

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761139Orig1s028

Trade Name: ENHERTU

Generic or Proper Name: fam-trastuzumab deruxtecan-nxki

Sponsor: Daiichi Sankyo, Inc.

Approval Date: April 5, 2024

Indication: Enhertu is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) breast cancer who have received a prior anti-HER2-based regimen either:
 - in the metastatic setting, or
 - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months or completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-

small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.*

- adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.
- adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.*

* These indications are approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s028

APPROVAL LETTER



BLA 761139/S-028

ACCELERATED APPROVAL

Daiichi Sankyo, Inc.
Attention: Susie J Flores
211 Mount Airy Road
Basking Ridge, NJ 07920

Dear Susie J Flores:

Please refer to your supplemental biologics license application (sBLA), dated and received November 30, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Enhertu (fam-trastuzumab deruxtecan-nxki) 100 mg lyophilized powder for solution for intravenous injection.

This Prior Approval supplemental biologics license application provides for the use of Enhertu for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,¹ that is identical to the enclosed labeling (Prescribing Information and

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effectuated” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761139/S-028.**” Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated March 28, 2024. These requirements are listed below.

- 4624-1 Complete Cohort A in Part 2 of the ongoing DESTINY-PanTumor02 trial intended to verify and describe the clinical benefit of Enhertu in adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options. Include a minimum of 40

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

patients across all tumor types, other than breast, colorectal, lung, and gastric/GEJ cancer, including a sufficient number of patients with and representation of HER2-positive (IHC3+) tumor types that require additional characterization. In order to characterize response rate and duration of response, patients should be followed for at least 12 months from the onset of response.

Final Protocol Submission:	11/2023 (completed)
Trial Completion:	12/2026
Final Report Submission:	06/2027

Submit clinical protocols to your IND 149506 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each study and clinical trial required under section 506(c) (listed above) to this BLA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). One report will be a standalone submission and the other report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval of the original BLA (with a 60-day grace period). Submit the other 180-day report with your application’s ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.³ Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics*, to submit your 180-day reports.⁴

180-day reports must be clearly designated “**BLA 761139/S-028 180-Day AA PMR Progress Report.**”

FDA will consider the submission of your application’s ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval of the original BLA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

³ You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

⁴ FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at <https://www.fda.gov/about-fda/reports-manuals-forms/forms>.

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Silver Spring, MD 20993

www.fda.gov

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated “**Subpart E Postmarketing Requirement(s).**”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to <1 month old because necessary studies are impossible or highly impracticable due to the rarity of pediatric patients in this age group who would be eligible for investigational treatment with Enhertu.

We are deferring submission of your pediatric study for ages 1 month to < 17 years old for this application because additional pediatric nonclinical data are needed to inform the design of the pediatric clinical study.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

- 4624-2 Conduct a clinical study of Enhertu to evaluate dosing, pharmacokinetics, safety, and efficacy of Enhertu in a sufficient number of pediatric patients ages 1 month to <17 years of age with unresectable or metastatic HER2-expressing solid tumors, that have progressed following prior treatment or who have no satisfactory alternative treatment options, deferred until results of completed or planned nonclinical in vitro and in vivo studies or available pediatric clinical data are submitted to and reviewed by FDA, and have been found to support a clinical investigation in the pediatric population.

Draft Protocol Submission	03/2026
Final Protocol Submission:	06/2026
Study Completion:	06/2032
Final Report Submission:	12/2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁵

Submit the protocol(s) to your IND 149506, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 4624-3 Conduct a new pragmatic clinical trial with a sufficient number of patients to verify and describe the efficacy of Enhertu in adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors with disease that has progressed following prior treatment and have no satisfactory alternative treatment options. The trial should include a sufficient number of tumor types, other than breast, colorectal, lung, and gastric/GEJ cancer. In order to characterize response rate and duration of response, patients should be followed for at least 12 months from the onset of response.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2024
Final Protocol Submission:	02/2025
Trial Completion:	08/2028
Final Report Submission:	02/2029

Submit the datasets with the final report submission.

- 4624-4 Commitment to submit appropriate analytical and clinical validation study data using the DESTINY-PanTumor02, DESTINY-CRC02, and DESTINY-Lung01 clinical trials, to support labeling of an immunohistochemistry-based in-vitro diagnostic device that is essential for the safe and effective use of Enhertu for treatment of adults with unresectable or metastatic HER2-positive (IHC3+) solid tumors.

⁵ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocol(s) to your IND 149506, with a cross reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁶

⁶ <https://www.fda.gov/media/128163/download>
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REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Alice Lee, Senior Regulatory Project Manager, at (301) 796-8881 or at Alice.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LALEH AMIRI KORDESTANI
04/05/2024 02:18:46 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENHERTU safely and effectively. See full prescribing information for ENHERTU.

ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

Initial U.S. Approval: 2019

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms. (2.3, 5.1)
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception. (5.4, 8.1, 8.3)

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.4, 1.5)	04/2024
Dosage and Administration (2.1, 2.2, 2.3, 2.4)	04/2024
Dosage and Administration (2.2, 2.4)	02/2024
Warnings and Precautions (5.1, 5.2, 5.3)	02/2024
Warnings and Precautions (5.1, 5.2, 5.3)	04/2024

INDICATIONS AND USAGE

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) breast cancer who have received a prior anti-HER2-based regimen either:
 - in the metastatic setting, or
 - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy. (1.1)
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. (1.2)
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.* (1.3)
- adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. (1.4)
- adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.* (1.5)

* These indications are approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (14.3, 14.5)

DOSAGE AND ADMINISTRATION

- Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine. (2.2, 2.4)

- For intravenous infusion only. Do not administer as an intravenous push or bolus. DO NOT use Sodium Chloride Injection, USP. (2.4)
- Premedicate for prevention of chemotherapy-induced nausea and vomiting. (2.2)
- The recommended dosage of ENHERTU for HER2-positive or HER2-low breast cancer, HER2-mutant NSCLC, and HER2-positive (IHC 3+) solid tumors is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for HER2-positive gastric cancer is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- Management of adverse reactions (ILD, neutropenia, thrombocytopenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of ENHERTU. (2.3)

DOSAGE FORMS AND STRENGTHS

For injection: 100 mg lyophilized powder in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Neutropenia: Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Manage through treatment interruption or dose reduction. (2.3, 5.2)
- Left Ventricular Dysfunction: Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage through treatment interruption or discontinuation. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF). (2.3, 5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥20%), including laboratory abnormalities, in patients with:

- HER2-positive or HER2-low metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive (including IHC 3+) solid tumors are nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, vomiting, increased blood alkaline phosphatase, alopecia, constipation, decreased appetite, decreased blood potassium, diarrhea, musculoskeletal pain, and abdominal pain. (6.1)
- HER2-positive gastric cancer are decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhea, decreased blood potassium, vomiting, constipation, increased blood bilirubin, pyrexia, and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of ENHERTU. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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- 1.5 HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].**
- **Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception [see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].**

1 INDICATIONS AND USAGE

1.1 HER2-Positive Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) breast cancer who have received a prior anti-HER2-based regimen either:

- in the metastatic setting, or
- in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

1.2 HER2-Low Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy [see Dosage and Administration (2.1)].

1.3 HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate and duration of response [see *Clinical Studies* (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 HER2-Positive Locally Advanced or Metastatic Gastric Cancer

ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

1.5 HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on objective response rate and duration of response [see *Clinical Studies* (14.5)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

HER2-Low Unresectable or Metastatic Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer with ENHERTU based on HER2 expression (IHC 1+ or IHC 2+/ISH-) [see *Clinical Studies* (14.2)].

HER2-Mutant Unresectable or Metastatic NSCLC

Select patients for the treatment of unresectable or metastatic HER2-mutant NSCLC with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in tumor or plasma specimens [see *Clinical Studies* (14.3)]. If no mutation is detected in a plasma specimen, test tumor tissue.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer

Select patients with locally advanced or metastatic HER2-positive gastric cancer based on HER2 protein overexpression or HER2 gene amplification (IHC 3+ or IHC 2+/ISH positive). Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

Select patients for treatment of unresectable or metastatic solid tumors with ENHERTU based on HER2-positive (IHC 3+) specimens [see *Clinical Studies* (14.5)]. An FDA-approved test for the detection of HER2-positive (IHC 3+) solid tumors for treatment with ENHERTU is not currently available.

Additional Patient Selection Information

Information on FDA-approved tests for the detection of HER2 protein expression, HER2 gene amplification, and activating HER2 mutations is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage and Schedules

Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine.

Slow or interrupt the infusion rate if the patient develops infusion-related symptoms.

Permanently discontinue ENHERTU in case of severe infusion reactions.

Premedication

ENHERTU is highly emetogenic [see *Adverse Reactions* (6.1)], which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting.

Recommended Dosage for HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant Unresectable or Metastatic NSCLC, and HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors.

The recommended dosage of ENHERTU is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Recommended Dosage for HER2-Positive Locally Advanced or Metastatic Gastric Cancer

The recommended dosage of ENHERTU is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

2.3 Dosage Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described in Tables 1 and 2.

Do not re-escalate the ENHERTU dose after a dose reduction is made.

If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.

Table 1: Dosage Reduction Schedule

Dose Reduction Schedule	Breast Cancer, NSCLC, and IHC 3+ Solid Tumors	Gastric Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment.	Discontinue treatment.

Table 2: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Treatment Modification
Interstitial Lung Disease (ILD)/Pneumonitis [see <i>Warnings and Precautions</i> (5.1)]	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt ENHERTU until resolved to Grade 0, then: - if resolved in 28 days or less from date of onset, maintain dose. - if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). - consider corticosteroid treatment as soon as ILD/pneumonitis is suspected.
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	- Permanently discontinue ENHERTU. - Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected.
Neutropenia	Grade 3 (less than 1.0 to 0.5 x 10 ⁹ /L)	Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.

Adverse Reaction	Severity		Treatment Modification
[see Warnings and Precautions (5.2)]	Grade 4 (less than $0.5 \times 10^9/L$)		- Interrupt ENHERTU until resolved to Grade 2 or less. - Reduce dose by one level (see Table 1).
Febrile Neutropenia [see Warnings and Precautions (5.2)]	Absolute neutrophil count of less than $1.0 \times 10^9/L$ and temperature greater than $38.3^\circ C$ or a sustained temperature of $38^\circ C$ or greater for more than one hour		- Interrupt ENHERTU until resolved. - Reduce dose by one level (see Table 1).
Thrombocytopenia [see Adverse Reactions (6.1)]	Grade 3 (platelets less than 50 to $25 \times 10^9/L$)		Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.
	Grade 4 (platelets less than $25 \times 10^9/L$)		- Interrupt ENHERTU until resolved to Grade 1 or less. - Reduce dose by one level (see Table 1).
Left Ventricular Dysfunction [see Warnings and Precautions (5.3)]	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	- Continue treatment with ENHERTU. - Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	- Interrupt ENHERTU. - Repeat LVEF assessment within 3 weeks. - If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. - If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
		LVEF less than 40% or absolute decrease from baseline is greater than 20%	- Interrupt ENHERTU. - Repeat LVEF assessment within 3 weeks. - If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
	Symptomatic congestive heart failure (CHF)		Permanently discontinue ENHERTU.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v.5.0).

2.4 Preparation and Administration

In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU (fam-trastuzumab deruxtecan-nxki) and not trastuzumab or ado-trastuzumab emtansine.

Reconstitute and further dilute ENHERTU prior to intravenous infusion. Use appropriate aseptic technique.

ENHERTU (fam-trastuzumab deruxtecan-nxki) is a hazardous drug. Follow applicable special handling and disposal procedures.¹

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed [see *Dosage and Administration* (2.2)].
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours from the time of reconstitution, protect the vial from light. Do not freeze.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

- Withdraw the calculated amount from the vial(s) using a sterile syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing **100 mL of 5% Dextrose Injection, USP**. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene).
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- Discard any unused portion left in the vials.

Administration

- If not used immediately, store the diluted ENHERTU in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature between 20°C to 25°C (68°F to 77 °F) for up to 4 hours including preparation and infusion time.
- Protect from light. Do not freeze.
- The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours.
- If the prepared infusion solution was stored refrigerated (2°C to 8°C [36°F to 46°F]), allow the solution to reach room temperature prior to administration. Cover the infusion bag to protect from light.
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene.
- Administer ENHERTU with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.
- Do NOT administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light during administration.
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.

3 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of fam-trastuzumab deruxtecan-nxki as a white to yellowish white lyophilized powder in a single-dose vial for reconstitution and further dilution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU [see *Adverse Reactions* (6.1)]. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment.

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥ 0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery [see *Dosage and Administration* (2.3)]. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥ 1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD [see *Dosage and Administration* (2.3)].

HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

5.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction [see *Dosage and Administration* (2.3)].

HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 63% of patients. Seventeen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1% of patients.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

5.3 Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see *Dosage and Administration* (2.3)].

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.8% of patients, of which 0.6% were Grade 3.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see *Use in Specific Populations* (8.1), *Clinical Pharmacology* (12.1), *Nonclinical Toxicology* (13.1)]. Advise patients of the potential risks to a fetus.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.1)]
- Neutropenia [see *Warnings and Precautions* (5.2)]
- Left Ventricular Dysfunction [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

HER2-Positive and HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 1799 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 65% were exposed for greater than 6 months and 38% were exposed for greater than 12 months. In this pooled safety population, the most common ($\geq 20\%$) adverse reactions (including laboratory abnormalities) were nausea (73%), decreased white blood cell count (70%), decreased hemoglobin (66%), decreased neutrophil count (63%), decreased lymphocyte count (58%), fatigue (56%), decreased platelet count (48%), increased aspartate aminotransferase (47%), increased alanine aminotransferase (43%), vomiting (40%), increased blood alkaline phosphatase (38%), alopecia (34%), constipation (33%), decreased appetite (32%), decreased blood potassium (31%), diarrhea (29%), musculoskeletal pain (24%), and abdominal pain (20%).

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

The data described in WARNINGS and PRECAUTIONS reflect exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01.

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03 [see *Clinical Studies (14.1)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU and 7 months (range: 0.7 to 25) for patients who received ado-trastuzumab emtansine.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, decreased hemoglobin, decreased lymphocyte count, increased alanine aminotransferase, decreased platelet count, fatigue, vomiting, increased blood alkaline phosphatase, alopecia, decreased blood potassium, constipation, musculoskeletal pain, diarrhea, decreased appetite, headache, respiratory infection, abdominal pain, increased blood bilirubin, and stomatitis.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast03.

Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast03

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	7	30	0.4
Vomiting	49	1.6	10	0.8
Constipation	34	0	20	0
Diarrhea	29	1.2	7	0.4
Abdominal pain ^a	21	0.8	8	0.4
Stomatitis ^b	20	0.8	5	0
Dyspepsia	11	0	6	0
General Disorders and Administration Site Conditions				
Fatigue ^c	49	6	35	0.8
Blood and Lymphatic System Disorders				
Anemia ^d	33	7	17	6
Skin and Subcutaneous Tissue Disorders				
Alopecia ^e	37	0.4	3.1	0

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^f	31	1.2	25	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.6	17	0.4
Investigations				
Decreased weight	17	1.2	6	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Respiratory infection ^g	22	0.8	12	1.1
Epistaxis	11	0	16	0.4
Cough	11	0.4	10	0
Interstitial lung disease ^h	11	0.8	1.9	0
Nervous System Disorders				
Headache ⁱ	22	0.4	16	0
Peripheral neuropathy ^j	13	0.4	14	0.4
Dizziness	13	0.4	8	0

Events were graded using NCI CTCAE version 5.0.

a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain

b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption

c Including fatigue, asthenia, malaise, and lethargy

d Including anemia, decreased hemoglobin, and decreased red blood cell count

e This Grade 3 event was reported by the investigator. Per NCI CTCAE v.5.0, the highest NCI CTCAE grade for alopecia is Grade 2.

f Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort

g Including respiratory tract infection, lower and upper respiratory tract infection, pneumonia, influenza, influenza-like illness, viral upper respiratory infection, bronchitis, and respiratory syncytial virus infection

h Interstitial lung disease includes events that were adjudicated as drug-induced ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For ado-trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism.

i Including headache and migraine

j Including peripheral neuropathy, peripheral sensory neuropathy, and paresthesia

Other clinically relevant adverse reactions reported in less than 10% of patients in the ENHERTU-treated group were:

- **Respiratory, Thoracic and Mediastinal Disorders:** dyspnea (8%)
- **Skin and Subcutaneous Tissue Disorders:** pruritus (8%) and skin hyperpigmentation (6%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- **Nervous System Disorders:** dysgeusia (6%)
- **Metabolism and Nutrition Disorders:** dehydration (4.3%)
- **Eye Disorders:** blurred vision (3.5%)
- **Cardiac Disorders:** asymptomatic left ventricular ejection fraction decrease (2.7%) [see **Warnings and Precautions** (5.3)]
- **Injury, Poisoning and Procedural Complications:** infusion-related reactions (2.3%) [including hypersensitivity and infusion-related reactions]
- **Blood and Lymphatic System Disorders:** febrile neutropenia (0.8%)

Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03

Laboratory Parameter	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	74	8	24	0.8
Decreased neutrophil count	70	18	30	2.3
Decreased hemoglobin	64	7	38	6
Decreased lymphocyte count	55	14	23	3.9
Decreased platelet count	52	7	79	24
Chemistry				
Increased aspartate aminotransferase	67	0.8	83	5
Increased alanine aminotransferase	53	1.6	67	6
Increased blood alkaline phosphatase	49	0.8	46	0.8
Decreased blood potassium	35	4.7	39	1.5
Increased blood bilirubin	20	0	14	0
Increased blood creatinine	16	0.8	8	0.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-Breast02

The safety of ENHERTU was evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02 [see *Clinical Studies (14.1)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 11 months (range: 0.7 to 45) for patients who received ENHERTU.

Serious adverse reactions occurred in 26% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were COVID-19, ILD, pneumonia, vomiting, fatigue, and nausea. Fatalities due to adverse reactions occurred in 2.5% of patients including pneumonitis (2 patients), acute myeloid leukemia, brain edema, COVID-19, hemorrhage, hepatitis B, malignant pleural effusion, pneumonia, and vasogenic cerebral edema (one patient each).

ENHERTU was permanently discontinued in 20% of patients, of which ILD accounted for 9%. Dose interruptions due to adverse reactions occurred in 45% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, COVID-19, anemia, fatigue, leukopenia, upper respiratory tract infection, and thrombocytopenia. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, neutropenia, and vomiting.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased alanine aminotransferase, vomiting, increased aspartate aminotransferase, alopecia, increased blood alkaline phosphatase, constipation, decreased appetite, decreased blood potassium, diarrhea, musculoskeletal pain, increased blood bilirubin, abdominal pain, and headache.

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast02.

Table 5: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast02

Adverse Reactions	ENHERTU 5.4 mg/kg N=404		Treatment of Physician's Choice N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	73	7	37	2.6
Vomiting	38	3.7	13	1
Constipation	35	0.3	11	0.5
Diarrhea	27	2.7	54	7
Abdominal pain ^a	22	1	20	2.1
Dyspepsia	12	0	9	0
Stomatitis ^b	12	1	21	1
General Disorders and Administration Site Conditions				
Fatigue ^c	62	9	37	1
Skin and Subcutaneous Tissue Disorders				
Alopecia	37	0.3	4.1	0
Metabolism and Nutrition Disorders				
Decreased appetite	31	1.7	18	0.5
Blood and Lymphatic System Disorders				
Anemia ^d	29	8	14	3.1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^e	25	0.7	18	0.5
Nervous System Disorders				
Headache ^f	20	0.3	6	0
Investigations				
Decreased weight	18	0.3	3.6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	13	0	10	0
Interstitial lung disease ^g	10	0.7	0.5	0.5

Events were graded using NCI CTCAE version 5.0.

a Including abdominal discomfort, abdominal pain, upper abdominal pain, lower abdominal pain, and gastrointestinal pain

b Including aphthous ulcer, mouth ulceration, and stomatitis

c Including asthenia, fatigue, lethargy, and malaise

d Including anemia, decreased hemoglobin, and decreased red blood cell count

e Including back pain, bone pain, limb discomfort, musculoskeletal chest pain, musculoskeletal pain, muscle spasms, myalgia, neck pain, and pain in extremity

f Including headache and migraine

g Interstitial lung disease includes events that were adjudicated as drug-induced ILD for ENHERTU: pneumonitis, interstitial lung disease, idiopathic interstitial pneumonia, lung disorder, pulmonary toxicity, and pneumonia.

Other clinically relevant adverse reactions reported in less than 10% of patients in the ENHERTU-treated group were:

- *Respiratory, Thoracic and Mediastinal Disorders*: dyspnea (8%) and epistaxis (8%)
- *Skin and Subcutaneous Tissue Disorders*: rash (8%) [including rash, pustular rash, maculo-papular rash, and pruritic rash], pruritis (5%), skin hyperpigmentation (5%) [including skin hyperpigmentation and pigmentation disorder]
- *Nervous System Disorders*: dizziness (8%) and dysgeusia (8%)
- *Cardiac Disorders*: asymptomatic left ventricular ejection fraction decrease (4.2%) [see *Warnings and Precautions* (5.3)]
- *Eye Disorders*: dry eye (6%) and blurred vision [including blurred vision and visual impairment] (3%)
- *Metabolism and Nutrition Disorders*: dehydration (2.7%)
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (1.2%)
- *Blood and Lymphatic System Disorders*: febrile neutropenia (0.3%)

Table 6: Selected Laboratory Abnormalities in Patients in DESTINY-Breast02

Laboratory Parameter	ENHERTU 5.4 mg/kg N=404		Treatment of Physician's Choice N=195	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	70	12	42	3.2
Decreased hemoglobin	67	9	54	3.2
Decreased neutrophil count	64	16	34	4.7
Decreased lymphocyte count	58	17	38	4.7
Decreased platelet count	48	2.7	31	1.6
Chemistry				
Increased alanine aminotransferase	43	1	32	1.6
Increased aspartate aminotransferase	37	0.7	29	2.1
Increased blood alkaline phosphatase	37	0	17	0
Decreased blood potassium	30	3.7	29	8
Increased blood bilirubin	23	0.3	44	2.1
Increased blood creatinine	7	0.3	13	0

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-Breast01 and Study DS8201-A-J101

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900) [see *Clinical Studies* (14.1)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

In the pooled 234 patients, the median age was 56 years (range: 28-96), 74% of patients were <65 years, 99.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an Eastern Cooperative Oncology

Group (ECOG) performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, decreased blood potassium, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, fatigue, vomiting, alopecia, increased aspartate aminotransferase, increased alanine aminotransferase, decreased platelet count, constipation, decreased appetite, diarrhea, decreased blood potassium, and cough.

Tables 7 and 8 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients in DESTINY-Breast01 and Study DS8201-A-J101.

Table 7: Common Adverse Reactions ($\geq 10\%$ All Grades or $\geq 2\%$ Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	79	7
Vomiting	47	3.8
Constipation	35	0.9
Diarrhea	29	1.7
Abdominal pain ^a	19	1.3
Stomatitis ^b	14	0.9
Dyspepsia	12	0
General Disorders and Administration Site Conditions		
Fatigue ^c	59	6
Skin and Subcutaneous Tissue Disorders		
Alopecia	46	0.4 ^d
Rash ^e	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	32	1.3
Blood and Lymphatic System Disorders		
Anemia ^f	31	7
Respiratory, Thoracic and Mediastinal Disorders		

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Cough	20	0
Dyspnea	13	1.3
Epistaxis	13	0
Interstitial lung disease ^g	9	2.6 ^h
Nervous System Disorders		
Headache ⁱ	19	0
Dizziness	10	0
Infections and Infestations		
Upper respiratory tract infection ^j	15	0
Eye Disorders		
Dry eye	11	0.4 ^k

Events were graded using NCI CTCAE version 4.03.

a Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain

b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).

c Including fatigue and asthenia

d This Grade 3 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for alopecia is Grade 2.

e Including rash, pustular rash, and maculo-papular rash

f Including anemia, decreased hemoglobin, decreased hematocrit, and decreased red blood cell count

g Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

h All events had fatal outcomes (n=6).

i Including headache, sinus headache, and migraine

j Including influenza, influenza-like illness, and upper respiratory tract infection

k This Grade 4 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for dry eye is Grade 3.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (2.6%)
- *Blood and Lymphatic System Disorders*: febrile neutropenia (1.7%)

Table 8: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU in DESTINY-Breast01 and Study DS8201-A-J101

Laboratory Parameter	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased white blood cell count	70	7
Decreased hemoglobin	70	7
Decreased neutrophil count	62	16
Decreased platelet count	37	3.4
Chemistry		
Increased aspartate aminotransferase	41	0.9

Laboratory Parameter	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Increased alanine aminotransferase	38	0.4
Decreased blood potassium	26	3

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

HER2-Low Metastatic Breast Cancer

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast04 [see *Clinical Studies (14.2)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4.0% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, constipation, increased blood alkaline phosphatase, decreased appetite, musculoskeletal pain, diarrhea, and decreased blood potassium.

Tables 9 and 10 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast04.

Table 9: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	76	4.6	30	0
Vomiting	40	1.6	13	0
Constipation	34	0.8	22	0
Diarrhea	27	1.3	22	1.7
Abdominal pain ^a	18	0.5	13	0

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Stomatitis ^b	13	0.3	12	0.6
General Disorders and Administration Site Conditions				
Fatigue ^c	54	9	48	4.7
Pyrexia	12	0.3	13	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	40	0	33	0
Rash ^d	13	0	23	4.7
Blood and Lymphatic System Disorders				
Anemia ^e	39	10	27	5
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	19	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^f	32	1.3	31	0.6
Investigations				
Decreased weight	16	0.3	8	0
Vascular Disorders				
Hemorrhage ^g	16	0	3.5	0
Nervous System Disorders				
Headache ^h	15	0.3	6	0
Peripheral neuropathy ⁱ	13	0	29	5
Dizziness ^j	11	0.5	6	0
Infections and Infestations				
Upper respiratory tract infection ^k	14	0.3	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease ^l	12	1.3	0.6	0
Dyspnea	10	1.3	9	1.2

Events were graded using NCI CTCAE version 5.0.

a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain

b Including stomatitis, aphthous ulcer, mouth ulceration, and pharyngeal inflammation

c Including fatigue, asthenia, and malaise

d Including rash, pustular rash, pruritic rash, maculo-papular rash, palmar-plantar erythrodysesthesia syndrome, papular rash, macular rash, eczema, erythema multiforme, dermatitis, urticarial dermatitis, drug eruption, and dermatitis bullous

e Including anemia, decreased hemoglobin, and decreased red blood cell count

f Including back pain, myalgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, arthralgia, noncardiac chest pain, musculoskeletal stiffness, arthritis, spinal pain, and neck pain

g Including esophageal varices, hemorrhage, hemorrhoidal hemorrhage, epistaxis, hematuria, conjunctival hemorrhage, vaginal hemorrhage, gingival bleeding, genital hemorrhage, eye hemorrhage, hemoptysis, hemorrhagic cystitis, pharyngeal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, and esophageal hemorrhage

h Including headache and migraine

- i Including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia
- j Including dizziness, postural dizziness, and vertigo
- k Including upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis
- l Interstitial lung disease includes events that were adjudicated as drug-induced ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

Other clinically relevant adverse reactions reported in less than 10% of patients treated with ENHERTU:

- *Nervous System Disorders*: dysgeusia (10%)
- *Respiratory, Thoracic and Mediastinal Disorders*: cough (10%)
- *Gastrointestinal Disorders*: abdominal distension (5%), gastritis (2.7%), flatulence (2.4%)
- *Eye Disorders*: blurred vision (4.9%) [including blurred vision and visual impairment]
- *Skin and Subcutaneous Tissue Disorders*: pruritus (3.2%) and skin hyperpigmentation (2.7%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Metabolism and Nutrition Disorders*: dehydration (1.9%)
- *Blood and Lymphatic System Disorders*: febrile neutropenia (1.1%)
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (0.5%) [including injection-site reaction and chills]

Table 10: Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased white blood cell count	70	9	78	25
Decreased hemoglobin	64	8	53	6
Decreased neutrophil count	64	14	73	38
Decreased lymphocyte count	55	18	40	11
Decreased platelet count	44	6	21	0.6
Chemistry				
Increased aspartate aminotransferase	38	2.2	38	4.1
Increased alanine aminotransferase	36	0.8	38	4.1
Increased blood alkaline phosphatase	34	0.3	24	0
Decreased blood potassium	25	3.3	17	1.2
Increased blood bilirubin	16	2.7	15	0.6
Increased blood creatinine	15	1.1	9	0.6

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

HER2-Mutant Unresectable or Metastatic NSCLC

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients in DESTINY-Lung02 [see *Clinical Studies* (14.3)]. Patients received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity.

Nineteen percent of patients were exposed for greater than 6 months. The median age was 59 years (range 30 to 83); 64% were female; 23% were White, 64% were Asian, and 14% were other races.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued due to an adverse reaction in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, decreased blood potassium, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia.

Tables 11 and 12 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Lung02.

Table 11: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	61	3.0
Constipation	31	1.0
Vomiting ^a	26	2.0
Diarrhea	19	1.0
Stomatitis ^b	12	0
Blood and Lymphatic System Disorders		
Anemia	34	10
General Disorders and Administration Site Conditions		
Fatigue ^c	32	4.0
Metabolism and Nutrition Disorders		
Decreased appetite	30	1.0
Skin and Subcutaneous Tissue Disorders		
Alopecia	21	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^d	15	1.0

Events were graded using NCI CTCAE version 5.0.

a Including vomiting and retching

b Including mucosal inflammation and stomatitis

c Including asthenia, fatigue, and malaise

d Including back pain, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, musculoskeletal pain, myalgia, and pain in extremity

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- **Respiratory, Thoracic and Mediastinal Disorders:** interstitial lung disease (6%) [including interstitial lung disease that was adjudicated as drug-induced ILD including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure], dyspnea (5%), and epistaxis (3%)
- **Gastrointestinal Disorders:** abdominal pain (9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]
- **Skin and Subcutaneous Disorders:** rash (3%) [including rash and maculo-papular rash]
- **Infections and Infestations:** upper respiratory tract infection (4%) [including upper respiratory tract infection, pharyngitis, and laryngitis]
- **Nervous System Disorders:** headache (4%) [including headache and migraine]

Table 12: Select Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Laboratory Parameter	ENHERTU 5.4 mg/kg N=101 ^a	
	All Grades ^b %	Grades 3 or 4 ^b %
Hematology^c		
Decreased white blood cell count	60	4.0
Decreased hemoglobin	58	10
Decreased neutrophil count	52	12
Decreased lymphocyte count	43	16
Decreased platelet count	40	4.0
Chemistry		
Decreased albumin	39	0
Increased aspartate aminotransferase	35	1.0
Increased alanine aminotransferase	34	2.0
Increased alkaline phosphatase	22	0
Decreased blood potassium	17	2.0

a Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

b Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

c The denominator used to calculate the rate varied from 98 to 99 based on the number of patients with a baseline value and at least one post-treatment value.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 [see *Clinical Studies (14.4)*]. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia,

ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and decreased blood potassium. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhea, decreased blood potassium, vomiting, constipation, increased blood bilirubin, pyrexia, and alopecia.

Tables 13 and 14 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 13: Adverse Reactions in $\geq 10\%$ All Grades or $\geq 2\%$ Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

Adverse Reactions	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	63	4.8	47	1.6
Diarrhea	32	2.4	32	1.6
Vomiting	26	0	8	0
Constipation	24	0	23	0
Abdominal pain ^a	14	0.8	15	3.2
Stomatitis ^b	11	1.6	4.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	60	17	45	13
Dehydration	6	2.4	3.2	1.6
Blood and Lymphatic System Disorders				
Anemia ^c	58	38	31	23
Febrile neutropenia	4.8	4.8	3.2	3.2
General Disorders and Administration Site Conditions				
Fatigue ^d	55	9	44	4.8
Pyrexia	24	0	16	0
Peripheral edema	10	0	0	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	22	0	15	0

	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
Adverse Reactions	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease ^e	10	2.4	0	0
Hepatobiliary Disorders				
Abnormal hepatic function	8	3.2	1.6	1.6

Events were graded using NCI CTCAE version 4.03.

^a Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain

^b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering

^c Including anemia, decreased hemoglobin, decreased red blood cell count, and decreased hematocrit

^d Including fatigue, asthenia, and malaise

^e Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Cardiac Disorders*: asymptomatic left ventricular ejection fraction decrease (8%) [see *Warnings and Precautions* (5.3)]
- *Infections and Infestations*: pneumonia (6%)
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (1.6%)

Table 14: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased hemoglobin	75	38	55	23
Decreased white blood cell count	74	29	53	13
Decreased neutrophil count	72	51	45	23
Decreased lymphocyte count	70	28	53	12
Decreased platelet count	68	12	12	5
Chemistry				
Increased aspartate aminotransferase	58	9	32	8
Increased blood alkaline phosphatase	54	8	34	10
Increased alanine aminotransferase	47	9	17	1.7
Decreased blood potassium	30	4.8	18	8
Increased blood bilirubin	24	7	5	3.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who received ENHERTU 5.4 mg/kg in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and

DESTINY-CRC02 [see *Clinical Studies (14.1 and 14.5)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8.3 months (range 0.7 to 30.2).

The median age was 60 years (range 23 to 96); 74% were female; 51% were White, 42% were Asian, 2.9% were Black or African American, 3.5% were of Hispanic or Latino ethnicity; and 40% had an ECOG performance status 0 and 41% had an ECOG performance status of 1.

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection.

Tables 15 and 16 summarize the common adverse reactions and laboratory abnormalities in DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-Breast01, and DESTINY-CRC02.

Table 15: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in HER2-positive (IHC 3+) Patients Treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Adverse Reactions	ENHERTU 5.4 mg/kg N= 347	
	All Grades %	Grade 3 or 4 %
Gastrointestinal Disorders		
Nausea	69	7
Vomiting	35	3.5
Diarrhea	31	4.3
Constipation	28	0.6
Stomatitis ^a	20	0.9
Abdominal pain ^b	18	2.0
Dyspepsia	12	0.3
General Disorders and Administration Site Conditions		
Fatigue ^c	59	10
Pyrexia	11	0

Adverse Reactions	ENHERTU 5.4 mg/kg N= 347	
	All Grades %	Grade 3 or 4 %
Edema ^d	11	0.6
Metabolism and Nutrition Disorders		
Decreased appetite	34	2.6
Skin and Subcutaneous Tissue Disorders		
Alopecia	34	0.3
Rash ^e	13	0.6
Infections and Infestations		
Upper respiratory tract infection ^f	20	0
Pneumonia	6	2.3
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^g	19	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough ^h	18	0
Interstitial lung disease ⁱ	16	0.6
Dyspnea ^j	12	1.7
Nervous System Disorders		
Headache ^k	15	0
Investigations		
Decreased weight	10	0.3

^a Including stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption, tongue ulceration, cheilitis.

^b Including abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, gastrointestinal pain.

^c Including fatigue, asthenia, malaise, lethargy.

^d Including peripheral edema, edema, localized edema, face edema, skin edema, periorbital edema, eyelid edema

^e Including rash, pustular rash, maculo-papular rash, papular rash, macular rash, pruritic rash dermatitis acneiform, dermatitis, eczema, palmar-plantar erythrodysesthesia syndrome.

^f Including influenza, influenza-like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis.

^g Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, limb discomfort.

^h Including cough, productive cough, upper-airway cough syndrome

ⁱ Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, organizing pneumonia, respiratory failure, acute respiratory failure, alveolitis, lung opacity, lymphangitis, pneumonia, bacterial pneumonia, pulmonary fibrosis, and radiation pneumonitis. Grade 5 adjudicated drug-induced ILD events were pneumonitis, respiratory failure, acute respiratory failure, lymphangitis, pulmonary fibrosis.

^j Including dyspnea, exertional dyspnea

^k Including migraine, headache, sinus headache.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Respiratory, thoracic and mediastinal disorders*: epistaxis (9%)
- *Nervous System Disorders*: dizziness (9%) [including dizziness, postural dizziness, and vertigo] and dysgeusia (6%)
- *Skin and Subcutaneous Disorders*: pruritus (5%) and skin hyperpigmentation (4.3%) [including skin hyperpigmentation, skin discoloration, pigmentation disorder]
- *Eye Disorders*: blurred vision (4.0%) [including blurred vision, visual impairment]
- *Metabolism and Nutrition Disorders*: dehydration (3.2%)
- *Gastrointestinal Disorders*: abdominal distension (2.6%), flatulence (1.7%) and gastritis (0.9%)
- *Blood and Lymphatic System Disorders*: febrile neutropenia (1.7%)
- *Injury, Poisoning, and Procedural Complications*: infusion-related reactions (1.4%) [including administration related reaction, anaphylactic reaction, hypersensitivity, infusion-related reaction and infusion-related hypersensitivity reaction]

Table 16: Selected Laboratory Abnormalities in HER2-positive (IHC 3+) Patients Treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Laboratory Parameter	ENHERTU 5.4 mg/kg	
	N= 347 ^a	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased white blood cell count	75	11
Decreased hemoglobin	67	10
Decreased neutrophil count	66	21
Decreased lymphocyte count	58	21
Decreased platelet count	51	7
Chemistry		
Increased aspartate aminotransferase	45	1.5
Increased alanine aminotransferase	44	1.5
Increased blood alkaline phosphatase	36	1.2
Decreased blood potassium	29	6
Decreased sodium	22	2.9
Increased blood bilirubin	15	0.6
Increased blood creatinine	14	0.6

^a Percentages were calculated using the number of patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (*see Data*). Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [*see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)*]. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with fam-trastuzumab deruxtecan-nxki.

8.2 Lactation

Risk Summary

There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception

Females

ENHERTU can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose [*see Nonclinical Toxicology (13.1)*].

Infertility

Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1287 patients with HER2-positive or HER2-low breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 3.8% were 75 years or older. No overall differences in efficacy within clinical studies were observed between patients ≥ 65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (59%) as compared to younger patients (49%).

Of the 101 patients with HER2-mutant unresectable or metastatic NSCLC treated with ENHERTU 5.4 mg/kg, 40% were 65 years or older and 8% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

Of the 125 patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg in DESTINY-PanTumor02, DESTINY-Lung01 or DESTINY-CRC02, 39% were 65 years or older and 9% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

8.6 Renal Impairment

No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance [CLcr] ≥ 60 and < 90 mL/min) or moderate (CLcr ≥ 30 and < 60 mL/min) renal impairment [see *Clinical Pharmacology* (12.3)]. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment [see *Warnings and Precautions* (5.1)]. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr < 30 mL/min) [see *Clinical Pharmacology* (12.3)].

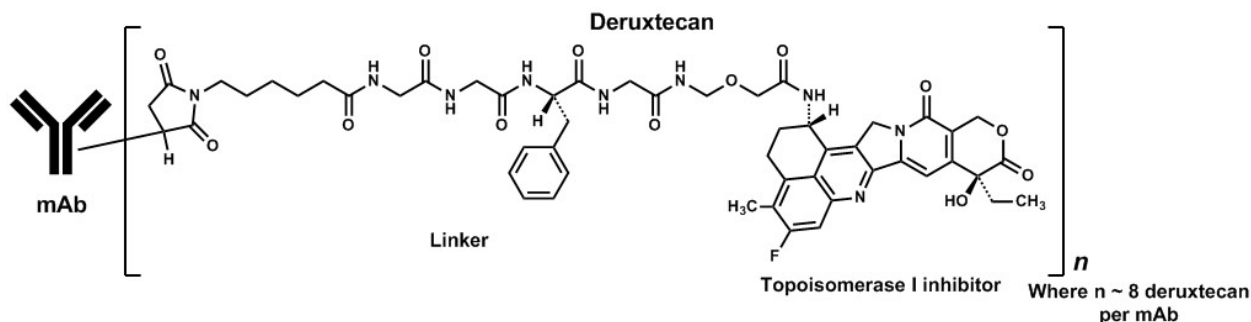
8.7 Hepatic Impairment

No dose adjustment of ENHERTU is required in patients with mild (total bilirubin $\leq$ ULN and any AST $>$ ULN or total bilirubin > 1 to 1.5 times ULN and any AST) or moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see *Dosage and Administration* (2.3)]. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin > 3 times ULN and any AST) [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody and topoisomerase inhibitor conjugate. Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb), covalently linked to 2) a topoisomerase inhibitor, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of a protease-cleavable maleimide tetrapeptide linker and the topoisomerase inhibitor, DXd, which is an exatecan derivative.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology, and the topoisomerase inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule. Fam-trastuzumab deruxtecan-nxki has the following structure:



ENHERTU (fam-trastuzumab deruxtecan-nxki) is a sterile, white to yellowish white, preservative-free lyophilized powder in single-dose vials. Each vial delivers 100 mg of fam-trastuzumab deruxtecan-nxki, L-histidine (4.45 mg), L-histidine hydrochloride monohydrate (20.2 mg), polysorbate 80 (1.5 mg), and sucrose (450 mg). Following reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting concentration of fam-trastuzumab deruxtecan-nxki is 20 mg/mL with a pH of 5.5. The resulting solution is administered by intravenous infusion following dilution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody-drug conjugate. The antibody is a humanized anti-HER2 IgG1. The small molecule, DXd, is a topoisomerase I inhibitor attached to the antibody by a cleavable linker. Following binding to HER2 on tumor cells, fam-trastuzumab deruxtecan-nxki undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death.

12.2 Pharmacodynamics

Exposure-Response Relationships

Exposure relationship for efficacy has not been fully characterized. Higher systemic exposure to fam-trastuzumab deruxtecan-nxki was associated with a higher incidence rate of any grade ILD.

Cardiac Electrophysiology

The administration of multiple doses of ENHERTU 6.4 mg/kg every 3 weeks did not show a large mean effect (i.e., >20 ms) on the QTc interval in an open-label, single-arm study in 51 patients with metastatic HER2-positive cancer.

12.3 Pharmacokinetics

The pharmacokinetics of fam-trastuzumab deruxtecan-nxki was evaluated in patients with cancer. Following a single dose, exposures (C_{max} and AUC) of fam-trastuzumab deruxtecan-nxki and released topoisomerase inhibitor (DXd) increased proportionally over a dose range of 3.2 mg/kg to 8 mg/kg (approximately 0.6 to 1.5 times the recommended dose in breast cancer, NSCLC, and HER2-positive (IHC 3+) solid tumors and 0.5 to 1.25 times the recommended dose in gastric cancer).

At the recommended dosage of ENHERTU for patients with metastatic breast cancer, NSCLC, and HER2-positive (IHC 3+) solid tumors, the geometric mean (coefficient of variation [CV]%) C_{max} of fam-trastuzumab deruxtecan-nxki and DXd were 132 µg/mL (20%) and 4.7 ng/mL (48%), respectively, and the AUC of fam-trastuzumab deruxtecan-nxki and DXd were 772 µg·day/mL (27%) and 29 ng·day/mL (48%), respectively. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 35% at steady-state (Cycle 3).

At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the geometric mean $C_{max,ss}$ of fam-trastuzumab deruxtecan-nxki and DXd were 126 µg/mL (18%) and 5.2 ng/mL (42%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan-nxki and DXd were 743 µg·day/mL (26%) and 33 ng·day/mL (43%), respectively. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 39% at steady-state (Cycle 3).

Distribution

The estimated volume of distribution of the central compartment (V_c) of fam-trastuzumab deruxtecan-nxki was 2.68 L.

DXd plasma protein binding is approximately 97% and the blood-to-plasma ratio is approximately 0.6, in vitro.

Elimination

The median elimination half-life ($t_{1/2}$) of fam-trastuzumab deruxtecan-nxki is 5.4-5.7 days. The estimated systemic clearance of fam-trastuzumab deruxtecan-nxki was 0.41 L/day.

The median elimination half-life ($t_{1/2}$) of DXd is 5.4-6.1 days. The estimated systemic clearance of DXd was 18.3 L/h.

Metabolism

The humanized HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In vitro, DXd is primarily metabolized by CYP3A4.

Specific Populations

No clinically significant differences in the pharmacokinetics of fam-trastuzumab deruxtecan-nxki or DXd were observed for age (20-96 years); race (Asian vs Non-Asian), including White, and Black or African American; sex; body weight (27.3-125.4 kg); tumor types; mild hepatic impairment; mild or moderate renal impairment.

The pharmacokinetics of fam-trastuzumab deruxtecan-nxki or DXd in patients with moderate to severe hepatic impairment or severe renal impairment is unknown.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A Inhibitors on DXd: Coadministration of itraconazole, a strong CYP3A inhibitor, with multiple doses of ENHERTU increased steady state $AUC_{0-17 \text{ days}}$ of fam-trastuzumab deruxtecan-nxki by 11% and DXd by 18%. The impact of these changes is not clinically meaningful.

Effect of OATP Inhibitors on DXd: Coadministration of ritonavir, a dual inhibitor of OATP1B/CYP3A, with multiple doses of ENHERTU increased steady state $AUC_{0-17 \text{ days}}$ of fam-trastuzumab deruxtecan-nxki by 19% and DXd by 22%. The impact of these changes is not clinically meaningful.

In Vitro Studies

Effects of DXd on CYP Enzymes: DXd does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A nor induce CYP1A2, CYP2B6, or CYP3A.

