s) for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent(s) go to Medical Records; a copy is placed in the research record.

All patients must have a signed informed consent form before entering on study.

14.4.1 Participation of subjects unable to give consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary, and there is a possibility, though unlikely, that subjects could lose decision-making capacity during the course of the study. For this reason, and because there is a prospect of direct benefit from research participation, all subjects ≥ age 18 **at the NCI only** will be offered the opportunity to fill in their wishes for research and care and appoint a legally authorized representative (LAR) using the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their treatment and research participation in the event that they lose

capacity during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects who lose capacity and do not have pre-determined LAR, the procedures described in NIH OHSRP Policy 403 will be followed.

14.4.2 Informed consent of non-English speaking subjects (at the NCI only)

We do not anticipate consistent enrollment of any particular group of non-English speaking research participants into this study. In the event there is enrollment of a non-English speaking research participant, the IRB approved full consent document will be translated into that language at that time. If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document and it is determined by the Principal Investigator that it is justified to proceed because it is in the participant's best interest to enroll prior to the translation, the PI and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process, as described in NIH OHSRP Policy 301 and the Guidance for Obtaining Consent to Participate in Research from Non-English Speaking Subjects. The PI's determination and the reasons for using the short form process will be documented in the research record and/or CRIS as part of the consent note and the NIH IRB will be informed of the use of the short form within 7 calendar days by submitting a Reportable New Information (RNI) form in the NIH eIRB system (PROTECT). Signed copies of both the English version of the consent and the translated short form will be given to the subject or, if applicable, their legally authorized representative and the signed original will be filed in the medical record. When available, the translated full consent form will be submitted to the external IRB for approval and then given to the participant.

14.5 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication and from undergoing blood and biopsy sampling procedures. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects. If patients suffer any physical injury as a result of the participation in this study at the NCI, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland.

14.6 Patient Advocate

At the NCI only, the patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their

medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

REFERENCES

1. Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C et al (2016) DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. Clinical cancer research : an official journal of the American Association for Cancer Research 22(20): 5097-5108. https://doi.org/10.1158/1078-0432.Ccr-15-2822

2. Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T (2016) 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): 1039-46. https://doi.org/10.1111/cas.12966

3. Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y et al (2017) 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. The Lancet Oncology 18(11): 1512-1522. https://doi.org/https://doi.org/10.1016/S1470-2045(17)30604-6

4. Iwata TN, Ishii C, Ishida S, Ogitani Y, Wada T et al (2018) A HER2-Targeting Antibody-Drug Conjugate, Trastuzumab Deruxtecan (DS-8201a), Enhances Antitumor Immunity in a Mouse Model. Mol Cancer Ther 17(7): 1494-1503. https://doi.org/10.1158/1535-7163.Mct-17-0749

5. Kubo K, Azuma A, Kanazawa M, Kameda H, Kusumoto M et al (2013) Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respiratory investigation 51(4): 260-77. https://doi.org/10.1016/j.resinv.2013.09.001

6. Patel AG, Flatten KS, Peterson KL, Beito TG, Schneider PA et al (2016) Immunodetection of human topoisomerase I-DNA covalent complexes. Nucleic acids research 44(6): 2816-2826. https://doi.org/10.1093/nar/gkw109

7. Wilsker DF, Barrett AM, Dull AB, Lawrence SM, Hollingshead MG et al (2019) Evaluation of Pharmacodynamic Responses to Cancer Therapeutic Agents Using DNA Damage Markers. Clinical cancer research : an official journal of the American Association for Cancer Research 25(10): 3084-3095. https://doi.org/10.1158/1078-0432.Ccr-18-2523

8. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB et al (2018) Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. 36(20): 2105-2122. https://doi.org/10.1200/jco.2018.77.8738

9. *This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.*

10. *The frequencies of infusion related reaction and ejection fraction decreased are <3%.*

11. *Pneumonitis/interstitial lung disease is considered an important identified risk and can, in rare instances be life-threatening or fatal.*

12. Oitate M, Shiozawa H, Ando O (2018) Comprehensive preclinical pharmacokinetic evaluations of trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody-drug conjugate, in cynomolgus monkeys AU - Nagai, Yoko. Xenobiotica: 1-11. https://doi.org/10.1080/00498254.2018.1531158