Effects of DXd on Transporters: At clinically relevant concentrations (steady-state C_{max} of $\sim 0.2 \mu\text{mol/L}$), DXd has a low potential to inhibit OAT1 (IC_{50} value of $12.7 \mu\text{mol/L}$), OAT3, OCT1, OCT2, OATP1B1 (IC_{50} value of $14.4 \mu\text{mol/L}$), OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

Effects of Other Drugs on DXd: DXd is a substrate of OATP1B1, OATP1B3, MATE2-K, P-gp, MRP1, and BCRP.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of ENHERTU or of other anti-HER2 products.

Among patients who received ENHERTU as a single agent and were tested for ADA over a 6 to 9-month treatment period in 12 clinical trials, anti-fam-trastuzumab deruxtecan-nxki antibodies developed in 1.5% (27/1798) of patients who received ENHERTU 5.4 mg/kg every three weeks and in 2.6% (21/793) of patients who received ENHERTU 6.4 mg/kg

every three weeks. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, safety, or effectiveness of fam-trastuzumab deruxtecan-nxki.

The incidence of neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0.06% and 0% for the respective dosages. Due to the limited number of patients who developed neutralizing antibodies against fam-trastuzumab deruxtecan-nxki, the effect of neutralizing antibodies is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with fam-trastuzumab deruxtecan-nxki.

The topoisomerase inhibitor component of fam-trastuzumab deruxtecan-nxki, DXd, was clastogenic in both an in vivo rat bone marrow micronucleus assay and an in vitro Chinese hamster lung chromosome aberration assay and was not mutagenic in an in vitro bacterial reverse mutation assay.

Fertility studies have not been conducted with fam-trastuzumab deruxtecan-nxki. In a six-week repeat-dose toxicity study in rats, intravenous administration of fam-trastuzumab deruxtecan-nxki resulted in spermatid retention at 20 mg/kg and 60 mg/kg (approximately 4 and 9 times the human recommended dose of 5.4 mg/kg based on AUC, respectively). Decreased testes and epididymides weights, tubular atrophy/degeneration in testes, and reduced sperm count in epididymides were observed at a dose of 197 mg/kg (19 times the human recommended dose of 5.4 mg/kg based on AUC). In a three-month repeat-dose toxicity study in monkeys, intravenous administration of fam-trastuzumab deruxtecan-nxki resulted in decreased numbers of round spermatids in the testes at seminiferous tubule stages V to VI at ≥ 30 mg/kg (≥ 7 times the human recommended dose of 5.4 mg/kg based on AUC). Evidence of reversibility was observed in monkeys by the end of a three-month recovery period.

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

The efficacy of ENHERTU was evaluated in study DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids, ILD/pneumonitis at screening, or clinically significant cardiac disease. Patients were also excluded for untreated and symptomatic brain metastases, ECOG performance status >1 , or prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting.

Patients were randomized 1:1 to receive either ENHERTU 5.4 mg/kg (N=261) or ado-trastuzumab emtansine 3.6 mg/kg (N=263) by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and visceral versus non-visceral disease. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for all patients at baseline. The major efficacy outcomes were progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and overall survival (OS). Confirmed objective response rate (ORR) was an additional outcome measure.

The median age was 54 years (range: 20-83); 80% were <65 years; 99.6% were female; 60% were Asian, 27% were White, and 3.6% were Black; 11% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (63%) or 1 (37%) at baseline. Seventy-three percent had visceral disease, 16% had brain metastases at baseline, 52% were hormone receptor positive (HR+), and 48% of patients had received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 10%.

Efficacy results are summarized in Table 17 and Figures 1 and 2.

Table 17: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	ENHERTU 5.4 mg/kg	Ado-trastuzumab emtansine 3.6 mg/kg
Progression-Free Survival (PFS) per BICR		
N	261	263
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value [†]	p< 0.0001	
Overall Survival (OS)		
N	261	263
Number of events (%)	72 (27.6)	97 (36.9)
Median, months (95% CI)	NR (40.5, NE)	NR (34.0, NE)
Hazard ratio (95% CI)	0.64 (0.47, 0.87)	
p-value [§]	p=0.0037	
Confirmed Objective Response Rate (ORR) per BICR*		
N	248	241
n (%)	205 (82.7)	87 (36.1)
95% CI	(77.4, 87.2)	(30.0, 42.5)
Complete Response n (%)	39 (15.7)	20 (8.3)
Partial Response n (%)	166 (66.9)	67 (27.8)

CI = confidence interval; NR = not reached; NE = not estimable

[†] The stratified log-rank test p-value is compared with the allocated alpha of 0.0002 for this interim analysis (with 73% of the planned number of events for final analysis).

[§] The stratified log-rank test p-value is compared with the allocated alpha of 0.013 for this interim analysis (with 68% of the planned number of events for final analysis).

*Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.

**Figure 1: Kaplan-Meier Plot of Progression-Free Survival per BICR
(Intent-to-Treat Analysis Set)**

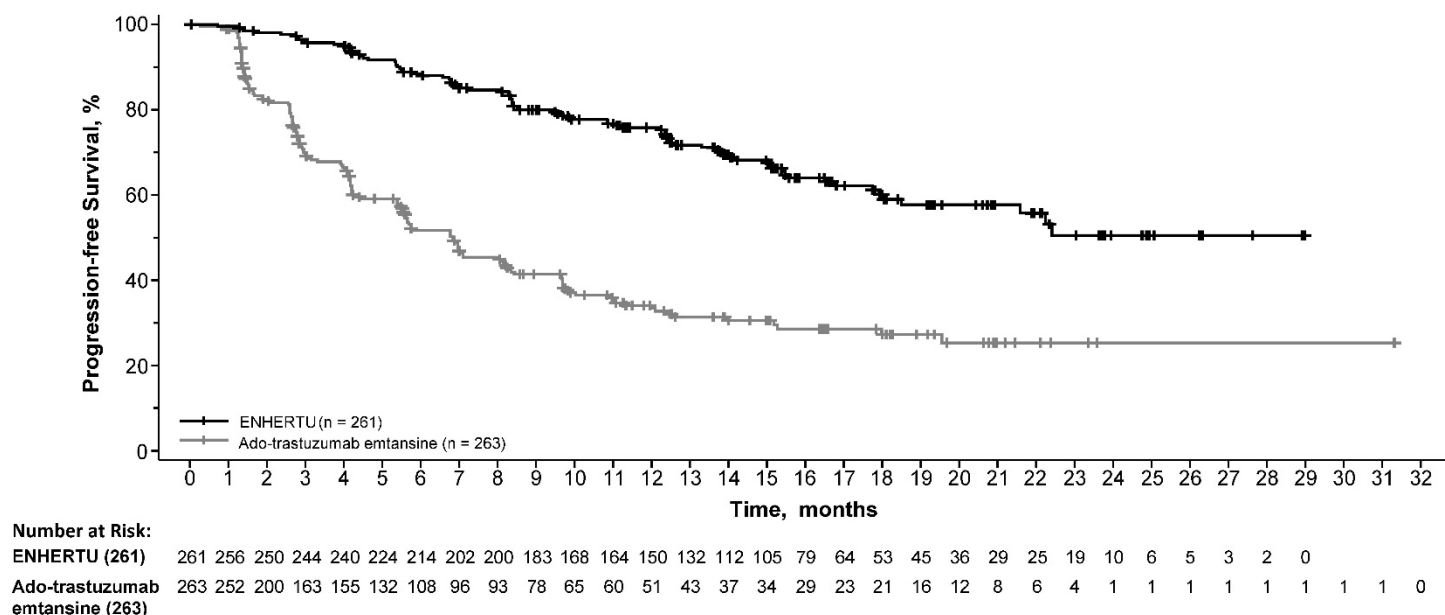
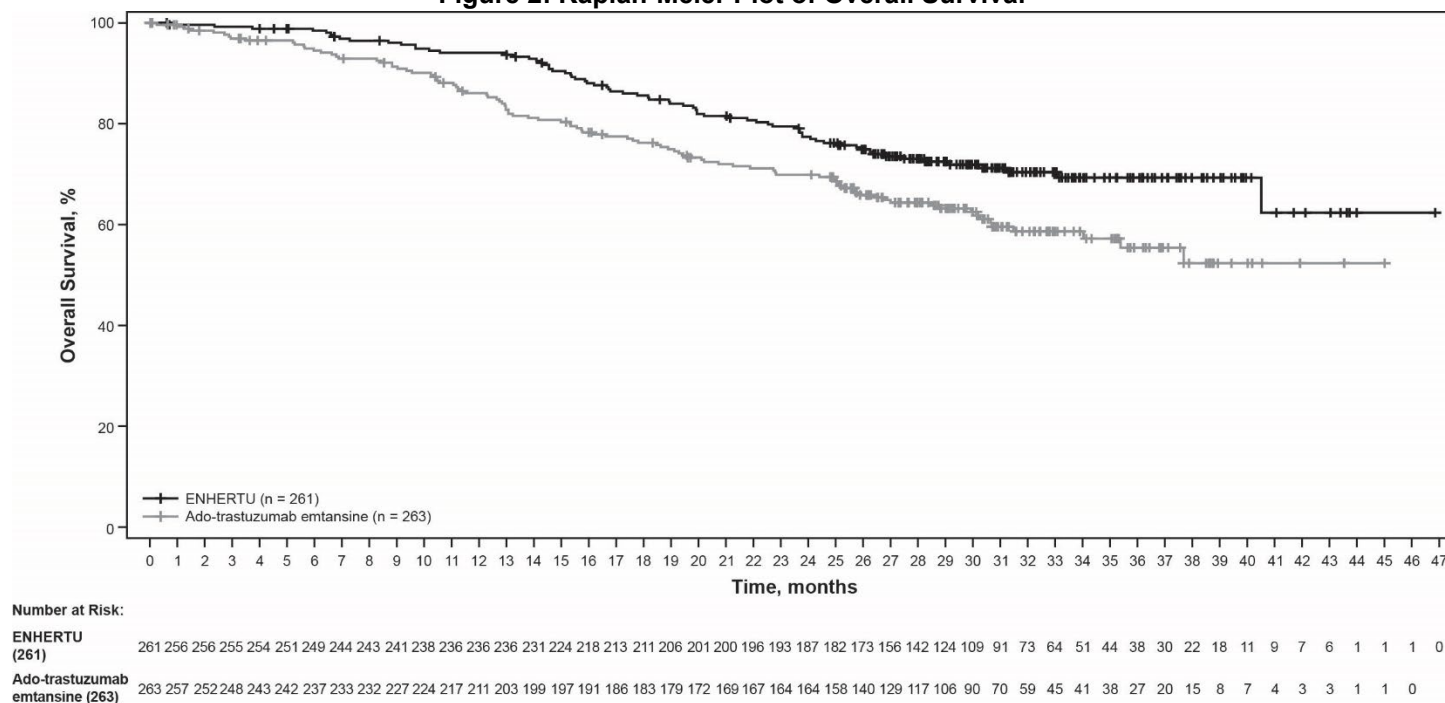


Figure 2: Kaplan-Meier Plot of Overall Survival



DESTINY-Breast02

The efficacy of ENHERTU was evaluated in study DESTINY-Breast02 (NCT03523585), a multicenter, open-label, randomized study that enrolled 608 patients with HER2-positive, unresectable and/or metastatic breast cancer who were previously treated with ado-trastuzumab emtansine. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=406) by intravenous infusion every 3 weeks or treatment of physician's choice (TPC) (N=202, trastuzumab plus capecitabine or lapatinib plus capecitabine) until unacceptable toxicity or disease

progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and visceral versus non-visceral disease. The major efficacy outcomes were PFS as assessed by BICR based on RECIST v1.1 and OS.

The median age was 54 years (range: 22 to 88); 80% were <65 years; 99% were female; 63% were White, 29% were Asian, and 3% were Black or African American; 11% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (57%) or 1 (42%) at baseline. Seventy-eight percent had visceral disease, 18% had brain metastases at baseline, 59% were hormone receptor positive (HR+), and 5% of patients had received one line of prior systemic therapy in the metastatic setting.

Efficacy results are summarized in Table 18 and Figures 3 and 4.

Table 18: Efficacy Results in DESTINY-Breast02

Efficacy Parameter	ENHERTU N=406	Treatment of Physician's Choice N=202
PFS per BICR		
Number of events (%)	200 (49.3)	125 (61.9)
Median, months (95% CI)	17.8 (14.3, 20.8)	6.9 (5.5, 8.4)
Hazard ratio (95% CI)	0.36 (0.28, 0.45)	
p-value	p<0.0001	
Overall Survival (OS)		
Number of events (%)	143 (35.2)	86 (42.6)
Median, months (95% CI)	39.2 (32.7, NE)	26.5 (21.0, NE)
Hazard ratio (95% CI)	0.66 (0.50, 0.86)	
p-value ^a	p=0.0021	
Confirmed Objective Response Rate (ORR) per BICR		
n (%)	283 (69.7)	59 (29.2)
95% CI	(65.0, 74.1)	(23.0, 36.0)
Complete Response n (%)	57 (14.0)	10 (5.0)
Partial Response n (%)	226 (55.7)	49 (24.3)
Duration of Response per BICR		
Median, months (95% CI)	19.6 (15.9, NE)	8.3 (5.8, 9.5)

CI = confidence interval; NE=not estimable

^a The stratified log-rank test p-value is compared with the allocated alpha of 0.004 for this interim analysis (with 53% of the planned number of events for final analysis)

Figure 3: Kaplan-Meier Plot of Progression-free Survival Per BICR

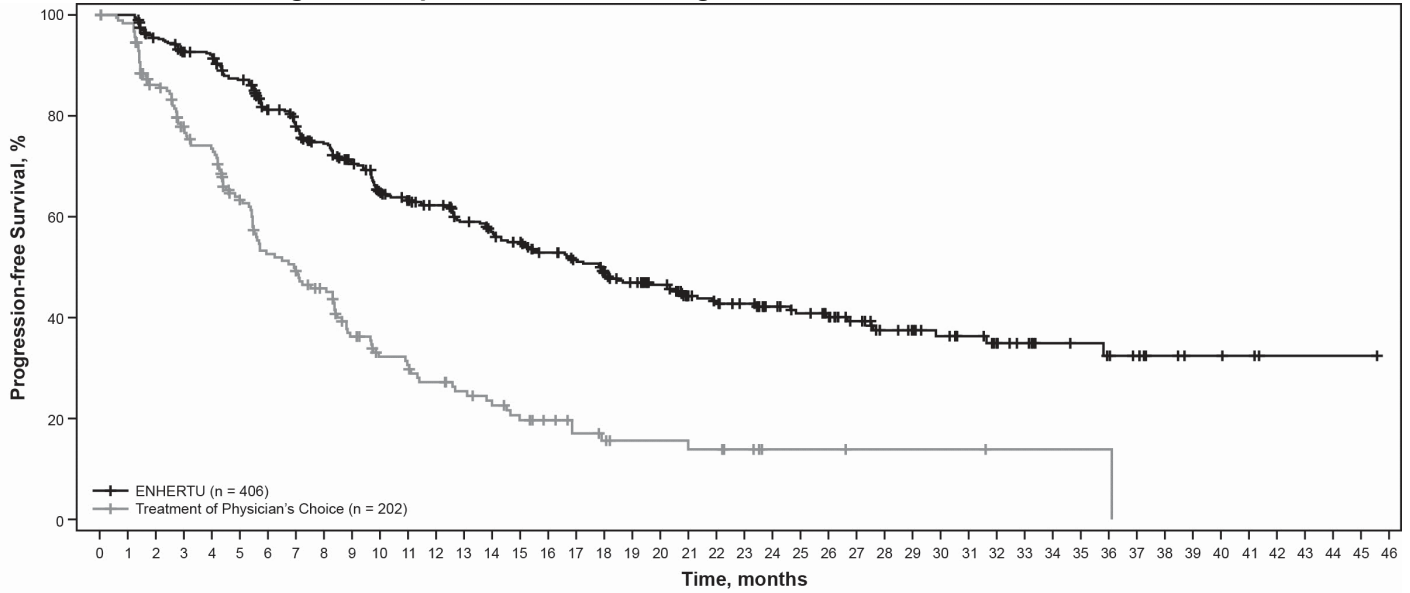
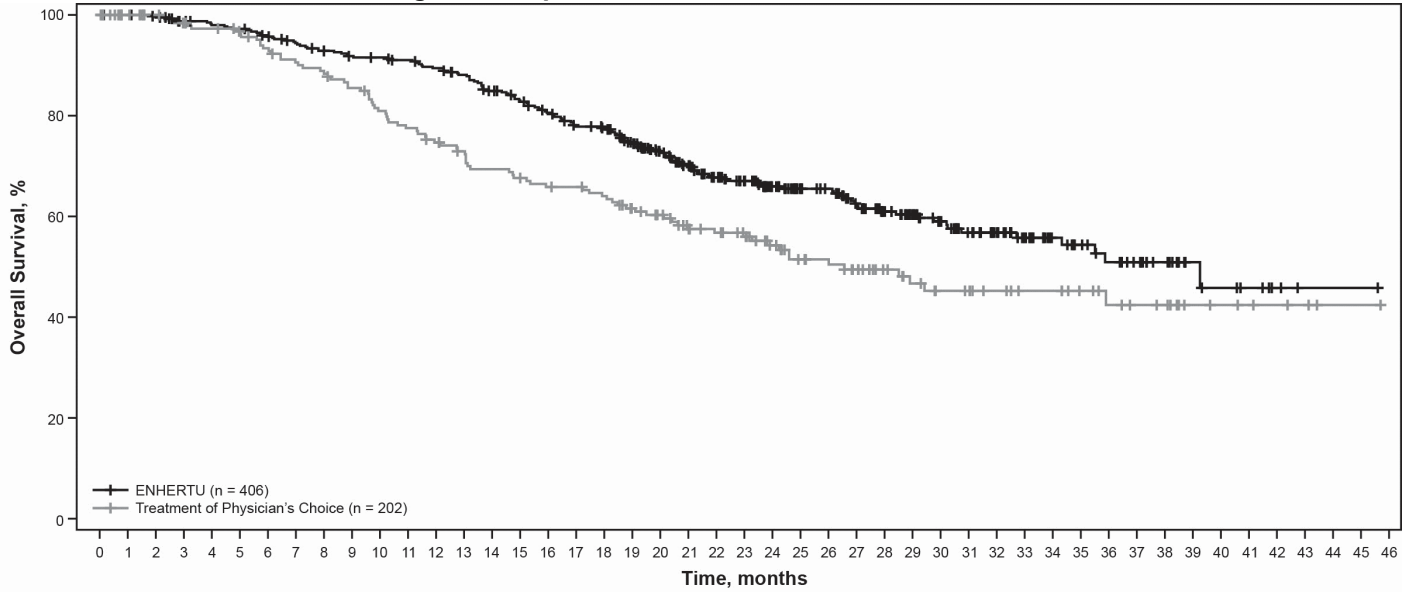


Figure 4: Kaplan-Meier Plot of Overall Survival



DESTINY-Breast01

The efficacy of ENHERTU was evaluated in study DESTINY-Breast01 (NCT03248492), a multicenter, single-arm, trial that enrolled 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients were excluded for a history of treated ILD or current ILD at screening. Patients were also excluded for history of clinically significant cardiac disease, active brain metastases, and ECOG performance status >1. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive.

Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with brain metastases at baseline. The major efficacy outcomes were confirmed objective response rate (ORR) assessed by independent central review (ICR) using RECIST v1.1 and duration of response (DOR).

The median age was 55 years (range: 28-96); 76% of patients were <65 years. All 184 patients were female, and the majority were White (55%) or Asian (38%). Patients had an ECOG performance status of 0 (55%) or 1 (44%) at baseline. Ninety-two percent had visceral disease, 29% had bone metastases, and 13% had brain metastases. Fifty-three percent were HR+. Sum of diameters of target lesions were <5 cm in 42%, and ≥5 cm in 50% (not evaluable by central review in 8% of patients).

The median number of prior cancer regimens in the locally advanced/metastatic setting was 5 (range: 2-17). All patients received prior trastuzumab, ado-trastuzumab emtansine, and 66% had prior pertuzumab.

Efficacy results are summarized in Table 19.

Table 19: Efficacy Results by Independent Central Review in DESTINY-Breast01

Efficacy Parameter	DESTINY-Breast01 N=184
Confirmed Objective Response Rate (95% CI)	60.3% (52.9, 67.4)
Complete Response	4.3%
Partial Response	56.0%
Duration of Response* Median, months (95% CI)†	14.8 (13.8, 16.9)

ORR 95% CI calculated using Clopper-Pearson method.

*DOR is based on median duration of follow-up of 11.1 months.

†Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method.-

14.2 HER2-Low Metastatic Breast Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Breast04 (NCT03734029), a randomized, multicenter, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor-positive (HR+) patients and 63 hormone receptor-negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined at a central laboratory using Ventana's PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=373) by intravenous infusion every 3 weeks or physician's choice of chemotherapy (N=184, eribulin, capecitabine, gemcitabine, nab paclitaxel, or paclitaxel). Randomization was stratified by HER2 IHC status of tumor samples (IHC 1+ or IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for untreated or symptomatic brain metastases or ECOG performance status >1.

The major efficacy outcome measure was PFS in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Additional efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomized HR+ and HR- patients), OS in HR+ patients, and OS in the overall population.

The median age was 57 years (range: 28 to 81); 24% were age 65 or older; 99.6% were female; 48% were White, 40% were Asian, and 2% were Black or African American; 3.8% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (55%) or 1 (45%) at baseline; 58% were IHC 1+, 42% were IHC 2+/ISH-; 70% had liver metastases, 33% had lung metastases, and 6% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 58% having 1 and 41% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6i treatment.

Efficacy results are summarized in Table 20 and Figures 5 and 6.

Table 20: Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Overall Survival				
Number of events (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)		0.64 (0.49, 0.84)	
p-value	0.0028		0.001	
Progression-Free Survival per BICR				
Number of events (%)	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)		0.50 (0.40, 0.63)	
p-value	<0.0001		<0.0001	
Confirmed Objective Response Rate per BICR				
n (%)	175 (52.9)	27 (16.6)	195 (52.3)	30 (16.3)
95% CI	47.3, 58.4	11.2, 23.2	47.1, 57.4	11.3, 22.5
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.5)	26 (16.0)	183 (49.1)	28 (15.2)
Duration of Response per BICR				
Median, months (95% CI)	10.7 (8.5, 13.7)	6.8 (6.5, 9.9)	10.7 (8.5, 13.2)	6.8 (6.0, 9.9)

CI = confidence interval

Figure 5: Kaplan-Meier Plot of Overall Survival (Overall Population)

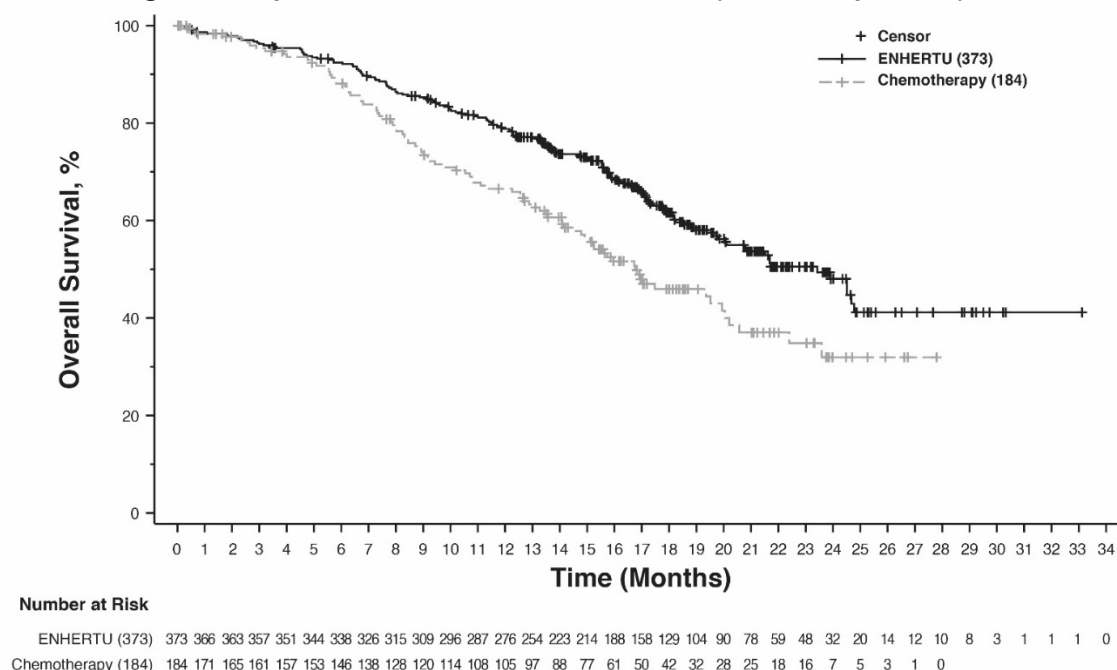
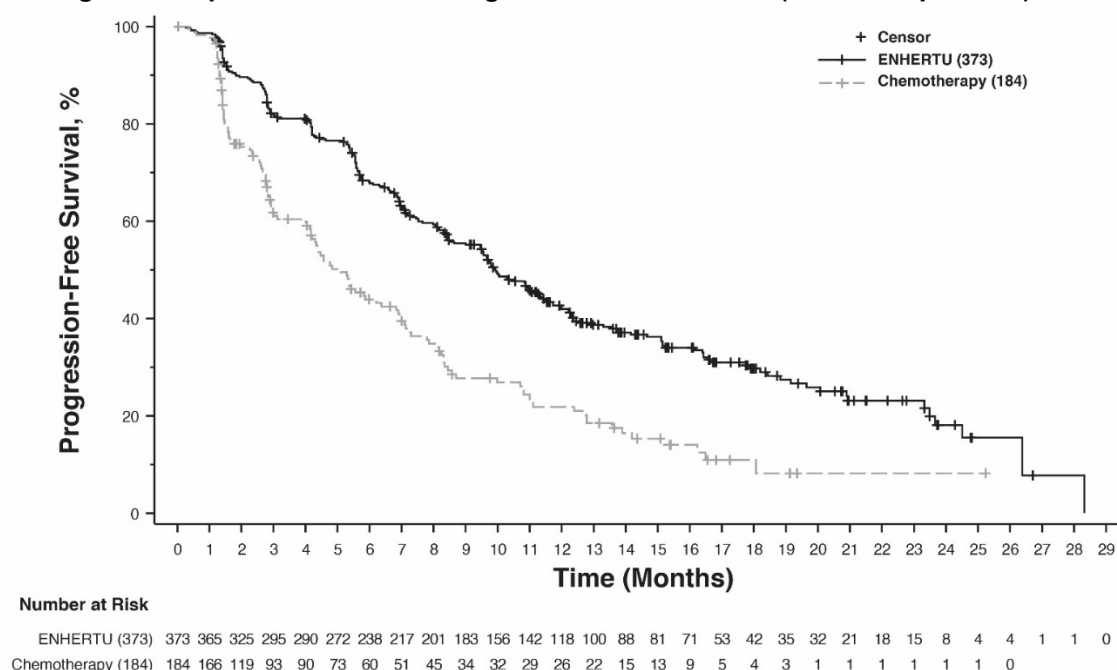


Figure 6: Kaplan-Meier Plot of Progression-Free Survival (Overall Population)



14.3 HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer

ENHERTU was evaluated in DESTINY-Lung01 (NCT03505710) and at two dose levels in DESTINY-Lung02 (NCT04644237). Patients were prospectively selected for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations by local testing using tissue. Samples from DESTINY-Lung01 were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation, Tissue-test) and Guardant360® CDx test (Guardant Health Inc., Plasma test). Demographic and baseline disease characteristics were similar for patients in DESTINY-Lung01 and DESTINY-Lung02, except for race (34% Asian vs 79% Asian, respectively). Response rates were consistent across dose levels. Increased rates of ILD/pneumonitis were observed at the higher dose. The approved recommended dose of 5.4 mg/kg intravenously every 3 weeks in the DESTINY-Lung02 study is described below [see *Adverse Reactions* (6.1)].

The efficacy of ENHERTU was evaluated in DESTINY-Lung02, a multicenter, multicohort, randomized, blinded, dose-optimization trial. Eligible patients were required to have unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after one prior systemic therapy. Patients with a history of steroid dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status >1 were excluded. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with stable brain metastases at baseline.

Results from an interim efficacy analysis in a pre-specified patient cohort are described below. The major efficacy outcomes were confirmed ORR as assessed by BICR using RECIST v1.1 and DOR.

The median age was 58 years (range 30 to 78); 69% were female; 79% were Asian, 12% were White, and 10% were other races; 29% had an ECOG performance status of 0 and 71% had 1; 33% had stable brain metastases; 94% had a mutation in the ERBB2 kinase domain and 6% had a mutation in the extracellular domain. The median number of prior regimens was 2 (range: 1 to 12); 100% of patients received prior platinum therapy, 71% received prior immunotherapy, and 44% received both in combination. Fifty percent of patients were never-smokers and 50% were former smokers; 96% of patients had adenocarcinoma histology.

Efficacy results are provided in Table 21.

Table 21: Efficacy Results for DESTINY-Lung02*

Efficacy Parameter	DESTINY-Lung02 N=52
Confirmed Objective Response Rate (95% CI)	57.7% (43.2, 71.3)
Complete Response	1.9%
Partial Response	55.8%
Duration of Response Median, months (95% CI)[†]	8.7 (7.1, NE)

ORR 95% CI calculated using Clopper-Pearson method

NE=not estimable

*Data cut-off: 22 June 2022

[†]Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method

14.4 HER2-Positive Locally Advanced or Metastatic Gastric Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Gastric01 (NCT03329690), a multicenter, open-label, randomized trial conducted in Japan and South Korea that enrolled 188 adult patients with HER2-positive (IHC 3+ or IHC 2+/ISH positive), locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. HER2 expression was determined by a central lab on tissue obtained either before or after prior trastuzumab treatment. Patients were excluded for a history of treated or current ILD, a history of clinically significant cardiac disease, active brain metastases, or ECOG performance status >1.

Patients were randomized 2:1 to receive ENHERTU (N=126) 6.4 mg/kg intravenously every 3 weeks or physician's choice of chemotherapy: irinotecan monotherapy (N=55) 150 mg/m² intravenously every 2 weeks or paclitaxel monotherapy (N=7) 80 mg/m² intravenously weekly. Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH+), ECOG performance status (0 or 1), and region (Japan or South Korea). Tumor imaging assessments were performed at screening and every 6 weeks from the first treatment dose. Treatment was administered until unacceptable toxicity or disease progression. The major efficacy outcomes were ORR assessed by ICR according to RECIST v1.1 and OS in the intent-to-treat population. Additional efficacy outcomes were PFS and DOR.

The median age was 66 years (range 28 to 82); 76% were male; and 100% were Asian. All patients received a trastuzumab product. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH+; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; 45% had three or more prior regimens in the locally advanced or metastatic setting. A total of 30% of patients were identified as HER2-positive using tissue obtained following prior treatment with a trastuzumab product.

Efficacy results are summarized in Table 22, and the Kaplan-Meier curve for OS is shown in Figure 7.

Table 22: Efficacy Results in DESTINY-Gastric01

Efficacy Parameter	ENHERTU N=126	Irinotecan or Paclitaxel N=62
Overall Survival (OS)*		
Median, months (95% CI)†	12.5 (9.6, 14.3)	8.4 (6.9, 10.7)
Hazard ratio (95% CI)‡	0.59 (0.39, 0.88)	
p-value*	0.0097	
Progression-Free Survival (PFS)§		
Median, months (95% CI)†	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)‡	0.47 (0.31, 0.71)	
Confirmed Objective Response Rate (ORR)§		
n (%)	51 (40.5)	7 (11.3)
95% CI¶	(31.8, 49.6)	(4.7, 21.9)
p-value#	<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Duration of Response (DOR)§		
Median, months (95% CI)†	11.3 (5.6, NR)	3.9 (3.0, 4.9)

CI = confidence interval; NR = not reached

*OS was evaluated following a statistically significant outcome of ORR.

†Median based on Kaplan-Meier estimate; 95% CI for median calculated using Brookmeyer-Crowley method

‡Based on the stratified Cox proportional hazards regression model (stratified by region)

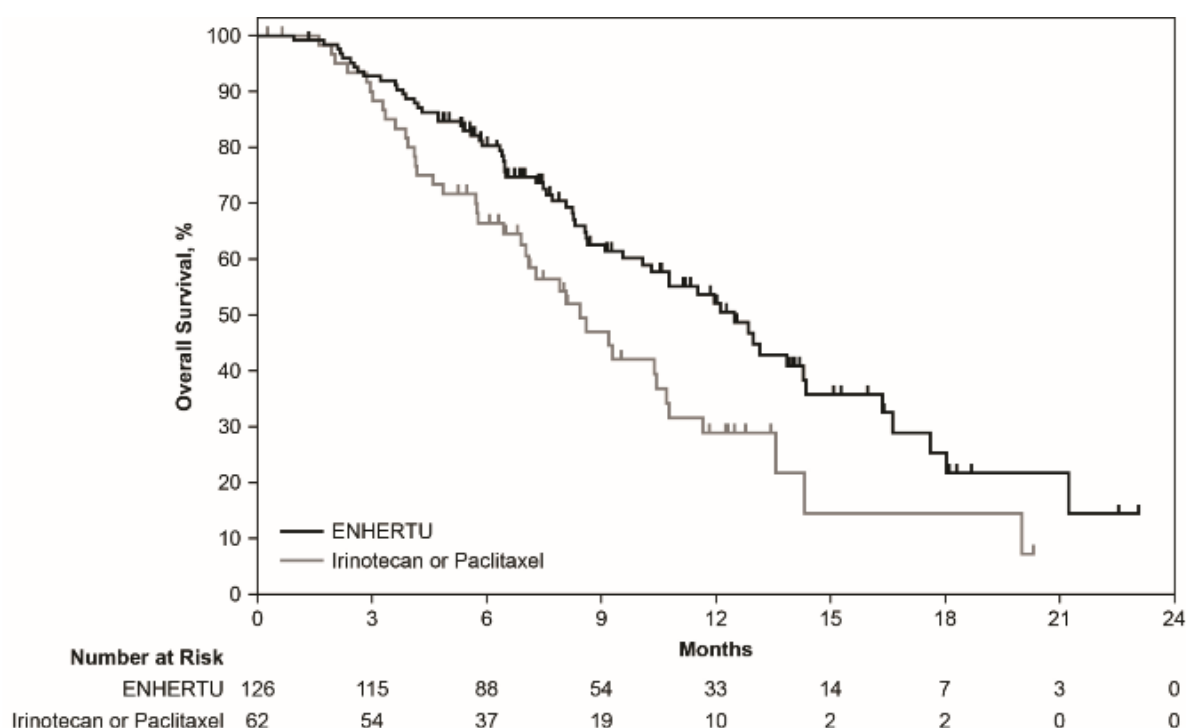
§Based on the stratified log-rank test (stratified by region)

¶Assessed by independent central review

¶95% exact binomial confidence interval

#Based on the stratified Cochran-Mantel-Haenszel test (stratified by region)

Figure 7: Kaplan-Meier Plot of Overall Survival



14.5 HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

The efficacy of ENHERTU was evaluated in 192 adult patients with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three multicenter trials: DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. All three studies excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every three weeks. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The major efficacy outcome measure in all three of the studies was confirmed objective response rate (ORR) and an additional efficacy outcome measure was duration of response (DOR). All outcomes were assessed by independent central review (ICR) based on RECIST v1.1.

DESTINY-PanTumor02

DESTINY-PanTumor02 (NCT04482309) was a multicenter, multicohort, open-label trial that included 111 adult patients with locally advanced, unresectable, or metastatic HER2-positive (IHC 3+ by either local or central assessment) solid tumors that progressed following at least one prior systemic regimen in the advanced/metastatic setting or that had no satisfactory alternative treatment option.

The median age was 64 years (range 23 to 85); 59% were female; 58% were White, 34% were Asian, and 4% were Black or African American; 3% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of either 0 (49%) or 1 (51%) at baseline. The median number of prior regimens in any treatment setting was 2.

DESTINY-Lung01

DESTINY-Lung01 (NCT03505710) was a multicenter, open-label, 2-cohort trial that included 17 patients with previously treated, unresectable, or metastatic, centrally confirmed HER2-positive (IHC 3+) NSCLC. Patients must have relapsed from or be refractory to standard treatment or have no available standard treatment.

The median age was 59 years (range 31 to 74); 59% were male; 65% were White, 18% were Asian, and 12% were Black or African American. Patients had an ECOG performance status of either 0 (12%) or 1 (88%) at baseline. The median number of prior regimens in any treatment setting was 3.

DESTINY-CRC02

DESTINY-CRC02 (NCT04744831) was a multicenter, randomized, 2-arm trial that included 64 patients with previously treated, unresectable or metastatic centrally confirmed HER2-positive (IHC 3+) colorectal cancer (CRC). Unless contraindicated, patients must have received fluoropyrimidine, oxaliplatin and irinotecan. If clinically indicated, patients must have received anti-EGFR treatment, anti-VEGF treatment and anti-PDL1 therapy.

The median age was 58 years (range 25 to 78); 53% were male; 55% were Asian and 41% were White; 1.6% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of either 0 (58%) or 1 (42%) at baseline. The median number of prior regimens in any treatment setting was 4.

Efficacy results are summarized in Table 23 and Table 24.

Table 23: Efficacy Results in HER2-Positive (IHC 3+) Patients in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Efficacy Parameter	DESTINY-PanTumor02 N=111	DESTINY-Lung01 N=17	DESTINY-CRC02 N=64
Confirmed ORR (95% CI)^{†‡}	51.4% (41.7, 61.0)	52.9% (27.8, 77.0)	46.9% (34.3, 59.8)
Complete Response Rate	2.7%	5.9%	0%
Partial Response Rate	48.6%	47.1%	46.9%
Duration of Response[†]			
Median [§] , months (range)	19.4 (1.3, 27.9+)	6.9 (4.0, 11.7+)	5.5 (1.3+, 9.7+)

CI=Confidence interval

[†]Assessed by independent central review

[‡]CI is derived based on the Clopper-Pearson method

[§]Calculated using the Kaplan-Meier technique

+ Denotes ongoing response

Table 24: Efficacy Results in HER2-positive (IHC 3+) Patients by Tumor Type in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Tumor Type	Patients	Confirmed ORR[†]	DOR[†] Range
	N	% (95% CI)[‡]	(months)
Colorectal Cancer	64	46.9 (34.3, 59.8)	(1.3+, 9.7+)
Bladder Cancer	27	37.0 (19.4, 57.6)	(2.8, 19.7+)
Biliary Tract Cancer	22	45.5 (24.4, 67.8)	(2.1, 22.0+)
NSCLC	17	52.9 (27.8, 77.0)	(4.0, 11.7+)
Endometrial Cancer	16	56.3 (29.9, 80.2)	(5.8, 23.7+)
Ovarian Cancer	15	66.7 (38.4, 88.2)	(1.3, 27.9+)
Cervical Cancer	10	70.0 (34.8, 93.3)	(7.2+, 25.0+)
Salivary Gland Cancer	9	66.7 (29.9, 92.5)	(5.6, 20.1)
Pancreatic Cancer	5	0 (0, 52.2)	NA
Oropharyngeal Neoplasm	1	PR	15.3
Vulvar Cancer	1	PR	2.6
Extramammary Paget's Disease	1	PR	19.4
Lacrimal Gland Cancer	1	PR	19.8+
Lip and/or Oral Cavity Cancer	1	SD	NA
Esophageal Adenocarcinoma	1	PR	2.8
Esophageal Squamous Cell Carcinoma	1	PD	NA

CI=Confidence interval, NA=Not applicable, PD=Progressive disease, PR=Partial response, SD=Stable disease

[†]Assessed by independent central review

[‡]CI is derived based on the Clopper-Pearson method

+ Denotes ongoing response

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied/Storage

ENHERTU (fam-trastuzumab deruxtecan-nxki) for injection is a white to yellowish white lyophilized powder supplied as:

Carton Contents	NDC
One 100 mg single-dose vial	NDC 65597-406-01

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of reconstitution. Do not freeze. Do not shake the reconstituted or diluted solution [see *Dosage and Administration* (2.4)].

Special Handling

ENHERTU (fam-trastuzumab deruxtecan-nxki) is a hazardous drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Interstitial Lung Disease

- Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see *Warnings and Precautions* (5.1)].

Neutropenia

- Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection [see *Warnings and Precautions* (5.2)].

Left Ventricular Dysfunction

- Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see *Warnings and Precautions* (5.3)].

Embryo-Fetal Toxicity

- Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.1)].
- Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose [see *Use in Specific Populations* (8.3)].
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose [see *Use in Specific Populations* (8.3)].

Lactation

- Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see *Use in Specific Populations* (8.2)].

Infertility

- Advise males of reproductive potential that ENHERTU may impair fertility [see *Use in Specific Populations* (8.3)].

Manufactured by:
Daiichi Sankyo, Inc., Basking Ridge, NJ 07920

U.S. License No. 2128

Marketed by:

Daiichi Sankyo, Inc., Basking Ridge, NJ 07920 and AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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USPI-ENH-C16-0424-r008

Medication Guide

ENHERTU® (en-HER-too)
(fam-trastuzumab deruxtecan-nxki) for injection

What is the most important information I should know about ENHERTU?

ENHERTU can cause serious side effects, including:

- **Lung problems that may be severe, life-threatening, or that may lead to death.** If you develop lung problems your healthcare provider may treat you with corticosteroid medicines. Tell your healthcare provider right away if you get any of the following signs and symptoms:
 - cough
 - trouble breathing or shortness of breath
 - fever
 - other new or worsening breathing symptoms (such as chest tightness, wheezing)
- **Low white blood cell count (neutropenia).** Low white blood cell counts are common with ENHERTU and can sometimes be severe. Your healthcare provider will check your white blood cell counts before starting ENHERTU and before starting each dose. Tell your healthcare provider right away if you develop any signs or symptoms of an infection or have fever or chills during treatment with ENHERTU.
- **Heart problems that may affect your heart's ability to pump blood.** Your healthcare provider will check your heart function before starting treatment with ENHERTU. Tell your healthcare provider right away if you get any of the following signs and symptoms:
 - new or worsening shortness of breath
 - coughing
 - feeling tired
 - swelling of your ankles or legs
 - irregular heartbeat
 - sudden weight gain
 - dizziness or feeling light-headed
 - loss of consciousness

Your healthcare provider will check you for these side effects during your treatment with ENHERTU. Your healthcare provider may reduce your dose, delay treatment, or completely stop treatment with ENHERTU if you have severe side effects.

- **Harm to your unborn baby.** Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with ENHERTU.
 - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with ENHERTU.
 - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with ENHERTU and for 7 months after the last dose.
 - **Males** who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with ENHERTU and for 4 months after the last dose.

See **“What are the possible side effects of ENHERTU?”** for more information about side effects.

What is ENHERTU?

ENHERTU is a prescription medicine used to treat adults who have:

- human epidermal growth factor receptor 2 (HER2)-positive breast cancer that cannot be removed by surgery or that has spread to other parts of the body (metastatic), and who have received a prior anti-HER2 breast cancer treatment:
 - for metastatic disease, **or**
 - have breast cancer that has come back during or within 6 months of completing treatment for their early-stage breast cancer.
- HER2-low breast cancer that cannot be removed by surgery or that has spread to other parts of your body (metastatic), and who have received a prior chemotherapy:
 - for metastatic disease, **or**
 - your disease has returned during or within 6 months of completing adjuvant chemotherapy (after surgery). Your healthcare provider will perform a test to make sure ENHERTU is right for you.
- non-small cell lung cancer (NSCLC) that has a certain mutation in the HER2 gene and cannot be removed by surgery or has spread to other parts of your body (metastatic), and who have received a prior treatment. Your healthcare provider will perform a test to make sure ENHERTU is right for you.
- stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that is HER2-positive and has spread to areas near your stomach (locally advanced) or that has spread to other parts of your body (metastatic), and who have received a prior trastuzumab-based regimen.
- solid tumors that are HER2-positive (IHC 3+) and that cannot be removed by surgery or have spread to other parts of your body (metastatic), and who have received a prior treatment and have no other satisfactory treatment options. Your healthcare provider will perform a test to make sure ENHERTU is right for you.

It is not known if ENHERTU is safe and effective in children.

Before you receive ENHERTU, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems.
- have signs or symptoms of an infection.
- have or have had any heart problems.
- are breastfeeding or plan to breastfeed. It is not known if ENHERTU passes into your breast milk. Do not breastfeed during treatment with ENHERTU and for 7 months after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ENHERTU?

- You will receive ENHERTU into your vein through an intravenous (IV) line by your healthcare provider.
- ENHERTU is given 1 time every three weeks (21-day treatment cycle).
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will give you medicines before your infusion to help prevent nausea and vomiting.
- Your healthcare provider may slow down or temporarily stop your infusion of ENHERTU if you have an infusion-related reaction, or permanently stop ENHERTU if you have severe infusion reactions.
- If you miss a planned dose of ENHERTU, call your healthcare provider right away to schedule an appointment. Do not wait until the next planned treatment cycle.

What are the possible side effects of ENHERTU?

ENHERTU can cause serious side effects. See "What is the most important information I should know about ENHERTU?"

The most common side effects of ENHERTU, when used in people with metastatic breast cancer, HER2-mutant non-small cell lung cancer, and other HER2-positive solid tumors include:

- | | |
|----------------------------------|---------------------------------|
| • nausea | • hair loss |
| • low white blood cell counts | • constipation |
| • low red blood cell counts | • decreased appetite |
| • feeling tired | • low levels of blood potassium |
| • low platelet counts | • diarrhea |
| • increased liver function tests | • muscle or bone pain |
| • vomiting | • stomach-area pain |

The most common side effects of ENHERTU, when used in people with HER2-positive gastric or GEJ adenocarcinoma, include:

- | | |
|----------------------------------|---------------------------------|
| • low red blood cell counts | • diarrhea |
| • low white blood cell counts | • low levels of blood potassium |
| • low platelet counts | • vomiting |
| • nausea | • constipation |
| • decreased appetite | • fever |
| • increased liver function tests | • hair loss |
| • feeling tired | |

ENHERTU may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of ENHERTU. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ENHERTU.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about ENHERTU that is written for healthcare professionals.

What are the ingredients in ENHERTU?

Active Ingredient: fam-trastuzumab deruxtecan-nxki.

Inactive Ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and sucrose.

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USMG-ENH-C16-0424-r007

For more information, call 1-877-437-7763 or go to <https://www.ENHERTU.com>.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 04/2024

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s028

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplemental BLA (sBLA)
Application Number(s)	761139 S-28
Priority or Standard	Priority
Submit Date(s)	November 30, 2023
Received Date(s)	November 30, 2023
PDUFA Goal Date	May 30, 2024
Division/Office	DO1/OOD
Review Completion Date	<i>Electronic Stamp Date</i>
Established Name	fam-trastuzumab deruxtecan-nxki
(Proposed) Trade Name	ENHERTU
Pharmacologic Class	Antibody drug conjugate
Applicant	Daiichi Sankyo, Inc.
Formulation(s)	100 mg single-use vial
Dosing Regimen	5.4mg/kg intravenous infusion every 3 weeks
Applicant Proposed Indication(s)/Population(s)	ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

	approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
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NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADA	Anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BC	Breast cancers
BICR	Blinded independent central review
BLA	biologics license application
BOR	Best overall responses
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BTC	Biliary tract cancer
BTB	Breakthrough Therapy Designation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CBR	Clinical benefit rate
CEAS	Centrally-determined efficacy analysis set
CFR	Code of Federal Regulations
CI	Confidence interval
CMC	chemistry, manufacturing, and controls
CNS	Central nervous system

COA	Clinical Outcome Assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	Confirmed responders
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DCR	Disease control rate
DMC	data monitoring committee
DoR	Duration of response
EAS	Enrolled Analysis Set
ECG	electrocardiogram
eCTD	electronic common technical document
EDC	Electronic data capture
ETASU	elements to assure safe use
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GC	Gastric cancers
GCP	good clinical practice
GEJ	Gastroesophageal junction
GI	Gastrointestinal

GLP	good laboratory practice
GRMP	good review management practice
IA	Interim Analysis
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IND	Investigational New Drug
INR	International Normalized Ratio
INV	Investigator
IRR	Infusion-related reactions
IRT	Interactive Response Technology
ISE	integrated summary of effectiveness
ISH	In-situ hybridization
ISS	integrated summary of safety
ITT	intent to treat
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	Not reported
NSCLC	Non-small cell lung cancer

OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	Objective response rate
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Progressive disease
PFS	Progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PRR	Platinum resistant recurrent
PSUR	Periodic Safety Update report
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumours
REMS	risk evaluation and mitigation strategy
RES	Response evaluable set
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety analysis set
SGE	special government employee

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

SOC	standard of care
SoD	Sum of diameters
SOP	Standard operating procedures
TEAE	treatment emergent adverse event
ULN	Upper limit of normal

1 Executive Summary

1.1. Product Introduction

Fam-trastuzumab deruxtecan-nxki (Enhertu, T-DXd, DS-8201a) is a HER2-directed antibody and topoisomerase I inhibitor conjugate. The anti-HER2 component, MAAL-9001, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb). The released drug, MAAA-1181a, is a topoisomerase I inhibitor derivative of deruxtecan. The mAb is covalently conjugated to a drug linker, MAAA-1162a, that is composed of a cleavable maleimide tetrapeptide linker and the released drug.

The currently approved indications for T-DXd include treatment of:

- adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
 - in the metastatic setting, or
 - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
 - this indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

In the current supplemental Biological Licensing Application (sBLA), the Applicant seeks approval for the following proposed indication:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

The recommended indication for accelerated approval is:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

For treatment of HER2 positive (IHC 3+) unresectable or metastatic solid tumors, the recommended dose of T-DXd is 5.4mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review team recommends granting accelerated approval for T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options, in accordance with 21 Code of Federal Regulations (CFR), Part 601.41, Subpart E of the Biological Licensing Regulations.

Data supporting this approval is from 192 patients in one of three trials: DESTINY-PanTumor02 (DP-02, 111 patients), DESTINY-CRC02 (DC-02, 64 patients) and DESTINY-Lung01 (DL-01, 17 patients). DP-02 was a multicenter, multi-cohort, open-label trial that enrolled 267 adult patients with locally advanced, unresectable, or metastatic HER2-expressing (IHC 3+, IHC 2+, and select IHC1+) solid tumors that progressed following at least one prior systemic regimen in the advanced or metastatic setting or that had no satisfactory alternative treatment options. DC-02 was a multicenter, randomized, 2-arm trial that enrolled 120 patients with previously treated, unresectable or metastatic HER2-expressing (IHC 3+, or IHC 2+/ISH+) colorectal cancer (CRC). DL-01 was a multicenter, open-label, 2-cohort trial that enrolled 181 patients with previously treated, unresectable or metastatic, HER2-expressing (IHC 3+, or IHC 2+) or HER2-mutant non-small cell lung cancer (NSCLC). HER2 positivity (IHC 3+) was assessed by either local or central assessment for DP-02 and by central assessment for trials DC-02 and DL-01. The primary endpoint of DP-02 was objective response rate (ORR) per RECIST v1.1 by investigator assessment; however, ORR per RECIST v1.1 by independent committee review (ICR)

assessment was also submitted for all patients enrolled in the IHC3+ population and was used for FDA's assessment of efficacy. The primary endpoint of DC-02, DL-01, DB-01, and DG-02 was ORR per ICR.

The pooled population of 192 patients included 15 different tumor types [biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, and rare cancers (salivary, extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, esophageal (squamous and non-squamous), and oropharyngeal]. The median number of prior systemic therapies (in any setting) was 3 (range 0-14) for this pooled population. Treatment with T-DXd resulted in a clinically meaningful ORR based on ICR across trials. In DP-02, ORR was 51.4% (95% CI: 41.7, 61.0) and median DOR was 19.4 months (range 1.3, 27.9+). In DL-01, ORR was 52.9% (95% CI: 27.8, 77.0) and median DOR was 6.9 months (range 4.0, 11.7+). In DC-02, ORR was 46.9% (95% CI: 34.3, 59.8), and DOR was 5.5 months (range 1.3+, 9.7+). In the pooled population of 192 patients, ORR was 50.0% (95% CI: 42.7, 57.3) with a median DOR of 9.9 months (95% CI: 7.0, 19.4). Responses were seen across multiple tumor types, except in pancreatic cancer. There were no observed responses in the 5 patients with IHC3+ pancreatic cancer. The FDA review team felt the lack of response in this limited number of patients may be due to chance and enrolling additional patients with pancreatic cancer in a confirmatory postmarketing trial could address this concern and better verify the clinical benefit.

The most common ($\geq 20\%$) TEAEs across the 4 trials evaluated for safety in the IHC3+ population (DP-02, DL-01, DC-02, and DB-01), including laboratory abnormalities, were decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection. Serious AEs occurred in 34% of patients, including sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea in $>1\%$ of the IHC3+ population. Fatalities due to AEs occurred in 6.3% of patients including interstitial lung disease (ILD)/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). ILD/pneumonitis remains as a serious and life-threatening toxicity and is already included as a boxed warning in labeling. The toxicities of T-DXd noted in these trials were generally consistent with the known safety profile of T-DXd.

The results for the IHC3+ population from trials DP-02, DC-02 and DL-01 with HER2-positive advanced/metastatic solid tumors treated with T-DXd at 5.4mg intravenously every 3 weeks each showed a clinically meaningful overall response rate (ORR) and duration of response (DOR).

Although the primary pooled population of 192 patients included 15 tumor types, the number of responders of some tumor types was relatively small and no responses were observed in pancreatic cancer; additionally due to limited follow-up time, the median DOR was not estimable in several tumor types. Therefore, the FDA review team felt that the data were not adequate to support a traditional approval, and more data is required to assess the efficacy of T-DXd in tumor types under-represented in the HER2 IHC3+ population. A postmarketing requirement has been issued for results on an additional cohort of patients that will be enrolled into DP-02 to collect further data on HER-positive (IHC3+) tumors and additional follow-up on ORR and DOR in this population and across various tumor types. Additionally, a PMC was also issued for a pragmatic trial of T-DXd in IHC3+ solid tumors to obtain further efficacy data.

The FDA review team concluded that for the HER2-positive (IHC 3+) advanced and metastatic population, the benefit-risk assessment was favorable given the clinically meaningful ORR and DOR across trials and tumor types, and the toxicities are appropriately managed by mitigation strategies in the USPI. The indication for accelerated approval is:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

This accelerated approval represents the first FDA approved tissue agnostic therapy for patients with HER2-positive (IHC3+), unresectable or metastatic solid tumors in a late line setting after prior systemic therapy. An FDA-approved test for the detection of HER2-positive (IHC 3+) solid tumors for treatment with T-DXd is not currently available and a postmarketing commitment (PMC) was issued by the FDA for development of a companion diagnostic. Additionally, a pediatric PMR was issued deferring submission of a pediatric study for T-DXd for ages 1 month to < 17 years old because additional pediatric nonclinical data are needed to inform the design of the pediatric clinical study.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Fam-trastuzumab deruxtecan-nxki (Enhertu, T-DXd, DS-8201a) a HER2-directed antibody linked to a topoisomerase I inhibitor conjugate, is recommended for accelerated approval for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options.

HER2 is a proto-oncogene involved in signal transduction pathways leading to tumor cell proliferation, migration, apoptosis, and differentiation. Generally, HER2 expression has been defined in breast and gastric cancers as IHC 3+, or IHC 2+ with amplification, but HER2-expression, with or without ERBB2 amplification has been described more widely, including in biliary tract cancer, bladder cancer, NSCLC, and colorectal cancer. In a study with approximately 40,000 patient samples by Yan et al 2015, HER2 expression (IHC 3+) was observed in 2.7% of samples, including a range of tumor types outside of breast and gastric cancers, most frequently in bladder cancer, esophageal cancer, gallbladder cancer, cervical cancer, and uterine cancer but also in cancer of unknown primary, testicular, ovarian, head and neck, pancreatic, small intestinal cancers, and melanoma. Available standard treatment options for most patients with unresectable locally advanced or metastatic solid tumors in later lines of therapy are not curative, are generally not biomarker targeted, and provide only modest clinical benefit. The objective response rate (ORR) in second line and beyond for many of these tumor types range from 5-44%. The presence of HER2 IHC 3+ expression in a diverse range of tumor types, along with the poor prognosis for patients with these advanced/metastatic solid tumors, presents the opportunity to treat these tumors in a biomarker selected (HER2 IHC 3+ expressing) tissue agnostic approach. Outside of breast cancer and gastric/GEJ cancer, there are currently no drugs specifically approved for the treatment of patients with other HER2-over expressing (IHC 3+) advanced or metastatic solid tumors.

The efficacy assessment of T-DXd for this sBLA is primarily based on results from 192 patients from one of three trials: DESTINY-PanTumor02 (DP-02), DESTINY-CRC02 (DC-02) and DESTINY-Lung01 (DL-01) with HER2 IHC 3+ advanced/metastatic solid tumors treated with T-DXd at 5.4 mg intravenously every 3 weeks.

DP-02 was a multicenter, multi-cohort, open-label trial that enrolled 267 adult patients with locally advanced, unresectable, or metastatic HER2-

expressing (IHC 3+, IHC 2+) solid tumors that progressed following at least one prior systemic regimen in the advanced/metastatic setting or that had no satisfactory alternative treatment options. Efficacy was assessed in the subgroup of patients (N=111) with HER2-positive (IHC 3+ by either local or central assessment) solid tumors.

DC-02 was a multicenter, randomized, 2-arm trial that enrolled 120 patients with previously treated, unresectable or metastatic HER2-expressing (IHC 3+, or IHC 2+/ISH+) colorectal cancer (CRC). Unless contraindicated, patients must have received fluoropyrimidine, oxaliplatin and irinotecan. If clinically indicated, patients must have received anti-EGFR treatment, anti-VEGF treatment and anti-PDL1 therapy. Efficacy was assessed in the subgroup of patients (N=64) with centrally confirmed HER2-positive (IHC 3+) CRC.

DL-01 was a multicenter, open-label, 2-cohort trial that enrolled 181 patients with previously treated, unresectable or metastatic, HER2-expressing (IHC 3+, or IHC 2+) or HER2-mutant non-small cell lung cancer (NSCLC). Patients must have relapsed from or be refractory to standard treatment or have no available standard treatment. HER2 positivity (IHC 3+) was assessed by either local or central assessment for Study DP-02 and by central assessment for studies DC-02 and DL-01. Efficacy was assessed in a subgroup of patients (N=17) with centrally confirmed HER2-positive (IHC 3+) NSCLC cancer.

All three studies excluded patients with a history of interstitial lung disease (ILD)/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Patients received T-DXd 5.4 mg/kg by intravenous infusion every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity in all these three trials. The major efficacy outcome measure in all three of the trials was confirmed objective response rate (ORR) and an additional efficacy outcome measure was duration of response (DOR). The primary endpoint in DP-02 was ORR assessed by investigator, while in DC-02 and DL-01 ORR was assessed by ICR. The efficacy results in DP-02 were consistent when assessed by investigator and ICR. Applicant reported all the efficacy outcomes as assessed by independent central review (ICR) based on RECIST v1.1 for the sBLA review.

This pooled population of 192 patients included 15 different tumor types [biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, and rare cancers (salivary, extramammary Paget's disease, vulvar, head and neck (lacrima), lip and/or oral cavity cancer, esophageal (squamous and non-squamous), and oropharyngeal]. The median number of prior systemic therapies (in any setting) was 3 (range 0-

14) for this pooled population. Treatment with T-DXd in this pooled population of 192 patients resulted in a clinically meaningful ORR based on ICR. In DP-02, ORR was 51.4% (95% CI: 41.7, 61.0) and median DOR was 19.4 months (range 1.3, 27.9+). In DL-01, ORR was 52.9% (95% CI: 27.8, 77.0) and median DOR was 6.9 months (range 4.0, 11.7+). In DC-02, ORR was 46.9% (95% CI: 34.3, 59.8), and DOR was 5.5 months (range 1.3+, 9.7+). In the pooled population of 192 patients, ORR was 50.0% (95% CI: 42.7, 57.3) with a median DOR of 9.9 months (95% CI: 7.0, 19.4). Responses were seen across multiple tumor types when treated with T-DXd, except in pancreatic cancer. There were no observed responses in the 5 patients with IHC3+ pancreatic cancer.

A larger pooled analysis with the 192 patients from the primary efficacy cohort in combination with an additional 222 patients with HER2 positive (IHC 3+) advanced/metastatic breast cancer and gastric/GEJ cancer from trials DESTINY-Breast01 (DB-01) and DESTINY-Gastric02 (DG-02) was considered supportive. Patients with HER2 positive (IHC 3+) advanced/metastatic breast cancer and gastric/GEJ cancer were not included in the primary efficacy cohort since T-DXd is already approved for these indications. In addition, the dose of T-DXd approved for the gastric/GEJ patient population is different (6.4 mg/kg). DB-01 was an open-label, single-arm study of T-DXd that enrolled 253 patients with HER2-positive unresectable and/or metastatic breast cancer resistant or refractory to ado-trastuzumab emtansine (T-DM1). The 154 patients with HER2 positive (IHC 3+) disease treated with T-DXd at 5.4mg/kg were included in the pooled analysis. DG-02 was an open-label, single-arm study of T-DXd study that enrolled 79 patients with HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma that had progressed on or after a trastuzumab-containing regimen. The 68 patients with HER2 positive (IHC 3+) were included in the pooled analysis. All patients on DG-02 were treated with T-DXd 6.4 mg/kg. This combined population of 414 patients included 17 different tumor types. The ORR by ICR remained consistent with an ORR of 54.1% (95% CI: 49.2, 59.0).

The safety assessment of T-DXd included a pooled population of 347 patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who received T-DXd 5.4 mg/kg in the DB-01, DP-02, DC-02 and DL-01 trials. DG-02 was not included in the primary safety pool due to the different dose of T-DXd used in the trial. Fatalities occurred in 6.3% of patients due to adverse reactions, including 2.3% due to interstitial lung disease (ILD)/pneumonitis. Serious adverse reactions occurred in 34% of patients, and the most common ($\geq 20\%$) adverse reactions included decreased white blood cell count, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection. ILD/pneumonitis and left ventricular (LV) dysfunction are adverse events of special interest for T-DXd. Adjudicated

ILD/pneumonitis occurred in 16% of patients, of which 0.6% were grade 3-4 in severity. LV dysfunction occurred in 2.9%, and 1.2% of patients had grade 3-4 LV dysfunction; two patients experienced fatal AEs attributed to cardiac arrest. ILD/pneumonitis is a serious and life-threatening toxicity and remains a boxed warning in labeling, and LV dysfunction remains as a Warning and Precaution. These AEs were generally consistent with the known safety profile for T-DXd and no new safety signals were noted.

The submitted evidence from trials DP-02, DC-02 and DL-01, plus supportive data from DB-01 and DG-02, meet the statutory evidentiary standard for accelerated approval of T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options. The ORR and DOR observed with T-DXd treatment in patients with multiple advanced/metastatic solid tumor types that have been previously treated is considered clinically meaningful. Although the primary pooled population of 192 patients included 15 tumor types, the number of responders of some tumor types was relatively small and due to limited follow-up time, the median DOR was not estimable in several tumor types. Therefore, the Applicant has agreed to a post marketing requirement (PMR) to further characterize ORR and DOR across HER2-positive (IHC3+) tumor types by enrolling additional patients and to obtain longer follow up on the responding patients in DP-02, as well as a postmarketing commitment (PMC) to conduct a pragmatic trial that may further inform on T-DXd efficacy in various IHC3+ solid tumors. A PMC has also been issued to support development of an in vitro diagnostic device as a companion diagnostic was not approved contemporaneously for the selection of IHC3+ tumors. The safety profile was consistent with known risks of T-DXd; these risks were manageable with close monitoring and dose modifications noted in USPI. This evidence supports the first approval for a HER2 directed tissue agnostic indication for patients with the HER2-positive (IHC 3+) advanced/metastatic solid tumors. T-DXd is recommended for accelerated approval for the following indication:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HER2 is a proto-oncogene involved in signal transduction pathways leading to tumor cell proliferation, migration, apoptosis, and differentiation. • In a study with approximately 40,000 patient samples, HER2 expression (IHC 3+) was observed in 2.7% of samples, including a range of tumor types outside of breast and gastric cancers. • The presence of HER2 IHC 3+ expression in a diverse range of tumor types, along with the poor prognosis for patients with these advanced/metastatic solid tumors, presents the opportunity to treat these tumors in a biomarker selected (HER2 IHC 3+) tissue agnostic approach. • Available standard treatment options for most patients with unresectable locally advanced or metastatic solid tumors are not curative, are not biomarker targeted, and provide only modest clinical benefit.	Unresectable or metastatic HER2 positive (IHC 3+) cancer is a serious and life-threatening condition.
Current Treatment Options	• Treatment goals for unresectable or metastatic HER2-positive (IHC 3+) solid tumors are to delay disease progression, prolong survival and reduce cancer related symptoms. • The objective response rate (ORR) ranges from 5-44% for many HER2 positive (IHC 3+) solid tumors. • Outside of breast cancer and gastric/GEJ cancer, there are currently no drugs specifically approved for the treatment of patients with other HER2-over expressing (IHC 3+) advanced or metastatic solid	Treatment options for HER2-positive (IHC3+) tumors are palliative. There is an unmet medical need to improve the outcomes of patients with HER2-positive (IHC 3+) unresectable or metastatic cancer, especially for tumors with no satisfactory alternative treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	tumors.	
Benefit	• Trials DESTINY-PanTumor02 (DP-02), DESTINY-CRC02 (DC-02) and DESTINY-Lung01 (DL-01) enrolled a total of 192 patients with HER2 IHC 3+ advanced/metastatic solid tumors treated with T-DXd at 5.4mg intravenously every 3 weeks. • All three trials required prior systemic therapy. The median of prior systemic therapies (in any setting) was 3 (range 0-14) for this pooled population. • The pooled population of 192 patients included 15 different tumor types [biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, and rare cancers (salivary, extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, esophageal (squamous and non-squamous), and oropharyngeal]. • Treatment with T-DXd in the pooled population of 192 patients resulted in a clinically meaningful ORR based on ICR (ORR: 50.0%; 95% CI: 42.7, 57.3) with a median DOR of 9.9 months (95% CI: 7.0, 19.4). • Responses were seen across multiple tumor types when treated with T-DXd, except in pancreatic cancer. There were no observed responses in the 5 patients with IHC3+ pancreatic cancer.	Trials DP-02, DC-02 and DL-01 resulted in a clinically meaningful ORR and DOR improvement of T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options. The submitted evidence meets the statutory evidentiary standard for accelerated approval.
Risk and Risk Management	• The most common ($\geq 20\%$) TEAEs across the 4 trials evaluated for safety in the IHC3+ population (DP-02, DL-01, DC-02, and DB-01), including laboratory abnormalities, were decreased white blood cell	The safety of T-DXd is acceptable for the intended population and is manageable with current labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection. • Serious AEs occurred in 34% of patients, including sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea in >1% of the IHC3+ population. • Fatalities due to AEs occurred in 6.3% of patients including interstitial lung disease (ILD)/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). • ILD/pneumonitis is a serious and life-threatening toxicity and remains a boxed warning in labeling, and LV dysfunction remains as a Warning and Precaution.	No REMS is indicated.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
X	Other: (Please specify)	No COA data was submitted as part of this sBLA. Refer to Section 8.1.2
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

X

Preeti Narayan, MD

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

HER2 is a proto-oncogene involved in signal transduction pathways leading to tumor cell proliferation, migration, apoptosis, and differentiation. Historically, HER2 expression has been defined in breast and gastric cancers as IHC 3+, or IHC 2+ with amplification, but HER2-expression, with or without ERBB2 amplification has been described more widely, including in biliary tract cancer, bladder cancer, NSCLC, and colorectal cancer (Yan et al 2015). In a comprehensive study with approximately 40,000 patient samples (Yan et al 2015), HER2 expression (IHC 3+) was observed in 2.7% of samples, including a range of tumor types outside of breast and GCs, most frequently in bladder cancer, esophageal cancer, gallbladder cancer, cervical cancer, and uterine cancer but also in cancer of unknown primary, testicular, ovarian, head and neck, pancreatic, small intestinal cancers and melanoma. A recent publication (Uzunparmak et al 2023) evaluated HER2 IHC expression in 4701 patients with solid tumors treated at The University of Texas MD Anderson Cancer Center between November 2020 and May 2022 confirmed the findings of Yan et al 2015. IHC 3+ expression was identified in a broad range of tumor types most frequently in gastric, biliary tract, endometrial, salivary gland, bladder, endometrial, cervical and breast cancers and less frequently (<5% samples tested) in ovarian, colorectal, lung, pancreatic and cancers of unknown primary. The presence of HER2 IHC 3+ expression in diverse cancers and the poor prognosis for the patients with these cancers offer the opportunity for T-DXd to improve clinical outcomes for patients, regardless of tumor type, through a biomarker-selected approach.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of HER2 expression (IHC 3+) in a variety of solid tumors, including breast cancer or gastric/GEJ cancer.

2.2. Analysis of Current Treatment Options

The information presented here focuses on providing a summary of the current treatment landscape for the more common tumors that express HER2. Response rate and duration of response data for the most effective current SOC treatments by tumor type are shown in Applicant - Table 1.

Applicant - Table 1: Current Standard of Care Therapeutic Options

Tumor type	Publication	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)
Biliary tract cancer	Hurvitz et al 2023 Lamarca et al 2021	2L FOLFOX (N = 81)	5% (NR)	NR
Bladder cancer	Rosenberg et al 2019	2L enfortumab vedotin (N = 125)	44% (35.1, 53.2)	7.6 months (4.9, 7.5)
	Shitara et al 2020 Tagawa et al 2021	3L sacituzumab govitecan (N = 113)	27.4% (19.5, 36.6)	7.2 months (4.7, 8.6)
	Bellmunt et al 2017	2L pembrolizumab (N = 270)	21.1% (16.4, 26.5)	NR
Endometrial cancer	Makker et al 2022	2/3L pembrolizumab + lenvatinib (N = 411)	31.9% (27.4, 36.6)	14.4 months (NR)
Cervical cancer	Weiss et al 1990	2L CTx (carboplatin) (N = 41)	15% (6, 29)	NR
	Chung et al 2019	2L+ pembrolizumab (N = 77)	14.3% (7.4, 24.1)	NR
	Oaknin et al 2022	2/3L ipilimumab + nivolumab (N = 43)	34.9% (NR)	NR
Ovarian cancer (PRR)	Pujade-Lauraine et al 2014	2/3L Non-platinum CTx + bevacizumab (N = 179)	27.3% (NR)	NR
Pancreatic cancer	Mita et al 2019	2L CTx (gemcitabine + Nab-paclitaxel) (N = 30)	13.3% (5.3, 29.7)	NR

Tumor type	Publication	Treatment regimen (N)	Confirmed ORR, % (95% CI)	Median DoR (95% CI)
Colorectal cancer	Giantonio et al 2007	2L bevacizumab + FOLFOX4 (N = 286)	22.7% (NR)	NR
	Strickler et al 2022 TUKYSA [®]	2L+ tucatinib + trastuzumab (N = 84)	38% (28, 49)	12.4 months (8.5, 20.5)
Non-small cell lung cancer	Herbst et al 2016	2L pembrolizumab (N = 344)	18% (NR)	NR
	Garon et al 2014	2L ramucirumab + docetaxel (N = 628)	23% (NR)	NR
BC	Hurvitz et al 2023	2L+ trastuzumab deruxtecan (N = 261)	79% (73.1, 83.4)	36.6 months (22.4, NE)
GC	Shitara et al 2020	3L+ trastuzumab deruxtecan (N = 125)	51% (42, 61)	11.3 months (5.6, NE)

2L, second-line treatment; 3L, third-line treatment; cORR, confirmed objective response rate; CI, confidence interval; mDoR, median duration of response; NE, not evaluable; NR, not reported; PRR, platinum resistant recurrent, SoC, standard of care.

The Applicant's Position:

Available standard treatment options for most patients with unresectable locally advanced or metastatic solid tumors are not curative, are not targeted toward biomarker identifiable vulnerabilities, and provide only modest clinical benefit. Therefore, better treatments are needed that can improve overall survival and quality of life in patients in the metastatic setting. By targeting molecular characterization and drivers of therapeutic vulnerabilities such as HER2-positive (IHC 3+) across tumor types, T-DXd offers the opportunity to improve therapeutic outcomes for patients. The presence of HER2 IHC 3+ expression in diverse cancers and the poor prognosis for these patients offers the opportunity to improve clinical outcomes for patients, agnostic to tumor type, through a biomarker selected approach. Several tissue-agnostic targeted therapies in biomarker-selected populations are approved, including in tumors with MSI-H/dMMR, TMB, BRAF V600E, NTRK fusions and RET rearrangements (Tateo V et al 2023). However, there are no drugs specifically approved (i.e., available therapy) to date, outside of BC and GC, for the treatment of patients with other HER2-expressing advanced or metastatic solid

tumors where patients continue to have poor outcomes with the currently available standard of care treatments in the second or later lines of therapy, where available.

The FDA's Assessment:

FDA agrees that there are no drugs approved for patients with HER2 expressing advanced/metastatic solid tumors, other than in breast cancer and gastric/GEJ cancer. Although the prognosis for patients with HER2 expressing (IHC 3+) advanced/metastatic solid tumors treated in the second line and beyond has not been characterized in all tumor types, it does appear to be poor based on the available literature. Therefore, FDA agrees additional therapies are needed in these populations of patients.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Enhertu® (trastuzumab deruxtecan; T-DXd) has been in development under Investigational New Drug (IND) 127553 since 2016. T-DXd is being investigated as a single agent and in combination regimens for the treatment of BC, GC, NSCLC, and other tumor types. ENHERTU is approved under Biologics License Application (BLA) 761139 for BC, GC, and NSCLC.

Date	Approval
20 December 2019	Accelerated approval granted for the treatment of adult patients with unresectable or metastatic HER2-positive BC who have received 2 or more prior anti-HER2-based regimens in the metastatic setting (5.4 mg/kg Q3W)
15 January 2021	Regular approval granted for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen (6.4 mg/kg Q3W)
05 May 2022	Regular approval was granted for the treatment of adult patients with unresectable or metastatic HER2-positive BC who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
06 August 2022	Regular approval was granted for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) BC who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy
12 August 2022	Accelerated approval was granted for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

The FDA's Assessment:

FDA agrees with the Applicant's summary of the regulatory actions and marketing history for T-DXd.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key regulatory interactions regarding T-DXd development in HER2-positive metastatic solid tumors is provided in Applicant - Table 2.

Applicant - Table 2: Key Regulatory Interactions

Date	Regulatory Interaction
14 Oct 2023	Type B Pre-sBLA Meeting (Written Responses Only) Alignment with FDA that the updated HER2 IHC3+ data from DP-02, DL-02, DC-02, DB-01, and DG-02 is acceptable to support sBLA filing in IHC3+ solid tumors
30 Aug 2023	Breakthrough Therapy Designation (BTD) granted for T-DXd in “treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options”
03 Jul 2023	Submission of a BTD Request in HER2-positive (IHC 3+) solid tumors
13 Jun 2023	Type C Meeting: Follow-up meeting to EOP meeting (19 Sep 2022) requested by AZ to share data from the Primary Analysis DCO from DP-02 as well as data from DL-01 and DC-02 to support the proposed indication in patients with HER2-expressing (IHC 3+) solid tumors. FDA agreed with the proposed submission package to support sBLA filing in IHC 3+ solid tumors.
13 Mar 2023	Pre-BTD Teleconference: FDA was supportive of submission of a full BTD Request for a tissue agnostic indication in HER2-positive (IHC 3+) solid tumors.
06 Mar 2023	Submitted preliminary Breakthrough Therapy Designation (pBTD) Request for a tissue agnostic indication in HER2-positive (IHC 3+) solid tumors.
19 Sep 2022	Type B (EOP) meeting: The meeting was requested by AZ to share preliminary clinical data from Study DP-02 and to discuss the potential of these data to support a proposed indication in patients with (b) (4).

The FDA’s Assessment:

In general, FDA agrees with the Applicant’s summary of key regulatory interactions. FDA notes the following additional information:

At the EOP2 Meeting in September 2002, the FDA expressed multiple concerns with the Applicant’s proposal for a potential agnostic indication for T-DXd in (b) (4) including:

- DP-02 excluded tumors where there were separate studies in HER2-positive tumors (such as NSCLC, gastric, colorectal cancers). In addition, gastric and GEJ tumors were approved at a dose of 6.4mg/kg while the Applicant was seeking an agnostic indication at 5.4mg/kg. The Applicant was informed that DP-02 by itself has an insufficient number of tumor types to solely support an agnostic indication.

- Applicant must harmonize definition for HER2 and IHC cutoffs across tumor types across the various studies that should be included for consideration.

(b) (4)

At the time of the Type C Meeting in June 2023, the Applicant proposed

(b) (4)

FDA also stated

(b) (4)

the Applicant should enroll additional patients with IHC3+ tumors into DP-02. In response to the Applicant's proposal of enrolling 40 additional patients in the mixed tumor cohort, FDA encouraged enrollment of additional patients in tumor types under-represented in the IHC3+ population currently available and to consider enrolling more than 40 patients in the mixed tumor cohort, as well as enroll additional patients into the rare tumor cohort. In addition, at this meeting, FDA agreed to the Applicant submitting a sBLA application only for patients with HER2-positive (IHC 3+) advanced/metastatic solid tumors. FDA stated that the approval pathway (accelerated approval vs. regular approval) for this supplement (IHC3+) would be a review issue. FDA stated

(b) (4)

The BTd granted for T-DXd was for the following indication, "*Treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.*" At the time of the pre-sBLA meeting in October 2023, FDA noted that if the proposed indication for this sBLA does not match the recent indication granted for BTd, this application may not be reviewed under BTd. Final wording of the indication will be a review issue.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to perform site inspections as part of the review for this supplemental BLA. Reference is made to the Clinical Inspection Summary by Dr. Regina Zopf dated 2/27/2024. The clinical site was chosen as it was a high enrolling site, and the clinical investigator had not been inspected previously. The CRO was selected for inspection to confirm data integrity related to independent radiology review and adjudication. The classification given to the clinical site and study contract research organization (CRO) are provided in FDA - Table 3.

FDA - Table 3: OSI Findings in DESTINY-PanTumor02 Study

Inspection	Site # and # of patients enrolled	Inspection Date	Final Classification
Dr. Funda Meric-Bernstam MD Anderson 1515 Holcombe Blvd, Houston, TX, 77030-4009 US	7801/ (b) (4) patients	January 29, 2024-February 1, 2024	NAI
CRO		(b) (4)	NAI

NA=not applicable; NAI=no action indication

Reviewer Comment: The OSI inspections did not find significant concerns regarding the oversight of the clinical trials or Good Clinical Practice (GCP) or regulatory compliance. Based on these results, data generated by the inspected clinical investigator and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

4.2. Product Quality

No CMC related changes were reported in the current submission. The assays used in the immunogenicity assessment were adequately validated and their performance during analysis of

the clinical samples is acceptable. No approvability issues were identified with respect to the validation and performance of the immunogenicity assays.

See the review by Dr. Jun Liu for full details.

4.3. **Clinical Microbiology**

No new information for clinical microbiology was submitted with this sBLA.

4.4. **Devices and Companion Diagnostic Issues**

The tissue agnostic indication in this sBLA for patients with HER2 IHC 3+ advanced/metastatic solid tumors is predominantly based on results from trials DP-02, DL-01 and DC-02. These three trials used different devices for assessment of HER2 IHC status.

(b) (4)

Since there will not be a contemporaneous companion diagnostic approval with this sBLA, a PMC was requested for the companion diagnostic. Refer to Section 13 of this Assessment Aid for additional details on PMCs issued for this sBLA.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

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6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted this BLA supplement for Enhertu (T-DXd) and accelerated approval is being granted for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and have no satisfactory alternative treatment options. For this tissue agnostic tumor indication, the proposed recommended dosage is 5.4 mg/kg Q3W for HER2-positive (IHC 3+) solid tumors.

The primary evidence of effectiveness comes from integrated efficacy analyses of three studies (DP-02, DL-01, DC-02) and two supportive studies (DB-01 and DG-02). The proposed dosages are supported by the overall efficacy of T-DXd across tissue-agnostic tumors. In DP-02, ORR was 51.4% (95% CI: 41.7, 61.0) and median DOR was 19.4 months (range 1.3, 27.9+). In DL-01, ORR was 52.9% (95% CI: 27.8, 77.0) and median DOR was 6.9 months (range 4.0, 11.7+). In DC-02, ORR was 46.9% (95% CI: 34.3, 59.8), and DOR was 5.5 months (range 1.3+, 9.7+). The safety profile of T-DXd is consistent with previous clinical trials, with no new safety signals identified.

The results of the population PK (popPK) analysis and exposure-response (E-R) analyses support the recommended dosage as (1) the E-R analyses are consistent with the approved dosages of T-DXd for the treatment of patients with unresectable or metastatic HER2-positive breast cancer (BC), non-small cell lung cancer (NSCLC), and gastric cancer (GC), (2) no dosage adjustment is necessary for specific populations based on updated popPK analyses after inclusion of data from Studies DP-02, DP-01, DC-02, and DC-01.

Updated integrated immunogenicity analyses showed the incidence of anti-drug antibodies (ADA) against T-DXd remained low at 1 - 3% of patients in DP-02 and across all completed T-DXd studies with no apparent effect of ADAs on the PK, safety, or efficacy of T-DXd.

Action:
The Office of Clinical Pharmacology has reviewed the information submitted in BLA761139 (S 0028). This BLA supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in FDA - Table 4.

FDA - Table 4: Key Clinical Pharmacology Review Issues by FDA

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
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Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from integrated efficacy analyses of five studies (DP-02, DL-01, DC-02, DB-01, and DG-02) with DB-01, and DG-02) considered supportive. The proposed dosages are supported by the overall efficacy of Enhertu with an objective response rate (ORR) of 54.1% (95% CI: 49.2%, 59%) across tumor types in the indicated patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options. Refer to the FDA's assessment in Section 8.1 for additional details.
General dosing instructions	The proposed recommended dosage of 5.4 mg/kg Q3W for HER2-positive (IHC 3+) solid tumors is acceptable from a clinical pharmacology perspective as they are supported by: • Favorable anti-tumor activity: This dosage demonstrated an ORR of 54%. There was no significant but positive E-R relationship for ORR or OS. • The proposed recommended dosage is consistent with the approved dosages of T-DXd for the treatment of patients with unresectable or metastatic HER2- positive BC and NSCLC. • E-R safety analyses continue to support these dosages in HER2-positive (IHC 3+) solid tumors. No new safety signals observed in this population.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dosage modification recommendations for specific populations remain unchanged. Results of updated popPK analysis are consistent with previously conducted analysis with no clinically significant differences in the PK of T-DXd and DXd based on sex, age, renal function, hepatic function, ECOG performance status, HER2 status, ethnicity (Japanese vs. non-Japanese), IHC class, tumor type, formulation, concomitant ritonavir or itraconazole administration, baseline albumin level, baseline tumor size, baseline bilirubin level, and baseline AST level. Body weight was identified as a significant covariate; however, consistent with previously conducted popPK analysis, it supports the body weight based dosing regimen.

Immunogenicity	The incidence of immunogenicity for T-DXd remained low. The ADAs against T-DXd were detected in 0.6 – 3% of patients in Study DP-02 and across all completed T-DXd studies. Updated integrated immunogenicity analyses showed no apparent effect of development of ADAs on the PK, safety, or efficacy of T-DXd.
Labeling	Overall, the proposed labeling recommendations are acceptable contingent upon the Applicant's agreement with the FDA revisions to the labeling. Clinical pharmacology labeling recommendations are detailed in labeling sections 8.5, 12.3 and 12.6.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The PK and immunogenicity of T-DXd have been well-characterized and are summarized in the current prescribing information. No noncompartmental analysis was conducted for Study DP-02, due to sparse PK sampling. An update of the popPK analysis of T-DXd that includes previously submitted data from 12 studies and new data from 4 Phase II studies (DP-01, DP-02 and DC-01 and DC-02) was performed where no new covariates were found and no clinically relevant covariates required dose adjustment. The ER analyses for efficacy and safety in patients with IHC 3+ tumors from Studies DP-02 (N = 111), DC-02 (N = 98), and DL-01 (N = 28) at 5.4 mg/kg and 6.4 mg/kg support the recommended dosing regimen of T-DXd 5.4 mg/kg Q3W for the treatment of patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors and support that dose adjustments for special populations are not necessary. An analysis of the immunogenicity of T-DXd based on pooled data from 12 clinical studies (Studies DB-01, DB-02, DB-03, DB-04, DG-01, DG-02, DL-01, DL-02, J101, DP-02, DC-01, and DC-02) was conducted. The prevalence and incidence of ADA to T-DXd across the 4 pooled immunogenicity datasets ranged from 6.6% to 9.0% and 0.6% to 3.0%, respectively. The majority of ADA+ patients were ADA+ at baseline only, and the majority of TE-ADA+ patients were transiently ADA+ and were nAb-negative. The medians of maximum anti-T-DXd post-baseline ADA titer of patients with TE-ADA were low relative to the minimum required dilution of 45 (range: 45 to 405). Both integrated immunogenicity analysis and population PK analysis showed the lack of impact of ADA on T-DXd PK. In addition, there was no apparent effect of ADA on safety or efficacy of T-DXd. Collectively, a positive benefit-risk balance is observed with T-DXd treatment regardless of ADA status.

The Applicant's Position:

The pharmacokinetics of T-DXd is well characterized using the same PopPK models established previously. The PopPK analysis continues to indicate that none of covariates, showed clinically meaningful impact on PK for T-DXd and DXd. The incidence of immunogenicity remains low, and the integrated immunogenicity analysis showed the lack of impact of ADA on T-DXd PK. In addition, there was no apparent effect of ADA on safety or efficacy of T-DXd.

The FDA's Assessment:

FDA agrees with the Applicant's position that integrated immunogenicity analysis and popPK analysis did not show an effect of ADAs on T-DXd PK and that ADAs have no apparent effect on PK, safety, and efficacy of T-DXd. Given that only 1 patient developed neutralizing antibody (NAb) against T-DXd, the effect of NAb on PK, safety, and efficacy of T-DXd is unknown. See Section 6.3.1 General Pharmacology and Pharmacokinetic Characteristics for more details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The recommended dosing regimen for T-DXd in HER2-positive (IHC 3+) cancer patients is 5.4 mg/kg Q3W, except for GC where the recommended dose is 6.4 mg/kg Q3W. The efficacy and safety data continue to support the approved dosing regimen of 5.4 mg/kg in tissue-agnostic tumors and 6.4 mg/kg in GC patients.

T-DXd and DXd exposures in patients with IHC 3+ tumors in Studies DP-02, DC-02, and DC-01 were consistent with patients in the prior studies included in the previous applications based on the PopPK analysis. No new covariates of T-DXd were identified as statistically significant from the previous analysis with data from 12 studies. Identified statistically significant covariates in the PopPK analysis did not appear to have a clinically meaningful impact on the steady-state exposure of intact T-DXd and DXd, and no dose adjustment was needed based on covariates or special populations.

Data from patients from Studies DP-02, DC-02, and DL-01, the PopPK analysis, and the E-R efficacy and safety analyses support a favorable benefit-risk profile for T-DXd 5.4 mg/kg Q3W in patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors that have received prior treatment or who have no satisfactory alternative treatment options, and data from Study DG-02 continue to support a favorable benefit-risk profile of T-DXd 6.4 mg/kg in GC. The previous E-R efficacy and safety analyses for GC patients have shown that the optimal dose in GC is 6.4 mg/kg Q3W as based on the locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma application (DS8201-A-J202 [Study DG-01]) The E-R efficacy and safety

analyses support a clinically meaningful but flat concentration-efficacy (ORR and OS) relationship and a generally tolerable and manageable safety profile at 5.4 mg/kg, supporting the use of the 5.4 mg/kg dose in patients with IHC 3+ tumors, except for GC patients.

In conclusion, the clinically meaningful efficacy, combined with a generally tolerable and manageable safety profile, observed in Studies DP-02, DC-02, and DL-01, and the results from the E-R efficacy and safety analyses support a favorable benefit-risk profile for T-DXd at a dose of 5.4 mg/kg Q3W in adult patients with unresectable or metastatic HER2-expressing (IHC 3+) solid tumors (except GC) that have received prior treatment or who have no satisfactory alternative treatment options. Efficacy and safety data from Study DG-02 continue to support a favorable benefit-risk profile for T-DXd at a dose of 6.4 mg/kg Q3W in gastric cancer.

The Applicant's Position:

The recommended dosing regimen for T-DXd in HER2-expressing (IHC3+) cancer patients is 5.4 mg/kg Q3W, except for GC where the recommended dose is 6.4 mg/kg Q3W. The efficacy and safety data continue to support the approved dosing regimen of 5.4 mg/kg in tissue-agnostic tumors and 6.4 mg/kg in GC patients.

The E-R analyses support a clinically meaningful efficacy (cORR, DoR and OS) at 5.4 mg/kg and a generally tolerable and manageable safety profile, supporting the use of the 5.4 mg/kg dose in patients with IHC 3+ tumors and 6.4 mg/kg Q3W in GC patients and support the proposed indication for the treatment of patients with unresectable or metastatic HER2-expressing (IHC 3+) solid tumors that have progressed following received prior treatment or who have no satisfactory alternative treatment options with T-DXd 5.4 mg/kg Q3W as the recommended dose in this population.

The FDA's Assessment:

FDA agrees with the Applicant that the proposed dosage of T-DXd 5.4 mg/kg Q3W in patients with HER2-positive (IHC 3+) solid tumors provides a favorable benefit-risk profile based on data from patients in Studies DP02, DC02, and DL01, updated popPK analysis, and E-R efficacy and safety analyses.

PopPK modeling and simulation indicates comparable steady state exposure parameters between GC on 6.4 mg/kg and other tumor types on 5.4 mg/kg with same Q3W dosing schedule. Refer to FDA's assessment in Section 19.4. OCP Appendices for details.