13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-47. https://doi.org/10.1016/j.ejca.2008.10.026

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Procedure for Blood Samples for Pharmacokinetics and ADA Analysis

PK and ADA Sample Collection and Processing

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Collect a blood sample into the gold-top serum separation tube. Fill tube completely. **It is important to thoroughly mix the blood with the clotting activation agent by inverting the tube not less than 5 times.** Blood samples should be allowed a clotting time of minimum 30 minutes at room temperature, and then centrifuged (room temperature) within 1 hour of collection. If clotting procedure exceeds 45 minutes, the sample should be placed on ice until centrifugation.
2. The blood samples will be centrifuged at 1300 – 2000 x g for 10 min. at room temperature.
    - **For PK samples:** serum will be collected at the top of each tube and should be equally transferred into 4 cryovials labeled: "PK-A," "PK-B," "PK-C," and "PK-D."
    - **For ADA samples:** serum will be collected at the top of each tube and should be equally transferred into 2 cryovials labeled: "ADA-A," and "ADA-B."
3. Freeze immediately and store at -70°C until time of shipment. If a -70°C freezer is not available, samples can be stored at -20°C (only non-cycling freezer should be used). Storage should not exceed 1 month.

Sample Shipping

1. Complete the "PK/ADA Specimen Receipt Criteria Worksheet A" and "Electronic Manifest for PK/ADA Sample Shipping" (see below). **Do not include personally identifiable patient information**, such as patient name, initials, social security number, address, or date of birth, in the manifest.
2. Ship first set of **PK aliquots** (PK-A) and (PK-B) and **ADA aliquot** (ADA-A) on dry ice monthly via **UPS or World Courier overnight delivery**. Ship second set of **PK aliquots** (PK-C) and (PK-D) and **ADA aliquot** (ADA-B) on dry ice via **UPS or World Courier overnight delivery** at least one week after shipment of the previous aliquot(s). All samples should be shipped to:

    PPD
    2246 Dabney Road
    Richmond, VA 23230
    Attn: Specimen/Mgmt. Dept
    Phone: +1 804-977-8459

If possible, **ship samples Monday, Tuesday, or Wednesday** to minimize sample loss or damage.

3. Notify PPD of the pending shipment on the day the shipment is retrieved by the courier.
    - Notification should be done through an email sent to the following addresses:
        - richmondsmopeners@ppd.com
        - richmond_data@ppd.com
    - Notification email should include the following information:
        - Sponsor and sponsor contact name if known
        - Courier used and the tracking number

- Site and/or clinic or central lab where the shipment is originating from and associated phone and fax numbers
- Number of samples being shipped
- Electronic Manifest for PK Sample Shipping

PK/ADA SPECIMEN RECEIPT CRITERIA WORKSHEET A

To assist PPD in ensuring the identity of the specimens to be shipped, PPD's Richmond, VA laboratory requires the section listed below to be completed by the site and/or clinic responsible for collecting the specimens. All this information is considered relevant and critical in properly identifying the specimens upon receipt. Failure to complete the form in its entirety may result in the return of the specimens to the site or clinic shipping the specimens, at their expense.

After completion of the form, please retain a copy for your records, include a copy in the shipment of specimens, and email a copy to:

- **RichmondSMOpeners@ppdi.com**
- **richmond_data@ppdi.com**

Unless otherwise communicated, all specimens are to be shipped to the following address:
PPD
2246 Dabney Road
Richmond, VA 23230 USA
Attn: Specimen/Mgmt. Dept/LiMajor Pittman
Phone +1 804.977.8459

*Client protocol number _____

*Client/Sponsor name _____

*Site/Clinic study number _____

*Analyte/Drug name(s) _____

*Matrix type _____
(Plasma, urine, serum, etc.)

*Matrix species _____
(rat, dog, human, etc.)

*Matrix additive/preservative _____
(EDTA, sodium hep, etc.)

*Total number of tubes sent _____ *Primary or backup specimens _____

*Site/Clinic contact name (print) _____

*Site/Clinic contact phone number _____ *Site/Clinic contact fax number _____

Note: all asterisked (*) fields are considered mandatory information to be completed by the site and/or clinic collecting the specimens.

I have reviewed the above information and have determined such to be accurate in content.