FDA concurs with the Applicant's conclusion that a flat E-R for efficacy was observed. However, E-R analyses for efficacy was conducted with data from two dose levels (5.4 mg/kg and 6.4 mg/kg). The exposure range is considered narrow from 5.4 mg/kg and 6.4 mg/kg and sample size (n=44, 18% of E-R efficacy population n=236) at 6.4 mg/kg was limited. Therefore, E-R relationship for efficacy has not been fully characterized.

6.2.2.2. Therapeutic Individualization

No new information is provided in the current application.

The FDA's Assessment:

Not applicable.

6.2.2.3. Outstanding Issues

No new information is provided in the current application.

The FDA's Assessment:

No outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Population-pharmacokinetics analysis

The previous PopPK analysis based on T-DXd and DXd PK data from 12 clinical studies (J102, DB-01, DB-02, DB-03, DB-04, A103, DG-01, DG-02, DL-01, DL-02, J101, A104) was updated to include data from Studies DP-01, DP-02, DC-01, and DC-02 (N = 2829). Across all tumor types, 314 (46.4%) patients were identified as HER2-positive (IHC 3+), 701 patients as HER2-positive (IHC 1+) or HER2-positive (IHC 2+), and 383 patients as HER2 status unknown. Patients were predominantly female (77.2%). The median age of patients included in the analysis was 58.0 years and median body weight was 61.0 kg; the racial distribution was Asian (47.8%), White (43.5%), African American (2.0%), and other (5.8%).

Consistent with the previous PopPK analysis, the PK of T-DXd was adequately described by a two-compartment model with linear elimination, and DXd was described by a one-compartment model, with time-varying release of drug from T-DXd. The same covariates as in the previous PopPK model were retained on T-DXd with exception of the impact of NSCLC on the clearance of T-DXd. The same covariate effects as the previous PopPK model were retained on DXd, with the addition of cancer type (colorectal cancer and 'Other') on VDXd and cancer type (GC and 'Other') on CLDXd. T-DXd exposures of subjects dosed at 5.4 mg/kg and 6.4 mg/kg Q3W were similar among BC, colorectal cancer, NSCLC and other tumor types; however, exposure in GC at steady-state appeared lower at the same dose level compared to other tumor types. The T-DXd

exposure estimates were also comparable across the categories of hepatic function, renal function, IHC class, ECOG status, HER2 status and Japanese ethnicity status, suggesting these covariates have no clinically meaningful impact on the exposure of either T-DXd or The point estimate of the T-DXd and DXd exposure ratios in the highest body weight category (> 91.5 kg, 95th percentile) versus the median body weight (61 kg, reference patient) fell outside the 0.8 to 1.25 range, being around 1.3 to 1.4-fold (range: 1.29 to 1.44-fold). These are consistent with the previous PopPK analysis but are not considered clinically relevant for dose adjustment.

For each of the other selected continuous covariates, the point estimate for the median exposure in each quantile group fell within the limits of the 80% to 125% range of the overall median, suggesting no substantial impact of the selected covariate on the exposure to DXd, though a trend towards reduced exposure was noted in those patients with the lowest levels of albumin at baseline.

The point estimate of the median exposure for each stratum of Japanese status, sex, formulation, ritonavir coadministration status, and itraconazole coadministration status all fell within the limits of the 80% to 125% range of the overall reference median, suggesting no substantial impact of the selected covariates on the exposure to T-DXd or DXd.

Overall, the steady-state exposure to both T-DXd and DXd is not sensitive to ethnicity, IHC class, HER2 status or renal impairment status. When tumor type is considered, there is an apparent reduction in steady-state exposure (AUC, C_{max} and C_{trough}) for T-DXd in gastric cancer patients when compared to other tumor types at 5.4 mg/kg; however, DXd exposures are consistent across tumor types and doses.

When data from Study DP-02 with additional tumor types are compared with other tumor types at the 5.4 mg/kg dose, the steady-state exposure to either T-DXd or DXd appear to be similar.

Exposure-Response for Efficacy

The ER-efficacy analyses evaluated exposure-efficacy relationships in patients with IHC 3+ tumors from Studies DP-02 (solid tumors), DC-02 (CRC), and DL-01 (NSCLC). ER-efficacy analyses were conducted for the key efficacy endpoints of ORR and OS. A total of 236 patients with IHC 3+ tumors treated with T-DXd were included; their median age was 62 years and females accounted for 52.1% of patients. Correlation between ORR and a range of steady-state exposure metrics were explored. The most influential ($p = 0.0443$) was C_{max} at steady state. As the relationship between exposure and ORR seems to be strongly confounded by baseline albumin level, no further exploration of relationships between exposure metrics and ORR was performed. In summary, baseline albumin level was considered a predictor of ORR, while exposure metrics were not significantly associated with ORR. In the E-R analysis, the relationship between T-DXd exposure and ORR in Studies DP-02, DC-02, and DL-01 was not statistically significant, suggesting a flat E-R relationship to the narrow exposure range resulting

from the single-dose level (5.4 mg/kg Q3W) in all studies.

The relationship between T-DXd exposure and OS in Studies DP-02, DC-02, and DL-01 was explored. When a relationship between steady-state T-DXd exposure and OS is considered, the strongest relationship, but still not significant, is between $C_{max,ss}$ and OS ($p=0.21$) however the highest quartile showed the lowest OS (12.9 months for Q4 versus 22.6 months for Q1). When albumin is considered in the relationship the trend with C_{max} at steady state reverses to lower concentration with either high albumin or low albumin is related to lower OS while higher concentrations with either high albumin or low albumin are related to higher OS (Applicant – Figure 6). As the relationship between exposure and OS seems to be strongly confounded by baseline albumin level, no further exploration of relationships between exposure metrics and OS was performed, and no covariate analysis was undertaken. The analyses support clinically meaningful efficacy across the entire exposure range with the T-DXd 5.4 mg/kg dose in patients with IHC 3+ tumors.

Exposure-Response for Safety

The ER-safety analysis was performed utilizing data from Studies DP-02, DC-02, and DL-01: the safety data comprised 236 patients who were in the safety analysis set and had modeled PK exposures (111 patients were from Study DP-02). The safety endpoints were ILD events irrespective of Grade and $\geq$ Grade 3 ILD events versus selected exposure metrics for both T-DXd and DXd. The exposure metric chosen to represent incidence of any grade ILD was the steady-state AUC of T-DXd ($p = 0.02875$).

There were no investigations of any exposure metric and $\geq$ Grade 3 ILD due to only 5 events of $>$ Grade 3 ILD occurring. Age and region were shown to have potential impact on the incidence rate of ILD. The final model contained age and regional differences between Europe, Japan, USA and Other to Asia and can be considered the final model. Steady-state exposure to T-DXd was shown to correlate with the incidence rate of any grade ILD (14.8% of patients; 35 events), no evaluation between exposure metrics and $\geq$ Grade 3 ILD was investigated due to the low incidence rate (2.1% of patients; 5 events).

Immunogenicity

Immunogenicity data collected from 12 clinical studies (Studies DP-02, DC-02, DL-01, DB-01, DG-02, J101, DL-02, DB-02, DB-03, DB-04, DG-01, and DC-01) were integrated to assess T-DXd ADA responses and the potential impact of immunogenicity on the clinical PK, efficacy and safety.

ADA prevalence (percentage of ADA+) was numerically similar across the pools (range: 6.6% to 9.0%) across IHC 3+ status or dosing regimen. The majority of ADA-positive patients were ADA-positive at baseline only (range: 4.4% to 6.0%). ADA incidence (percentage of TE-ADA+) was low across the pools (range: 0.6% to 3.0%). A total of 8 patients tested positive for NAb

(one classified as TE-NAb+). Across all pools, ADA response to T-DXd was mostly transient in nature. The medians of maximum T-DXd post-baseline ADA titer of patients with TE-ADA were low relative to the minimum required dilution of 45 (range: 45 to 405).

The Applicant's Position:

Overall, the results indicate that T-DXd has a low immunogenicity risk profile. T-DXd showed relatively low ADA incidence and transient ADA response. Both integrated immunogenicity analysis and PopPK analysis showed the lack of effect of ADA on T-DXd PK. In addition, there was no apparent effect of ADA on safety or efficacy of T-DXd. Collectively, a positive benefit-risk balance was observed with T-DXd treatment regardless of ADA status.

The FDA's Assessment:

FDA concurs with the Applicant's position that there is no apparent effect of ADAs on the PK, efficacy, or safety of T-DXd. PopPK analysis did not show effect of ADAs on the PK of T-DXd. This conclusion is supported by the following data analyses illustrated in the tables and plots below.

ADA Impact on PK

- Across all tumor types, T-DXd C_{trough} in patients with TE-ADA+ status were comparable to those with ADA- status at all PK sampling time points from C2D1 to C8D1, except for the ICH 3+ pools (FDA - Table 5 and FDA - Table 6 and FDA Figure 1). The difference observed in the ICH 3+ 5.4 mg/kg and 6.4 mg/kg pools is likely due to the low number of TE-ADA+ (n = 2 in each pool) patients in these pools.
- Consistent with previous popPK analysis (Analysis Report PMx023, dated 09 December 2022), the impact of T-DXd ADAs on the PK of T-DXd was not found to be a significant covariate in this updated popPK analysis.

FDA - Table 5: Abbreviated Summary of T-DXd C_{trough} Concentration ($\mu\text{g/mL}$) by Visit and ADA Status (Immunogenicity Analysis Set) – 5.4 mg/kg Pool

Visit/Statistic	ICH3+ Pool T-DXd 5.4 mg/kg (N=347)				All Tumor Types Pool T-DXd 5.4 mg/kg (N=1798)			
	TE-ADA+ N=2	non-TE-ADA+ N=21	ADA – N=324	TE-NAb+* N=0	TE-ADA+ N=27	non-TE-ADA+ N=118	ADA – N=1653	TE-NAb+* N=1
Baseline								
n (n < LLOQ)	1 (1)	21 (21)	316 (314)	0	26 (26)	114 (112)	1601 (1585)	1 (1)
Geometric mean	NQ	NQ	NC		NQ	NC	NC	NQ
Geo CV (%)	NC	NC	NC		NC	NC	NC	NC
C2D1								
n (n < LLOQ)	2 (0)	21 (1)	308 (17)	0	27 (0)	115 (2)	1482 (47)	1 (0)

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Geometric mean	6.1142	2.4128	3.0489		4.4077	4.1579	3.7057	3.7900
Geo CV (%)	73.0764	104.2993	119.3450		72.3796	107.2248	105.1540	NC
C3D1								
n (n < LLOQ)	2 (0)	13 (0)	202 (1)	0	24 (0)	95 (1)	1184 (1)	1 (0)
Geometric mean	12.0000	5.4282	5.7447		7.8564	7.6217	6.7510	13.4000
Geo CV (%)	26.2187	78.9602	92.9580		61.3219	91.0664	80.0140	NC
C4D1								
n (n < LLOQ)	2 (0)	15 (0)	280 (3)	0	26 (0)	101 (1)	1317 (6)	1 (0)
Geometric mean	14.4312	5.3067	6.7547		9.2961	8.9571	8.0062	16.4000
Geo CV (%)	30.3360	93.0005	104.4370		73.3761	88.3254	89.5588	NC
C6D1								
n (n < LLOQ)	2 (0)	6 (1)	182 (2)	0	22 (0)	78 (1)	1110 (4)	1 (0)
Geometric mean	12.4625	6.6116	8.4004		11.6385	11.6132	10.1530	17.8000
Geo CV (%)	34.5245	248.7505	79.2814		45.6549	82.3558	81.6598	NC
C8D1								
n (n < LLOQ)	0	5 (0)	105 (0)	0	15 (0)	65 (0)	877 (1)	1 (0)
Geometric mean		4.9566	9.9859		15.2559	12.2319	11.1333	19.9000
Geo CV (%)		105.6397	81.2504		26.1744	75.3569	73.0772	NC

Abbreviation: NC = Not Calculated; NQ = Non-quantifiable;

* NAb test results are not available for DB01.

TE-ADA+ is defined as subjects who were either treatment-boosted ADA+ or treatment-induced ADA+.

Non TE-ADA positive is defined as subjects who are ADA positive but not fulfilling the conditions for TE-ADA+.

ADA negative is defined as participants who are ADA negative at all assessments, including baseline and post-baseline.

TE-NAb+ is defined as treatment-emergent ADA+ subjects with any positive NAb assessment post-baseline.

At a time point where ≤ 50% of the concentration values are NQ, all NQ values were set to the LLOQ, and all descriptive statistics calculated accordingly.

At a time point where > 50% (but not all) of the values are NQ, the geomean, geoCV(%) were set to NC. The max value from the individual data, and the min and median were set to NQ.

If all concentrations were NQ at a time point, no descriptive statistics were calculated for that time point. The geomean was reported as NQ, and geoCV(%) as NC.

Source: Applicant ISI Table 2.7.4.7.2.1. Module 5.3.5.3

FDA - Table 6: Abbreviated Summary of T-DXd C_{trough} Concentration (µg/mL) by Visit and ADA Status (Immunogenicity Analysis Set) – 6.4 mg/kg Pools

Visit/Statistic	IHC3+ Pool T-DXd 6.4 mg/kg (N=67)				All Tumor Types Pool T-DXd 6.4 mg/kg (N=793)			
	TE-ADA+ N=2	non-TE-ADA+ N=4	ADA – N=61	TE-NAb+* N=0	TE-ADA+ N=21	non-TE-ADA+ N=41	ADA – N=731	TE-NAb+* N=0
Baseline								
n (n < LLOQ)	2 (2)	4 (4)	58 (58)	0	20 (20)	41 (41)	722 (719)	0

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Geometric mean	NQ	NQ	NQ		NQ	NQ	NC	
Geo CV (%)	NC	NC	NC		NC	NC	NC	
C2D1								
n (n < LLOQ)	2 (0)	4 (0)	55 (1)	0	21 (1)	30 (0)	515 (8)	0
Geometric mean	3.0532	3.0601	4.1461		4.7793	4.8052	4.4369	
Geo CV (%)	72.3253	138.1145	90.7719		89.0809	73.1719	84.7990	
C3D1								
n (n < LLOQ)	2 (0)	4 (0)	49 (0)	0	17 (0)	24 (0)	407 (4)	0
Geometric mean	4.4345	6.9963	7.7922		6.7054	7.1910	7.7901	
Geo CV (%)	7.0217	74.4457	136.3073		69.9212	62.8864	86.5145	
C4D1								
n (n < LLOQ)	2 (0)	4 (0)	46 (0)	0	13 (0)	22 (0)	377 (1)	0
Geometric mean	3.5557	8.2267	9.0262		10.9291	8.8993	9.9380	
Geo CV (%)	30.4818	39.6328	84.2427		71.2653	61.3822	68.7138	
C6D1								
n (n < LLOQ)	2 (0)	3 (0)	31 (0)	0	11 (0)	23 (0)	402 (2)	0
Geometric mean	5.8040	11.7763	11.0679		13.4178	10.3539	11.7237	
Geo CV (%)	70.1887	41.9269	64.4038		115.1821	91.7687	72.5328	
C8D1								
n (n < LLOQ)	1 (0)	2 (0)	23 (0)	0	3 (0)	9 (0)	195 (0)	0
Geometric mean	5.8400	20.3652	9.6230		11.3202	14.8196	12.3313	
Geo CV (%)	NC	19.2130	95.9782		65.0110	57.1003	73.4062	

* NAb test results are not available for DB01.

At a time point where $\leq 50\%$ of the concentration values are NQ, all NQ values were set to the LLOQ, and all descriptive statistics calculated accordingly.

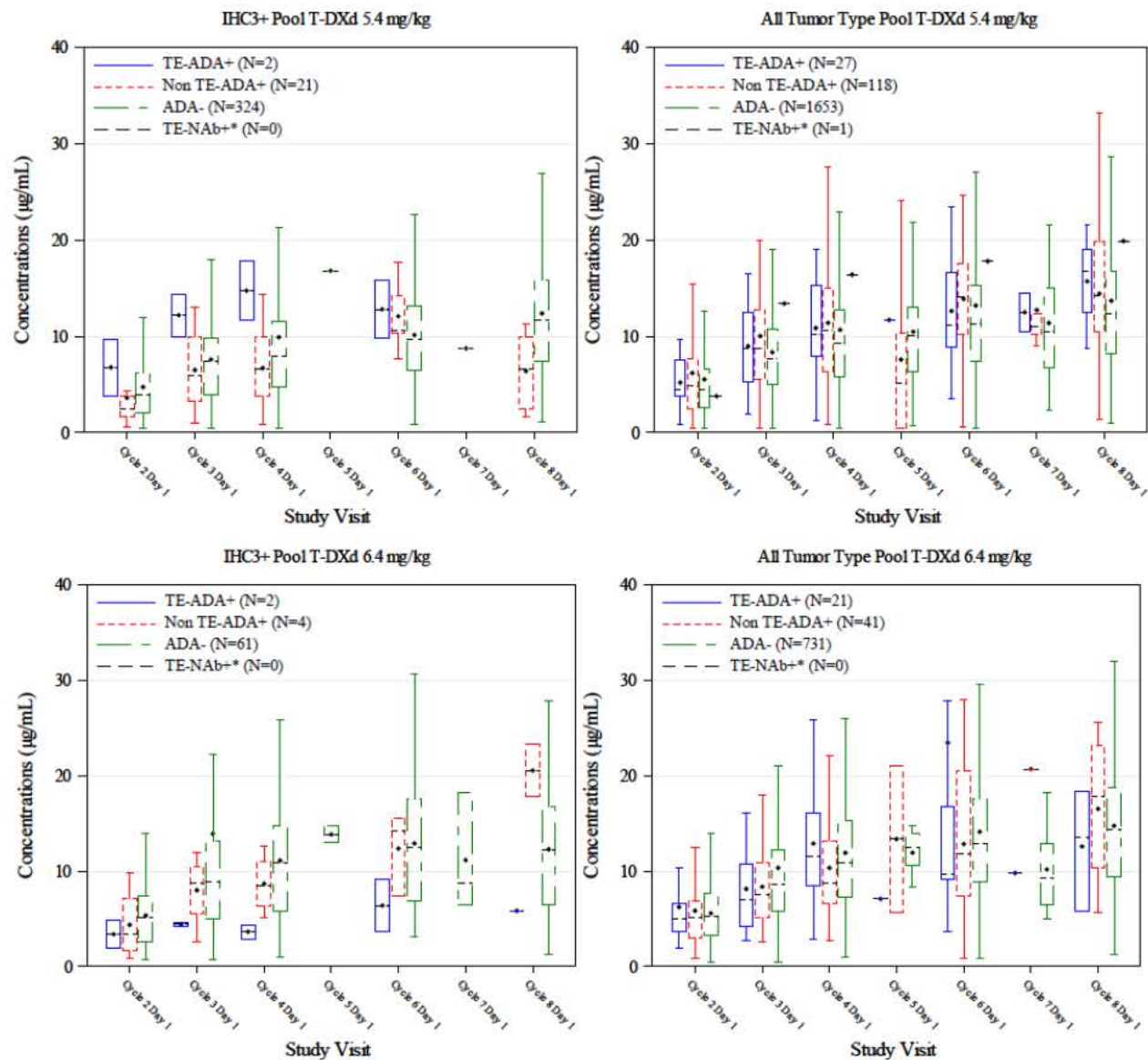
At a time point where $> 50\%$ (but not all) of the values are NQ, the geomean, geoCV(%) were set to NC. The max value from the individual data, and the min and median were set to NQ.

If all concentrations were NQ at a time point, no descriptive statistics were calculated for that time point. The geomean was reported as NQ, and geoCV(%) as NC.

Source: Applicant ISI Table 2.7.4.7.2.1. Module 5.3.5.3

FDA Figure 1: Box Plots of T-DXd C_{trough} by Visit and ADA Status and by Pools (Immunogenicity Analysis Set)

Trastuzumab deruxtecan (T-DXd, DS-8201a)



Boxplot = median (dotted line), arithmetic mean (diamond) and 1.5 * IQR (spindles).

* NAb test results are not available for DB01.

Source: Applicant ISI Figure 2.7.4.7.2.3, Module 5.3.5.3

ADA impact on efficacy

Across all tumor types, ORR in patients with TE-ADA+ status was generally similar to those with ADA- status, except for the ICH 3+ pools (

FDA - Table 7). The difference observed in the ICH 3+ 5.4 mg/kg and 6.4 mg/kg pools is likely due to the low number of TE-ADA+ (n = 2 in each pool) patients in these pools.

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FDA - Table 7: Summary of Clinical Response Parameters by Pools and ADA Status (Immunogenicity Analysis Set)

	IHC3+ Pool				All Tumor Types Pool			
	TE-ADA+	non-TE-ADA+	ADA –	TE-NAb+*	TE-ADA+	non-TE-ADA+	ADA –	TE-NAb+*
T-DXd 5.4 mg/kg	(N=2)	(N=21)	(N=324)	(N=0)	(N=27)	(N=118)	(N=1653)	(N=1)
Confirmed ORR, n (%)	0	12 (57.1)	181 (55.9)	0	16 (59.3)	70 (59.3)	944 (57.1)	1 (100.0)
Duration of confirmed response (months), n ^a	n=0	n=12	n=181	n=0	n=16	n=70	n=944	n=1
Median	NE	7.9	19.4	NE	11.3	20.0	16.8	2.8
95% CI	NE	5.6 to NE	11.4 to NE	NE	3.8 to 24.9	13.7 to NE	15.0 to 19.5	NE
T-DXd 6.4 mg/kg	(N=2)	(N=4)	(N=61)	(N=0)	(N=21)	(N=41)	(N=731)	(N=0)
Confirmed ORR, n (%)	1 (50.0)	1 (25.0)	30 (49.2)	0	12 (57.1)	19 (46.3)	295 (40.4)	0
Duration of confirmed response (months), n ^a	n=1	n=1	n=30	n=0	n=12	n=19	n=295	n=0
Median	NE	5.5	8.3	NE	9.3	14.1	10.4	NE
95% CI	NE	NE	6.9 to NE	NE	2.9 to NE	4.2 to NE	8.5 to 12.8	NE

[a] Calculated using the Kaplan-Meier technique. CI for median is derived based on Brookmeyer-Crowley method.

*NAb test results are not available for DB01.

DP02 reported clinical responses according to investigator as primary, but DP02 results per Independent Central Review are included for consistency with other studies.

Source: Applicant ISI Table 2.7.4.7.3.1, Module 5.3.5.3

ADA impact on IRR

No trend in the proportion of TE-ADA+ or ADA- patients who experienced IRRs was observed in any pool (FDA - Table 8).

FDA - Table 8: Summary of Infusion Related Reactions by Pools and ADA Status (Immunogenicity Analysis Set)

	IHC3+ Pool				All Tumor Types Pool			
	TE-ADA+	non-TE-ADA+	ADA –	TE-NAb+*	TE-ADA+	non-TE-ADA+	ADA –	TE-NAb+*
T-DXd 5.4 mg/kg	(N=2)	(N=21)	(N=324)	(N=0)	(N=27)	(N=118)	(N=1653)	(N=1)
Patients with any IRR, n (%)	0	1 (4.8)	4 (1.2)	0	0	3 (2.5)	16 (1.0)	0
Patients with no IRR, n (%)	2 (100%)	20 (95.2%)	320 (98.8%)	0	27 (100%)	115 (97.5%)	1637 (99%)	1 (100%)
T-DXd 6.4 mg/kg	(N=2)	(N=4)	(N=61)	(N=0)	(N=21)	(N=41)	(N=731)	(N=0)
Patients with any IRR, n (%)	0	0	0	0	0	1 (2.4%)	6 (0.8%)	0
Patients with no IRR, n (%)	2 (100%)	4 (100%)	61 (100%)	0	21 (100%)	40 (97.6%)	725 (99.2%)	0

* NAb test results are not available for DB01.

IRR is defined as any adverse event (AE) occurring within 24 hours of the completed infusion, at any cycle, with one of the following Preferred Terms (PTs) that were considered related to study drug by the investigator: administration related reaction; anaphylactic reaction; hypersensitivity; infusion related hypersensitivity reaction; or infusion related reaction.

Source: Applicant ISI Table 2.7.4.7.4.2, Module 5.3.5.3

NAb impact on PK, efficacy and safety

The occurrence of TE-nAb+ was low (n = 1 in the 5.4 mg/kg and 0 in the 6.4 mg/kg pools for all tumor types); therefore, the potential impact of NAb on PK, efficacy, or safety could not be assessed.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Refer to Section 6.3.1.

The Applicant's Position:

Patients treated with T-DXd in Studies DP-02, DC-02, and DL-01 demonstrated high response rates with long durability leading to meaningful survival outcomes across multiple HER2-

positive (IHC 3+) tumor types. T-DXd demonstrated a tolerable and manageable safety profile in the intended patient population and showed consistent safety findings with the established safety profile in the T-DXd clinical program at the dose of 5.4 mg/kg Q3W. No new safety signals were observed in the IHC 3+ T-DXd 5.4 mg/kg Pool or in Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg).

The FDA's Assessment:

FDA agrees that the clinical pharmacology program provides supportive evidence of effectiveness. Refer to FDA's assessment in Section 8.1.3. Trial Results for details.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Refer to Section 0.

The Applicant's Position:

The ERES analyses support a clinically meaningful but flat concentration-efficacy (ORR and OS) relationship and a generally tolerable and manageable safety profile at 5.4 mg/kg based on DL-01, DC02 and DP-02 patients and tumors, supporting the use of the 5.4 mg/kg dose in patients with IHC 3+ tumors and 6.4 mg/kg Q3W in patients with GC as shown in the earlier GC submission.

The FDA's Assessment:

FDA agrees that the proposed recommended dosing regimen is appropriate for patients with HER2-positive (IHC 3+) solid tumors.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

T-DXd exposures of subjects dosed at 5.4 mg/kg and 6.4 mg/kg Q3W were similar among BC, CRC, NSCLC and other tumor types; however, exposure in GC at steady-state appeared lower at the same dose level compared to other tumor types. The T-DXd exposure estimates were also comparable across the categories of hepatic function, renal function, IHC class, ECOG status, HER2 status and Japanese ethnicity status, suggesting these covariates have no clinically meaningful impact on the exposure of either T-DXd or The point estimate of the T-DXd and DXd exposure ratios in the highest body weight category (> 91.5 kg, 95th percentile) versus the median body weight (61 kg, reference patient) fell outside the 0.8 to 1.25 range, being around 1.3 to 1.4-fold (range: 1.29 to 1.44-fold). These are consistent with the previous PopPK analysis but

are not considered clinically relevant for dose adjustment.

For each of the other selected continuous covariates, the point estimate for the median exposure in each quantile group fell within the limits of the 80% to 125% range of the overall median, suggesting no substantial impact of the selected covariate on the exposure to DXd, though a trend towards reduced exposure was noted in those patients with the lowest levels of albumin at baseline.

The point estimate of the median exposure for each stratum of Japanese status, sex, formulation, ritonavir coadministration status, and itraconazole coadministration status all fell within the limits of the 80% to 125% range of the overall reference median, suggesting no substantial impact of the selected covariates on the exposure to T-DXd or DXd.

The Applicant's Position:

Overall, the steady-state exposure to both T-DXd and DXd is not sensitive to ethnicity, IHC class, HER2 status or renal impairment status. When tumor type is considered, there is an apparent reduction in steady-state exposure (AUC, C_{max} and C_{trough}) for T-DXd in gastric cancer patients when compared to other tumor types at 5.4 mg/kg; however, DXd exposures are consistent across tumor types and doses. When data from Study DP-02 with additional tumor types are compared with other tumor types at the 5.4 mg/kg dose, the steady-state exposure to either T-DXd or DXd appear to be similar. Therefore, the GC patients require a 6.4 mg/kg dose adjustment to achieve similar exposure to other indications as the only dose adjustment necessary.

The FDA's Assessment:

FDA concurs with Applicant's position. Results of updated popPK analysis are consistent with previously conducted analysis with no clinically significant differences in the PK of T-DXd and DXd based on sex, age, renal function, hepatic function, ECOG performance status, HER2 status, ethnicity (Japanese vs. non-Japanese), IHC class, tumor type, formulation, concomitant ritonavir or itraconazole administration, baseline albumin level, baseline tumor size, baseline bilirubin level, and baseline AST level.

Body weight was identified as a significant covariate; however, consistent with previously conducted popPK analysis, it supports the body weight-based dosing regimen. Refer to FDA's assessment in Section 19.4. OCP Appendices for details.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

No new information is provided in the current application.

The Applicant's Position:

No dose adjustment is needed for food-drug or drug-drug interactions.

The FDA's Assessment:

Not applicable.

X

X

X

X

Primary Reviewer

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Lily Leu, PharmD

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The basis of this application are the clinical studies presented in the below table and which are described comprehensively in Section 8.1.

Applicant - Table 9: Listing of Relevant Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Studies to Support Efficacy and Safety</i>								
DESTINY-PanTumor02 (DP-02)	NCT 04482309	Phase II, open-label, single-arm, non-randomized, multicenter study of T-DXd	T-DXd IV infusion 5.4 mg/kg Q3W	<u>Primary:</u> confirmed ORR by RECIST v1.1 <u>Secondary:</u> Safety, tolerability, DoR, DCR, PFS, OS, and PK.	<u>Data cut-off (DCO):</u> 08 Jun 2023 <u>Median treatment duration:</u> 5.59 months (range 2.07 to 8.97) <u>Median duration of OS follow-up (FAS):</u> 13.4 months	268 enrolled 267 treated	Locally advanced unresectable or metastatic selected HER2-expressing tumors that had progressed following prior treatment or had no satisfactory alternative treatment options. Prior HER2-	65 study centers 15 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							targeting therapy was permitted	
DESTINY-CRC02 (DC-02; DS8201-A-U207)	NCT 04744831	Phase II, open-label, single-arm, randomized, multicenter, 2-part study of T-DXd	Part 1: patients randomized 1:1 to T-DXd 5.4 mg/kg or T-DXd 6.4 mg/kg IV Q3W Part 2: T-DXd 5.4 mg/kg IV Q3W	<u>Primary:</u> confirmed ORR by RECIST v1.1 <u>Secondary:</u> DoR, DCR, CBR, PFS, OS.	<u>Data cut-off (DCO):</u> 01 Nov 2022 <u>Median treatment duration in 5.4 mg/kg group:</u> 5.49 months (range 0.7 to 13.2) <u>Median treatment duration in 6.4 mg/kg group:</u> 4.90 months (range 0.7 to 13.8) <u>Median duration of OS follow-up (FAS) in 5.4 mg/kg group:</u> 13.4 months <u>Median duration of OS follow-up (FAS) in 6.4 mg/kg group:</u> Not evaluable	122 enrolled and treated	HER2-overexpressing locally advanced, unresectable, or metastatic CRC	40 study centers 9 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
DESTINY-Lung01 (DL-01; DS8201-A-U204)	NCT 03505710	Phase II, open-label, single-arm, non-randomized, multicenter	T-DXd 5.4 mg/kg or 6.4 mg/kg IV infusion Q3W	<u>Primary:</u> confirmed ORR by RECIST v1.1 <u>Secondary:</u> DoR, DCR, CBR, PFS, OS.	<u>Data cut-off (DCO):</u> 03 Dec 2021 <u>Median treatment duration in Cohort 1 (6.4 mg/kg):</u> 4.1 months (range 0.7 to 20.7) <u>Median treatment duration in Cohort 1a (5.4 mg/kg):</u> 5.5 months (range 0.7 to 16.5) <u>Median treatment duration in Cohort 2 (HER2-mutant 6.4 mg/kg):</u> 6.9 months (range 0.7 to 26.4) <u>Median duration of OS follow-up (FAS) in Cohort 1:</u> 12.4 months <u>Median duration of OS follow-up</u>	181 enrolled and treated	HER2-over-expressing and/or HER2-mutated advanced NSCLC	20 study centers 5 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
					(FAS) in Cohort 1a: 11.2 months <u>Median duration of OS follow-up (FAS) in Cohort 2:</u> 18.6 months			
DESTINY-Breast01 (DB-01; DS8201-A-U201)	NCT 03248492	Phase II, open-label, single- arm, randomized, multicenter, 2- part study of T-DXd	Part 1: PK stage: randomized 1:1:1 to T-DXd 5.4, 6.4, or 7.4 mg/kg Dose finding stage randomized 1:1 to T-DXd 5.4 or 6.4 mg/kg Part 2: nonrandomized and received T-DXd 5.4 mg/kg	<u>Primary:</u> confirmed ORR by RECIST v1.1 <u>Secondary:</u> DoR, DCR, CBR, PFS, OS.	<u>Data cut-off (DCO):</u> 21 Mar 2019 (efficacy evaluation); 08 Jun 2020 (safety evaluation) <u>Median treatment duration:</u> 7.0 months (range 0.7 to 16.2) <u>Median duration of OS follow-up (FAS):</u> Not estimable	253 enrolled and treated	HER2-positive unresectable and/or metastatic BC resistant or refractory to T DM1	72 study centers 8 countries
DESTINY-Gastric02 (DG-02;	NCT 04014075	Phase II, open-label, single-arm, multicenter study of T-DXd	T-DXd 6.4 mg/kg	<u>Primary:</u> confirmed ORR by RECIST v1.1	<u>Data cut-off (DCO):</u> 08 Nov 2021	79 enrolled and treated	HER2-positive unresectable or metastatic gastric or GEJ	24 study centers 5 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
DS8201-A-U205)				<u>Secondary:</u> DoR, DCR, CBR, PFS, OS.	<u>Median treatment duration:</u> 4.3 months (range 0.7 to 22.1) <u>Median duration of OS follow-up (FAS):</u> 10.2 months		adenocarcinoma that had progressed on or after a trastuzumab-containing regimen	
<i>Studies to Support Safety</i>								
DESTINY-Breast02	NCT 03523585	Phase III, open-label, active-controlled, multicenter study of T-DXd vs investigator's choice	T-DXd 5.4 mg/kg	<u>Primary:</u> PFS by BICR <u>Secondary:</u> OS, ORR, DoR, PFS by investigator	<u>Data cut-off (DCO):</u> 30 Jun 2022 <u>Median treatment duration:</u> T-DXd: 11.3 months (range 0.7 – 45.1) TPC: 4.4 months (range 0.1 – 43.0) <u>Median duration of OS follow-up (FAS):</u> T-DXd: 39.2 months TPC: 26.5 months	608 randomized	HER2-positive, unresectable and/or metastatic BC previously treated with T-DM1	186 study centers 15 countries
DESTINY-Breast03	NCT 03529110	Phase III, open-label, active-controlled,	T-DXd 5.4 mg/kg	<u>Primary:</u> PFS by BICR	<u>Data cut-off (DCO):</u> 25 Jul 2022	524 randomized	HER2-positive, unresectable and/or metastatic	118 study centers

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		multicenter study of T-DXd vs trastuzumab emtansine (T-DM1)		<u>Secondary:</u> OS, ORR, DoR, PFS by investigator	<u>Median treatment duration:</u> T-DXd: 14.3 months (range 0.7 – 29.8) TPC: 6.9 months (range 0.7 – 25.1) <u>Median duration of OS follow-up (FAS):</u> Not estimable		BC previously treated with trastuzumab and taxane	14 countries
DESTINY-Breast04	NCT 03734029	Phase III, open-label, active-controlled, multicenter study of T-DXd vs investigator's choice	T-DXd 5.4 mg/kg	<u>Primary:</u> PFS by BICR in the hormone receptor-positive cohort <u>Secondary:</u> PFS by BICR in the FAS, OS in the hormone receptor-positive cohort, and OS in the FAS	<u>Data cut-off (DCO):</u> 11 Apr 2022 <u>Median treatment duration:</u> T-DXd: 8.2 months (range 0.2 – 33.3) TPC: 3.5 months (range 0.3 – 17.6) <u>Median duration of OS follow-up (FAS):</u> 18.4 months	T-DXd: 373 enrolled/ randomized TPC: 184 enrolled/ randomized	HER2-low, unresectable and/or metastatic BC	161 study centers 19 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
J101	NCT 02564900	Phase I, two-part, open-label, non-randomized, multiple dose, first-in-human study of T-DXd	T-DXd 5.4 mg/kg T-DXd 6.4 mg/kg	<u>Primary:</u> Dose escalation: Safety and tolerability, determine maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) Dose expansion: safety and tolerability at MTD/RP2D, efficacy at MTD/RP2D <u>Secondary:</u> PK, efficacy, ADA	<u>Data cut-off (DCO):</u> 01 Aug 2019 <u>Median treatment duration:</u> 7.4 months (range 0.7 – 40.4) <u>Median duration of OS follow-up (FAS):</u> 29.4 months	292 enrolled	Patients with advanced solid malignant tumors	14 study centers 2 countries
DESTINY-Lung02	NCT 04644237	Phase II, randomized,	T-DXd 5.4 mg/kg	<u>Primary:</u> ORR by BICR	<u>Data cut-off (DCO):</u> 23 Dec 2022	152 randomized	HER2-mutated metastatic NSCLC	47 study centers

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Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		multicenter study of T-DXd	T-DXd 6.4 mg/kg	<u>Secondary:</u> ORR by investigator, DoR, DCR, PFS, OS	<u>Median treatment duration:</u> 5.4 mg/kg: 3.71 months (range 0.7 – 11.8) 6.4 mg/kg: 3.27 months (range 0.7 – 12.6) <u>Median duration of OS follow-up (FAS):</u> OS not reported interim study report			
DESTINY-Gastric01	NCT 03329690	Phase II, open-label study of T-DXd	T-DXd 6.4 mg/kg	<u>Primary:</u> ORR by independent central review <u>Secondary:</u> OS, PFS, DoR, DCR, time to treatment failure, ORR	<u>Data cut-off (DCO):</u> 03 Jun 2020 <u>Median treatment duration:</u> T-DXd: 4.4 months (range 0.7 – 22.3) <u>Median duration of OS follow-up (FAS):</u> T-DXd: 12.5 months	233 enrolled	HER2-expressing advanced gastric or GEJ adenocarcinoma	63 study centers 2 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
DESTINY-CRC01	NCT 03384940	Phase II, open-label, multicenter, 3-cohort study of T-DXd	T-DXd 6.4 mg/kg	<u>Primary:</u> ORR by independent central review <u>Secondary:</u> DOR, DCR, PFS, OS, ORR by investigator, PK	<u>Data cut-off (DCO):</u> 28 Dec 2020 <u>Median treatment duration:</u> 3.0 months (range 0.7 – 22.3) <u>Median duration of OS follow-up (FAS):</u> 12.3 months	86 enrolled	HER2-expressing advanced CRC	25 study centers 5 countries

The FDA's Assessment:

The primary efficacy and safety analyses for this supplement are based on results for tumors with IHC3+ expression from trials DESTINY-PanTumor02 (DP-02), DESTINY-CRC02 (DC-02) and DESTINY-Lung 01 (DL-02). Results from DESTINY-Breast01 (DB-01) and DESTINY-Gastric02 (DG-02) for the IHC3+ population were considered supportive for some of the pooled analyses. The other trials listed in Table 3 were not reviewed by the efficacy and safety reviewers for this sBLA. (b) (4)

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies Supporting Efficacy

Trial Design

The Applicant's Description:

See Applicant - Table 10.

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial designs in Table 4.

Eligibility Criteria

The Applicant's Description: See Applicant - Table 10.

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria in Table 4. Of note, DP-02 allowed patients to be enrolled based on HER2 IHC results from either local or central testing. Central testing for HER2 IHC was required for the other four studies listed in Table 4. All patients were required to have received prior therapy; however, the prior treatment requirements varied per study as outlined in Table 4.

Given the AESI for T-DXd, patients with a history of ILD/pneumonitis or evidence of ILD/pneumonitis on imaging at screening were excluded. Patients with LVEF<50% were also excluded across trials.

Study Endpoints

The Applicant's Description: See Applicant - Table 10.

The FDA's Assessment:

The primary endpoint of DP-02 was objective response rate (ORR) per RECIST v1.1 by investigator assessment; however, ORR per RECIST v1.1 by independent committee review (ICR) assessment was also submitted for all patients enrolled in the IHC3+ population and was used for FDA's assessment of efficacy. The primary endpoint of DC-02, DL-01, DB-01, and DG-02 was ORR per ICR. Common secondary endpoints across the five trials included duration of response (DOR), progression free survival (PFS), and overall survival (OS).

Safety endpoints across trials included adverse events (AEs), including AESIs, and serious adverse events (SAEs).

Statistical Analysis Plan and Amendments

The Applicant's Description: See Applicant - Table 10.

The initial efficacy population for DP-02 submitted to the sBLA included 75 patients that were enrolled with IHC3+ per central testing only. The efficacy population from the DP-02 study has been updated to include 111 patients that were enrolled with IHC 3+ per either local testing or central testing in response to the FDA information request received on 09Jan24.

The FDA's Assessment:

For DP-02, a sample size of 40 patients per cohort was determined to provide sufficient precision for the estimation of ORR in the respective populations. For DC-02, the sample size was determined based on the probability evaluation that the 95% Clopper-Pearson CI exceeds and excludes the ORR benchmark of 20%. For DL-01, a sample size of 40 response evaluable patients in Cohort 1a was required so that the average distance from the limits of the respective 95% CIs to the observed ORR was approximately 14%, assuming the expected ORR was 30%. Overall, the sample sizes for the small cohorts of

patients with HER2 IHC 3+ solid tumors in the 3 studies appeared to be based on natural enrollment.

FDA required the efficacy population for DP-02 to be updated by the Applicant in the draft USPI and review to include 111 patients that were enrolled with HER2 IHC 3+ status per either local testing or central testing as this reflects the study eligibility criteria. For the integrated analysis of efficacy across the five trials, ORR and DOR by ICR were used.

Protocol Amendments

The Applicant's Description: See Applicant - Table 10.

The FDA's Assessment:

In general, FDA agrees with the Applicant's summary of protocol amendments in Table 4.

There was an additional amendment submitted to DP-02 that is not listed in Table 4. Amendment 3 for DP-02 was submitted to IND 149506 in October 2023. The main changes for this amendment included the addition of Part 2, which included 5 additional cohorts (40 patients each). One of these cohorts included a mixed tumor cohort for patients with HER2 IHC 3+ advanced/metastatic solid tumors. In an Information Request (IR) response dated February 9, 2024, the Applicant stated that no patients have been enrolled to study DP-02 yet. The Applicant stated there have been delays to initiating Part 2 of the study due to the requirement for central testing using centrally performed HercepTest HER2 IHC testing at the (b) (4) facility in (b) (4). The Applicant anticipates that central HER2 IHC testing will be available to enable enrollment starting from April 2024.