_____ _____
(Signature of site/clinic contact) **(Date)**

ELECTRONIC MANIFEST FOR PK/ADA SAMPLE SHIPPING

In addition to the shipping manifest, an electronic file must be sent via email to PPD. This file should contain the specifics of each sample contained in the pending shipment. The file can be either a text file type (.txt or .csv) or a standard Excel worksheet (.xls) and should be included as an attachment to the shipment notification email described above. The file should contain at a minimum, and where the variables are available, the following information (or working equivalent of such) as it appears on the sample tube label and/or collection sheet for the sample:

- Protocol ID
- Biological matrix
- Compound (analyte) name if known
- Barcode/accession number
- Subject number or animal number
- Visit (such as period, nominal day, nominal timepoint)
- Treatment group (for multi-arm studies only)
- Collection date
- Collection time
- Aliquot assignment

Additional Expectations when providing an electronic manifest to PPD:

- The order of the specimens on the specimen manifest should match the order of the specimens in the specimen containers when possible.
- The specimen manifest should also detail any issues noted with the samples by the sender to make the sample handling personnel aware of such issues.
- Primary, as well as, duplicate/back-up samples should be clearly labeled as such in the shipment manifest.
- For clinical studies, it is requested that within each shipment all samples from a single subject where possible be grouped together to aid the sample log-in process.
- **Do not include personally identifiable patient information**, such as patient name, initials, social security number, address, or date of birth, in the manifest.

Example of an Acceptable Electronic Manifest for Reporting to PPD:

Protocol	Biological Matrix	Analyte	Accession Number	Subject Number	Period	Day	Timepoint (hr)	Collect Date	Collect Time	Aliquot ID
ABC123	Human Serum	Drug 1	0123456	01	1	1	0	01/01/2011	09:00	1
ABC123	Human Serum	Drug 1	0123457	01	1	1	0.5	01/01/2011	09:30	1
ABC123	Human Serum	Drug 1	0123458	01	1	1	1	01/01/2011	10:00	1
ABC123	Human Serum	Drug 1	0123459	01	1	1	2	01/01/2011	11:15	1
ABC123	Human Serum	Drug 1	0123460	01	1	1	4	01/01/2011	13:00	1
ABC123	Human Serum	Drug 1	0123461	01	1	1	6	01/01/2011	15:05	1
ABC123	Human Serum	Drug 1	0123465	01	1	2	16	01/02/2011	02:00	1
ABC123	Human Serum	Drug 1	0123466	01	1	2	24	01/02/2011	08:30	1

APPENDIX C: Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information:
1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX D: PK/PD Sample Collection Worksheets

Date:	PK/PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 1	
CTEP Protocol P10346 **Dose level:** **DS-8201a Dose:** **Patient ID:**	**Page _____** **for Sample Pick-up** **Lab phone: _____**	**Research Nurse:** Phone: **Lead AI/PI:** Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Cycle 1 Day 1	**Prior to drug administration**	**PK 200 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		
Cycle 1 Day 1	**Prior to drug administration**	**ADA 700 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		
Cycle 1 Day 1	**Prior to drug administration**	**PD 800A** 7.5 mL into Streck tube **PD 800B** 7.5 mL into Streck tube Label tubes: sample number, date and time	**Morning of drug administration**		
Cycle 1 Day 1	**End of drug infusion**	**PK 201 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		
Cycle 1 Day 1	**5 hours post-end of infusion**	**PK 202 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Afternoon of drug administration**		

PK/PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1, TIME OF ON-TREATMENT BIOPSY (48-96 H POST-DAY 1 DOSE)

Date:

CTEP Protocol P10346

Dose level: **DS-8201a Dose:**

Patient ID:

Page _____
for Sample Pick-up
Lab phone: _____

Research Nurse:
Phone:

Lead AI/PI:
Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Cycle 1, time of on-treatment biopsy	±3 hours from time of biopsy	**PK 203 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time			
Cycle 1, time of on-treatment biopsy	±24 hours from time of biopsy	**PD 801A** 7.5 mL into Streck tube **PD 801B** 7.5 mL into Streck tube Label tubes: sample number, date and time			

Date:	PK/PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 2 DAY 1	
CTEP Protocol P10346 **Dose level:** **DS-8201a Dose:** **Patient ID:**	**Page _____** **for Sample Pick-up** **Lab phone: _____**	**Research Nurse:** Phone: **Lead AI/PI:** Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Cycle 2 Day 1	**Prior to drug administration**	**PK 204 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		
Cycle 2 Day 1	**Prior to drug administration**	**ADA 701 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		
Cycle 2 Day 1	**End of drug infusion**	**PK 205 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 3 DAY 1**

CTEP Protocol P10346
Dose level: **DS-8201a Dose:**
Patient ID:

Page _____
for Sample Pick-up
Lab phone: _____

Research Nurse:
Phone:

Lead AI/PI:
Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Cycle 3 Day 1	**Prior to drug administration**	**PK 206 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		
Cycle 3 Day 1	**Prior to drug administration**	**PD 802A** 7.5 mL into Streck tube **PD 802B** 7.5 mL into Streck tube Label tubes: sample number, date and time	**Morning of drug administration**		
Cycle 3 Day 1	**End of drug infusion**	**PK 207 (4 mL, serum separation [gold-top] tube)** Label tube: sample number, date and time	**Morning of drug administration**		

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 4 DAY 1**

CTEP Protocol P10346
Dose level: **DS-8201a Dose:**
Patient ID:

Page _____
for Sample Pick-up
Lab phone: _____

Research Nurse:
Phone:
Lead AI/PI:
Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Cycle 4 Day 1	Prior to drug administration	PK 208 (4 mL, serum separation [gold-top] tube) Label tube: sample number, date and time	Morning of drug administration		
Cycle 4 Day 1	Prior to drug administration	ADA 702 (4 mL, serum separation [gold-top] tube) Label tube: sample number, date and time	Morning of drug administration		
Cycle 4 Day 1	End of drug infusion	PK 209 (4 mL, serum separation [gold-top] tube) Label tube: sample number, date and time	Morning of drug administration		

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: CYCLE __ DAY 1**

CTEP Protocol P10346
Dose level: **DS-8201a Dose:**
Patient ID:

Page _____
for Sample Pick-up
Lab phone: _____

Research Nurse:
Phone:
Lead AI/PI:
Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Cycle _ Day 1	Prior to drug administration	ADA 70_ (4 mL, serum separation [gold-top] tube) Label tube: sample number, date and time	Morning of drug administration		

PK/PD BLOOD SAMPLE COLLECTION SHEET: RESTAGING FOLLOW-UP OR PROGRESSION BIOPSY*					
Date:					
CTEP Protocol P10346 **Dose level:** **DS-8201a Dose:** **Patient ID:**			**Page _____** **for Sample Pick-up** **Lab phone: _____**		**Research Nurse:** Phone: **Lead AI/PI:** Phone: Pager:
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
___	**Restaging follow-up or progression biopsy***	**PD 803A** 7.5 mL into Streck tube **PD 803B** 7.5 mL into Streck tube Label tubes: sample number, date and time			

*Restaging follow-up or progression biopsies are optional, as are the associated blood samples for PK or PD analysis.

PK/PD BLOOD SAMPLE COLLECTION SHEET: TIME OF DISEASE PROGRESSION					
Date:					
CTEP Protocol P10346 **Dose level:** **DS-8201a Dose:** **Patient ID:**			**Page _____** **for Sample Pick-up** **Lab phone: _____**		**Research Nurse:** Phone: **Lead AI/PI:** Phone: Pager:
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
___	**Disease progression**	**PD 804A** 7.5 mL into Streck tube **PD 804B** 7.5 mL into Streck tube Label tubes: sample number, date and time			

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: TIME OF 40-DAY FOLLOW-UP**

CTEP Protocol P10346
Dose level: **DS-8201a Dose:**
Patient ID:

Page _____
for Sample Pick-up
Lab phone: _____

Research Nurse:
Phone:
Lead AI/PI:
Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
40-day follow up	Any	ADA 70_ (4 mL, serum separation [gold-top] tube) Label tube: sample number, date and time	Any		

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: OPTIONAL SAMPLE FOR PATIENTS EXPERIENCING INTERSTITIAL LUNG DISEASE**

CTEP Protocol P10346
Dose level: **DS-8201a Dose:**
Patient ID:

Page _____
for Sample Pick-up
Lab phone: _____

Research Nurse:
Phone:
Lead AI/PI:
Phone: Pager:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
_____ (please specify)	Any	PK 210 (4 mL, serum separation [gold-top] tube) Label tube: sample number, date and time	Any		

APPENDIX E: Acceptable Birth Control Methods

The effect of DS-8021a on the developing human fetus are unknown, For this reason and because a HER2 antibody conjugated to a topoisomerase 1 inhibitor is known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for at least 7 months after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of DS-8201a administration. Methods considered as highly effective methods of contraception include:

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

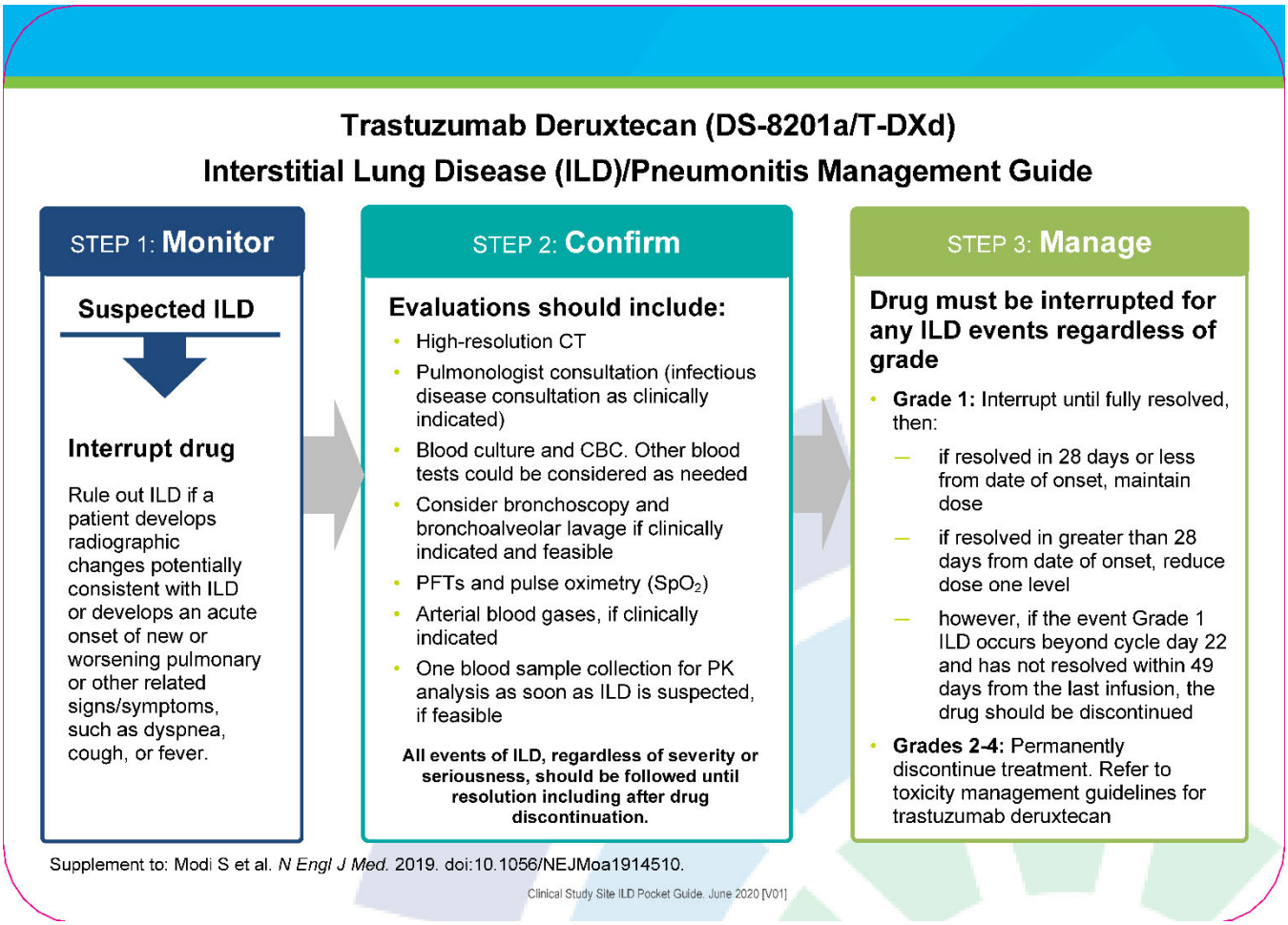
Progestogen-only hormonal contraception associated with inhibition of ovulation:

- Oral
- Injectable
- Implantable

Acceptable non-hormonal birth control methods include:

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months (for women) or 4 months (for men) after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

APPENDIX F: DS-8201a ILD Site Pocket Guide



Trastuzumab Deruxtecan (DS-8201a/T-DXd)
Interstitial Lung Disease (ILD)/Pneumonitis Management Guide

	Grade 1	Grade 2	Grade 3 / 4

Toxicity Management	• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
	• Consider follow-up imaging in 1-2 weeks (or as clinically indicated).
	• Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks.
	• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.*
		• Promptly start systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent), for at least 14 days or until complete resolution of clinical symptoms and chest CT findings followed by gradual taper over at least 4 weeks.
		• Monitor symptoms closely.
		• Re-image as clinically indicated.
		• If worsening or no improvement in clinical or diagnostic observations in 5 days,
		  • Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone).
		  • Re-consider additional work-up for alternative etiologies as described above.
		  • Escalate care as clinically indicated.
			• Hospitalization required.
			• Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical symptoms and chest CT findings, then followed by a gradual taper over at least 4 weeks.
			• Re-image as clinically indicated.
			• If still no improvement within 3 to 5 days,
			  • Re-consider additional work-up for alternative etiologies as described above.
			  • Consider other immuno-suppressants and/or treat per local practice.

* If patient is asymptomatic, then patient should still be considered as Grade 1 even if steroid treatment is given.

Clinical Study Site ILD Pocket Guide, June 2020 [V01]

APPENDIX G: SHIPPING MANIFEST FOR BLOOD SAMPLES FOR GENETIC ANALYSIS

Protocol 10346	Shipping date:	**Carrier:** FedEx (MoCha Account number)	
Ship FROM:	Ordering Physician/PI:	**Ship TO:**	MoCha Laboratory
Address:		**Address:**	Attn: Lindsay Dutko MoCha Histology Lab Frederick National Laboratory for Cancer Research Leidos Biomedical Research, Inc. 1050 Boyles Street Building 321 Room 107 Frederick, MD 21702
Contact Name:		**Contact Name:**	Alyssa Chapman
Telephone:		**Telephone:**	301-846-1718
Email:		**Email:**	MoChaSampleReceiving@nih.gov

Item	**Sample ID** (Study#_SiteID_Patient#_Specimen Series ID)	**Diagnosis**	**No. Tubes (w/ volumes)**	**Collection:**			**Storage Temp**
				Date	**Time**	**Time Point**	
1							
2							
3							
4							
5							
6							
7							
8							
		TOTAL No. ITEMS					

COMMENTS: *DO NOT include patient identifiers

APPENDIX H: SHIPPING MANIFEST FOR FORMALIN FIXED BIOPSY SAMPLES FOR IHC ANALYSIS

Protocol 10346	Shipping date:	**Carrier:** FedEx (MoCha Account number)	
Ship FROM:	Ordering Physician/PI:	**Ship TO:**	MoCha Laboratory
Address:		**Address:**	Attn: Lindsay Dutko MoCha Histology Lab Frederick National Laboratory for Cancer Research Leidos Biomedical Research, Inc. 1050 Boyles Street Building 321 Room 107 Frederick, MD 21702
Contact Name:		**Contact Name:**	Lindsay Dutko
Telephone:		**Telephone:**	301-846-6019
Email:		**Email:**	MoChaSampleReceiving@nih.gov

Item	**Sample ID** (Study#_SiteID_Patient#_Specimen Series ID)	**Diagnosis**	**Site of Biopsy**	**Collection:**			**Storage Temp**
				Date	**Time**	**Time Point**	
Ex	*10346_NCIDTC_0001_500A*	*Colon cancer*	*Liver*	*03/17/23*	*0900 hrs*	*Baseline*	*Room temp*
1							
2							
3							
4							
5							
6							
7							
		TOTAL No. ITEMS					

COMMENTS: *DO NOT include patient identifiers