Applicant - Table 10 **Studies Supporting Efficacy**

	DESTINY-PanTumor02	DESTINY-CRC02	DESTINY-Lung01	DESTINY-Breast01	DESTINY-Gastric02
Trial Design	Open-label, single-arm, multicenter, multi-cohort Phase II 40 patients planned per cohort: biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, and rare tumors.	Multicenter, randomized, 2-arm, parallel, Phase II study Stage 1: 80 patients with HER2-overexpressing CRC randomized to either 5.4 mg/kg or 6.4 mg/kg Stage 2: 40 patients with HER2-positive CRC in T-DXd 5.4 mg/kg arm to further inform on the efficacy and safety of this dose in metastatic CRC.	Phase II, open-label, multicenter, 2-cohort study Cohort 1: 40 patients with NSCLC received 6.4 mg/kg Cohort 1a: 40 patients with NSCLC received 5.4 mg/kg Cohort 2: 90 patients with mutant NSCLC received 6.4 mg/kg	Phase II, open-label, global, multicenter, 2-part study Part 1: randomized and had a PK stage (60 patients), and a dose finding stage (54 patients) Part 2: non-randomized and included all patients who received 5.4 mg/kg	Phase II, open-label, multicenter, single-arm study
Diagnostic criteria	IHC2+/IHC 3+ or IHC 1+ by local or central assessment	Locally advanced, unresectable or metastatic HER2-overexpressing (IHC 3+ or IHC 2+/ISH-positive CRC	IHC 3+ or IHC 2+; using modified Ventana anti-HER2 [4B5] IHC assay) or HER2-mutant NSCLC	HER2-positive (assessed centrally using ASCO/CAP guidelines)	HER2-positive (defined as IHC 3+, or IHC 2+ and evidence of HER2 amplification by ISH using ASCO/CAP guidelines)

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Trial location	North America, Europe, Asia Pacific	US, Europe, Asia-Pacific	North America, Japan, Europe	US, Asia, Europe	US, Europe
Choice of Control Group	Not applicable				
Dose Selection	5.4 mg/kg dose: Based on clinical data from Studies J101 and U201, as well as PopPK and ER analyses. 6.4 mg/kg dose: Based on clinical data and PK data from Studies J101 and DESTINY-CRC01.				
Study Treatment	T-DXd at 5.4 mg/kg IV Q3W	T-DXd at 5.4 mg/kg or 6.4 mg/kg IV Q3W	T-DXd at 5.4 mg/kg or 6.4 mg/kg IV Q3W	T-DXd at 5.4 mg/kg or 6.4 mg/kg IV Q3W	T-DXd at 6.4 mg/kg IV Q3W
Assignment to Treatment	Not applicable	Assignment via IRT	Assignment via Interactive Web/Voice Response System	Assignment via Interactive Web/Voice Response System	Assignment via IRT
Blinding	Not applicable	Blinded: Patients, investigators, central imaging readers, ILD AC, study site personnel (except unblinded pharmacist and other staff deemed necessary for site operation)	Not applicable	Not applicable	Not applicable
Dose Modification/Dose Discontinuation	Guidelines for dose delay or dose modification and treatment discontinuation in response to specific TEAEs were detailed in the protocol.				
Administrative Structure	Responsibility for conduct of study was shared between the Sponsor and CROs. A study Steering Committee was created to provide clinical guidance on study implementation, study conduct, and interpretation of results. An Independent Data Monitoring Committee consisting of qualified physicians and scientists, who were not investigators in the study and not otherwise directly				

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	associated with the Sponsor, was created to further protect the rights, safety, and well-being of subjects who were participating in this study by monitoring their progress and results. The Independent Data Monitoring Committee periodically reviewed unblinded safety data. An independent ILD AC established for the T-DXd program was responsible for reviewing all cases of potential ILD/pneumonitis, including relationship to T-DXd, onset date, and grade.				
Procedures and Schedule	Tumor evaluation (RECIST v1.1) conducted at screening and every 6 weeks ($\pm$ 1 week) for first 48 weeks after first dose of T-DXd and then every 12 weeks ($\pm$ 1 week) thereafter until investigator-assessed objective PD per RECIST v1.1 or until withdrawal of consent.	Tumor evaluation (RECIST v1.1) conducted at screening and every 6 weeks ($\pm$ 1 week) and after 12 months, and then then every 12 weeks ($\pm$ 1 week) thereafter until investigator-assessed objective PD per RECIST v1.1 or until withdrawal of consent.	Tumor evaluation (RECIST v1.1) conducted at screening and every 6 weeks ($\pm$ 1 week) until PD or starting new anticancer treatment.	Tumor evaluation (RECIST v1.1) conducted at screening and every 6 weeks ($\pm$ 1 week).	Tumor evaluation (RECIST v1.1) conducted at screening and every 6 weeks ($\pm$ 1 week) for first year and then every 12 weeks ($\pm$ 1 week) until PD or starting new anticancer treatment.
Concurrent Medications	Prohibited: other anti-cancer therapies, chloroquine or hydroxychloroquine, other investigational agents, radiotherapy, chronic systemic corticosteroids, or other immunosuppressants				
Treatment Compliance	As T-DXd was administered by IV under the supervision of site clinical study personnel, compliance was ensured if subjects attended scheduled visits.				
Subject Completion, Discontinuation, or Withdrawal	Patients continued to receive study treatment until RECIST v1.1-defined disease progression, unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation was met.				
Eligibility Criteria	- Age $\geq$ 18 years - WHO/ECOG of 0 to 1 - Advanced, unresectable, or metastatic solid tumors, who had progressed	- age $\geq$ 18 - unresectable, recurrent, or metastatic colorectal adenocarcinoma	- age $\geq$ 18 years - unresectable and/or metastatic non-squamous NSCLC - relapsed after or were refractory to	- age $\geq$ 18 years - unresectable or metastatic BC - HER2-positive (assessed centrally using ASCO/CAP	- age $\geq$ 18 years - unresectable or metastatic GC or GEJ cancer - HER2 status (IHC 3+ or IHC 2+ using ASCO/CAP

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	following at least one prior systemic treatment for metastatic or advanced disease, or who had no satisfactory alternative treatment option HER2-expressing tumors (defined as IHC 2+/IHC 3+ or, under certain circumstances also IHC 1+) as determined by local or central assessment (using HercepTest™ [Agilent]; assessed using current ASCO/CAP guidelines for scoring HER2 for GC)	- previous treatment included chemotherapy, targeted therapy, or anti-programmed cell death ligand 1 therapy - BRAF wild-type cancer and RAS status identified in primary or metastatic site by central assessment - HER2 status (IHC 3+ or IHC 2+/ISH-positive; using Ventana anti-HER2 [4B5] IHC assay) - ECOG PS of 0 or 1	standard treatment or no standard treatment was available - ECOG PS of 0 or 1 - Cohort 1 and 1a only: HER2-overexpressing (IHC 3+ or IHC 2+; using modified Ventana anti-HER2 [4B5] IHC assay) status	guidelines) status refractory or resistant to T-DM1, with documented clinical or radiographic progression of disease during or after treatment with T-DM1	guidelines) and evidence of HER2 amplification by ISH - experienced disease progression per RECIST v1.1 on or after first-line therapy with a trastuzumab-containing regimen - ECOG PS of 0 or 1.
Study Endpoints	Primary: ORR according to RECIST v1.1 as assessed by investigator Key secondary: DoR, DCR, PFS, OS	Primary: ORR by BICR Key secondary: DoR, DCR, CBR, PFS, OS	Primary: ORR by BICR Key secondary: DoR, DCR, CBR, PFS, OS	Primary: ORR by BICR Key secondary: DCR, CBR, PFS, OS, best percent change in SOD	Primary: ORR by independent central imaging facility using RECIST v1.1 Key secondary: PFS, OS, ORR by investigator, DoR
Statistical Analysis Plan for Integrated Summary of Efficacy	The SAP Version 1.0 was prepared to describe the detailed procedures and methods used for an analysis of efficacy data for the Integrated Summary of Efficacy to support T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive solid tumors that have progressed following prior treatment or who have no satisfactory alternative treatment options. The clinical efficacy results from patients with HER2 positive (IHC3+) expressing tumors who received T-DXd 5.4 mg/kg every Q3W in DP-02, DC-02, DL-01, DG-02, and DB-01 was used to evaluate the efficacy profile and risk/benefit of T-DXd.				

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	HER2-positive IHC 3+ tumor Population includes enrolled/randomized patients with HER2-positive IHC 3+ expressing tumors in cohorts/arms with T-DXd 5.4 mg/kg Q3W for non-gastric studies and the arm with T-DXd 6.4 mg/kg Q3W for DG-02. No adjustment for multiplicity was performed. Analysis based on subgroups were explored to assess the consistency of treatment effect. The FAS includes all patients in who were treated (DP-02 and DG-02), enrolled (DL-01), randomized (DC-02 and DB-01 Part 1) or registered (DB-01 Part 2). The FAS in DL01 and DC-02 included all enrolled/registered/randomized patients, whereas FAS of DP-02/DB-01/DG-02 included patients who have received at least one dose of study treatment. The difference of FAS definition across studies has minimum impact on integrity of ISE analysis since in general all patients enrolled, registered, or randomized have received at least one dose of study treatment across studies except in DP-02, one enrolled patient not treated thus not in FAS. All summary analysis was based on FAS, summarized by tumor cohort, subtotal and overall total for IHC 3+ population.				
Protocol Amendments	Amendment 1: added pre-screening option Amendment 2: Updated end of study definition; revised frequency of tumor assessments and serum sample collections	There were no protocol amendments	Amendment 1: updated inclusion and exclusion criteria, and management of AESI Amendment 2: updated inclusion criteria Amendment 3 and 4: Increased enrolment period and study duration Amendment 5: Addition of Cohort 1a, updated inclusion and exclusion criteria Amendment 6: updated inclusion and exclusion criteria, changes in dose reduction level	Amendment 1: added endpoints (determination of RP2D, TEAEs, AESIs), updated exclusion criteria and restrictions Amendment 2: updated inclusion and exclusion criteria Amendment 3: updated starting dose for Part 2 based on RP2D, updated dose modifications	Amendment 1: Interim version not sent to study sites due to typographical errors Amendment 2: added dose modification plan and analysis to evaluate impact of COVID-19, updated end of treatment visit

8.1.2. Study Results

The results in this section present data to evaluate efficacy signals across tumor types from the studies in Applicant - Table 10 which include 17 HER2-positive (IHC 3+) solid tumor types (biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, and rare tumors [salivary, extramammary Paget's disease, vulvar, head and neck (lacrima), lip and/or oral cavity cancer, oesophageal (squamous and non-squamous), and oropharyngeal]) in DP-02, CRC in DC-02, NSCLC in DL-01, BC in DB-01, and GC in DG-02. In addition, to further characterize the population, 2 aggregate pools for the IHC 3+ Population are provided as described in Applicant – Table 11.

Applicant – Table 11 Summary of Groups Included in the Efficacy Data Presentation

Population Evaluation	Dose	Number of patients
IHC 3+ Population		
<u>Data presentation by tumor type</u>	T-DXd 5.4 mg/kg or 6.4 mg/kg in Study DG-02 only	Study DP-02 (111): biliary tract (22), bladder (27), cervical (10), endometrial (16), ovarian (15), pancreatic (5), rare tumors: (16 [salivary (9), extramammary Paget's disease (1), vulvar (1), head and neck (lacrima) (1), lip and/or oral cavity cancer (1), non-squamous oesophageal (1), squamous oesophageal (1), oropharyngeal (1)]); Study DC-02 , colorectal: 64; Study DL-01 , NSCLC: 17; Study DB-01 , breast: 154; Study DG-02 , gastric: 68
<u>IHC 3+ Pool (without BC and GC), referred to as “IHC 3+ Subtotal” in tables and figures</u>	T-DXd 5.4 mg/kg	N = 192 Study DP-02: 111; Study DC-02: 64; Study DL-01: 17
<u>Total IHC 3+ Pool (with BC and GC), referred to as “IHC 3+ Overall” in tables and figures</u>	T-DXd 5.4 mg/kg or 6.4 mg/kg in Study DG-02 only	N = 414 Study DP-02: 111; Study DC-02: 64; Study DL-01: 17; Study DB-01: 154; Study DG-02: 68

The FDA's Assessment:

The key efficacy results in this supplement are based on 192 patients across DP-02, DC-02 and DL-01 with HER2-positive (IHC 3+) advanced/metastatic solid tumors treated with T-DXd 5.4mg/kg. Results from DB-01 and DG-02 are considered supportive as there are already

approved indications for T-DXd in patients with HER2 IHC 3+ advanced/metastatic breast cancer and HER2 IHC 3+ advanced/metastatic gastric/GEJ cancer. In addition, the dose used in DG-02 is a different dose of T-DXd (6.4 mg/kg) than that proposed for the tissue agnostic indication in this supplement.

Compliance with Good Clinical Practices

The Applicant's Position:

The Sponsor's procedures, internal quality control measures and audit programs provide reassurance that the clinical study program was carried out in accordance with GCP, as documented by the International Conference on Harmonisation (ICH).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA was not made aware of any compliance or ethical misconduct during conduct of the trial.

Financial Disclosure

Data:

Financial disclosures are addressed in Appendix 19.2.

The Applicant's Position:

The integrity of the data was not affected by the financial interest of the investigators.

The FDA's Assessment:

In general, FDA agrees that there were no findings presented in the financial disclosure information provided by the Applicant that indicated any compromise of the study data integrity. Refer to Section 19.2 of this Assessment Aid for additional details.

Patient Disposition

Data:

Patient disposition data is provided in Applicant – Table 12.

The Applicant's Position:

The disposition of patients in the studies is summarized in Applicant – Table 12. Among the IHC 3+ patients who discontinued the study treatment, the most common reason for discontinuation in most tumor types was objective disease progression and the rate of

study drug discontinuation was low.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of patient disposition. The rates of discontinuation other than objective disease progression varied by tumor type.

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Applicant – Table 12: Patient Disposition by All Tumor Types in the IHC 3+ Population

	Number (%) of Patients												
	Biliary tract cancer	Bladder cancer	Cervical cancer	Endometrial cancer	Ovarian cancer	Pancreatic cancer	Rare	Colorectal cancer	NSCLC	BC	GC	IHC 3+ subtotal	IHC 3+ overall total
Patients in Full Analysis Set	22	27	10	16	15	5	16	64	17	154	68	192	414
Patients ongoing study treatment at data cut-off ^a	2 (9.1)	2 (7.4)	5 (50.0)	6 (37.5)	5 (33.3)	0	2 (12.5)	9 (14.1)	2 (11.8)	95 (61.7)	10 (14.7)	33 (17.2)	138 (33.3)
Patients who discontinued treatment ^a	20 (90.9)	25 (92.6)	5 (50.0)	10 (62.5)	10 (66.7)	5 (100)	14 (87.5)	55 (85.9)	15 (88.2)	59 (38.3)	58 (85.3)	159 (82.8)	276 (66.7)
Objective disease progression	9 (40.9)	16 (59.3)	3 (30.0)	3 (18.8)	9 (60.0)	3 (60.0)	5 (31.3)	45 (70.3)	9 (52.9)	30 (19.5)	40 (58.8)	102 (53.1)	172 (41.5)
Subjective disease progression	0	1 (3.7)	1 (10.0)	1 (6.3)	0	2 (40.0)	2 (12.5)	3 (4.7)	3 (17.6)	0	4 (5.9)	13 (6.8)	17 (4.1)
Death	4 (18.2)	3 (11.1)	0	2 (12.5)	0	0	1 (6.3)	0	0	5 (3.2)	1 (1.5)	10 (5.2)	16 (3.9)
Adverse event	6 (27.3)	3 (11.1)	1 (10.0)	2 (12.5)	0	0	4 (25.0)	5 (7.8)	2 (11.8)	14 (9.1)	9 (13.2)	23 (12.0)	46 (11.1)
Subject decision	1 (4.5)	2 (7.4)	0	2 (12.5)	0	0	1 (6.3)	0	0	6 (3.9)	2 (2.9)	6 (3.1)	14 (3.4)
Investigator decision	0	0	0	0	1 (6.7)	0	0	0	0	2 (1.3)	1 (1.5)	1 (0.5)	4 (1.0)
Pregnancy	0	0	0	0	0	0	0	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0	0	0	0	0	0	0	0
Subject lost to follow-up	0	0	0	0	0	0	0	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	1 (6.3)	2 (3.1)	1 (5.9)	2 (1.3)	1 (1.5)	4 (2.1)	7 (1.7)
Duration of Follow-up (Months)													
n	22	27	10	16	15	5	16	64	17	154	68	192	414
Mean	11.32	12.17	18.73	17.24	17.97	10.05	19.55	9.32	10.69	7.73	10.67	12.77	10.55
Standard Deviation	9.064	7.639	8.592	8.975	8.745	5.872	8.928	3.165	4.467	2.634	5.402	7.662	6.302
Median	7.41	12.62	19.94	21.34	19.98	8.77	22.83	9.28	11.17	7.34	11.09	11.02	8.72

Applicant – Table 12: Patient Disposition by All Tumor Types in the IHC 3+ Population

	Number (%) of Patients												
	Biliary tract cancer	Bladder cancer	Cervical cancer	Endometrial cancer	Ovarian cancer	Pancreatic cancer	Rare	Colorectal cancer	NSCLC	BC	GC	IHC 3+ subtotal	IHC 3+ overall total
Min, Max	1.6, 29.1	0.4, 24.7	3.9, 31.0	0.8, 26.0	3.6, 30.6	2.4, 16.0	0.7, 31.6	0.5, 17.1	1.9, 16.0	1.9, 17.1	0.7, 22.1	0.4, 31.6	0.4, 31.6

^a Percentages are calculated from the number of patients in the cohort who received treatment.

Rare tumor cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal, oropharyngeal.

Biliary tract cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and rare tumor are from DP-02; colorectal cancer is from DC-02; NSCLC is from DL-01; BC is from DB-01; GC is from DG-02.

IHC 3+ Subtotal pool includes patients who received the 5.4 mg/kg dose from studies DP02/DC02/DL01 with IHC 3+ tumors; IHC 3+ Overall total pool includes patients who received the 5.4 mg/kg dose (6.4 mg/kg dose in DG-02) from studies DP02/DC02/DL01/DB01/DG02 with IHC 3+ tumors. Percentages are calculated based on FAS per tumor cohort.

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Protocol Violations/Deviations

Data:

- Study DP-02: 13.9% of patients had at least one important protocol deviation (PD) with the most common related to the inclusion criterion that all patients must provide an existing formalin-fixed paraffin-embedded tumor sample for tissue-based IHC staining to centrally determine HER2-expression and other correlatives (4.5%), with most of these occurring in the rare tumor cohort (9 of 12 patients).
- Study DC-02: 28.7% subjects had at least one major PD with the most common related to study procedures (19.5%), informed consent (7.3%), SAE reporting (6.1%), and investigational product (7.5%).
- Study DL-01: 28.6% subjects with HER2 mutation (Cohort 2), 8.2% in Cohort 1, and 39.0% in Cohort 1a met at least one major PD, with the most frequent in Cohort 2 related to visit/procedure required (12.1%), and non-compliance (9.9%). All other major PDs were reported in < 5% of subjects.
- Study DB-01: 46.2% of subjects met at least one major PD with the most common related to study procedures criteria (18.2%), laboratory assessment criteria (13.8%), informed consent (9.5%), investigational product compliance (7.1%), and eligibility and entry criteria (6.3%).
- Study DG-02: 49.4% subjects met at least one major PD. The most frequent category of major protocol deviation was “visit/procedure required”.

The Applicant’s Position:

The protocol deviations observed in the studies do not raise any concerns regarding the overall conduct or quality of the study, or the clinical interpretation of data within the patient population enrolled.

The FDA’s Assessment:

FDA agrees that the protocol deviations observed in the study likely did not impact the efficacy results.

Table of Demographic Characteristics

Data:

Demographic characteristics data are provided in Applicant - Table 13.

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Applicant - Table 13: Demographics, and Baseline Characteristics in the IHC 3+ Population (FAS)

Demographic characteristic	Biliary tract cancer (N = 22)	Bladder cancer (N = 27)	Cervical cancer (N = 10)	Endometrial cancer (N = 16)	Ovarian cancer (N = 15)	Pancreatic cancer (N = 5)	Rare (N = 16)	Colorectal cancer (N = 64)	NSCLC (N = 17)	BC (N = 154)	GC (N = 68)	IHC 3+ subtotal ^a (N = 192)	IHC 3+ overall total ^b (N = 414)
Age (years)													
N	22	27	10	16	15	5	16	64	17	154	68	192	414
Median	66.0	68.0	49.0	68.5	56.0	52.0	62.5	58.0	59.0	57.0	59.5	61.0	59.0
Min, Max	31, 80	43, 85	31, 78	56, 79	34, 70	23, 68	38, 75	25, 78	31, 74	28, 96	20, 77	23, 85	20, 96
Age group (years) n (%)													
< 65	10 (45.5)	12 (44.4)	9 (90.0)	4 (25.0)	11 (73.3)	4 (80.0)	9 (56.3)	45 (70.3)	13 (76.5)	118 (76.6)	41 (60.3)	117 (60.9)	276 (66.7)
≥ 65	12 (54.5)	15 (55.6)	1 (10.0)	12 (75.0)	4 (26.7)	1 (20.0)	7 (43.8)	19 (29.7)	4 (23.5)	36 (23.4)	27 (39.7)	75 (39.1)	138 (33.3)
Sex n (%)													
Male	12 (54.5)	17 (63.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	13 (81.3)	34 (53.1)	10 (58.8)	0 (0.0)	47 (69.1)	89 (46.4)	136 (32.9)
Female	10 (45.5)	10 (37.0)	10 (100)	16 (100)	15 (100)	2 (40.0)	3 (18.8)	30 (46.9)	7 (41.2)	154 (100)	21 (30.9)	103 (53.6)	278 (67.1)
Race n (%)													
White	12 (54.5)	16 (59.3)	7 (70.0)	10 (62.5)	6 (40.0)	3 (60.0)	10 (62.5)	26 (40.6)	11 (64.7)	75 (48.7)	61 (89.7)	101 (52.6)	237 (57.2)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	1 (6.7)	1 (20.0)	0 (0.0)	0 (0.0)	2 (11.8)	4 (2.6)	1 (1.5)	6 (3.1)	11 (2.7)
Asian	10 (45.5)	11 (40.7)	1 (10.0)	3 (18.8)	8 (53.3)	1 (20.0)	4 (25.0)	35 (54.7)	3 (17.6)	67 (43.5)	2 (2.9)	76 (39.6)	145 (35.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.5)	0 (0.0)	2 (0.5)
Other	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	3 (4.7)	1 (5.9)	3 (1.9)	3 (4.4)	7 (3.6)	13 (3.1)
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	2 (1.0)	5 (1.2)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Demographic characteristic	Biliary tract cancer (N = 22)	Bladder cancer (N = 27)	Cervical cancer (N = 10)	Endometrial cancer (N = 16)	Ovarian cancer (N = 15)	Pancreatic cancer (N = 5)	Rare (N = 16)	Colorectal cancer (N = 64)	NSCLC (N = 17)	BC (N = 154)	GC (N = 68)	IHC 3+ subtotal ^a (N = 192)	IHC 3+ overall total ^b (N = 414)
Ethnicity n (%)													
Hispanic or Latino	1 (4.5)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	8 (5.2)	5 (7.4)	4 (2.1)	17 (4.1)
Not Hispanic or Latino	21 (95.5)	27 (100)	8 (80.0)	16 (100)	15 (100)	5 (100)	16 (100)	60 (93.8)	15 (88.2)	118 (76.6)	60 (88.2)	183 (95.3)	361 (87.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.7)	0 (0.0)	0 (0.0)	3 (4.4)	3 (1.6)	6 (1.4)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	27 (17.5)	0 (0.0)	0 (0.0)	27 (6.5)
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Region n (%)													
Asia	10 (45.5)	11 (40.7)	1 (10.0)	1 (6.3)	8 (53.3)	1 (20.0)	4 (25.0)	32 (50.0)	2 (11.8)	61 (39.6)	0 (0.0)	70 (36.5)	131 (31.6)
North America	3 (13.6)	6 (22.2)	2 (20.0)	8 (50.0)	2 (13.3)	0 (0.0)	5 (31.3)	6 (9.4)	6 (35.3)	39 (25.3)	24 (35.3)	38 (19.8)	101 (24.4)
Europe	9 (40.9)	10 (37.0)	7 (70.0)	7 (43.8)	5 (33.3)	4 (80.0)	5 (31.3)	19 (29.7)	9 (52.9)	54 (35.1)	44 (64.7)	75 (39.1)	173 (41.8)
ROW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	7 (10.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (4.7)	9 (2.2)

Rare tumor cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal, oropharyngeal.

Biliary tract cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and rare tumors are from DP02; colorectal cancer is from DC02; NSCLC is from DL01; BC is from DB01; GC is from DG-02.

^a IHC 3+ Subtotal pool includes patients who received the 5.4 mg/kg dose from studies DP02/DC02/DL01 with IHC 3+ tumors

^b IHC 3+ Overall total pool includes patients who received the 5.4 mg/kg dose (6.4 mg/kg dose in DG-02) from studies DP02/DC02/DL01/DB01/DG-02 with IHC 3+ tumors.

N: Number of patients in full analysis set.

The Applicant's Position:

Overall, across the tumor types, the patients with IHC 3+ expressing tumors comprised a pre-treated population of adults with unresectable or metastatic HER2-positive (IHC 3+) tumors that have progressed after prior therapies or with no satisfactory alternative treatment options. The patient population is considered representative of those who will receive this treatment post-approval.

The FDA's Assessment:

FDA agrees that the patient population with HER2 IHC 3+ solid tumors represent a variety of tumor types. The primary efficacy cohort of 192 patients includes patients with 8 different tumor types, plus a rare tumor cohort. The rare tumor cohort in DP-02 includes 7 different tumor types as listed in the footnote for Table 7, with single patients being enrolled in most of these tumor types, bringing the total tumor types in the primary efficacy cohort to 15.

Patients in DP-02, DC-02 and DL-01 were enrolled from around the world, including 38 (out of the 192) patients from the US in the primary efficacy cohort. Three percent of the enrolled patients were Black or African American and only 2% were Hispanic or Latino, which is lower than the demographics of patients with these malignancies. The majority of enrolled patients were of either White or Asian race. Though this was a limitation, the FDA review team determined that the results, based upon other important disease characteristics and prior therapies, were applicable to the solid tumor population treated in the U.S. and supportive of the intended indication.

For the patients with HER2-positive (IHC 3+ by either local or central assessment, N = 111) solid tumors in DP-02, the median age was 64 years (range 23 to 85); 59% were female; 58% were White, 34% were Asian, and 4% were Black or African American; 3% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of either 0 (49%) or 1 (51%) at baseline. The median number of prior regimens in any treatment setting was 2.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Data on baseline characteristics are provided in Applicant - Table 14.

The Applicant's Position:

Across tumor types the patients were pre-treated. The median number of prior regimens of systemic therapy ranged from 1 prior regimen in patients with pancreatic and GC to 6 prior regimens in patients with BC.

The FDA's Assessment:

FDA agrees that most of the patients were pre-treated. The median and range of prior therapies listed in Table 8 represent prior therapies in any setting (both early stage and advanced/metastatic setting).

However, the Applicant confirmed in an IR response dated February 13, 2024, that two out of the 192 patients in the primary efficacy cohort did not receive prior systemic treatment in any setting. One patient was from (b) (6) and had urothelial cancer that was documented to be extensive disease at the start of study. Per the treating investigator, the patient was not a suitable candidate for available standard therapy options of platinum and gemcitabine, and the patient was not eligible to receive immunotherapy under local reimbursement in the (b) (6). The other patient was from (b) (6) and had endometrial clear cell carcinoma that was documented to be extensive disease. The treating investigator considered the patient to have no suitable alternative treatments. The other 190 patients had received prior systemic therapy.

The patients represented in the primary efficacy cohort had an excellent performance status, with almost all patients having an ECOG performance status of 0 or 1.

Applicant - Table 14: Baseline Characteristics in the IHC 3+ Population (FAS)

Demographic characteristic	Biliary tract cancer (N = 22)	Bladder cancer (N = 27)	Cervical cancer (N = 10)	Endometrial cancer (N = 16)	Ovarian cancer (N = 15)	Pancreatic cancer (N = 5)	Rare (N = 16)	Colorectal cancer (N = 64)	NSCLC (N = 17)	BC (N = 154)	GC (N = 68)	IHC 3+ subtotal ^a (N = 192)	IHC 3+ overall total ^b (N = 414)
ECOG													
0	8 (36.4)	13 (48.1)	6 (60.0)	8 (50.0)	12 (80.0)	1 (20.0)	6 (37.5)	37 (57.8)	2 (11.8)	84 (54.5)	26 (38.2)	93 (48.4)	203 (49.0)
1	14 (63.6)	14 (51.9)	4 (40.0)	8 (50.0)	3 (20.0)	4 (80.0)	10 (62.5)	27 (42.2)	15 (88.2)	69 (44.8)	42 (61.8)	99 (51.6)	210 (50.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Number of prior regimens													
n	22	27	10	16	15	5	16	64	17	154	68	192	414
Median	2.0	3.0	2.5	2.0	3.0	1.0	1.5	4.0	3.0	6.0	1.0	3.0	3.0
Min, Max	1, 4	0, 9	1, 6	0, 7	1, 8	1, 4	1, 3	1, 14	1, 5	2, 19	1, 2	0, 14	0, 19

Rare tumor cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal, oropharyngeal.

Biliary tract cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and rare tumors are from DP02; colorectal cancer is from DC02; NSCLC is from DL01; BC is from DB01; GC is from DG-02.

^a IHC 3+ Subtotal pool includes patients who received the 5.4 mg/kg dose from studies DP02/DC02/DL01 with IHC 3+ tumors;

^b IHC 3+ Overall total pool includes patients who received the 5.4 mg/kg dose (6.4 mg/kg dose in DG-02) from studies DP02/DC02/DL01/DB01/DG-02 with IHC 3+ tumors.

N: Number of patients in full analysis set.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

T-DXd was administered via IV infusions at study centers. Most subjects received concomitant medications.

The Applicant's Position:

Treatment compliance indicated that the treatment regimens were tolerated by most patients. Overall, the concomitant treatments administered were representative of those commonly described for the patient population.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of treatment compliance, and concomitant medications.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Primary endpoint data is provided in Applicant - Table 16.

The Applicant's Position:

Data presented in this application demonstrate that T-DXd shows substantial efficacy across tumor types in an IHC 3+ biomarker selected population, as evidenced by the consistently high and clinically meaningful confirmed ORR by ICR across IHC 3+ solid tumor types.

The FDA's Assessment:

FDA agrees with the data presented in Table 9. The primary endpoint for DP-02 was ORR by investigator assessment; however, ORR results by ICR were also provided. The primary endpoint of DC-2, DL-01, DB-01, and DG-02 was ORR per ICR. Overall, ORR per RECIST v1.1 by ICR assessment was used for FDA's assessment of efficacy.

The ORR results by ICR across DP-02, DL-01 and DC-02 were summarized in

FDA - Table 15: ORR by ICR Assessment Across DCP-02, DL-01 and DC-02.

FDA - Table 15: ORR by ICR Assessment Across DCP-02, DL-01 and DC-02

	DP-02 (N = 111)	DL-01 (N = 17)	DC-02 (N = 64)
Confirmed ORR (95% CI)	51.4% (41.7, 61.0)	52.9% (27.8, 77.0)	46.9% (34.3, 59.8)
Complete Response Rate	2.7%	5.9%	0%
Partial Response Rate	48.6%	47.1%	46.9%

Source: FDA analysis

Overall, T-DXd shows efficacy with clinically meaningful ORR by ICR in most of the HER2-positive IHC 3+ tumor types included in the primary efficacy cohort. However, there were no responses in a small sample of 5 patients with pancreatic cancer. ORR in the pooled population of 192 patients in the IHC3+ population was 54.1% (95% CI: 42.7, 57.3) by ICR assessment with ORRs ranging from 37-70% in the tumor types that had responders, and was 46.4% (95% CI: 39.1, 53.7) by investigator assessment.

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Applicant - Table 16: Primary Endpoint of ORR by ICR in the IHC 3+ Population (FAS)

	Biliary Tract Cancer	Bladder Cancer	Cervical Cancer	Endometrial Cancer	Ovarian Cancer	Pancreatic Cancer	Rare	CRC	NSCLC	BC	GC	IHC 3+ ^a Subtotal	IHC 3+ ^b Overall Total
	(N = 22)	(N = 27)	(N = 10)	(N = 16)	(N = 15)	(N = 5)	(N = 16)	(N = 64)	(N = 17)	(N = 154)	(N = 68)	(N = 192)	(N = 414)
ORR, n (%)	10 (45.5)	10 (37.0)	7 (70.0)	9 (56.3)	10 (66.7)	0	11 (68.8)	30 (46.9)	9 (52.9)	96 (62.3)	32 (47.1)	96 (50.0)	224 (54.1)
95% CI	24.4, 67.8	19.4, 57.6	34.8, 93.3	29.9, 80.2	38.4, 88.2	0, 52.2	41.3, 89.0	34.3, 59.8	27.8, 77.0	54.2, 70.	34.8, 59.6	42.7, 57.3	49.2, 59.0

^a IHC 3+ Subtotal pool includes patients who received the 5.4 mg/kg dose from studies DP02/DC02/DL01 with IHC 3+ tumors.

^b IHC 3+ Overall total pool includes patients who received the 5.4 mg/kg dose (6.4 mg/kg dose in DG-02) from studies DP02/DC02/DL01/DB01/DG-02 with IHC 3+ tumors.

Rare tumor cohort includes 9 patients with salivary, 1 each with extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, non-squamous oesophageal, squamous oesophageal, oropharyngeal.

Biliary tract cancer, Bladder cancer, Cervical cancer, Endometrial cancer, Ovarian cancer, Pancreatic cancer, and rare tumor are from DP02; Colorectal cancer is from DC02; Non-small cell lung cancer is from DL01; Breast cancer is from DB01; Gastric cancer is from DG-02.

N: number of patients in FAS.

Data Quality and Integrity

Data:

AstraZeneca procedures, internal quality control measures and audit programs provide reassurance that the clinical study program was carried out in accordance with GCP, as documented by the International Conference on Harmonisation (ICH).

The Applicant's Position:

There were no data quality issues that impacted the integrity of the data.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary and other relevant endpoints

Data:

Data from secondary endpoints are presented in Applicant - Table 19.

The Applicant's Position:

T-DXd single-agent treatment has demonstrated robust clinical benefit in a comprehensive dataset of 414 patients across 17 tumor types. Across these diverse tumor types, consistently long duration of response, and long survival times have been observed in patients with IHC 3+ expressing tumors.

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis results of the secondary endpoints presented in Table 10. As expected in patients with advanced/metastatic solid tumor cancers, most patients with a tumor response had a partial response (PR) and very few patients had a complete response (CR). In the small cohort of 5 patients with pancreatic cancer, four had stable disease (SD) and one had progressive disease (PD) as best overall response.

The median (range) duration of follow-up in DP-02, DC-02, and DL-01 were 12.8 (0.4, 31.6), 9.3 (0.5, 17.1), and 11.2 (1.9, 16.0) months, and the median DOR in these three studies were summarized in FDA - Table 17: DOR by ICR Assessment Across DP-02, DL-01 and DC-02. Due to limited follow-up time, the median DOR was not estimable in multiple tumor types. The range of DOR per tumor type across DP-02, DC-02, and DL-01 were

summarized in FDA - Table 18: DOR by ICR Assessment per Tumor Type Across DP-02, DL-01 and DC-02.

FDA - Table 17: DOR by ICR Assessment Across DP-02, DL-01 and DC-02

	DP-02 (N = 111)	DL-01 (N = 17)	DC-02 (N = 64)
Median, month (range)	19.4 (1.3, 27.9+)	6.9 (4.0, 11.7+)	5.5 (1.3+, 9.7+)

+ denotes ongoing response

Source: FDA analysis

FDA - Table 18: DOR by ICR Assessment per Tumor Type Across DP-02, DL-01 and DC-02

Tumor Type	Patients	DOR Range
	N	(months)
Colorectal Cancer	64	(1.3+, 9.7+)
Bladder Cancer	27	(2.8, 19.7+)
Biliary Tract Cancer	22	(2.1, 22.0+)
NSCLC	17	(4.0, 11.7+)
Endometrial Cancer	16	(5.8, 23.7+)
Ovarian Cancer	15	(1.3, 27.9+)
Cervical Cancer	10	(7.2+, 25.0+)
Salivary Gland Cancer	9	(5.6, 20.1)
Pancreatic Cancer	5	NA
Oropharyngeal Neoplasm	1	15.3
Vulvar Cancer	1	2.6
Extramammary Paget's Disease	1	19.4
Lacrimal Gland Cancer	1	19.8+
Lip and/or Oral Cavity Cancer	1	NA
Esophageal Adenocarcinoma	1	2.8
Esophageal Squamous Cell Carcinoma	1	NA

+ denotes ongoing response.

Source: FDA analysis

In DP-02, the FDA identified 5 patients who were censored with duration of response less than 6 months and sent an Information Request to ask the Applicant for clarification on censoring reasons. For four of those five patients, no further scans were available for ICR assessment beyond investigator determined PD (progressive disease). For the other patient, treatment was discontinued due to investigator decision despite PR (partial

response), and then patient then withdrew consent for all further study related procedures including RECIST scan. FDA does not consider time-to-event endpoints, including PFS and OS, to be interpretable in the context of single-arm trials.

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Applicant - Table 19: Secondary Endpoints by ICR in the IHC 3+ Population (FAS)

	Biliary Tract Cancer	Bladder Cancer	Cervical Cancer	Endometrial Cancer	Ovarian Cancer	Pancreatic Cancer	Rare	CRC	NSCLC	BC	GC	IHC 3+ ^a Subtotal	IHC 3+ ^b Overall Total
	(n = 22)	(n = 27)	(n = 10)	(n = 16)	(n = 15)	(n = 5)	(n = 16)	(n = 64)	(n = 17)	(n = 154)	(n = 68)	(N = 192)	(N = 414)
BOR n (%)													
CR	1 (4.5)	0	1 (10.0)	1 (6.3)	0	0	0	0	1 (5.9)	5 (3.2)	3 (4.4)	4 (2.1)	12 (2.9)
PR	9 (40.9)	10 (37.0)	6 (60.0)	8 (50.0)	10 (66.7)	0	11 (68.8)	30 (46.9)	8 (47.1)	91 (59.1)	29 (42.6)	92 (47.9)	212 (51.2)
SD	9 (40.9)	11 (40.7)	3 (30.0)	6 (37.5)	3 (20.0)	4 (80.0)	4 (25.0)	30 (46.9)	5 (29.4)	54 (35.1)	27 (39.7)	75 (39.1)	156 (37.7)
Progression	3 (13.6)	6 (22.2)	0	1 (6.3)	1 (6.7)	1 (20.0)	1 (6.3)	3 (4.7)	3 (17.6)	3 (1.9)	7 (10.3)	19 (9.9)	29 (7.0)
NE	0	0	0	0	0	0	0	1 (1.6)	0	1 (0.6)	2 (2.9)	1 (0.5)	4 (1.0)
No evidence of disease	0	0	0	0	1 (6.7)	0	0	0	0	0	0	1 (0.5)	1 (0.2)
Median TTR (months)	1.5	1.3	1.4	1.4	1.8	NE	2.8	2.1	2.8	1.6	1.4	1.6	1.5
DCR n (%) [95% CI]	19 (86.4 [65.1, 97.1])	21 (77.8 [57.7, 91.4])	10 (100 [69.2, 100])	15 (93.8 [69.8, 99.8])	14 (93.3 [68.1, 99.8])	4 (80.0 [28.4, 99.5])	15 (93.8 [69.8, 99.8])	60 (93.8 [84.8, 98.3])	14 (82.4 [56.6, 96.2])	150 (97.4 [93.5, 99.3])	59 (86.8 [76.4, 93.8])	172 (89.6 [84.4, 93.5])	381 (92.0 [89.0, 94.4])
Median PFS (months)	6.8	6.8	NE	NE	13.9	7.0	21.0	7.0	7.5	NE	7.1	7.5	9.7
95% CI	2.8, 15.0	2.6, 9.9	2.9, NE	3.9, NE	4.4, NE	1.4, NE	5.6, 22.9	5.7, 8.2	3.1, 11.0	NE, NE	4.7, 9.7	7.0, 9.8	8.2, 11.2
Median OS (months)	7.6	12.6	NE	26.0	20.0	8.8	24.3	15.1	12.5	NE	12.8	17.2	18.1
95% CI	4.6, NE	6.7, 17.2	3.9, NE	4.5, NE	7.2, NE	2.4, NE	11.1, NE	12.6, NE	9.3, NE	NE, NE	9.7, 18.1	14.2, 21.1	15.4, 21.0
DoR	(n = 10)	(n = 10)	(n = 7)	(n = 9)	(n = 10)	(n = 0)	(n = 11)	(n = 30)	(n = 9)	(n = 96)	(n = 32)	(n = 96)	(n = 224)
Median DoR (months)	10.9	5.7	NE	NE	NE	NE	19.4	5.5	6.9	NE	8.1	9.9	11.3
95% CI	2.1, NE	4.1, 10.0	9.3, NE	5.8, NE	5.1, NE	NE	2.8, NE	4.2, 8.1	4.0, 9.8	NE, NE	5.5, NE	7.0, 19.4	9.3, 20.1

^a IHC 3+ Subtotal pool includes patients who received the 5.4 mg/kg dose from studies DP02/DC02/DL01 with IHC 3+ tumors.

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^b IHC 3+ Overall total pool includes patients who received the 5.4 mg/kg dose (6.4 mg/kg dose in DG-02) from studies DP02/DC02/DL01/DB01/DG-02 with IHC 3+ tumors.

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Dose/Dose Response

Data:

No new data on dose/dose response is being submitted. Refer to Section 6.3.1 for general pharmacology and pharmacokinetic characteristics.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to Section 6 of this Assessment Aid for details of the FDA clinical pharmacology review for this sBLA.

Durability of Response

Data:

Refer to DoR data in Applicant - Table 19.

The Applicant's Position:

Across the diverse tumor types, responses were durable and clinically meaningful in patients with IHC 3+ solid tumors.

The FDA's Assessment:

Refer to the "Secondary and other relevant endpoints" subsection.

Persistence of Effect

Data:

Refer to data in Applicant - Table 19.

The Applicant's Position:

In the IHC 3+ Population, persistence of efficacy of T-DXd is demonstrated by the long DoR and time to progression (PFS) observed across tumor types in patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

The FDA's Assessment:

Persistence of effect in these studies is assessed by the duration of response. As noted previously, due to limited follow-up time, the median DOR was not estimable in multiple

tumor types. FDA does not consider PFS to be interpretable in the context of single-arm trials.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. No PRO data was submitted; and therefore FDA team could not consider PRO as part of the benefit:risk assessment for this supplement.

Additional Analyses Conducted on the Individual Trial

Data:

No additional analyses have been conducted.

The Applicant’s Position:

No new information is provided in the current submission.

The FDA’s Assessment:

FDA agrees with the Applicant’s position.

8.1.3. Integrated Review of Effectiveness

The FDA’s Assessment:

FDA’s conclusions regarding efficacy are primarily based on results including 192 patients with HER2 IHC 3+ advanced/metastatic solid tumors across Studies DP-02, DC-02 and DL-01. Refer to Integrated Assessment of Effectiveness in Section 8.1.5 for further details.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Primary endpoint data, including pooled data across studies, are presented in Applicant - Table 16.

The Applicant's Position:

In the IHC 3+ Pool (without BC and GC), there was a clinically meaningful ORR based on ICR (ORR: 50.0%; 95% CI: 42.7, 57.3). When including BC and GC into the Total IHC 3+ Pool, the ORR by ICR remained consistent with an ORR of 54.1% (95% CI: 49.2, 59.0). The ORR by investigator assessment was consistent with the ORR by ICR across the IHC 3+ Pool (without BC and GC) and the Total IHC 3+ Pool.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Refer to the "Primary Endpoint (Including Sensitivity Analyses)" subsection for details regarding FDA analysis.

Secondary and Other Endpoints

Data:

Secondary endpoint data, including pooled data across studies, are presented in Applicant - Table 19.

The Applicant's Position:

The proportion of patients with BOR by investigator assessment of CR, PR, SD, or PD was consistent with the BOR by ICR in the IHC 3+ Pool (without BC and GC) and in the Total IHC 3+ Pool (with BC and GC).

The median DoR by investigator assessment was consistent with the analysis of DoR by ICR in the IHC 3+ Pool (without BC and GC) and in the Total IHC 3+ Pool (with BC and GC).

The median TTR by investigator assessment was consistent with the analysis of TTR by ICR and responses occurred early in treatment in the IHC 3+ Pool (without BC and GC) and in the Total IHC 3+ Pool (with BC and GC).

The DCR by investigator assessment was consistent with DCR by ICR assessment across tumor types, in the IHC 3+ Pool (without BC and GC), and in the Total IHC 3+ Pool (with BC and GC).

The PFS by investigator assessment was consistent with PFS by ICR assessment across tumor types, in the IHC 3+ Pool (without BC and GC), and in the Total IHC 3+ Pool (with BC and GC).

In the IHC 3+ Pool (without BC and GC), there were 47.9% of patients with OS events and the median OS was 17.2 months (95% CI: 14.2, 21.1). Additionally, when BC and GC are considered in the Total IHC 3+ Pool, there were 35.0% of patients with OS events and a median OS of 18.1 months (95% CI: 15.4, 21.0).

The FDA's Assessment:

In general, FDA agrees with the Applicant's position, however, FDA does not consider time-to-event endpoints such as PFS and OS to be interpretable in the context of single-arm trials. Refer to the "Secondary and other relevant endpoints" subsection.

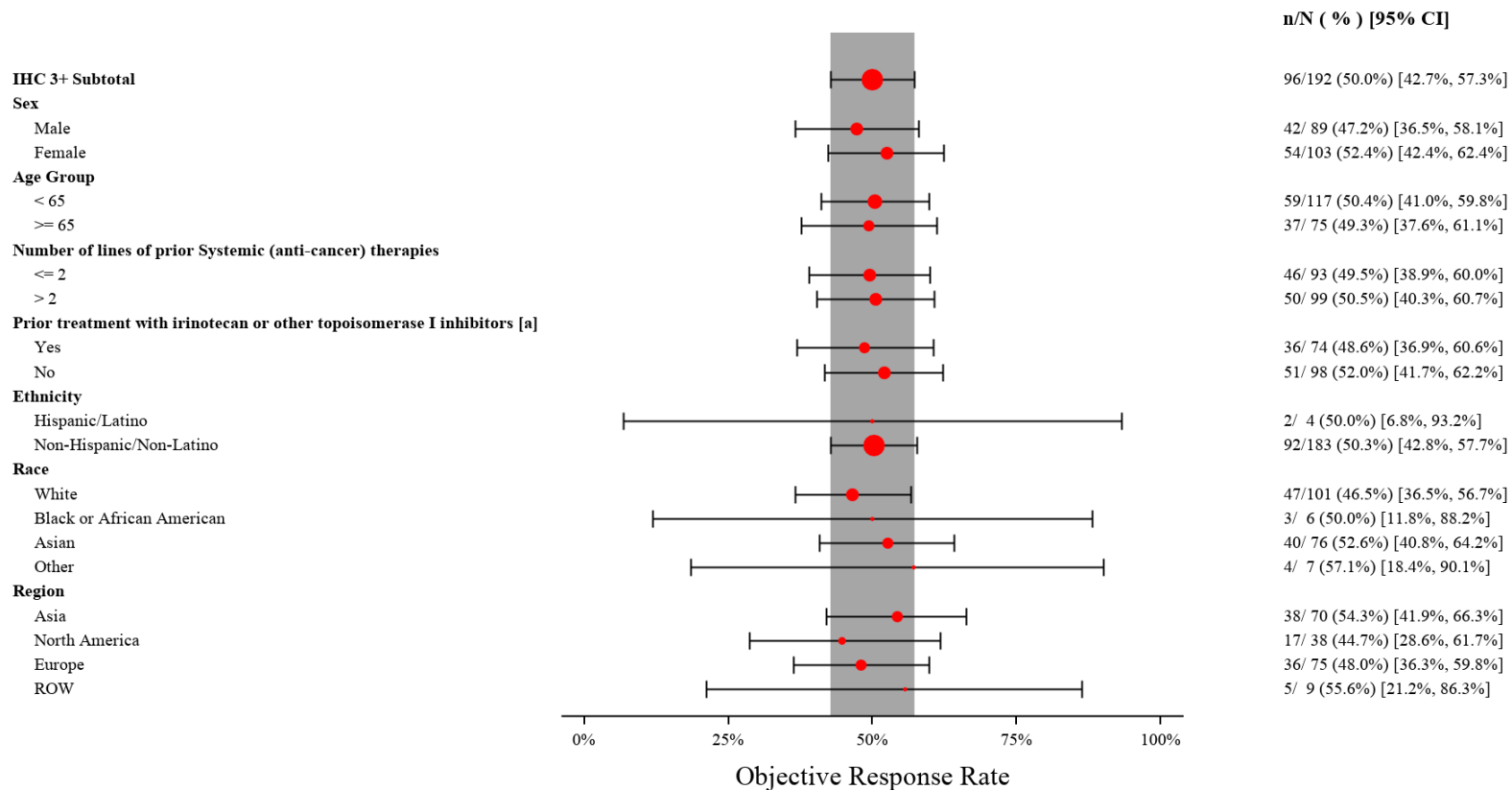
Subpopulations

Data:

Subgroup analyses of ORR were conducted in the pre-specified demographic and baseline disease characteristics. In the IHC 3+ Pool (without BC and GC), a forest plot of ORR based on ICR by subgroup is presented in Applicant – 2. In the Total IHC 3+ Pool (with BC and GC) similar results were observed.

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Applicant – Figure 2 Forest Plot of ORR by ICR Assessment by Subgroups in IHC 3+ Pool (without BC and GC) (FAS)



^a Prior treatment with irinotecan or other topoisomerase I inhibitors is only applicable in DP-02 and DC-02.

Responses determined by ICR. Size of circle is proportional to the number of patients within a subgroup. Grey band represents the 95% confidence interval for the ORR of all patients in the pool. Statistics presented are n/N where n=number of patients with response and N=number of patients in the specific subgroup. The objective response rate and corresponding 95% confidence interval calculated using the Clopper-Pearson method. Unknown/Not reported/Missing are not listed in plot. IHC 3+ Subtotal pool includes patients who received the 5.4 mg/kg dose from studies DP02/DC02/DL01 with IHC 3+ tumors.

The Applicant's Position:

The efficacy benefit in ORR by ICR was consistent across the pre-specified subgroups in the IHC 3+ population.

The FDA's Assessment:

In general, FDA agrees with the results of the Applicant's subgroup analyses of ORR by ICR, and the Applicant's position that ORR by ICR appeared consistent across the pre-specified subgroups in the pooled population of 192 patients with HER2 IHC 3+ advanced/metastatic solid tumors from Studies DP-02, DC-02, and DL-01. However, the number of participants in some subgroups is relatively small to draw any definitive conclusions. Therefore, the subgroup results should be interpreted with caution.

Additional Efficacy Considerations

The FDA's Assessment:

FDA performed an additional exploratory subgroup analysis based on RAS status in the pooled population of 192 patients with HER2 IHC 3+ advanced/metastatic solid tumors from Studies DP-02, DC-02, and DL-01. This exploratory analysis was conducted as there is some literature in tumor types such as colorectal cancer, (Smith et al, Nature Communications 2021), that suggest that there may be resistance to HER2 targeting due to the presence of a concurrent RAS mutation.

There were only 18 patients with a concurrent RAS mutation and the ORR was 50.0% (95% CI: 26.0, 74.0), and the ORR among 174 patients with RAS wild type was 50.0% (95% CI: 42.3, 57.7). Although the data for concurrent RAS mutation is limited in these trials and should be interpreted with caution, partial responses were seen across available tumor types with the concurrent mutations of RAS and IHC3+, including colorectal cancer.

8.1.5. Integrated Assessment of Effectiveness

Data:

For integrated data, refer to Applicant - Table 16 and Applicant - Table 19.

The Applicant's Position:

The available data for T-DXd, across multiple different tumor types, demonstrates that T-DXd is a highly effective treatment for patients with HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options. T-DXd single-agent treatment has demonstrated robust clinical benefit in a comprehensive dataset of 414

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patients across 17 tumor types including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, BC, GC, and rare cancers (salivary, extramammary Paget's disease, vulvar, head and neck (lacrima), lip and/or oral cavity cancer, esophageal (squamous and non-squamous), and oropharyngeal). Across these diverse tumor types, consistently high response rates, long duration of response, and long survival times have been observed in patients with IHC 3+ expressing tumors.

The FDA's Assessment:

FDA's conclusions regarding efficacy for treatment with T-DXd at 5.4 mg/kg are primarily based on results from 192 patients across trials DP-02, DC-02 and DL-01 with HER2 IHC 3+ advanced/metastatic solid tumors who have received prior treatment or who have no satisfactory alternative treatment options. This pooled population includes 15 different tumor types [biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, and rare cancers (salivary, extramammary Paget's disease, vulvar, head and neck (lacrima), lip and/or oral cavity cancer, esophageal (squamous and non-squamous), and oropharyngeal] from the three single arm trials. In the pooled population of 192 patients, treatment with T-DXd in this patient population resulted in a clinically meaningful ORR based on ICR (ORR: 50.0%; 95% CI: 42.7, 57.3) with a median DOR of 9.9 months (95% CI: 7.0, 19.4; range: 1.3+, 27.9+). In DP-02, ORR was 51.4% (95% CI: 41.7, 61.0) and median DOR was 19.4 months (range 1.3, 27.9+). In DL-01, ORR was 52.9% (95% CI: 27.8, 77.0) and median DOR was 6.9 months (range 4.0, 11.7+). In DC-02, ORR was 46.9% (95% CI: 34.3, 59.8), and DOR was 5.5 months (range 1.3+, 9.7+).

A larger pooled analysis with the 192 patients from the primary efficacy cohort in combination with an additional 222 patients with HER2 positive (IHC 3+) advanced/metastatic breast cancer and gastric/GEJ cancer from trials DESTINY-Breast01 and DESTINY-Gastric02 was considered supportive, noting that the data for gastric cancer is at a higher dose (6.4 mg/kg) than the 5.4 mg/kg indication proposed for IHC3+ advanced and metastatic solid tumors. Patients with HER2-positive (IHC 3+) advanced/metastatic breast cancer and gastric/GEJ cancer were not included in the primary efficacy cohort since T-DXd is already approved for these indications in earlier lines. In addition, the dose of T-DXd approved for the gastric/GEJ patient population is different (6.4 mg/kg) and patients with gastric cancer should be treated per the separate approved indication for gastric/GEJ cancers. DESTINY-Breast01 was an open-label, single-arm trial of T-DXd that enrolled 253 patients with HER2-positive (per ASCO-CAP guidelines) unresectable and/or metastatic breast cancer resistant or refractory to T DM1. The 154 patients with HER2-positive (IHC 3+) disease treated with T-DXd at 5.4mg/kg were included in the pooled analysis. DESTINY-Gastric02 was an open-label, single-arm trial of T-DXd that enrolled 79 patients with HER2-positive (IHC 3+/IHC 2+ and ISH positive) unresectable or metastatic gastric or GEJ adenocarcinoma that had progressed on or after a trastuzumab-containing regimen. The 68 patients with HER2-positive (IHC 3+) were included in the larger pooled analysis. All patients on DESTINY-Gastric02 were treated with T-DXd 6.4 mg/kg. This combined population of 414

patients included 17 different tumor types. The ORR by ICR remained consistent with an ORR of 54.1% (95% CI: 49.2, 59.0).

FDA agrees that the ORR and DOR observed with T-DXd treatment in patients with multiple advanced/metastatic solid tumor types that have been previously treated is considered clinically meaningful. In the context of single-arm trials, FDA does not consider time-to-event endpoints such as PFS or OS to be interpretable, and no conclusion should be drawn for PFS and OS from these trials. No confirmed responses were observed in patients with pancreatic cancer. Persistence of effect was assessed by DOR per ICR, and it was clinically meaningful in the overall cohort of HER2 IHC 3+ patients. Although the primary pooled population of 192 patients included 15 tumor types, the number of responders of some tumor types was relatively small and due to limited follow-up time, the median DOR was not estimable in several tumor types. Therefore, one post marketing requirement (PMR) and one post marketing commitment (PMC) have been issued to further characterize ORR and DOR across tumor types and to obtain DOR with longer follow-up on the responding patients.

8.2. Review of Safety

Data:

The assessment of safety and tolerability in the intended population is based on data from 347 patients with IHC 3+ solid tumors who received T-DXd 5.4 mg/kg Q3W in 4 studies. The characterization of the safety profile of T-DXd 6.4 mg/kg in 68 patients with IHC 3+ gastric or gastroesophageal junction cancer treated with T-DXd 6.4 mg/kg is provided by data from Study DG-02. To provide strength of evidence and robustness of the overall safety data for T-DXd at the 5.4 mg/kg and 6.4 mg/kg doses, data are also summarized by dose based on 2 pooled datasets that include supportive studies in a variety of tumor types (the All Tumor Types T-DXd 5.4 mg/kg Pool and the All Tumor Types T-DXd 6.4 mg/kg Pool). Following guidance from the FDA (IR 09Jan24), changes from ISS have been made: IHC 3+ patients from the DP-02 Study are selected based on HER2 status at the time of enrolment with either local test or central test, and Study DP-01 has been removed from the All Tumor Types T-DXd 5.4 mg/kg Pool, in the following summaries. Studies included are presented in Applicant – Table 20.

Applicant – Table 20: Number of Patients in Safety Data Presentations

Group for Evaluation	Dose of T-DXd	Number of Patients Treated
HER2 IHC 3+		
<u>IHC 3+ T-DXd 5.4 mg/kg Pool</u> Multi-study pool of data from study of patients with IHC 3+ solid tumors who received T-DXd 5.4 mg/kg	5.4 mg/kg	Total: 347 DP-02: 111; DL-01: 17; DC-02: 65; DB-01: 154

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Group for Evaluation	Dose of T-DXd	Number of Patients Treated
<u>Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg)</u> Data from patients with IHC 3+ gastric or gastroesophageal junction cancer who received T-DXd 6.4 mg/kg	6.4 mg/kg	DG-02: 68
All Tumor Types		
<u>All Tumor Types T-DXd 5.4 mg/kg Pool</u> Multi-study pool of data from patients across various tumor types and IHC expression levels who received the proposed registration dose of T-DXd 5.4 mg/kg	5.4 mg/kg	Total: 1799 DP-02: 267; DL-01: 41; DC-02: 83; DB-01: 184; DB-02: 404; DB-03: 257; DB-04: 371; J101: 91; DL-02: 101
<u>All Tumor Types T-DXd 6.4 mg/kg Pool</u> Multi-study pool of data from patients across various tumor types and IHC expression levels who received T-DXd 6.4 mg/kg	6.4 mg/kg	Total: 794 DL-01: 140; DC-02: 39; DB-01: 48; DG-02: 79; J101: 183; DL-02: 50; DG-01: 169; DC-01: 86

The Applicant's Position:

The safety data presented in this application allowed for a comprehensive and adequate assessment of the safety profile of T-DXd, including detection and characterization of common AEs, guidance on toxicity management, and an evaluation of the overall benefit-risk in the target population.

The FDA's Assessment:

FDA's safety analysis was primarily based on data from patients from three trials submitted for this sBLA treated with T-DXd at the 5.4mg/kg dose. References will be made in this safety section to different pooled safety populations evaluated to characterize the safety of T-DXd across tumor types. FDA will refer to these pools as the "4-trial", "3-trial", and "large" safety pools. The 4-trial safety pool and large safety pools are consistent with the Applicant description above and are further described below.

- 4-Trial safety pool: Patients with IHC3+ tumors treated with 5.4mg/kg T-DXd from the DP-02 (n=111), DB-01 (n= 154), DL-01 (n=17), DC-02 (n=65) trials with a total of 347 patients.
- 3-Trial safety pool: Patients with IHC3+ tumors treated with 5.4mg/kg T-DXd from DP-02 (n=111), DL-01 (n=17), DC-02 (n=65) trials with a total of 193 patients.
- Large safety pool: Patients from several trials treated with 5.4mg/kg T-DXd with multiple tumor types and varying IHC-HER2 expression. This included 1799 patients from the following trials DP 02 (n= 267), DL 01 (n= 41), DC-02 (n=83), DB 01 (n=184), DB-02 (n=404), DB-03 (n=257), DB-04 (n=371), J101 (n=91), and DL 02 (n=101).

In addition to the 3-Trial pool noted above, FDA also agreed to the inclusion of 154 breast cancer patients from DB-01 with IHC3+ HER2 expression tumors to support the safety analysis as this trial also enrolled patients in a similar treatment line setting. Therefore, the 4-trial pool was the focus for the assessment of toxicity associated with treatment with T-DXd across solid tumor types with IHC3+ HER2 expression for this sBLA. FDA separately analyzed data from the 3-Trial pool to ensure that safety signals were not masked by the number of patients with breast cancer included in DB-01, as the safety of T-DXd in breast cancer is well-established.

The safety population for the 4-Trial pool included 347 patients though the efficacy population was n=346. This was due to the inclusion of 1 patient (ID- (b) (6)) from the DC-02 study that was randomized to the 6.4mg/kg arm for T-DXd but received a dose of 5.4mg/kg in the study. This patient was included in the safety analyses for the 5.4mg/kg pool but in the efficacy analyses for the 6.4mg/kg pool.

As noted by the Applicant, all patients from DP-02 who had IHC3+ tumors by local *or* central testing, as per the eligibility criteria for the study, were included in the safety pool of patients treated with T-DXd at 5.4mg/kg. FDA considered the fact that many patients would be selected from treatment based on local tests available in their treatment centers upon approval of T-DXd and, therefore, inclusion of patients with local testing of tumor samples demonstrating IHC3+ expression would be consistent with clinical practice. An information request (IR) was sent to the Applicant, with agreement to make this change in the patient population in both labeling and this Assessment Aid document. This increased the number of patients in the 4-study pool of IHC3+ solid tumors to 347 patients vs. 311 originally proposed by the Applicant. The safety analyses in this review reflect this change.

Though FDA does not disagree with the proposed large safety pool of gastric cancer patients treated with 6.4mg/kg of T-DXd, the focus of the safety review were the patients included in the safety population who received the 5.4mg/kg every 3-weeks dosage of T-DXd, and FDA did not separately analyze patients who received 6.4mg/kg T-DXd for the review of this sBLA. Overall, FDA agrees that the safety data were consistent across the pooled analyses and provided a comprehensive review of safety of T-DXd across tumor types. Though the patients in these trials had tumors of different histology, all enrolled patients who had received prior line(s) of chemotherapy and were of similar treatment line settings. FDA safety analyses focused on evaluation of deaths, treatment-emergent adverse events (TEAEs), serious TEAEs, and AEs of special interest (AESIs). AESIs for T-DXd include ILD/pneumonitis, neutropenia, and left ventricular (LV) dysfunction.

Safety Review Approach

Data:

Results from the safety pools in Applicant – Table 20 are presented: To provide safety data with more precise estimates in the target indication at the recommended dose; to illustrate the maturity

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of the large safety database and the well-characterized safety profile of T-DXd at each of the 2 doses (5.4 mg/kg and 6.4 mg/kg).

The Applicant's Position:

The safety review approach was considered comprehensive and appropriate to evaluate the safety profile of T-DXd in the intended population.

The FDA's Assessment:

FDA agrees that the safety review approach was comprehensive and appropriate to evaluate the safety profile of T-DXd in the intended IHC3+ population.

8.2.1. **Review of the Safety Database****Overall Exposure**Data:

Overall exposure data is provided in Applicant – Table 21.

Applicant – Table 21: Summary of Exposure

	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Duration of treatment (months) ^a				
Mean	10.47	6.94	11.66	7.68
Std Dev	7.634	5.325	9.192	6.900
Median	8.28	5.62	8.74	5.52
Min, Max	0.7, 30.2	0.7, 22.1	0.2, 45.1	0.7, 41.0
Duration of treatment category, n (%) ^a				
0 to ≤3 months	61 (17.6)	22 (32.4)	310 (17.2)	251 (31.6)
>3 to ≤6 months	64 (18.4)	16 (23.5)	312 (17.3)	176 (22.2)
>6 to ≤9 months	71 (20.5)	7 (10.3)	301 (16.7)	123 (15.5)
>9 to ≤12 months	36 (10.4)	15 (22.1)	200 (11.1)	79 (9.9)
>12 to ≤18 months	38 (11.0)	4 (5.9)	246 (13.7)	92 (11.6)
>18 to ≤24 months	57 (16.4)	4 (5.9)	219 (12.2)	40 (5.0)
>24 months	20 (5.8)	0	211 (11.7)	33 (4.2)
Number of cycles				

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	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Mean	14.2	9.5	15.9	10.3
Std Dev	10.29	7.36	12.49	9.18
Median	11.0	7.5	12.0	7.0
Min, Max	1, 40	1, 32	1, 60	1, 53
Number of cycles category, n (%)				
≤6 cycles	95 (27.4)	32 (47.1)	479 (26.6)	373 (47.0)
>6 to ≤12 cycles	100 (28.8)	15 (22.1)	442 (24.6)	188 (23.7)
>12 to- ≤18 cycles	52 (15.0)	14 (20.6)	283 (15.7)	105 (13.2)
>18 to ≤24 cycles	23 (6.6)	3 (4.4)	176 (9.8)	55 (6.9)
>24 to ≤30 cycles	37 (10.7)	2 (2.9)	153 (8.5)	29 (3.7)
>30 cycles	40 (11.5)	2 (2.9)	266 (14.8)	44 (5.5)
Total patient-years of exposure ^b	302.7	39.4	1748.0	508.4
Cumulative dose level ^c				
Mean	73.70	59.15	82.37	61.60
Std Dev	53.337	45.525	63.928	52.882
Median	57.60	44.91	64.80	43.55
Min, Max	5.3, 225	6.4, 200.3	5.2, 321.3	6.2, 274.1
Dose intensity ^d				
Mean	4.96	5.95	5.02	5.77
Std Dev	0.598	0.588	0.739	0.730
Median	5.19	6.14	5.22	5.97
Min, Max	2.5, 5.7	3.9, 6.7	2.5, 22.7	3.2, 7.0
Relative dose intensity (%) ^e				
Mean	91.31	92.91	96.79	90.13
Std Dev	13.391	9.183	8.408	11.411
Median	96.18	95.91	99.68	93.26
Min, Max	46.1, 199.6	60.3, 104.0	46.1, 199.6	50.4, 109.3
Relative dose intensity (%) category, n (%)				
≥90%	230 (66.3)	51 (75.0)	1585 (88.1)	469 (59.1)
<90% to ≥80%	58 (16.7)	7 (10.3)	112 (6.2)	183 (23.0)
<80% to ≥60%	50 (14.4)	10 (14.7)	91 (5.1)	130 (16.4)

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	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
<60%	9 (2.6)	0	11 (0.6)	12 (1.5)
Patients with dose modification, n (%)	127 (36.6)	18 (26.5)	499 (27.7)	391 (49.2)
Dose reduction	98 (28.2)	17 (25.0)	442 (24.6)	310 (39.0)
Dose interruption	44 (12.7)	3 (4.4)	102 (5.7)	165 (20.8)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

The pooled analysis group is based on tumor type and first dose received for patients in each study.

- ^a Duration of treatment (months) = (date of the last dose - date of the first dose + 21 days)/30.44. 1 month = 365.25/12=30.44 days.
- ^b Total patient-years of exposure = sum of duration of treatment (months)/12.
- ^c Cumulative dose level (mg/kg) = sum of the actual dose level received (mg/kg).
- ^d Dose intensity ((mg/kg)/cycle length in weeks) = cumulative dose level (mg/kg) / (duration of treatment (days)/21 days).
- ^e RDI derivation/definition for each study follows the study convention specified in CSR SAPs. RDI is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation. Actual treatment duration = total treatment duration, excluding duration of dose delays.

The Applicant's Position:

Overall, the IHC 3+ T-DXd 5.4 mg/kg Pool and Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) provided adequate exposure and follow-up data to evaluate the safety profile of T-DXd in the intended patient population for its use in clinical practice.

The FDA's Assessment:

FDA agrees with the Applicants description of exposure to T-DXd at a dose of 5.4 mg/kg. FDA agrees that exposure is adequate to characterize safety of T-DXd across tumor types.

Relevant characteristics of the safety population:

Data: Refer to Section 8.1.2.

The Applicant's Position:

The safety database includes a population that is sufficiently diverse to adequately represent and characterize the safety profile in the target population.

The FDA's Assessment:

The diversity of patients treated with T-DXd across multiple trials was assessed in the large safety pool of 1799 patients as well as the 3-Trial safety pool for this sBLA in reference to demographics and disease characteristics. The majority of patients treated with T-DXd in the Large safety pool identified as White (49%) or Asian (41%). Only 2.3% of patients were Black and 7% were Hispanic or Latino; therefore, FDA did not find the safety population of T-DXd to be representative of the racial and ethnic diversity of breast cancer patients in the U.S. Though this was a limitation, FDA still determined that the results, based upon other important disease characteristics and prior therapies, were applicable to the solid tumor population treated in the U.S. and supportive of the intended indication.

Most of the 1799 patients (88%) treated with T-DXd in the Large safety pool were female which is likely due to the initial development of T-DXd in the breast cancer patient population. When considering the 3-Trial safety population of 193 patients with non-breast cancer solid tumors in studies DL-01, DC-02, and DP-02, there was a more representative proportion of male patients across the other tumors represented (46%).

The proportion of older cancer patients in the safety population for T-DXd was 27% for ≥ 65 years of age and only 5% for ≥ 75 years. FDA analyses did not reflect any distinct safety differences in older adults enrolled across trials though the overall number of patients in each of these age groups was limited, especially for the ≥ 75 cutoff.

Almost all 347 patients included in the 4-study safety pool had been treated with at least one prior regimen and the majority had received 2 or more prior therapies which FDA would consider to be representative of the population of solid tumor patients in the U.S. with advanced/metastatic disease considering treatment on T-DXd. Despite some limitations, FDA generally agrees that the diversity of the safety population was adequate for characterizing the safety profile of T-DXd 5.4mg/kg dose across tumor types.

Adequacy of the safety database:

Data:

The number of patients included in the safety database and their exposure to T-DXd treatment are provided in Applicant – Table 20 and Applicant – Table 21.

The Applicant's Position:

The available safety database allows for an adequate assessment of the overall safety profile of T-DXd in the intended population at the target dose.

The FDA's Assessment:

FDA agrees with the Applicant that the safety database is adequate for assessment of the T-DXd safety profile.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The Applicant's quality control and quality assurance activities, data management, and statistical analysis of the study data were implemented per the Applicant's Good Clinical Practice standard operating procedures. Monitors designated by the Applicant to ensure compliance of the investigators and other site staff members involved in this study were granted direct access to the source documents maintained at individual study sites and verified that case report form data were accurately reported and consistent with the source data. As applicable, Contract Research Organizations and central laboratories implemented data quality control activities based on their relevant in house standard operating procedures.

All potential ILD/pneumonitis cases were adjudicated by an independent ILD Adjudication Committee.

The Applicant's Position:

No meaningful concerns were observed in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections by the Applicant; data in the case report forms and AE databases were consistent.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of data integrity based on FDA review and clinical inspections from the FDA Office of Scientific Investigations (OSI). Please see Section 4.1 of this Assessment Aid for more information.

Categorization of Adverse Events

Data:

The safety profile observed with T-DXd was evaluated on the basis of the following:

- Frequency, type, severity, and causal relationship of AEs to study treatment
- Frequency of deaths, SAEs, AESI (ILD and LV dysfunction) and other clinically significant AEs (including AEs associated with study drug discontinuation, dose reduction, and/or study drug interruption)
- Frequency and type of AEs in key intrinsic and extrinsic factors (ie, age, race, ECOG PS,

- renal and hepatic function at baseline, geographic region, and country)
- Changes in laboratory variables, with particular attention to abnormalities of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4.

The Applicant's Position:

The categorization of AEs was considered appropriate for evaluating the safety data in the targeted population treated with T-DXd at the target dose.

The FDA's Assessment:

FDA agrees with the Applicant's description of adverse events (AEs). AEs were coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) and assigned grades based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) for DP-02, DC-02, DB-01, and DL-01 trials. AEs of special interest (AESI) for these studies included ILD/pneumonitis and cardiotoxicity/LV dysfunction. An ILD Adjudication Committee (AC) was established for each trial and reviewed all cases of potential ILD. It was required that response assessment scans be reviewed for evidence of ILD / pneumonitis prior to administration of the next scheduled dose of T-DXd.

Overall, the trials used for safety pooling were consistent in their safety monitoring. Echocardiogram/MUGA were required at screening, every 4 cycles, and at the EOT visit for all trials. Management of dose modifications were generally consistent across DP-02, DC-02, DB-01, and DL-01 trials. However, due to the onset of the COVID-pandemic, dose modification instructions for potential COVID-19 cases were included for DL-01, DC-02, and DP-02.

In the DP-02, DC02, DL-01 and DB-01 trials, a TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or worsened in severity or seriousness after initiating the study drug until the 47 days after the last dose of study drug. FDA's safety assessment focused on the frequency and severity of all AEs with particular focus on AEs leading to death, serious adverse events (SAEs), grade ≥ 3 AEs, and the adverse events of special interest (AESI) of ILD/pneumonitis which has been previously reported to be a serious risk of treatment with T-DXd. FDA considers all AEs in its safety analysis without attribution.

Routine Clinical Tests

Data:

The schedule of assessments in the protocol specified the time points at which laboratory evaluations were conducted. Per protocol, abnormal laboratory values that were considered clinically significant by the investigator were to be reported as AEs.

The Applicant's Position:

The clinical monitoring of subject safety (methods and time points) described in the protocol was considered to be reasonable and adequate for the population, disease, and indication being investigated.

The FDA's Assessment:

FDA agrees with the Applicant's description of laboratory assessments for this sBLA.

8.2.3. Safety Results**Deaths**Data:

In the IHC 3+ T-DXd 5.4 mg/kg Pool, the majority of deaths were due to disease progression and disease under investigation (110 of the 146 deaths) (Applicant – Table 22). Twenty-two (6.3%) of patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had Grade 5 TEAEs (Applicant – Table 23).

Applicant – Table 22: Summary of Deaths

	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Any Death	146 (42.1)	38 (55.9)	742 (41.2)	432 (54.4)
Adverse event	14 (4.0)	7 (10.3)	51 (2.8)	42 (5.3)
Disease progression	56 (16.1)	25 (36.8)	447 (24.8)	336 (42.3)
Related to disease under investigation	54 (15.6)	0	154 (8.6)	0
Unknown	13 (3.7)	4 (5.9)	59 (3.3)	39 (4.9)
Other	9 (2.6)	2 (2.9)	31 (1.7)	15 (1.9)
On-treatment death ^a	26 (7.5)	9 (13.2)	99 (5.5)	67 (8.4)
Adverse event	10 (2.9)	4 (5.9)	39 (2.2)	31 (3.9)
Disease progression	6 (1.7)	5 (7.4)	34 (1.9)	35 (4.4)
Related to disease under investigation	8 (2.3)	0	19 (1.1)	0

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	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Unknown	0	0	3 (0.2)	1 (0.1)
Other	2 (0.6)	0	4 (0.2)	0

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

^a On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug (28 days for Study J101) and before the initiation of the first subsequent anti-cancer therapy (whichever occurred first).

Applicant – Table 23: Adverse Events Associated with an Outcome of Death

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Patients with any TEAE	22 (6.3)	10 (14.7)	81 (4.5)	70 (8.8)
Death	3 (0.9)	0	6 (0.3)	0
Pneumonitis	3 (0.9)	1 (1.5)	8 (0.4)	7 (0.9)
Cardiac arrest	2 (0.6)	0	2 (0.1)	0
Acute kidney injury	1 (0.3)	0	2 (0.1)	0
Acute respiratory failure	1 (0.3)	0	1 (0.1)	0
COVID-19	1 (0.3)	1 (1.5)	3 (0.2)	2 (0.3)
COVID-19 pneumonia	1 (0.3)	0	1 (0.1)	0
Cerebrovascular accident	1 (0.3)	1 (1.5)	2 (0.1)	1 (0.1)
Disease progression	1 (0.3)	2 (2.9)	12 (0.7)	25 (3.1)
General physical health deterioration	1 (0.3)	0	2 (0.1)	1 (0.1)
Lymphangitis	1 (0.3)	0	1 (0.1)	0
Neoplasm malignant	1 (0.3)	0	1 (0.1)	0
Neutropenic sepsis	1 (0.3)	0	1 (0.1)	0
Pneumonia	1 (0.3)	0	6 (0.3)	1 (0.1)

Applicant – Table 23: Adverse Events Associated with an Outcome of Death

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Respiratory failure	1 (0.3)	0	5 (0.3)	3 (0.4)
Sepsis	1 (0.3)	0	4 (0.2)	1 (0.1)
Shock haemorrhagic	1 (0.3)	0	1 (0.1)	0
Acute hepatic failure	0	0	1 (0.1)	0
Acute myeloid leukaemia	0	0	1 (0.1)	0
Acute pulmonary oedema	0	0	0	1 (0.1)
Asthenia	0	0	0	1 (0.1)
Biliary obstruction	0	0	0	1 (0.1)
Brain oedema	0	0	1 (0.1)	0
Bronchospasm	0	0	0	1 (0.1)
Colitis ischaemic	0	0	1 (0.1)	0
Disseminated intravascular coagulation	0	0	1 (0.1)	2 (0.3)
Dyspnoea	0	0	1 (0.1)	1 (0.1)
Febrile neutropenia	0	0	1 (0.1)	1 (0.1)
Gastrointestinal perforation	0	0	1 (0.1)	0
General physical condition abnormal	0	0	0	1 (0.1)
Haemorrhage	0	0	1 (0.1)	0
Hepatic failure	0	0	1 (0.1)	0
Hepatic function abnormal	0	0	0	1 (0.1)
Hepatitis B	0	0	1 (0.1)	0
Hydrocephalus	0	0	0	1 (0.1)
Hypotension	0	0	1 (0.1)	0

Applicant – Table 23: Adverse Events Associated with an Outcome of Death

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Interstitial lung disease	0	1 (1.5)	1 (0.1)	5 (0.6)
Intestinal obstruction	0	1 (1.5)	0	2 (0.3)
Intestinal perforation	0	0	0	1 (0.1)
Large intestine perforation	0	0	0	1 (0.1)
Lung neoplasm malignant	0	0	2 (0.1)	0
Lymphangiosis carcinomatosa	0	1 (1.5)	0	1 (0.1)
Malignant neoplasm progression	0	2 (2.9)	2 (0.1)	2 (0.3)
Malignant pleural effusion	0	0	1 (0.1)	0
Mechanical ileus	0	0	0	1 (0.1)
Meningism	0	0	0	1 (0.1)
Neoplasm progression	0	0	0	2 (0.3)
Organising pneumonia	0	0	1 (0.1)	0
Pleural effusion	0	0	1 (0.1)	0
Pneumocystis jirovecii pneumonia	0	0	0	1 (0.1)
Pneumonia aspiration	0	0	0	1 (0.1)
Postoperative wound infection	0	0	1 (0.1)	0
Pulmonary embolism	0	0	1 (0.1)	0
Seizure	0	0	0	1 (0.1)
Sudden death	0	0	1 (0.1)	0
Upper gastrointestinal haemorrhage	0	0	0	1 (0.1)

Applicant – Table 23: Adverse Events Associated with an Outcome of Death

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Vasogenic cerebral oedema	0	0	1 (0.1)	0

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

A death could be associated with multiple PTs.

If a patient had multiple occurrences of the same PT, the patient was counted once for the specific PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

TEAEs are sorted by descending frequency in the IHC 3+T-DXd 5.4 mg/kg Pool.

The Applicant's Position:

Many of the solid tumors studied in the clinical studies supporting this submission are associated with advanced metastatic disease and significant mortality. The most common causes of death due to any cause across pools were disease progression and disease under investigation. Based on a review of deaths, no new AE patterns associated with T-DXd were identified.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. FDA performed an independent analysis of all patient deaths due to AEs and selected other patient deaths that occurred in the 4-Trial safety pool (N=347). FDA also evaluated rates of deaths due to AEs, disease progression, in the 4-Trial and 3-Trial safety pools and compared it to rates reported in the large safety pool to determine if the experience of patients from the trials supporting this sBLA differed from the overall experience across trials of T-DXd. Finally, FDA evaluated deaths due to AEs occurring within 47 days per the trial protocols of the last dose of T-DXd in the 4-study pool (FDA - Table 24 and FDA - Table 25). FDA agreed with the approach taken by the Applicant in Applicant – Table 23, that the AEs leading to death may be linked to multiple preferred terms, but FDA only counted each patient with a death due to AE once in the breakdown of causes for death. An IR request was sent to the Applicant during the review to clarify and the Applicant and FDA determined there were 22 deaths due to adverse events. FDA agrees with the Applicant that most deaths were due to disease progression or disease under investigation, noting that the term "disease under investigation" referred to the patient's underlying cancer by the Applicant. FDA agrees with the Applicant that 22 of the deaths in the 4-trial safety pool occurred due to AEs; however, there were some distinctions between the FDA and Applicant's assessment of which AE caused a patient's death in a few cases which are included in the patient narratives below. Information regarding fatalities were included in the USPI.

FDA - Table 24: Summary of Patient Deaths in DP-2, DB-01, DL-01, and DC-02 trials

	Pooled analysis (N=347) n (%)
Total deaths	146 (42)
Disease progression or “Disease under investigation)	102 (29)
Adverse event	22 (6.3)
Unknown/Other	22 (6.3)

Source: FDA analysis

FDA - Table 25: Analyses of Deaths due to AEs DP-02, DL-01, DC-02, and DB-01 Trials

	DP-02 N=111 N (%)	DL-01 N =17 N (%)	DC-02 N=65 N (%)	DB-01 N=154 N (%)	Pooled analysis N=347 N (%)
Death due to AE	12 (11)	2 (12)	1 (1.5)	7 (4.5)	22 (6.3)
Unknown	3 (2.7)	0	0	0	3 (0.9)
Cardiac arrest	2 (1.8)	0	0	0	2 (0.6)
Cerebrovascular accident	1 (0.9)	0	0	0	1 (0.3)
COVID-19	2 (1.8)	0	0	0	2 (0.6)
Sepsis*	1 (0.9)	1(6)	0	0	2 (0.6)
Pneumonia	1 (0.9)	0	0	0	1 (0.3)
Acute kidney injury	0	0	1 (1.5)	0	1 (0.3)
Hemorrhagic shock	0	0	0	1 (0.6)	1 (0.3)
General physical health deterioration	0	0	0	1 (0.6)	1(0.3)
ILD/Pneumonitis	2 (1.8)	1(6)	0	5 (3.2)	8 (2.3)

*Sepsis included sepsis (n=1) and neutropenic sepsis (n=1)

Source: FDA analysis

There were three patients noted by the Applicant to have experienced deaths due to the AE of “Death”, and all were from the DP-02 trial. FDA noted the causes of these deaths to be “Unknown/Other” in FDA - Table 24. FDA reviewed the narratives for each of these patients (details below) and notes confounding factors in these deaths as noted.

DP-02, Patient ID# (b) (6) – Applicant’s attribution: Death

38-year-old White female from (b) (6) enrolled in the rare tumor cohort (oral cavity tumor), received a total of 6 cycles of T-DXd and developed Grade 1 pneumonitis which was ongoing at the time of death. However, the patient died at home following the diagnosis of pneumonitis and maximum grade for this AE was reported as Grade 1. No autopsy was performed, and the pneumonitis was adjudicated as not ILD though it was determined to be related to T-DXd. Imaging revealed changes only in one lung and patient did not require any treatment for pneumonitis; this AE was noted to be improving as well in the case report files. FDA cannot rule out whether the event of pneumonitis contributed to the patient’s death and whether other factors contributed to this death.

DP-02, Patient ID# (b) (6) - Applicant’s attribution: Death

72-year-old female from (b) (6) with diagnosis of bladder cancer experienced an SAE (sepsis) which was noted to have improved. The patient was also diagnosed with acute kidney injury at the time of sepsis. FDA requested additional information from imaging studies performed during the study period. The patient was noted to have a nephroureteral stent and severe hydronephrosis at the time of acute renal insufficiency. The patient had no evidence of abnormalities on chest x-ray and had experienced dehydration, decreased oral intake prior to her death. The patient chose to stop study treatment and later died after being transferred to hospice. No autopsy was performed. FDA agrees with the Applicant’s assessment that the patient had an AE with the outcome of death and that the cause of death is difficult to further classify due to confounding factors, though contribution of underlying dehydration and acute kidney injury could not be ruled out.

DP-02, Patient ID# (b) (6) - Applicant’s attribution: Death

74-year-old Asian male from (b) (6) with diagnosis of biliary tract cancer and received 4 cycles of T-DXd. The patient had ongoing pneumonia at the time of his death. The event was considered an SAE and required hospitalization. The patient died in the hospital 26 days after the last dose of study drug. The narrative states the patient had been treated in the hospital for pneumonia for several days and did not have documentation of desaturation. FDA cannot rule out that pneumonia did not play a factor in this patient’s death.

FDA evaluated deaths due to causes that were not typically associated with T-DXd; all were from the DP-02 trial. Two of these were attributed to the AE of COVID-19. These deaths were notable given the timing of the trial during the COVID pandemic, but FDA agreed that COVID-19 infection was likely not directly attributable to T-DXd though patients with underlying cancer and receiving therapy may be at higher risk for this infection. There were also two deaths due to cardiac arrest and one due to hemorrhagic cerebrovascular accident that were reviewed, and FDA did not disagree with the Applicant's attribution. Two additional deaths in the DB-01 trial, one due to disease progression and another due to general physical deterioration, were also reviewed as they were included by the Applicant as deaths due to AEs. FDA did not consider disease progression to be a cause of death due to an AE and disagreed with the Applicant's inclusion of this in their deaths due to AEs above (Applicant – Table 23) but agreed with including the patient with general physical deterioration for the reasons outlined below.

DP-02, Patient ID# (b) (6) – Applicant's attribution: COVID-19 pneumonia

68-year-old Asian male from (b) (6) who enrolled in the biliary tract cohort experienced on treatment death attributed by the Applicant to COVID-19 pneumonia. The patient died on Study Day 231 after development of COVID-19 pneumonia. FDA agrees that the death was due to the AE of COVID-19 pneumonia and cannot rule out that T-DXd treatment did not contribute to the severity of the infection leading to death.

DP-02, Patient ID# (b) (4) – Applicant's attribution: COVID-19

63-year-old Asian male from (b) (6) who experienced on treatment death due to AE COVID-19 had a diagnosis of biliary tract cancer with a primary tumor location of gall bladder. On Study Day 39 an event of interstitial lung disease was reported. At onset, the CTCAE grade for the event was 1 which was the maximum grade during the event. T-DXd was interrupted in response to the event of ILD. On Study Day 53 a high-resolution CT was done, and the event of interstitial lung disease was reported as resolved. On Study Day 54, the treatment with T-DXd was restarted. This event of interstitial lung disease was adjudicated as ILD (drug-related). On Study Day 61 the patient developed a high-grade fever temperature of 38.8°C and low oxygenation with SpO2 level of 87% (self-measured by pulse oximeter). The patient went to the hospital and was diagnosed with COVID-19 infection, and this was reported as an SAE. He was reported to have low grade fever with more cough and received unspecified treatment for the event. Around the same time as the diagnosis of COVID-19 the patient also experienced non-serious adverse events of "alanine aminotransferase increased" and "blood creatinine increased". On Study Day 85 the patient died. The primary cause of death was reported as COVID-19. No autopsy was performed. The reporting investigator considered the death to be unrelated to their underlying cancer. Though FDA does not disagree with COVID-19 as the underlying cause of death, there is a possibility that the patient did not have full recovery of pneumonitis, and this could have contributed to his eventual death and complications from COVID-19 that were complicated by treatment with T-DXd.

DP-02, Patient ID# (b) (6) - Applicant's attribution: Cardiac arrest

80-year-old Asian male from (b) (6) had a diagnosis of biliary cancer. He had a history of a prior myocardial infarction at baseline. Approximately a month prior to his death, he had an echocardiogram reporting unchanged ejection fraction (61%). The patient's disease had metastasized to multiple lymph nodes in the mesenteric and aortocaval area. Shortly afterwards, this patient had death from cardiac arrest. Though FDA requested and reviewed the most recent EKG and echocardiogram on this patient, these studies showed overall normal findings during the month prior to the patient's death, and FDA considers there to be uncertainty around why the patient died of cardiac arrest and cannot rule out the contribution of T-DXd to the death.

DP-02, Patient ID# (b) (6) - Applicant's attribution: Cardiac arrest

85-year-old White female from (b) (6) who had a diagnosis of bladder cancer. The patient had liver, lung and pelvic metastases at baseline and a history of prior immunotherapy; she was also noted to have a past medical history that includes Lynch syndrome, atrial fibrillation and hypertension. She experienced gastric obstruction shortly after enrolling on the trial and was hospitalized and also diagnosed with COVID-19 prior to beginning treatment. Upon receiving two cycles of treatment, the patient was noted to have lower extremity edema and was diagnosed with a new thromboembolic event CTCAE grade 3; she was hospitalized. During this hospitalization the patient became unresponsive, coded and died. No autopsy was performed, and the patient was reported to have death from cardiac arrest. FDA does not disagree with the report of cardiac arrest though it is notable that the patient had a recent thromboembolic event that could have also contributed to the sudden death of the patient and there were other confounding factors where the contribution of T-DXd cannot be ruled out.

DP-02, Patient ID# (b) (6) - Applicant's attribution: Cerebrovascular accident

70-year-old White female from (b) (6) with a diagnosis of endometrial cancer, heavily pretreated with a history of hypertension, dyslipidemia. On Study Day 8 the SAE of dyspnea was reported. Bilateral pleural effusions were reported on imaging, and a pulmonary function test noted mixed obstructive and restrictive ventilatory patterns. A lung ventilation perfusion scan (VQ scan) showed low probability for pulmonary embolism and bilateral lung masses were appreciated, and no evidence of pneumonia was noted. On study day 19 the patient woke up with severe dyspnea and slurred speech. On the same day, she was hospitalized with a SAE of cerebrovascular accident and was intubated. On study day 23, the patient's family stopped all life-saving measures. On the same day, the patient was declared dead; the primary cause of the death was hemorrhagic stroke. FDA considered that the patient had only 1 cycle of T-DXd, multiple prior regimens and h/o dyslipidemia and hypertension and smoking. FDA agrees with

the Applicant's attribution of death due to stroke, but considers that multiple factors, including the patient's underlying disease contributed to the patient's death and did not find hemorrhagic stroke to be a new safety signal of treatment with T-DXd.

DB-01, Patient ID# (b) (6) - Applicant's attribution: Disease progression

39-year-old White female from (b) (6) initially diagnosed with breast cancer on (b) (6). The patient was diagnosed with grade 3 disease progression, considered an SAE as it required hospitalization. The patient received a total of 2 doses of T-DXd. After that hospitalization, she was readmitted for abdominal pain and a CT scan showed the presence of a peritoneal drain and new metastases in the lung, liver, and bone. An intestinal transit study showed gastroparesis in the absence of mechanical obstruction. On study day 57), the patient died due to disease progression which was considered by the Applicant to be the AE cause of death. FDA agrees with Applicant's attribution of death as due to disease progression but did not consider this to be a death due to an AE.

DB-01, Patient ID# (b) (6) - Applicant's attribution: General physical deterioration

66-year-old White female from (b) (6). On study day 106 she developed dyspnea grade 2, grade 1 vomiting, and then edema, decreased appetite, and ascites. General physical health deterioration was diagnosed as an SAE requiring hospitalization. She had received 10 doses of study drug and had multiple AEs at the time of her death. Her nausea/vomiting had worsened to Grade 3; she also was diagnosed with pulmonary sepsis, dyspnea, fatigue grade 3. She had impaired gastric emptying, sinus tachycardia, productive cough. At the time of her death the patient had sepsis, was intubated, and was reported to also have bacterial pneumonitis. Palliative treatment including pressors were initiated, but she was noted to die due to disease progression and grade 5 "general physical deterioration". FDA does not disagree with this attribution but considers it possible that the multiple other AEs could have also contributed to the patient's death.

FDA included an additional 5 patients as having deaths due to the AE of ILD/pneumonitis. Four of these patients were already included by the Applicant as having deaths due to an AE but the Applicant attributed their deaths to other causes. Another patient enrolled in DP-02 experienced ILD. However, though the Applicant included this as a death due to organizing pneumonia, it was not included in Applicant – Table 23. FDA included this patient as a death due to the AE of organizing pneumonia which was considered under the grouped term ILD/pneumonitis. Given FDA had removed one death attributed to disease progression, the overall numbers of deaths due to AEs did not differ between the Applicant and FDA.

DL-01 Patient ID# (b) (6) – Applicant’s attribution: Malignant Neoplasm

45-year-old White female from (b) (6) had a diagnosis of HER2-overexpressing IHC3+ non-small cell lung cancer. The Applicant attributed the patient’s death to “malignant neoplasm” and FDA disagrees with this attribution. The patient had a history of treatment with immunotherapy and was a former smoker. During cycle 2 of T-DXd the patient experienced Grade 3 pneumonia, Grade 3 sepsis, and Grade 3 pneumothorax, which were all considered not related to T-DXd by the Investigator. On the same day, the patient was also diagnosed with Grade 3 empyema, considered an SAE as it required hospitalization. She subsequently experienced Grade 3 respiratory failure with a CT showing pleural fluid, consolidative changes in the left lung and extensive metastatic disease. The ILD Adjudication committee (AC) noted that the ground glass opacities were more widely spread. The cause of death was reported as complications of malignant neoplasm, but the patient had respiratory failure, hypoxia, empyema. The ILD AC reviewed the case and adjudicated the death to be due to ILD; FDA agrees with this adjudication. FDA classified this as a death that could have been due to the AE, ILD and not just “malignant neoplasm” as noted by the Applicant.

DB-01- (b) (6) - Applicant’s attribution: Acute respiratory failure

45-year-old White female from (b) (6) also noted to have acute respiratory failure and ILD but was reported as having death due to disease progression. Given the ILD was ongoing, and the patient had respiratory failure, FDA considers this to possibly be the underlying cause of death and that this could be considered a death due to an AE of ILD. FDA considered ILD to possibly be the underlying cause of death and respiratory failure and disagrees with the Applicant’s classification as this patient’s death due to acute respiratory failure alone. FDA included this as a death due to ILD/pneumonitis.

DB-01- (b) (6) - Applicant’s attribution: Lymphangitis

62-year-old White female from (b) (6) with lymphangitis who was noted to have death due to lymphangitis; however, review of the narratives reflected that the patient had ongoing ILD and that she died due to ILD. FDA would consider the cause of death to possibly be related to the AE of ILD and not just lymphangitis and disease progression as noted by the Applicant. FDA included this as a death due to the AE of ILD/pneumonitis.

DB-01- (b) (6) - Applicant’s attribution: Respiratory failure

33-year-old White female from (b) (6) was diagnosed with grade 1 pneumonitis, with dose interruption after a high-resolution CT showed nodular densities and she was diagnosed with pneumonitis. She was started on methylprednisolone and on study day 134, pneumonitis worsened to Grade 2; on day 137, she presented with grade 3 hypoxia, dyspnea, and grade 5

respiratory failure. Of note, chest x-ray showed frosted glass opacities which were considered to be consistent with interstitial pneumonitis. She received Bactrim, but pneumonitis persisted at the time of respiratory failure. A repeat high-resolution CT (HRCT) was noted to show worsening “pneumopathy”. The ILD AC agreed with investigators’ original report of Grade 1 but adjudicated the outcome of death as due to ILD. FDA agrees with this attribution and considers this death to be due to the pneumonitis, not only respiratory failure as noted by the Applicant.

DP-02, Patient ID# (b) (6) - Applicant’s attribution: Organizing pneumonia

This was a 65-year-old female (race/ethnicity not provided) with endometrial cancer from (b) (6). On study day 382, an event of special interest, “organizing pneumonia” was reported to the investigator. At onset, this was reported to be grade 3. On study day 389, 31 days after permanently discontinuing T-DXd, the patient died in comfort care. The primary cause of death was organizing pneumonia. This event of organizing pneumonia was adjudicated as ILD (drug-related). At onset, the CTCAE grade for the event as assessed by the adjudication committee was Grade 3; the maximum CTCAE Grade during the event as assessed by the AC was Grade 5. FDA does not disagree with the adjudication but considers this as a death due to the AESI, ILD/pneumonitis. The Applicant’s narratives reflected that this was a death due to the AE of organizing pneumonia though it was not included in Applicant – Table 23 as a death due to AE. FDA disagrees with this attribution and included this as a death due to the AE of organizing pneumonia which falls under the grouped term, ILD/pneumonitis.

The following narratives were reviewed for potential deaths due to ILD/pneumonitis

DP-02, Patient ID# (b) (6) - Applicant’s attribution: LV heart failure/Disease under investigation

72-year-old White female from (b) (6) with diagnosis of biliary tract cancer, with metastatic disease to adrenal gland, intrahepatic bile duct, liver, lung, peritoneum and pleural effusion at baseline. The patient’s death was attributed by the Applicant to disease under investigation (LV heart failure) and underlying cholangiocarcinoma. She had a significant history of aortic arteriosclerosis, diabetes, and hypertension. However, on study day 92 the patient had developed the SAE, pneumonitis. At onset, the event was CTCAE grade 2, the maximum grade during the event was grade 3. The patient was receiving 4.4 mg/kg of T-DXd at the time of the event. A CT scan showed multiple areas of frosted glass and consolidation appearing against a background of thickening of the interstitium with signs of drug-related pneumonitis. T-DXd was discontinued, and the event was adjudicated to be ILD. The patient was hospitalized for shortness of breath and had treatment with steroids without improvement or resolution. On study day 108, 39 days after permanently discontinuing T-DXd, the patient died.

An autopsy was not performed. The reporting investigator considered the death to be related to disease under investigation, left ventricular failure. FDA reviewed this narrative as the event of pneumonitis was ongoing at the time of the subject's death and this event of pneumonitis was adjudicated as ILD with the maximum CTCAE grade 5. However, the patient also had pleural effusion, and significant heart disease. FDA agrees that the patient's ILD/pneumonitis contributed to their death; however, there was uncertainty around his heart disease and underlying disease.

DP-02, Patient ID# (b) (6) - Applicant's attribution: Cardiopulmonary failure/Disease under investigation

71-year-old White male from (b) (6) enrolled in the rare tumor cohort with a salivary gland tumor who experienced on treatment death attributed by the Applicant to "disease under investigation" (pulmonary heart failure). The patient's relevant past medical history included deep vein thrombosis from and pulmonary embolism. The patient was diagnosed with pneumonitis and treatment with T-DXd was permanently discontinued as a result of that AE. The patient presented with a fever, grade 2 weakness and dyspnea, with no cough. This event of pneumonitis was adjudicated as ILD (drug-related). At onset, the CTCAE grade for the event as assessed by the AC was grade 1. On Study Day 713, 34 days after permanently discontinuing T-DXd, the patient experienced hypotension and asystole and was pronounced dead. There was no autopsy. The maximum grade during the event of ILD was noted by the AC to be grade 5; however, the patient's cause of death was reported as cardiopulmonary failure. The secondary cause of death was reported as ILD. The reporting investigator considered the death to be related to underlying cancer. Though FDA does not disagree that the patient experienced cardiopulmonary failure, FDA considers it a possibility that the patient's ongoing pneumonitis could have contributed and that this death could have been a death due to an AE of ILD/pneumonitis, not "disease under investigation". However, FDA did not include this as a death due to the AE of ILD as there was some question as to the cause of death being due to underlying cancer as noted by the investigator. In addition, the presentation with fever and no cough and the eventual death due to asystole and hypotension were not definitive for cause of death being due to ILD. Therefore, FDA did not disagree with the Applicant's attribution.

DP-02, Patient ID# (b) (6) - Applicant's attribution: Pneumonia

79-year-old Asian female from (b) (6) enrolled in the endometrial cancer cohort with metastatic disease to liver, lungs, pleural effusion and left pleural nodule. She developed a kidney infection and then pneumonia. On (b) (6) the patient had a CT abd/pelvis showing no bleeding, bilateral ureteritis, cystitis, stable disease, and possible bilateral organizing pneumonia was diagnosed. She was treated with methylprednisolone for 4 days as well as broad spectrum antibiotics. The patient tested negative for COVID. Though oxygen saturation was 96%

originally, she eventually required intubation. On study day 136, 30 days after permanently discontinuing T-DXd, the patient died. The AEs of pneumonia and kidney infection were ongoing, and the Applicant attributed cause of death to pneumonia. FDA does not disagree with the attribution of death due to pneumonia. However, this was diagnosed as an “organizing pneumonia”, FDA considered this to be under the grouped term of ILD/pneumonitis. The organizing pneumonia was ongoing at the time of the patient’s death. However, with the descriptions from the imaging studies there was bilateral pneumonia and only a possibility of organizing pneumonia that was not confirmed. This was not included as a case of adjudicated ILD/pneumonitis by the Applicant. FDA reviewed the case due to the possible diagnosis of organizing pneumonia which is included in the grouped term for ILD/pneumonitis; however, on review of the narrative, FDA agreed with the Applicant that this was likely a death due to pneumonia.

Serious Adverse Events

Data:

The proportion of patients who experienced serious TEAEs across the pooled studies is presented in Applicant – Table 26.

Applicant – Table 26: Serious TEAEs Reported in $\geq 1\%$ of Patients in the IHC 3+ T-DXd 5.4 mg/kg Pool, by Preferred Term

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Patients with any Serious TEAE	117 (33.7)	27 (39.7)	528 (29.3)	305 (38.4)
Sepsis	11 (3.2)	0	22 (1.2)	9 (1.1)
Pneumonia	9 (2.6)	2 (2.9)	40 (2.2)	23 (2.9)
Vomiting	9 (2.6)	2 (2.9)	30 (1.7)	13 (1.6)
Urinary tract infection	8 (2.3)	2 (2.9)	19 (1.1)	7 (0.9)
Abdominal pain	7 (2.0)	1 (1.5)	12 (0.7)	6 (0.8)
Nausea	7 (2.0)	3 (4.4)	22 (1.2)	14 (1.8)
Pneumonitis	7 (2.0)	2 (2.9)	31 (1.7)	30 (3.8)
Pleural effusion	6 (1.7)	0	16 (0.9)	3 (0.4)

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
COVID-19	5 (1.4)	1 (1.5)	24 (1.3)	2 (0.3)
Fatigue	5 (1.4)	0	12 (0.7)	6 (0.8)
Anaemia	4 (1.2)	0	23 (1.3)	14 (1.8)
Cellulitis	4 (1.2)	0	10 (0.6)	2 (0.3)
Dyspnoea	4 (1.2)	0	17 (0.9)	6 (0.8)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

SAEs with an onset or worsening 48 days (29 days for Study J101) or more after the last dose of study drug, if considered related to the study treatment, were also considered to be TEAEs. In Study DP-02, SAEs considered to be related to study drug with onset or worsening 48 days or more after the last dose of study drug are not considered TEAEs.

If a patient had multiple occurrences of the same serious PT, the patient was counted once for that serious PT. If a patient had multiple serious PTs, the patient was counted once for each of the different PTs.

TEAEs are sorted by descending frequency in the IHC 3+ T-DXd 5.4 mg/kg Pool.

The Applicant's Position:

The most common SAEs in the T-DXd arm were generally consistent with the prior experience with T-DXd and characteristic of the target population under study. The SAEs were manageable by dose modification and routine clinical practice.

The FDA's Assessment:

FDA conducted an independent analysis of SAEs for this sBLA and agrees with the Applicant that SAEs occurred in 34% of patients in the 4-Trial safety pool (N=347). FDA separately evaluated the 193 patients in the 3-Trial safety pool of patients from DP-02, DL-01, and DC-02 to determine if the 154 breast cancer patients from DB-01 were diminishing the rates of any emerging, new SAEs. In this smaller safety pool, 75 patients experienced SAEs (38%). Many of these SAEs were infectious-related (9 patients with sepsis, 8 with UTI, 6 with wound/skin/device-related infections, and 8 with pneumonia). The most common SAEs occurring ($\geq 3\%$) were pneumonitis (5.4%), fatigue (5.4%), abdominal pain (5.4%), vomiting (5.4%), COVID-19 (5.4%), sepsis (4.7%), pneumonia (4.1%). Other miscellaneous infection-related SAEs were reported in patients from the DP-02 trial (wound infection in 2 patients, and liver abscess in two patients). Both patients with liver abscess had biliary cancers and prior abdominal procedures. Two patients with wound infections had ovarian and endometrial cancers with concurrent small bowel obstruction as well as a history of surgical procedures including exploratory laparotomy or ileostomy. Though infection-related SAEs occurred in patients enrolling in the DP-02 trial, given the disparate groups of patients in this trial and the variety of

types of infection-related SAEs, FDA did not consider this to be a new safety risk associated with T-DXd. In general, FDA considered the SAEs in these three studies to be consistent with the rate and types of SAEs occurring in the larger safety pools for T-DXd and what has previously been reported.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs associated with study drug discontinuation are presented in Applicant – Table 27.

Applicant – Table 27: TEAEs Leading to Study Drug Discontinuation in at Least One Patients in the IHC 3+ T-DXd 5.4 mg/kg Pool, by PT (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Patients with any TEAE	52 (15.0)	12 (17.6)	304 (16.9)	176 (22.2)
Pneumonitis	25 (7.2)	5 (7.4)	103 (5.7)	61 (7.7)
Interstitial lung disease	8 (2.3)	2 (2.9)	63 (3.5)	36 (4.5)
Platelet count decreased	3 (0.9)	0	6 (0.3)	3 (0.4)
Organising pneumonia	2 (0.6)	0	5 (0.3)	2 (0.3)
Pneumonia	2 (0.6)	0	14 (0.8)	7 (0.9)
Acute hepatitis B	1 (0.3)	0	1 (0.1)	0
Alveolitis	1 (0.3)	0	1 (0.1)	0
Cardiac failure congestive	1 (0.3)	0	1 (0.1)	0
Diarrhoea	1 (0.3)	0	1 (0.1)	1 (0.1)
Dyspnoea	1 (0.3)	0	4 (0.2)	2 (0.3)
Gamma-glutamyltransferase increased	1 (0.3)	0	1 (0.1)	0
Liver abscess	1 (0.3)	0	1 (0.1)	0
Neuropathy peripheral	1 (0.3)	0	1 (0.1)	1 (0.1)
Neutrophil count decreased	1 (0.3)	0	4 (0.2)	0
Pancytopenia	1 (0.3)	0	1 (0.1)	0

MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Performance status decreased	1 (0.3)	0	1 (0.1)	0
Sepsis	1 (0.3)	0	3 (0.2)	2 (0.3)
Thrombocytopenia	1 (0.3)	0	3 (0.2)	2 (0.3)
Venoocclusive liver disease	1 (0.3)	0	1 (0.1)	0
White blood cell count decreased	1 (0.3)	0	1 (0.1)	1 (0.1)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

If a patient had multiple occurrences of the same PT, the patient was counted once for that PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

The Applicant's Position:

ILD/pneumonitis is an important identified risk associated with T-DXd. The protocols for all studies in the IHC 3+ T-DXd 5.4 mg/kg Pool stipulated that study drug was to be discontinued in patients who had ILD events of $\geq$ Grade 2 which is the main cause of the discontinuation rates.

The FDA's Assessment:

FDA conducted an independent analysis of TEAEs leading to discontinuation in the pooled 4-study safety population (N=347) and generally agrees with the findings presented by the Applicant in Applicant – **Table 27** that 15% of patients in the experienced drug discontinuation due to AEs. FDA also evaluated drug discontinuations in each of the DP-02, DL-01, and DC-02 trials to determine if there were distinct TEAEs leading to drug discontinuation in these three trials across tumor types (**Error! Reference source not found.**); in this analysis, ILD/pneumonitis was also the most common reason for drug discontinuation. FDA considered the term ILD/Pneumonitis as a grouped term (GT) that included the Preferred Terms (PTs) of ILD, pneumonitis, and organizing pneumonia. In Section 6 of the USPI, ILD/pneumonitis was noted as the reason for drug discontinuation in 10% of patients.

It was notable that several patients (2.1 %) had to discontinue treatment due to infection-related events (pneumonia, sepsis, and liver abscess) in the 3-trial safety pool (FDA - **Table 28**). However, this is a risk associated with myelosuppressive therapies and a risk experienced by many cancer patients undergoing treatment. FDA did not consider this to be a new safety signal associated with T-DXd, given the low incidence. Overall, the rate of TEAEs leading to

discontinuation of T-DXd across trials was low and FDA did not consider drug discontinuation to significantly limit the exposure to T-DXd.

FDA - Table 28: Analyses of TEAEs Leading to Drug Discontinuation Reported in $\geq 1\%$ of Patients Treated with T-DXd 5.4 mg/kg from DP-2, DL-01, and DC-02 Trials

	DP-02 N = 111 N (%)	DL-01 N = 17 N (%)	DC-02 N = 65 N (%)	Pooled analysis N=193 N (%)
TEAEs leading to drug discontinuation	16 (14)	2 (12)	5 (8)	23 (12)
Pneumonitis (GT)	12 (11)	1 (6)	4 (6)	17 (9)
Pneumonia (GT)	2 (1.8)	0 0	0 0	2 (1)
Liver abscess	1 (0.9)	0	0	1 (0.5)
Platelet count decreased	1 (0.9)	0	0	1 (0.5)
Sepsis	0	1 (6)	0	1 (0.5)
Pancytopenia	0	0	1 (1.5)	1 (0.5)

Group Pneumonitis (GT) includes PT terms pneumonitis, interstitial lung disease, organizing pneumonia

Group Pneumonia (GT) includes PT terms pneumonia, lower respiratory tract infection, pneumonia bacterial

Source: FDA analysis

Dose Interruption/Reduction Due to Adverse Effects

Data:

TEAEs associated with dose reduction are presented in Applicant – Table 29.

A total of 166 (47.8%) patients had TEAEs that led to study drug interruption, with neutrophil count decreased, neutropenia, anaemia, COVID-19, fatigue, white blood cell count decreased, interstitial lung disease, and upper respiratory tract infection reported in $\geq 2\%$ of patients. The investigator assessed the TEAEs leading to study drug interruption to be related to study drug in 109 (31.4%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool, and 546 (30.4%) patients in the All Tumor Types T-DXd 5.4 mg/kg Pool. The investigator assessed the TEAEs leading to study drug interruption to be related to study drug in 7 (10.3%) patients in Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg).

Applicant – Table 29: TEAEs Associated with Dose Reduction Reported in $\geq 1\%$ of Patients in the IHC 3+ T-DXd 5.4 mg/kg Pool, by PT (Safety Analysis Set)

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MedDRA Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Patients with any TEAE	95 (27.4)	15 (22.1)	411 (22.8)	240 (30.2)
Fatigue	20 (5.8)	3 (4.4)	59 (3.3)	45 (5.7)
Nausea	18 (5.2)	5 (7.4)	87 (4.8)	46 (5.8)
Neutrophil count decreased	12 (3.5)	4 (5.9)	43 (2.4)	48 (6.0)
Diarrhoea	8 (2.3)	1 (1.5)	27 (1.5)	11 (1.4)
Platelet count decreased	7 (2.0)	0	34 (1.9)	20 (2.5)
Vomiting	7 (2.0)	0	24 (1.3)	4 (0.5)
Asthenia	6 (1.7)	0	26 (1.4)	9 (1.1)
Neutropenia	6 (1.7)	0	24 (1.3)	3 (0.4)
Blood bilirubin increased	5 (1.4)	0	12 (0.7)	3 (0.4)
Pneumonitis	5 (1.4)	0	10 (0.6)	4 (0.5)
Anaemia	4 (1.2)	0	21 (1.2)	12 (1.5)
Febrile neutropenia	4 (1.2)	2 (2.9)	8 (0.4)	11 (1.4)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

If a patient had multiple occurrences of the same PT, the patient was counted once for that PT. If a patient had multiple PTs, the patient was counted in each of the different PTs.

TEAEs are sorted by descending frequency in the IHC 3+ T-DXd 5.4 mg/kg Pool.

The Applicant's Position:

Observed TEAEs associated with dose reduction or study drug interruption were manageable and were consistent with those previously observed with T-DXd.

The FDA's Assessment:

FDA conducted an independent analysis of dose reductions and interruptions in the 4-Trial safety pool. FDA agrees that 27% of patients experienced TEAEs leading to dose reductions, and 48% of patients experienced TEAEs leading to dose interruptions.

FDA also assessed dose reductions and interruptions in the 3-Trial safety pool of 193 patients and found similar rates of dose reductions due to TEAEs (28%) and dose interruptions due to TEAEs (52%).

The most common TEAEs in the 3-Trial safety pool leading to dose reduction were fatigue (7%), nausea (5%), decreased neutrophil count (5%), pneumonitis (2.3%), and diarrhea (2.3%). FDA

considered the terms neutrophil count decreased and neutropenia together as their clinical applicability would be similar. FDA determined that dose reductions and interruptions for the 3-Trial pool were generally consistent with what has been previously reported in trials of T-DXd, what was demonstrated in the large safety pool and the 4-Trial safety pool, and what is reported in the USPI.

Significant Adverse Events

Data:

The following Selected ADRs were observed in the IHC 3+ T-DXd 5.4 mg/kg Pool and are further described below:

- A total of 115 (33.1%) patients had a TEAE of anemia (grouped term), including 44 (12.7%) who had events of $\geq$ Grade 3.
- A total of 131 (37.8%) patients had a TEAE of neutropenia (grouped term), including 76 (21.9%) who had events of $\geq$ Grade 3.
- Six (1.7%) patients had a TEAE of febrile neutropenia, all of whom had events of $\geq$ Grade 3 and all of whom recovered.
- A total of 60 (17.3%) patients had a TEAE of leukopenia (grouped term), including 21 (6.1%) who had events of $\geq$ Grade 3.
- A total of 34 (9.8%) patients had a TEAE of lymphopenia (grouped term), including 15 (4.3%) who had events of $\geq$ Grade 3.
- A total of 82 (23.6%) patients had a TEAE of thrombocytopenia (grouped term), including 24 (6.9%) who had events of $\geq$ Grade 3.
- A total of 40 (11.5%) patients had a TEAE of hypokalemia (grouped term), including 15 (4.3%) who had events of $\geq$ Grade 3.
- A total of 109 (31.4%) patients had a TEAE of diarrhoea, including 15 (4.3%) with events of $\geq$ Grade 3.
- A total of 122 (35.2%) patients had a TEAE of vomiting, including 12 (3.5%) who had events of $\geq$ Grade 3.
- A total of 62 (17.9%) patients had a TEAE of transaminases increased (grouped term), including 8 (2.3%) who had events of $\geq$ Grade 3.

The Applicant's Position:

Most selected ADRs were of GI or hematologic in nature, which is expected with this class of drugs. The events were mainly Grade 1 or Grade 2 (with no Grade 5 events) and most events were manageable (including dose reduction and study drug interruption and routine clinical

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practice), with few patients discontinuing due to the event. The results observed in the IHC 3+ 5.4 mg/kg Pool were similar to those in the All Tumor Types 5.4 mg/kg.

The FDA's Assessment:

FDA generally agrees with the Applicant's list of TEAEs and that the majority of these adverse events were GI or hematologic in nature. FDA did not consider the management and resolution of these TEAEs in the overall assessment of safety given that the incidence of these TEAEs, especially those $\geq$ Grade 3, impact patients' tolerability of treatment regardless of intervention and possible resolution. FDA considered myelosuppression terms such as anemia in the context of laboratory abnormalities reported across trials rather than what was just reported in the ADAE dataset. In the pooled safety analysis of patients from DP-02, DL-01, DC-02, and DB-01, decreased white blood cell count occurred in 75%, decreased hemoglobin in 67%, decreased neutrophil count in 66%, and decreased lymphocyte count in 58% of patients. FDA did not consider it clinically meaningful to separately consider lymphopenia, leukopenia and considered cytopenias to be well-reported risks of T-DXd.

Refer to FDA assessment below for TEAEs and laboratory analysis for further details on FDA analyses and information included in the T-DXd USPI.

Treatment Emergent Adverse Events and Adverse ReactionsData:**TEAEs**

An overview of TEAEs is provided in Applicant – Table 30.

Applicant – Table 30 Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Treatment-emergent Adverse Events (TEAE)	342 (98.6)	68 (100)	1786 (99.3)	794 (100)
TEAE with CTCAE $\geq$ Grade 3 ^a	217 (62.5)	38 (55.9)	999 (55.5)	561 (70.7)
SAE	117 (33.7)	27 (39.7)	528 (29.3)	305 (38.4)

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	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) Pool (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
TEAE associated with an outcome of death	22 (6.3)	10 (14.7)	81 (4.5)	70 (8.8)
TEAE associated with study drug discontinuation	52 (15.0)	12 (17.6)	304 (16.9)	176 (22.2)
TEAE associated with study drug interruption	166 (47.8)	22 (32.4)	792 (44.0)	381 (48.0)
TEAE associated with dose reduction	95 (27.4)	15 (22.1)	411 (22.8)	240 (30.2)
Drug-related TEAE ^c	327 (94.2)	65 (95.6)	1712 (95.2)	770 (97.0)
Drug-related TEAE with CTCAE $\geq$ Grade 3 ^b	170 (49.0)	23 (33.8)	769 (42.7)	442 (55.7)
SAE	52 (15.0)	8 (11.8)	225 (12.5)	147 (18.5)
Drug-related TEAE associated with an outcome of death ^b	6 (1.7)	2 (2.9)	21 (1.2)	15 (1.9)
Drug-related TEAE associated with study drug discontinuation	49 (14.1)	8 (11.8)	253 (14.1)	133 (16.8)
Drug-related TEAE associated with study drug interruption	109 (31.4)	7 (10.3)	546 (30.4)	278 (35.0)
Drug-related TEAE associated with dose reduction	86 (24.8)	12 (17.6)	382 (21.2)	227 (28.6)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

^a A patient was counted once at the maximum severity.

^b If relationship was missing, the TEAE was considered to be related to the drug.

Adverse Drug Reactions

ADRs are presented for the intended dose (T-DXd 5.4 mg/kg) for the indication. Applicant – Table 31 presents all ADRs reported in $\geq 10\%$ of patients and Grade 3 or 4 ADRs reported in $\geq 2\%$ of patients in the IHC 3+ T-DXd 5.4 mg/kg Pool.

Applicant – Table 31 Common ADRs in the IHC 3+ T-DXd 5.4 mg/kg Pool and the All Tumor Types T-DXd 5.4 mg/kg Pool (Events Reported in $\geq 10\%$ of Patients or Events of Grade 3 or 4 Reported in $\geq 2\%$ of Patients), by MedDRA System Organ Class PT (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)		All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Blood and Lymphatic System Disorders				
Neutropenia	131 (37.8)	76 (21.9)	629 (35.0)	313 (17.4)
Anemia	115 (33.1)	44 (12.7)	640 (35.6)	193 (10.7)
Thrombocytopenia	82 (23.6)	24 (6.9)	437 (24.3)	99 (5.5)
Leukopenia	60 (17.3)	21 (6.1)	391 (21.7)	107 (5.9)
Lymphopenia	34 (9.8)	15 (4.3)	173 (9.6)	77 (4.3)
Gastrointestinal Disorders				
Nausea	240 (69.2)	23 (6.6)	1308 (72.7)	103 (5.7)
Vomiting	122 (35.2)	12 (3.5)	710 (39.5)	48 (2.7)
Diarrhoea	109 (31.4)	15 (4.3)	526 (29.2)	45 (2.5)
Constipation	97 (28.0)	2 (0.6)	584 (32.5)	10 (0.6)
Abdominal pain	63 (18.2)	7 (2.0)	351 (19.5)	20 (1.1)
Stomatitis	51 (14.7)	3 (0.9)	253 (14.1)	11 (0.6)
Dyspepsia	41 (11.8)	1 (0.3)	189 (10.5)	1 (0.1)
General Disorders and Administration Site Conditions				
Fatigue	206 (59.4)	35 (10.1)	1007 (56.0)	156 (8.7)
Pyrexia	37 (10.7)	0	230 (12.8)	9 (0.5)
Hepatobiliary Disorders				
Transaminases increased	62 (17.9)	8 (2.3)	435 (24.2)	58 (3.2)
Infections and Infestations				
Upper respiratory tract infection	69 (19.9)	0	296 (16.5)	3 (0.2)

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MedDRA System Organ Class Preferred Term	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)		All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Pneumonia	21 (6.1)	8 (2.3)	100 (5.6)	28 (1.6)
Metabolism and Nutrition Disorders				
Decreased appetite	118 (34.0)	9 (2.6)	577 (32.1)	36 (2.0)
Hypokalaemia	40 (11.5)	15 (4.3)	214 (11.9)	67 (3.7)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	65 (18.7)	1 (0.3)	433 (24.1)	15 (0.8)
Nervous System Disorders				
Headache	52 (15.0)	0	297 (16.5)	3 (0.2)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	57 (16.4)	0	243 (13.5)	2 (0.1)
Interstitial lung disease ^a	54 (15.6)	2 (0.6)	216 (12.0)	13 (0.7)
Dyspnoea	42 (12.1)	6 (1.7)	179 (9.9)	18 (1.0)
Skin and Subcutaneous Tissue Disorders				
Alopecia	117 (33.7)	1 (0.3)	616 (34.2)	3 (0.2)
Rash	36 (10.4)	2 (0.6)	157 (8.7)	2 (0.1)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

System organ classes are presented by alphabetic order. PTs are presented by descending frequency in the All Grades column of the IHC 3+ T-DXd 5.4 mg/kg Pool.

If a patient had multiple occurrences of the same ADR, the patient was counted once for that specific ADR. If a patient had multiple ADRs, the patient was counted in each of the different ADRs.

^a Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd.

The Applicant's Position:

The overall frequency and type of TEAEs and ADRs were consistent with the established safety profile of T-DXd. No new ADRs were identified on the basis of the available data.

The FDA's Assessment:

FDA conducted an independent analysis for common all grade and grade 3-4 TEAEs in the 4-Trial safety pool. FDA did not perform repeat analyses of the safety pool of patients treated with 6.4mg/kg of T-DXd as the results for those patients have been previously reviewed in other sBLAs for T-DXd.

The Applicant has used the term adverse drug reactions to refer to AEs that are included in USPI as associated with T-DXd, but FDA has not used this distinction during the review. A TEAE was defined as an AE that occurred, having been absent before the first dose of study drug, or worsened in severity or seriousness after initiating the study drug until the 47 days after the last dose of study drug and FDA would agree with this definition. FDA agrees with the Applicant's overview of TEAEs noted in FDA - Table 28. FDA did not separately classify TEAEs to be "drug-related" as FDA consider safety regardless of attribution. FDA analyses demonstrated slight differences in the rates of stomatitis, rash, edema, cough, and dyspnea that were likely due to differences in PTs included under those grouped terms. FDA concluded that 20% of patients experienced stomatitis (including stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption, tongue ulceration, cheilitis), 18% experienced cough, 12% dyspnea (including dyspnea, exertional dyspnea), and 11% edema (including edema peripheral, edema, localized edema, face edema, skin edema, periorbital edema, eyelid edema). FDA agreed with the Applicant's summary that most patients (63%) experienced $\geq$ grade 3 TEAEs and 34% experienced SAEs. The FDA's analysis of all-grade and grade 3-4 TEAEs is shown in FDA - Table 32 below and this information was also included in Section 6 of the T-DXd USPI.

In addition, FDA separately analyzed the TEAEs, particularly the rates of grade 3-4 TEAEs in the DP-02, DL-01, and DC-02 trials. Though patients in DP-02 had a higher rate of grade 3-4 TEAEs the majority were cytopenias. There were small differences in the rates of the individual grade 3-4 TEAEs of fatigue (12% vs. 10%), nausea (3.6% vs. 7%), and diarrhea (6% vs. 4.3%) for this trial compared to that seen in the larger safety pool, but FDA did not consider these differences to be significant enough to alter the conclusions of safety for T-DXd.

FDA - Table 32: Common Adverse Reactions ($\geq 10\%$ All Grades or $\geq 2\%$ Grades 3 or 4) in HER2-positive (IHC 3+) Patients Treated with ENHERTU in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Adverse Reactions	ENHERTU 5.4 mg/kg	
	N= 347	
	All Grades %	Grade 3 or 4 %
Gastrointestinal Disorders		
Nausea	69	7
Vomiting	35	3.5
Diarrhea	31	4.3

Adverse Reactions	ENHERTU 5.4 mg/kg	
	N= 347	
	All Grades %	Grade 3 or 4 %
Constipation	28	0.6
Stomatitis ^a	20	0.9
Abdominal pain ^b	18	2.0
Dyspepsia	12	0.3
General Disorders and Administration Site Conditions		
Fatigue ^c	59	10
Pyrexia	11	0
Edema ^d	11	0.6
Metabolism and Nutrition Disorders		
Decreased appetite	34	2.6
Skin and Subcutaneous Tissue Disorders		
Alopecia	34	0.3
Rash ^e	13	0.6
Infections and Infestations		
Upper respiratory tract infection ^f	20	0
Pneumonia	6	2.3
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^g	19	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough ^h	18	0
Interstitial lung disease ⁱ	16	0.6
Dyspnea ^j	12	1.7
Nervous System Disorders		
Headache ^k	15	0
Investigations		

Adverse Reactions	ENHERTU 5.4 mg/kg	
	N= 347	
	All Grades	Grade 3 or 4
	%	%
Decreased weight	10	0.3

^a Including stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption, tongue ulceration, cheilitis.

^b Including abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, gastrointestinal pain.

^c Including fatigue, asthenia, malaise, lethargy.

^d Including peripheral edema, edema, localized edema, face edema, skin edema, periorbital edema, eyelid edema

^e Including rash, pustular rash, maculo-papular rash, papular rash, macular rash, pruritic rash dermatitis acneiform, dermatitis, eczema, palmar-plantar erythrodysesthesia syndrome.

^f Including influenza, influenza-like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis.

^g Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, limb discomfort.

^h Including cough, productive cough, upper-airway cough syndrome

ⁱ Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, organizing pneumonia, respiratory failure, acute respiratory failure, alveolitis, lung opacity, lymphangitis, pneumonia, bacterial pneumonia, pulmonary fibrosis, and radiation pneumonitis. Grade 5 adjudicated drug-induced ILD events were pneumonitis, respiratory failure, acute respiratory failure, lymphangitis, pulmonary fibrosis.

^j Including dyspnea, exertional dyspnea

^k Including migraine, headache, sinus headache.

Source: FDA analysis

Laboratory Findings

Data:

Hematology: The majority of shifts from baseline in hematology parameters were of 1 grade (eg, normal to Grade 1 or Grade 1 to Grade 2), with the exception of neutrophil count, for which 162 (47.5%) patients had shifts of 2 grades or more (ie, baseline normal to Grade 2, Grade 3, Grade 4 or baseline Grade 1 to Grade 3, Grade 4), lymphocyte count decreased, for which 127 (38%) patients had shifts of 2 grades or more, white blood cell count decreased, for which 149 (43.3%) patients had shifts of 2 grades or more.

Clinical Chemistry: Overall, shifts in chemistry parameters of > 1 grade were observed infrequently and even fewer patients had shifts to values $\geq$ Grade 3. The most frequent shifts in blood chemistry parameters following treatment were in liver function tests.

Liver Function Tests: Overall, 8 (2.3%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had post-baseline LFT values that met the biochemical criteria for potential Hy's Law (ALT or AST $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN). No event was categorized as Hy's Law; in all 8 patients in the IHC 3+ T-DXd 5.4 mg/kg Pool, the events of potential Hy's Law were determined not to be

causally associated with study drug due to alternative etiologies at the time of occurrence of the events (ie, liver metastases, infection, cirrhosis, retrogastric infiltration, subhepatic and peri duodenal fluid effusion, vesicular lithiasis, and metallic prosthesis in bile duct, progressive disease, cholecystitis and hepatic steatosis with multiple liver metastases).

The Applicant's Position:

Clinical laboratory data were consistent with the known safety profile of T-DXd and with the background disease state. No cases of potential Hy's Law were confirmed to be Hy's Law. Most laboratory abnormalities were of Grade 1 or Grade 2 and no new safety concerns were identified.

The FDA's Assessment:

FDA independently analyzed laboratory abnormalities in patients in the 4-Trial safety pool (N=347) and agrees with the Applicant that the majority of these abnormalities were grade 1 or grade 2. FDA found that a significant percentage of patients experienced increased aspartate aminotransferase (45%) and increased alanine aminotransferase (44%); however, this was similar to rates reported previously from other trials of T-DXd. FDA agrees with the Applicant that the liver function abnormalities were not categorized as Hy's Law. FDA analyses demonstrated that 22% of patients had decreases in sodium, of which 2.6% were grade 3 or 4 which the Applicant did not initially include in their list of common laboratory findings but was added by FDA to the USPI.

FDA - Table 33 below shows the FDA's analysis of lab abnormalities which was also included in Section 6 of the T-DXd USPI.

FDA - Table 33: Selected Laboratory Abnormalities in HER2-positive (IHC 3+) Patients Treated with T-DXd 5.4 mg/kg in DBr-01, DP-02, DL-01, and DC-02

Laboratory Parameter	ENHERTU 5.4 mg/kg N= 347 ^a	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased white blood cell count	75	11
Decreased hemoglobin	67	10
Decreased neutrophil count	66	21
Decreased lymphocyte count	58	21

Laboratory Parameter	ENHERTU 5.4 mg/kg N= 347 ^a	
	All Grades %	Grades 3 or 4 %
Decreased platelet count	51	7
Chemistry		
Increased aspartate aminotransferase	45	1.5
Increased alanine aminotransferase	44	1.5
Increased blood alkaline phosphatase	36	1.2
Decreased blood potassium	29	6
Decreased sodium	22	2.9
Increased blood bilirubin	15	0.6
Increased blood creatinine	14	0.6

^aPercentages were calculated using the number of patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Source: FDA analysis

Vital Signs

Data:

The vital sign parameters included heart rate, systolic and diastolic BP, respiratory rate, temperature, and SpO₂. In general, no clinically meaningful vital sign results were found for patients in the IHC 3+ T-DXd 5.4 mg/kg Pool. 4 (1.2%) patients had post-baseline systolic BP values ≥ 180 mmHg with an increase from baseline of ≥ 20 mmHg; 35 (10.1%) patients had post-baseline systolic BP values of ≤ 90 mmHg with a decrease from baseline of ≥ 20 mmHg; 5 (1.4%) patients had post-baseline diastolic BP values ≥ 105 mmHg with an increase from baseline of ≥ 15 mmHg; 39 (11.2%) patients had post-baseline diastolic BP values of ≤ 50 mmHg with a decrease from baseline of ≥ 15 mmHg.

The Applicant's Position:

Results from vital signs, physical findings, and other observations related to safety were consistent with the known safety profile of T-DXd and with the background disease state. No new safety concerns were identified.

The FDA's Assessment:

FDA did not conduct an independent analysis of vital sign data from the pooled studies and believes that any clinically significant changes would be captured as TEAEs.

Electrocardiograms (ECGs)

Data:

The ECG parameters included heart rate, QT interval, and QTcF. If triplicate ECG readings were collected at any assessment time point, the average of the readings at that time point was used. If multiple ECG measurements were taken at baseline, the average of all baseline values was used as the baseline value. The data include all ECG assessments collected up to 47 days after the last dose of study drug (28 days after the last dose in Study J101).

The Applicant's Position:

There were no clinically meaningful changes from baseline in mean heart rate, QT interval, and QTcF. Results were similar between the IHC3 + T-DXd 5.4mg/kg Pool, DG-02 (IHC3 + T-DXd 6.4mg/kg) and the All Tumor Types T-DXd 5.4 mg/kg Pool.

The FDA's Assessment:

FDA generally agrees with the Applicant regarding ECG findings. FDA did not independently analyze ECG changes reported in the safety populations and believes that significant changes in ECG would likely be captured as SAEs or TEAEs, which were not noted.

QT

Data:

Four (1.2%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had a QTcF of > 500 ms during treatment with T-DXd. Among these 4 patients, 3 had TEAEs of electrocardiogram QT prolonged; 1 had a Grade 1, non-serious, drug-related event that resolved in 3 days, after study drug was interrupted; 1 had a Grade 3, non-serious, non-drug-related event that resolved in 21 days, with no change to study drug; 1 had a Grade 3, drug-related event that resolved in 2 days, with no change to study drug. Twelve (3.6%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had a change from baseline QTcF interval of > 60 ms. Among these 12 patients, 3 had TEAEs of electrocardiogram QT prolonged (2 patients had Grade 3 events and 1 patient had a Grade 1 event). Eleven (3.2%) patients in the IHC 3+ T-DXd 5.4 mg/kg Pool had a TEAE with a PT of electrocardiogram QT prolonged, including Grade 3 events in 3 (0.9%) patients. The remaining patients had Grade 1 (3 [0.9%]) or Grade 2 (5 [1.4%]) events.

The Applicant's Position:

There were no clinically meaningful changes from baseline in mean QT interval.

The FDA's Assessment:

FDA noted that 12 patients in the 4-study safety pool experienced the AE “electrocardiogram QT prolonged”. However, 11 patients were from the DB-01 trial, a trial which included QT prolongation in the AESIs for that trial. None of these events were >grade 3; a designated QT study (DS8201-A-J102) was previously analyzed and did not support an association of T-DXd with clinically relevant QT prolongation. FDA did not consider QT prolongation to be a new safety signal associated with T-DXd at this time.

ImmunogenicityData:

Immunogenicity was reported as part of pharmacology. See Section 6.3.1.

The Applicant's Position:

See Section 6.3.1.

The FDA's Assessment:

Refer to Sections 4.2, 6.1, 6.2, and 6.3 of this Assessment Aid for details of the FDA review of immunogenicity.

Analysis of Submission-Specific Safety Issues**8.2.5.1 Interstitial Lung Disease**

Data: Data on ILD adjudicated as drug-related ILD is presented in Applicant – Table 34.

Applicant – Table 34 Interstitial Lung Disease by Adjudicated Grade (Safety Analysis Set)

Adjudicated Outcome/ CTCAE Grade by Adjudication Committee	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Adjudicated as drug-related ILD				
Any Grade	54 (15.6)	7 (10.3)	216 (12.0)	133 (16.8)
Grade 1	12 (3.5)	2 (2.9)	55 (3.1)	35 (4.4)
Grade 2	32 (9.2)	3 (4.4)	130 (7.2)	69 (8.7)

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Adjudicated Outcome/ CTCAE Grade by Adjudication Committee	Number (%) of Patients			
	IHC 3+ T-DXd 5.4 mg/kg Pool (N = 347)	Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg) (N = 68)	All Tumor Types T-DXd 5.4 mg/kg Pool (N = 1799)	All Tumor Types T-DXd 6.4 mg/kg Pool (N = 794)
Grade 3	2 (0.6)	0	13 (0.7)	10 (1.3)
Grade 4	0	0	0	1 (0.1)
Grade 5	8 (2.3)	2 (2.9)	18 (1.0)	18 (2.3)
≥ Grade 3	10 (2.9)	2 (2.9)	31 (1.7)	29 (3.7)

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

At the time of the DCO, ILD adjudication was pending for 2 patients in Study DG-02 (IHC3+ T-DXd 6.4 mg/kg) (both Grade 1 per investigator); 1 patient in the All Tumor Types 5.4 mg/kg Pool (Grade 3); and 3 patients in the All Tumor Types 6.4 mg/kg Pool (all Grade 1).

The Applicant's Position:

ILD/pneumonitis is an important identified risk for T-DXd and has been closely monitored from the beginning of the clinical study program. A well-established safety evaluation process was followed with robust data collection and adjudication by the independent ILD AC, which ensured a comprehensive assessment of the ILD events and an adequate management plan for ongoing studies. ILD requires proactive monitoring, dose modification, and supportive care instituted in a timely fashion. Data from the T-DXd clinical program support a boxed warning in the label and instructions to patients through a medication guide for early intervention.

The FDA's Assessment:

FDA agrees with the Applicant's finding of 216 patients with any grade ILD in the large safety pool of 1799 patients. FDA also agrees with the Applicant that 17 patients (1%) patients experienced fatal/grade 5 pneumonitis and determined that 2 of these patients were from the DP-02 study as noted in FDA - Table 25.

When considering the smaller, 4-trial patient pool, FDA found 2 cases of adjudicated ILD grade 3-4 out of the total 347 patients. The patient from the DL-01 trial ID# (b) (6) was also flagged to have adjudicated ILD grade 3 but as noted in the narratives of death, this patient experienced grade 5 ILD, so the case was included as a potential fatality due to ILD.

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability Data:

No data on COA analyses are included in this submission.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees that there were no COA analyses submitted by the Applicant for this sBLA.

8.2.4. Safety Analyses by Demographic Subgroups

Data:

TEAEs were evaluated for the intrinsic factors of sex (male, female), age group < 65, ≥ 65, < 75, ≥ 75 years), race (Asian, White, Other), ECOG performance status (0, 1), renal function at baseline (normal function, mild impairment, moderate impairment), hepatic function at baseline (normal function, mild impairment), and for the extrinsic factors of country (Japan, non-Japan), and geographic region (Asia, Europe, North America and RoW).

Patients ≥ 75 years of age had a higher incidence of ≥ Grade 3 TEAEs (overall and drug-related), TEAEs associated with death, TEAEs associated with study drug interruption (overall and drug-related), TEAEs PTs of diarrhoea, and neutrophil count decreased. Patients from Japan generally reported a higher incidence of hematologic TEAEs and a higher incidence of adjudicated drug-related ILD (all ILD events in patients from Japan were of Grade 1 or Grade 2).

The Applicant's Position:

No clinically relevant differences in the safety profile of T-DXd were identified between demographic subgroups.

The FDA's Assessment:

FDA performed separate analyses of patients ≥ 65 years of age vs. <65 years. In the safety population of DP02, DL01, and DC02 (N=193), most patient deaths due to AEs were in older patients ≥65 years of age (N=10 out of 14). In addition, there was a higher percentage of SAEs (47% vs. 34%) in older patients, of which the majority were due to pneumonia (GT). FDA reviewed these cases of pneumonia and found there to be multiple confounding factors in these cases and considered the toxicities of pneumonia and other infections to be known risks of treatment with T-DXd. Several of these cases are reviewed above as they were patients with deaths due to AEs or possibly attributed to ILD (8.2.3). In general, FDA considered the rate of SAEs due to pneumonia to be complicated by many different factors and did not find this to be a new safety risk in older patients. FDA also analyzed rates of drug discontinuation due to TEAEs by age group; 17% of patients ≥65 vs. 14% of patients <65 years of age discontinued treatment due to TEAEs which FDA considered to be a small difference that could have been explained by chance. In general, FDA considered it likely that many factors contributed to these small

differences in TEAEs in older patients. FDA did not believe this required a change in labeling for the geriatric population in the USPI for T-DXd.

There were 18 patients (9%) in the 3-study safety pool that were $\geq$ age of 75. FDA did evaluate deaths due to AEs, TEAEs, and discontinuations in this age group but considered the number of patients in this age group to be too small to draw conclusions about safety.

FDA did not conduct independent analyses of safety for patients by country, race, and ECOG performance status as sample sizes were small. FDA reviewed the Applicant's analyses and agreed that the differences in safety did not change the benefit: risk for T-DXd in any of these subgroups.

8.2.5. Specific Safety Studies/Clinical Trials

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

In the IHC3+ 5.4 mg/kg pool, 8 (2.3%) patients reported in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) System Organ Class did not provide any evidence of tumor development and were mainly non-specific (Basal cell carcinoma, Cancer pain, Malignant pleural effusion, Metastases to skin, Neoplasm malignant, Lipoma, Tumour associated fever and Tumour pain).

The Applicant's Position:

TEAEs have been reported at a low frequency in the MedDRA System Organ Class of Neoplasms Benign, Malignant and Unspecified and do not provide evidence of tumor development. Although carcinogenicity studies have not been conducted, limited long-term data preclude definitive evaluation of carcinogenicity.

The FDA's Assessment:

FDA agrees that no human carcinogenicity studies were submitted as a part of this sBLA.

Human Reproduction and Pregnancy

Data: No new information is provided in this application.

The Applicant's Position: No new information is provided in this application.

The FDA's Assessment:

FDA agrees.

Pediatrics and Assessment of Effects on Growth

Data:

Not applicable.

The Applicant's Position:

The Sponsor is planning to evaluate the potential use of T-DXd in the pediatric population for HER2-expressing solid tumors as outlined in the agreed initial Pediatric Study Plan (iPSP).

The FDA's Assessment:

The Applicant submitted a partial waiver for the evaluation of T-DXd in patients ages 0<1 months old and a deferral to evaluate patients 1 month to <17 years of age, based on the results of several nonclinical studies. A PMR was issued; refer to the Postmarketing Requirements and Commitment section in this review for the language in this PMR.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

A PT of overdose was reported as a TEAE in 1 patient in the IHC 3+ 5.4 mg/kg Pool. No action was taken, and the event resolved the same day.

Drug abuse and dependence with T-DXd have not been studied; however, given the nature of T-DXd and its IV administration, drug abuse is not anticipated. No studies have been conducted that assess withdrawal or rebound effects of T-DXd.

The Applicant's Position:

In the event of overdose, subjects should be observed, and appropriate supportive care should be given, if required. Given the nature of T-DXd and its IV administration, no abuse or dependence

is anticipated. Given the disease being treated and the nature of T-DXd, no withdrawal or rebound effects are anticipated.

The FDA's Assessment:

FDA generally agrees with the Applicant.

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Cumulatively, since the first approval of T-DXd on 20 Dec 2019 through 19 Jun 2023, there were (b) (4) vials of T-DXd distributed from Marketing Authorization Holder warehouses worldwide. Based on the average body weight of adults in the countries where the product is marketed, it is estimated that (b) (4) infusions were administered. Considering that an infusion of T-DXd is administered Q3W (21-day cycle) and 17.3 cycles per year, the estimated cumulative patient exposure up through 19 Jun 2023 was (b) (4) patient-years. According to the cumulative summary tabulations of serious and non-serious adverse reactions from postmarketing data, 10426 AEs that met the Periodic Benefit Risk-Evaluation Report criteria were reported, of which the majority (7544) were non-serious.

The Applicant's Position:

Review of spontaneous postmarketing events did not reveal any new safety information that would impact the overall benefit-risk profile of T-DXd. The reported events were generally consistent with the known safety profile of T-DXd.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA will continue to monitor postmarketing data as for any new safety information.

8.2.7. Integrated Assessment of Safety

Data:

217 (62.5%) number of patients had Grade 3 or above AEs and 117 (33.7%) patients had SAEs. AEs leading to death occurred in 6.3%, however those considered related to treatment by the investigator was low (1.7%), and in line with that observed for other T-DXd advanced cancer populations (1.2% in the All Tumor Types T-DXd 5.4 mg/kg Pool). Whilst 15.0% patients treated with T-DXd were discontinued due to AEs, the majority were not considered to be treatment related by the investigator.

ILD remains an important identified risk of T-DXd. Adjudicated drug-related ILD cases were

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mostly Grade 1 or Grade 2, with events of Grade 3 in 0.6% of patients, and no Grade 4 events. Grade 5 events were reported in 2.3% of the IHC 3+ T-DXd 5.4 mg/kg Pool.

Neutropenia (including febrile neutropenia) remains an important identified risk for T-DXd. Events of neutropenia were reported in 37.8% of patients: 3.2% with Grade 1, 12.7% with Grade 2, 18.2% with Grade 3, and 3.7% with Grade 4 neutropenia in the IHC 3+ T-DXd 5.4 mg/kg Pool. Six (1.7%) patients had events of febrile neutropenia (all $\geq$ Grade 3), which were manageable through standard clinical practice.

LV dysfunction was reported in 2.9% of patients; 1.2% of patients had events of $\geq$ Grade 3. No fatal events were reported. The causal association between T-DXd and LV dysfunction has not been established.

No new safety signals were observed in the IHC 3+ T-DXd 5.4 mg/kg Pool or in Study DG-02 (IHC 3+ T-DXd 6.4 mg/kg).

The Applicant's Position:

T-DXd 5.4 mg/kg demonstrated an acceptable and generally manageable safety profile in the intended patient population. The most common TEAEs and $\geq$ Grade 3 TEAEs were mainly GI or hematologic, which is consistent with the established safety profile in the T-DXd clinical program. TEAEs were manageable through dose modification (dose interruption and/or dose reduction of T-DXd), specific management guidelines and routine clinical practice. No new safety signals were identified. ILD/pneumonitis is an important identified risk for T-DXd. Adjudicated drug-related ILD cases were mostly Grade 1 or Grade 2; fatal events (2.3%) were observed in the IHC 3+ 5.4 mg/kg Pool. The ILD events were generally manageable by following the established ILD management guidelines, with the majority of patients having an outcome of recovered, recovered with sequelae, or recovering.

The totality of the data demonstrates the compelling clinical benefit of T-DXd in IHC 3+ population compared to the currently accepted SoCs, along with an acceptable and generally manageable safety profile. Therefore, the overall benefit-risk assessment is favorable and supports approval of T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

The FDA's Assessment:

FDA agrees with the Applicant that the safety database, comprised of a large pool of 1799 patients as well as a safety pool of 4-trials (DP-02, DL-01, DC-02, and DB-01) supporting this sBLA were adequate to characterize the safety of T-DXd.

In the 4-Trial safety pool there were 347 patients in the safety population. FDA focused its review of safety on these patients from the 4 trials supporting this sBLA.

The most common ($\geq 20\%$) TEAEs across the 4 trials, including laboratory abnormalities, were decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection. This information is noted in the USPI for the IHC3+ population.

Evaluation of the 3-Trial safety pool without the breast cancer patients (N=193) did not reveal new safety signals. Generally, these rates of TEAEs were consistent with those previously reported in the USPI for T-DXd.

Serious AEs occurred in 34% of patients, the most common from infectious causes which is a known risk of treatment with T-DXd as well as many approved therapies in this later line treatment setting. In general, the rate of serious AEs was slightly higher than that reported in labeling for breast cancer indications but similar or lower than that reported in lung, gastric cancer patients. FDA considered these to be small differences likely attributable to distinctions in prior therapies, surgical procedures across tumor types and generally manageable with close monitoring and supportive care, as noted in the USPI. Serious AEs in $>1\%$ of patients who received T-DXd in the IHC3+ population were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea.

Fatalities due to AEs occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

As the Applicant noted, the most common cause of AE related fatalities was ILD/pneumonitis. ILD is an AESI for all trials of T-DXd included in this sBLA and is a known serious risk included as a boxed warning in the USPI. It was reassuring that the rates of ILD/pneumonitis were not higher in the 4-trial safety pool compared to the larger safety pool and the risk of ILD/pneumonitis were not higher in any one tumor type. T-DXd was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to AEs occurred in 48% of patients.

Another AESI, left ventricular (LV) dysfunction, was also evaluated across the 4 trials; a small percentage of patients (2.3%) experienced LV dysfunction, and the majority was low grade. Rates of LV dysfunction were consistent with what has been reported in the larger safety pool of 1799 patients. Cardiac imaging is recommended at baseline and at regular intervals for all patients treated with T-DXd.

Overall, the safety profile of T-DXd across tumor types was manageable through instructions in labeling, close monitoring, and supportive care and is acceptable for the patients across trials with HER2-positive (IHC3+) solid tumors.

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SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues identified with this application. However, the sample sizes for some tumor types were relatively small, especially for those in the cohort of rare tumors in DP-02, many of which included only one patient per tumor type. Therefore, the ORR results from those small samples need to be interpreted with caution. In addition, the duration of follow-up was limited across DP-02, DC-02 and DL-01, making the median DOR not estimable for multiple tumor types. To further characterize the efficacy of T-DXd in these tumor types, the FDA issued a PMR for additional patients to be enrolled in DP-02 and data on longer follow-up, and one PMC to conduct a pragmatic trial to the Applicant. Refer to Section 13 for further details.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The efficacy assessment of T-DXd is primarily based on results from the pooled population of 192 patients from trials DESTINY-PanTumor02 (DP-02, 111 patients), DESTINY-CRC02 (DC-02, 64 patients) and DESTINY-Lung01 (DL-01, 17 patients) with HER2-positive IHC 3+ advanced/metastatic solid tumors treated with T-DXd at 5.4mg intravenously every 3 weeks. DP-02 was a multicenter, multi-cohort, open-label trial that enrolled 267 adult patients with locally advanced, unresectable, or metastatic HER2-expressing (IHC 3+, IHC 2+, IHC1+) solid tumors that progressed following at least one prior systemic regimen in the advanced/metastatic setting or that had no satisfactory alternative treatment option. DC-02 was a multicenter, randomized, 2-arm trial that enrolled 120 patients with previously treated, unresectable or metastatic HER2-expressing (IHC 3+, or IHC 2+/ISH+) colorectal cancer (CRC). Unless contraindicated, patients must have received fluoropyrimidine, oxaliplatin and irinotecan. If clinically indicated, patients must have received anti-EGFR treatment, anti-VEGF treatment and anti-PDL1 therapy. DL-01 was a multicenter, open-label, 2-cohort trial that enrolled 181 patients with previously treated, unresectable or metastatic, HER2-expressing (IHC 3+, or IHC 2+) or HER2-mutant non-small cell lung cancer (NSCLC). Patients must have disease that relapsed from or be refractory to standard treatment or have no available standard treatment. HER2 positivity (IHC 3+) was assessed by either local or central assessment for Study DP-02 and by central assessment for studies DC-02 and DL-01.

All three trials excluded patients with a history of interstitial lung disease (ILD)/pneumonitis

requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Patients received T-DXd 5.4 mg/kg by intravenous infusion every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The major efficacy outcome measure in all three of the studies was confirmed objective response rate (ORR) and an additional efficacy outcome measure was duration of response (DOR). DP-02 assessed ORR by investigator while DC-02 and DL-01 assessed ORR by ICR. All outcomes were assessed by independent central review (ICR) based on RECIST v1.1 for the sBLA review.

This pooled population of 192 patients included 15 different tumor types [biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, and rare cancers (salivary, extramammary Paget's disease, vulvar, head and neck (lacrimal), lip and/or oral cavity cancer, esophageal (squamous and non-squamous), and oropharyngeal]. The median of prior systemic therapies (in any setting) was 3 (range 0-14) for this pooled population. Treatment with T-DXd in this pooled population of 192 patients resulted in a clinically meaningful ORR based on ICR (ORR: 50.0%; 95% CI: 42.7, 57.3) with a median DOR of 9.9 months (95% CI: 7.0, 19.4). In DP-02, ORR was 51.4% (95% CI: 41.7, 61.0) and median DOR was 19.4 months (range 1.3, 27.9+). In DL-01, ORR was 52.9% (95% CI: 27.8, 77.0) and median DOR was 6.9 months (range 4.0, 11.7+). In DC-02, ORR was 46.9% (95% CI: 34.3, 59.8), and DOR was 5.5 months (range 1.3+, 9.7+). Responses were seen across multiple tumor types when treated with T-DXd, except in pancreatic cancer. There were no observed responses in the 5 patients with IHC3+ pancreatic cancer. Furthermore, the number of responders of some tumor types is relatively small, and due to limited follow-up time, the median DOR was not estimable in several tumor types. Therefore, the Applicant has agreed to a post marketing requirement (PMR) to further characterize ORR and DOR across HER2-positive (IHC3+) tumor types by enrolling additional patients and to obtain longer follow up on the responding patients in DP-02, as well as a postmarketing commitment (PMC) to conduct a pragmatic trial that may further inform on T-DXd efficacy in various IHC3+ solid tumors.

A larger pooled analysis with the 192 patients from the primary efficacy cohort in combination with an additional 222 patients with HER2 positive (IHC 3+) advanced/metastatic breast cancer and gastric/GEJ cancer from Trials DESTINY-Breast01 (DB-01) and DESTINY-Gastric02 (DG-02) was considered supportive. Patients with HER2-positive (IHC 3+) advanced/metastatic breast cancer and gastric/GEJ cancer were not included in the primary efficacy cohort since T-DXd is already approved for these indications. In addition, the dose of T-DXd approved for the gastric/GEJ patient population is different (6.4 mg/kg). DESTINY-Breast01 was an open-label, single- arm trial of T-DXd that enrolled 253 patients with HER2-positive unresectable and/or metastatic breast cancer resistant or refractory to ado-trastuzumab emtansine (T-DM1). The 154 patients with HER2 positive (IHC 3+) disease treated with T-DXd at 5.4mg/kg were included in

the pooled analysis. DESTINY-Gastric02 was an open-label, single-arm trial of T-DXd that enrolled 79 patients with HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma that had progressed on or after a trastuzumab-containing regimen. The 68 patients with HER2 positive (IHC 3+) were included in the pooled analysis. All patients on DESTINY-Gastric02 were treated with T-DXd 6.4 mg/kg. This combined population of 414 patients included 17 different tumor types. The ORR by ICR remained consistent with an ORR of 54.1% (95% CI: 49.2, 59.0).

The safety assessment of T-DXd included a pooled population of 347 patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who received T-DXd 5.4 mg/kg in the DB-01, DP-02, DC-02 and DL-01 trials. The most common ($\geq 20\%$) TEAEs across the 4 trials, including laboratory abnormalities, were decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection. Fatalities due to AEs occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock. No new safety signals were noted in this sBLA review. The safety profile of T-DXd across tumor types was manageable through instructions in labeling, close monitoring, and supportive care and is acceptable for the patients across trials with HER2-positive (IHC3+) solid tumors.

The FDA review team concluded that for the HER2-positive (IHC3+) advanced and metastatic population, the benefit-risk assessment was favorable given the clinically meaningful ORR and DOR across trials and tumor types, and the toxicities are appropriately documented by mitigation strategies in the USPI. The indication for accelerated approval is:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

This accelerated approval represents the first FDA approved tissue agnostic therapy for patients with HER2-positive (IHC3+), unresectable or metastatic solid tumors in a late line setting after prior systemic therapy. An FDA-approved test for the detection of HER2-positive (IHC 3+) solid tumors for treatment with T-DXd is not currently available and a postmarketing commitment

(PMC) was issued by the FDA for development of a companion diagnostic.

X

X

X

X

Zhou Feng, PhD
Primary Statistical Reviewer

Xin Gao, PhD
Statistical Team Leader

X

X

X

X

Suparna Wedam, MD (Efficacy)

Asma Dilawari, MD (Safety)

Preeti Narayan, MD

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Primary Clinical Reviewer

Clinical Team Leader

APPEARS THIS
WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No Advisory Committee was convened for this application.

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ON ORIGINAL

10 Pediatrics

The Applicant's Position:

The Sponsor is planning to evaluate the potential use of T-DXd in the pediatric population for HER2-expressing solid tumors as outlined in the agreed initial Pediatric Study Plan (iPSP).

The FDA's Assessment:

No pediatric patients were included in the DP-02, DL-01, and DC-02 that were the primary studies used to evaluate efficacy in this sBLA. FDA agrees with the Applicant that the iPSP submitted related to this application plans to conduct nonclinical studies and a potential pediatric study. Refer to Section 13 of this Assessment Aid for the postmarketing requirement (PMR) issued for partial deferral of clinical trials in the pediatric population based on results of ongoing nonclinical studies.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
<u>Section</u>	<u>Applicant's Proposed Labeling</u>	<u>FDA's proposed Labeling</u>
Prescribing Information		
Highlights	Updated to reflect changes made to the Full Prescribing Information.	- Updated indications to include IHC information for clarity. - Added reference to accelerated approval for both NSCLC and IHC3+ indications to avoid redundancy in label. - Revised most common adverse reactions. - Updated recommended dosage to include IHC3+ solid tumors. - Updated full prescribing information contents to reflect new heading titles throughout USPI that clarify HER2 status.
1 Indications and Usage	Added new indication for (b) (4) Unresectable or Metastatic Solid Tumors	- Updated HER2-positive breast cancer indication to include IHC information. - Updated gastric cancer indication to include IHC information. - Revised HER2-positive (IHC3+) solid tumor indication to include prior systemic treatment and to revise "or" to "and" for no satisfactory alternative treatment options
2 Dosage and Administration 2.1 Patient Selection 2.2 Recommended Dosage and Schedules 2.3 Dosage Modifications	Updated to include Patient Selection and Dosing Recommendations for (b) (4) Unresectable or Metastatic Solid Tumors (IHC3+, 5.4 mg/kg)	- Updated headings for each indication in Section 2.1 to include HER2 status for consistency. - Added IHC3+ to solid tumors in dosing Table 1 in Section 2.3
2 Dosage and Administration 2.4 Preparation and Administration	Updated for clarification.	Added clarification to Section 2.4 Preparation and Administration for dilution and administration instructions.

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

5 Warnings and Precautions 5.1 ILD/Pneumonitis 5.2 Neutropenia 5.3 Left Ventricular Dysfunction	Updated the pooled safety information for patients treated with ENHERTU 5.4 mg/kg to include (b) (4) Unresectable or Metastatic Solid Tumors.	- Modified the term “hypokalemia” to “decreased blood potassium” throughout the USPI. - Modified heading in Section 5 to include HER2 status for clarity. - Updated pooled safety information to include 111 patients from DP-02 instead of (b) (4).
6.1 Clinical Trials Experience	Updated the introductory paragraph for patients treated with ENHERTU 5.4 mg/kg to include (b) (4) Solid Tumors Added new subsection for (b) (4) Unresectable or Metastatic Solid Tumors data (IHC3+, 5.4 mg/kg safety pool)	- Added toxicities impacting >10% of patients to the list of common adverse reactions in Table 13 of Section 6. This included “stomatitis” (20%), and edema (11%). - Added “decreased sodium” to Table 14, list of selected laboratory abnormalities as grade 3-4 decreases in sodium were experienced by 2.6% of patients. - Modified “(b) (4)” to “drug-induced” ILD in all safety table footnotes where applicable to be consistent with label practices.
8.5 Geriatric Use	Added new subsection for outcomes from the IHC3+, 5.4 mg/kg safety pool	Updated Section with efficacy population of 192 patients
12.2 Pharmacodynamics 12.3 Pharmacokinetics	(b) (4)	- Added exposure-response relationships subsection to Section 12.2 per clinical pharmacology labeling guidance. - Updated Section 12.3 across both 5.4 and 6.4mg/kg doses.
12.6 Immunogenicity	Added consolidated paragraphs for patients treated across approved dosage strengths (5.4 mg/kg and 6.4 mg/kg and by individual dosages strengths. Deleted study specific paragraphs.	Updated Section 12.6
14 Clinical Studies	Added efficacy information (b) (4) Unresectable or Metastatic Solid Tumors (IHC3+, 5.4 mg/kg) from DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02	- Modified Section 14.5 to streamline description of clinical studies to support efficacy. - Removed (b) (4) (b) (4) (b) (4) included information on patients enrolled with IHC3+ solid tumors.

		- Updated efficacy results to include DOR range. - Modified Table 24 to include actual response (partial or stable) for single patient tumor cohorts.
Medication Guide		
What is ENHERTU?	Added Other Solid Tumors indication.	Modified indication to align with USPI approved indication.
What are the possible side effects of ENHERTU?	Updated to include Other Solid Tumors. Removed the term “cough” since it no longer meets the threshold of most common based on the updated safety pool.	Updated to reflect changes to Section 5 and 6 of the USPI.

The Applicant’s Position:

Based on the results from the studies presented in Section 8, the Applicant proposes the significant changes described in the table above for the Enhertu Prescribing Information and Medication Guide.

The FDA’s Assessment:

Refer to FDA proposed labeling in Table above for the summary of USPI changes for this sBLA.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS recommended for T-DXd.

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13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following 2 postmarketing requirements (PMRs) and 2 postmarketing commitments (PMCs) were issued for this sBLA. The Applicant agreed to the following language and milestones:

PMR 4624-1: Complete Cohort A in Part 2 of the ongoing DESTINY-PanTumor02 trial intended to verify and describe the clinical benefit of Enhertu in adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options. Include a minimum of 40 patients across all tumor types, other than breast, colorectal, lung, and gastric/GEJ cancer, including a sufficient number of patients with and representation of HER2-positive (IHC3+) tumor types that require additional characterization. In order to characterize response rate and duration of response, patients should be followed for at least 12 months from the onset of response.

Final Protocol Submission: 11/2023

Trial Completion: 12/2026

Final Report Submission: 06/2027

PMR 4624-2: Conduct a clinical study of Enhertu to evaluate dosing, pharmacokinetics, safety, and efficacy of Enhertu in a sufficient number of pediatric patients ages 1 month to <17 years of age with unresectable or metastatic HER2-expressing solid tumors, that have progressed following prior treatment or who have no satisfactory alternative treatment options, deferred until results of completed or planned nonclinical in vitro and in vivo studies or available pediatric clinical data are submitted to and reviewed by FDA, and have been found to support a clinical investigation in the pediatric population.

Draft Protocol Submission: 03/2026

Final Protocol Submission: 06/2026

Study Completion: 06/2032

Final Report Submission: 12/2032

PMC 4624-3: Conduct a new pragmatic clinical trial with a sufficient number of patients to verify and describe the efficacy of Enhertu in adult patients with unresectable or metastatic

HER2-positive (IHC3+) solid tumors with disease that has progressed following prior treatment and have no satisfactory alternative treatment options. The trial should include a sufficient number of tumor types, other than breast, colorectal, lung, and gastric/GEJ cancer. In order to characterize response rate and duration of response, patients should be followed for at least 12 months from the onset of response.

Draft Protocol Submission: 10/2024

Final Protocol Submission: 02/2025

Trial Completion: 08/2028

Final Report Submission: 02/2029

PMC 4624-4: Commitment to submit appropriate analytical and clinical validation study data using the DESTINY-PanTumor02, DESTINY-CRC02, and DESTINY-Lung01 clinical trials, to support labeling of an immunohistochemistry-based in-vitro diagnostic device that is essential for the safe and effective use of Enhertu for treatment of adults with unresectable or metastatic HER2-positive (IHC3+) solid tumors.

Final Report Submission: 06/2026

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed? No
☐	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	X Yes ___ No
☐	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	___ Yes X No
☐	Other considerations (e.g.: PK/PD), if applicable:	___ Yes X No

14 Division Director (DHOT) (NME ONLY)

X

X

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15 Division Director (OCP)

X

X

APPEARS THIS WAY ON
ORIGINAL

16 Division Director (OB)

X

X

APPEARS THIS WAY
ON ORIGINAL

17 Division Director (Clinical)

X

X

Laleh Amiri-Kordestani

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ON ORIGINAL

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

X

Laleh Amiri-Kordestani

APPEARS THIS WAY
ON ORIGINAL

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:

No concerns were raised regarding the overall integrity of the study data.

Covered Clinical Study (Name and/or Number):* DESTINY-PanTumor02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>763</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>2</u>		

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>7</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* DESTINY-CRC02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>578</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>2</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* DESTINY-Lung01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>385</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>5</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* DESTINY-Breast01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>957</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>5</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>5</u>		

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)
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*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* DESTINY-Gastric02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>592</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>17</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

FDA agrees with the Applicant that there were no apparent financial conflicts that would have impacted the overall integrity of the study data for the five studies (DP-02, DC-02, DL-01, DB-01 and DG-02) listed in the table above.

Out of 763 investigators in DP-02, the Applicant was unable to provide financial disclosure for 11 investigators and the following 2 investigators had disclosable financial interests:

1. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) received a grant totaling \$239,983. This site was expected to enroll (b) (6) out of 735 patients in Study DP-02. The grant was for a PARP inhibitor patient preference study. The financial disclosure is likely to have minimal impact due to the low expected overall enrollment at the site and the fact that the grant was not related to drug development to T-DXd.
2. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) received a grant totaling \$314,465. This site was expected to enroll (b) (6) out of 735 patients in Study DP-02. Upon further follow up with (b) (6), he confirmed that the reference grant was not for a clinical study. The grant was to develop a patient-facing app to measure patient-reported symptoms. The financial disclosure is likely to have minimal impact due to the low expected overall enrollment at the site and the fact that the grant was not related to drug development to T-DXd.

Out of 578 investigators in DC-02, the Applicant was unable to provide financial disclosure for 2 investigators and no investigators had disclosable financial interests.

Out of 385 investigators in DL-01, the Applicant was unable to provide financial disclosure for 5 investigators and 1 investigator had the following disclosable financial interests:

1. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) reported payments made by AstraZeneca in the past 3 years for advisory sessions and speaker programs that totaled more than \$25,000. These payments were unrelated to the T-DXd program. (b) (6) reported the sum of \$87,025.09 from AstraZeneca. This site enrolled 3 patients in Study DL-01. Given the above-mentioned study design including central assessments and the low enrollment, it is unlikely the payments impacted the integrity of study results.

Out of 957 investigators in DB-01, the Applicant was unable to provide financial disclosure for 5 investigators and the following 5 investigators had disclosable financial interests:

2. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) received payment from Daiichi Sankyo to the institution for preclinical research for DS-8201a in the (b) (6) lab totaling \$240,000. This site enrolled 15 patients in Study DB-01. Given the above-mentioned study design including central assessments, it is unlikely the payments impacted the integrity of study results.
3. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) received significant payments of other sorts (SPOOS) payments from the Sponsor totaling \$50,596.12. Of the payments, \$49,915.14 was granted for joint research with the Sponsor and \$680.98 was for honoraria. This site enrolled 3 patients in Study DB-01. Given the above-mentioned study design including central assessments, it is unlikely the payments impacted the integrity of study results.
4. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) received SPOOS payments from the Sponsor totaling \$77,429.16 for honoraria. This site enrolled 7 patients in Study DB-01. Given the above-mentioned study design including central assessments, it is unlikely the payments impacted the integrity of study results.
5. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) has been contracted as the medical advisor of DS8201-A-J101 and serves on the DS- 8201a advisory board. He received SPOOS payments from the Sponsor totaling \$53,230.60 for consultation or honoraria including DS-8201a and other compounds of the Sponsor. This site enrolled 2 patients in Study DB-01. Given the above-mentioned study design including central assessments, it is unlikely the payments impacted the integrity of study results.
6. (b) (6) (sub-investigator, Site (b) (6)): (b) (6) received SPOOS payments from the Sponsor totaling \$115,765.40. Of the payments, \$111,563.50 was granted for an Investigator initiated study of DS-8201a and \$4201.9 was for honoraria. This site enrolled 9 patients in Study DB-01. Given the above-mentioned study design including central assessments, it is unlikely the payments impacted the integrity of study results.

Out of 592 investigators in DESTINY-GASTRIC02, the Applicant was unable to provide financial disclosure for 17 investigators and no investigators had disclosable financial interests.

19.3. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology data is not included in this submission.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

In general, the applicant's population PK and exposure response analyses on efficacy and safety are considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		- Update an established PopPK model for both T-DXd and DXd with data from DP-01 and DP02 - Assess the impact of potential covariates on the PK of T-DXd and DXd - Estimate individual post-hoc PK parameters for use in subsequent ER analyses - Compare exposures among subpopulations of interest
Study Included		J102, DB01, DB02, DB03, DB04, A103, DG-01, DG-02, DL01, DL02, J101, A104, DP-01, DP02, DC01, and DC02
Dose(s) Included		0.8, 1.6, 3.2, 5.4, 6.4, 7.4, and 8.0 mg/kg
Population Included		BC, gastric/GEJ cancer, NSCLC, CRC and other cancers
Population Characteristics (Applicant – Table 35, Applicant – Table 36)	General	Age median: 58.0 years Median body weight: 61.0 kg. Race and ethnicity: Asian: 47.8% (26.7% of Japanese ethnicity and 21.1% of non-Japanese ethnicity), White 43.5% African American 2.0%

		Remainder were of another race or race unknown
	Organ Impairment	Hepatic: 1768 (62.5%) Normal, 948 (33.5%) mild, 14 (0.5%) Moderate, 2 (0.1%) Severe, 97 (3.4%) unknown Renal: 1314 (46.4%) Normal, 918 (32.4%) mild, 346 (12.2%) Moderate, 7 (0.2%) Severe, 244 (8.6%) unknown
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		2829 subjects received IV doses of Enhertu, at target doses ranging from 0.8 to 8 mg/kg. 67884 samples were included in the population PK data set, of which 34016 were for the intact T-DXd antibody, and 33868 were for the DXd warhead. There was a total of 34279 dosing events.
Sampling Schedule	Rich Sampling	Refer to previous submission
	In ITT Population	Before and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; and 5 hours (± 2 hours) after the start of infusion on Cycle 1.
Covariates Evaluated	Static	CL _{T-DXd} : baseline tumor size, albumin, body weight, race-country, cancer type (GC, CRC); V _{1,T-DXd} : body weight, cancer type (GC, NSCLC,CRC), sex V _{2,T-DXd} : race-country DXd Final Model: CL _{DXd} : body weight, total bilirubin, aspartate aminotransferase (AST), itraconazole co-administration, ritonavir co-administration V _{DXd} : formulation, age, body surface area (BSA), cancer type and race-country
	Time-varying	No time varying covariates evaluated

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	NonMEM 7.5, using First Order Conditional Estimation with Interaction (FOCE-I). All analysis parent data sets were created using SAS System for Windows version 9.3 TS Level 1M0. All manipulations of parent datasets, data visualizations and model output diagnostics were processed using R 4.1.1.	Acceptable
Model Structure	A two-compartment model with linear elimination, and DXd was described by a one-compartment model, with time-varying release of drug from T-DXd. The structural model was consistent with previous analyses	Acceptable
Model Parameter Estimates	Applicant – Table 37	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	For T-DXd parameters the BSV %CV were 26%, 16%, 64% and 28% for CLT-DXd, V1,T-DXd, V2,T-DXd and QT-DXd, respectively For DXd parameters the BSV %CV were 31%, 48%, 29%, and 77% for CLDXd, VDXd, Krel, and FPC1, respectively	Acceptable
BLQ for Parameter Accuracy	PK observations BLQ were retained in the dataset and were flagged as missing. As less than 1% of post-dose observations were BLQ for both T-DXd and DXd, likelihood-based approaches were not	Acceptable

	necessary and were not used to handle BLQ observations.	
GOF, VPC	Applicant – , Applicant – Figure 4	Acceptable
Significant Covariates and Clinical Relevance	Applicant – Figure 5 to Applicant – Figure 17	Acceptable. Body weight shows significant impact on exposure and supports body weight-based dosing.
Analysis Based on Simulation (optional)		
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	(b) (4).	Given that tumor type is not a significant covariate, recommended recalculating PK parameters based on all patients who have received the recommended 5.4 mg/kg dosage instead of reporting PK parameters per indication. A subset pool based on patients dosed at 5.4mg/kg (n=1475) was generated with the following criteria: •

		For studies that have been included in the USPI supporting existing approved indications, the subset popPK population was kept the same. • For new studies included in the tissue agnostic submission, the subset popPK population is restricted to patients with HER2 IHC 3+ solid tumors (as per eligibility for DP-02).
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NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Table 35 Continuous Demographic Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
Baseline age (year)																	
Mean	58.3	55.9	54.9	56.5	55.8	62.8	58.4	60.8	59.1	58.9	58.4	54.2	53.9	55.9	64.2	60.1	57.6
(SD)	(11.5)	(10.5)	(8.74)	(12.0)	(11.8)	(11.0)	(11.4)	(10.9)	(11.6)	(11.9)	(12.7)	(12.0)	(11.1)	(10.6)	(10.3)	(12.2)	(11.8)
Median	58.0	56.0	54.5	57.0	56.0	65.0	58.5	62.0	60.5	60.0	59.0	54.0	54.0	57.0	66.5	62.0	58.0
[Min, Max]	[23.0, 83.0]	[31.0, 79.0]	[36.0, 69.0]	[31.0, 80.0]	[28.0, 96.0]	[29.0, 82.0]	[27.0, 79.0]	[29.0, 88.0]	[20.0, 77.0]	[27.0, 85.0]	[25.0, 83.0]	[22.0, 88.0]	[27.0, 83.0]	[31.0, 80.0]	[36.0, 84.0]	[23.0, 85.0]	[20.0, 96.0]
Baseline weight (kg)																	
Mean	59.8	52.7	60.4	59.2	61.3	57.4	66.4	67.0	75.7	63.3	65.6	63.2	62.8	63.0	64.1	67.6	63.3
(SD)	(14.9)	(7.84)	(5.76)	(12.9)	(13.8)	(11.8)	(16.5)	(14.8)	(15.4)	(14.8)	(14.0)	(13.8)	(14.0)	(13.3)	(15.2)	(16.7)	(14.7)
Median	58.1	51.5	60.0	55.8	59.4	57.0	61.7	64.6	75.8	60.9	64.4	61.0	59.3	61.2	62.1	65.0	61.0
[Min, Max]	[34.6, 125]	[38.9, 75.2]	[51.0, 68.0]	[41.3, 90.7]	[35.6, 121]	[27.3, 109]	[38.0, 111]	[39.7, 110]	[41.9, 121]	[40.0, 111]	[39.9, 107]	[35.3, 116]	[39.7, 121]	[36.5, 121]	[35.7, 125]	[35.4, 138]	[27.3, 138]
Baseline height (cm)																	
Mean	161	155	159	161	160	164	167	167	172	163	167	160	159	160	164	164	162
(SD)	(8.46)	(6.41)	(5.91)	(8.48)	(7.16)	(8.75)	(9.10)	(9.21)	(10.9)	(9.53)	(10.4)	(7.27)	(6.29)	(7.10)	(9.34)	(9.23)	(8.84)
Median	160	156	159	160	160	165	165	167	174	163	167	160	159	160	164	164	161 [136, 198]
[Min, Max]	[138, 189]	[140, 171]	[145, 168]	[143, 178]	[139, 182]	[141, 182]	[149, 188]	[149, 198]	[148, 193]	[137, 190]	[144, 198]	[136, 185]	[142, 179]	[139, 183]	[147, 188]	[145, 198]	

Applicant – Table 35 Continuous Demographic Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
Baseline Body Mass Index (kg/m²)																	
Mean	23.2	21.8	23.9	22.8	24.4	21.3	27.0	24.7	26.2	24.1	24.1	24.6	24.9	24.7	24.3	25.1	24.3
(SD)	(5.55)	(2.86)	(2.44)	(4.04)	(6.03)	(3.56)	(14.3)	(8.69)	(7.99)	(8.68)	(8.44)	(5.17)	(5.15)	(6.03)	(7.16)	(6.17)	(6.69)
Median	22.5	21.4	24.2	22.0	23.1	20.7	23.1	23.4	25.2	23.0	23.4	23.4	24.0	24.0	23.4	24.0	23.3
[Min, Max]	[14.1, 61.5]	[16.8, 29.4]	[18.7, 27.1]	[16.3, 31.8]	[14.6, 65.8]	[13.5, 36.4]	[14.0, 94.1]	[15.3, 97.5]	[16.5, 85.8]	[15.8, 113]	[15.8, 105]	[14.1, 48.8]	[15.5, 44.3]	[14.9, 97.3]	[12.8, 69.3]	[13.9, 55.7]	[12.8, 113]
Baseline Body Surface Area (m²)																	
Mean	1.62	1.50	1.62	1.61	1.63	1.61	1.73	1.75	1.88	1.67	1.73	1.65	1.64	1.65	1.69	1.73	1.67
(SD)	(0.207)	(0.121)	(0.0890)	(0.188)	(0.181)	(0.182)	(0.218)	(0.212)	(0.228)	(0.208)	(0.206)	(0.175)	(0.172)	(0.171)	(0.220)	(0.216)	(0.201)
Median	1.60	1.49	1.63	1.57	1.62	1.64	1.66	1.72	1.93	1.65	1.72	1.63	1.61	1.63	1.67	1.73	1.64
[Min, Max]	[1.22, 2.33]	[1.22, 1.82]	[1.48, 1.77]	[1.33, 2.01]	[1.25, 2.23]	[1.06, 2.21]	[1.28, 2.30]	[1.32, 2.38]	[1.36, 2.45]	[1.22, 2.19]	[1.33, 2.31]	[1.25, 2.27]	[1.32, 2.23]	[1.22, 2.20]	[1.25, 2.42]	[1.28, 2.38]	[1.06, 2.45]
Baseline Tumor Size (mm)																	
Mean	74.2	65.2	63.3	60.7	62.1	65.0	109	69.6	78.7	59.4	95.2	58.3	51.5	67.7	73.8	82.2	68.7
(SD)	(53.3)	(38.2)	(32.1)	(36.0)	(40.7)	(44.1)	(59.8)	(44.9)	(52.7)	(38.9)	(58.4)	(41.5)	(38.8)	(44.6)	(46.9)	(63.3)	(48.9)
Median	58.0	55.0	56.5	54.0	51.0	55.0	93.5	61.0	64.0	52.0	83.0	48.0	41.0	57.0	55.0	67.0	55.0
[Min, Max]	[11.0, 381]	[17.0, 230]	[23.0, 132]	[16.0, 189]	[10.0, 212]	[11.0, 294]	[20.0, 308]	[10.3, 254]	[11.0, 306]	[10.0, 200]	[10.0, 245]	[10.0, 227]	[10.0, 277]	[10.0, 263]	[11.9, 267]	[11.0, 440]	[10.0, 440]

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Table 36 Categorical Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
Sex																	
Male	63 (21.8%)	0 (0%)	0 (0%)	18 (45.0%)	0 (0%)	129 (75.9%)	46 (53.5%)	83 (45.9%)	57 (73.1%)	51 (34.5%)	64 (52.5%)	3 (0.7%)	1 (0.4%)	2 (0.5%)	40 (40.0%)	89 (33.3%)	646 (22.8%)
Female	226 (78.2%)	51 (100%)	12 (100%)	22 (55.0%)	253 (100%)	41 (24.1%)	40 (46.5%)	98 (54.1%)	21 (26.9%)	97 (65.5%)	58 (47.5%)	401 (99.3%)	256 (99.6%)	369 (99.5%)	60 (60.0%)	178 (66.7%)	2183 (77.2%)
Race																	
White	82 (28.4%)	0 (0%)	0 (0%)	0 (0%)	132 (52.2%)	0 (0%)	53 (61.6%)	102 (56.4%)	69 (88.5%)	27 (18.2%)	50 (41.0%)	256 (63.4%)	71 (27.6%)	175 (47.2%)	50 (50.0%)	163 (61.0%)	1230 (43.5%)
Black/African American	8 (2.8%)	0 (0%)	0 (0%)	0 (0%)	5 (2.0%)	0 (0%)	0 (0%)	7 (3.9%)	1 (1.3%)	2 (1.4%)	0 (0%)	10 (2.5%)	10 (3.9%)	6 (1.6%)	1 (1.0%)	6 (2.2%)	56 (2.0%)
Asian	191 (66.1%)	51 (100%)	12 (100%)	40 (100%)	104 (41.1%)	170 (100%)	27 (31.4%)	48 (26.5%)	3 (3.8%)	93 (62.8%)	66 (54.1%)	121 (30.0%)	149 (58.0%)	151 (40.7%)	38 (38.0%)	87 (32.6%)	1351 (47.8%)
American Indian/Alaska Native	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (0.2%)
Native Hawaiian/ Pacific Islander	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	4 (0.1%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (2.0%)	0 (0%)	4 (4.7%)	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	11 (11.0%)	5 (1.9%)	28 (1.0%)
Other	6 (2.1%)	0 (0%)	0 (0%)	0 (0%)	4 (1.6%)	0 (0%)	2 (2.3%)	23 (12.7%)	3 (3.8%)	26 (17.6%)	6 (4.9%)	15 (3.7%)	25 (9.7%)	38 (10.2%)	0 (0%)	6 (2.2%)	154 (5.4%)

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Table 36 Categorical Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
Japanese Ethnicity																	
Japanese	177 (61.2%)	51 (100%)	0 (0%)	31 (77.5%)	55 (21.7%)	135 (79.4%)	26 (30.2%)	38 (21.0%)	0 (0%)	52 (35.1%)	43 (35.2%)	45 (11.1%)	36 (14.0%)	56 (15.1%)	9 (9.0%)	0 (0%)	754 (26.7%)
Asian (Non-Japanese)	14 (4.8%)	0 (0%)	12 (100%)	9 (22.5%)	49 (19.4%)	35 (20.6%)	1 (1.2%)	10 (5.5%)	3 (3.8%)	41 (27.7%)	23 (18.9%)	76 (18.8%)	113 (44.0%)	95 (25.6%)	29 (29.0%)	87 (32.6%)	597 (21.1%)
Other	98 (33.9%)	0 (0%)	0 (0%)	0 (0%)	149 (58.9%)	0 (0%)	59 (68.6%)	133 (73.5%)	75 (96.2%)	55 (37.2%)	56 (45.9%)	283 (70.0%)	108 (42.0%)	220 (59.3%)	62 (62.0%)	180 (67.4%)	1478 (52.2%)
Tumor type																	
Breast	184 (63.7%)	51 (100%)	12 (100%)	17 (42.5%)	253 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	404 (100%)	257 (100%)	0 (0%)	0 (0%)	0 (0%)	1178 (41.6%)
Gastric	40 (13.8%)	0 (0%)	0 (0%)	1 (2.5%)	0 (0%)	147 (86.5%)	0 (0%)	0 (0%)	78 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	266 (9.4%)
Lung	18 (6.2%)	0 (0%)	0 (0%)	6 (15.0%)	0 (0%)	0 (0%)	0 (0%)	181 (100%)	0 (0%)	148 (100%)	0 (0%)	0 (0%)	0 (0%)	371 (100%)	0 (0%)	0 (0%)	724 (25.6%)
Colorectal	20 (6.9%)	0 (0%)	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	86 (100%)	0 (0%)	0 (0%)	0 (0%)	122 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	229 (8.1%)
Other	27 (9.3%)	0 (0%)	0 (0%)	15 (37.5%)	0 (0%)	23 (13.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	100 (100%)	267 (100%)	432 (15.3%)
Renal Impairment Status																	
Normal	126 (43.6%)	23 (45.1%)	5 (41.7%)	19 (47.5%)	122 (48.2%)	49 (28.8%)	41 (47.7%)	64 (35.4%)	31 (39.7%)	50 (33.8%)	62 (50.8%)	240 (59.4%)	130 (50.6%)	201 (54.2%)	32 (32.0%)	119 (44.6%)	1314 (46.4%)
Mild	120 (41.5%)	0 (0%)	7 (58.3%)	21 (52.5%)	95 (37.5%)	0 (0%)	34 (39.5%)	73 (40.3%)	25 (32.1%)	67 (45.3%)	51 (41.8%)	129 (31.9%)	92 (35.8%)	123 (33.2%)	44 (44.0%)	37 (13.9%)	918 (32.4%)

185

Version date: August 2023 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Table 36 Categorical Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
Moderate	42 (14.5%)	28 (54.9%)	0 (0%)	0 (0%)	35 (13.8%)	0 (0%)	11 (12.8%)	42 (23.2%)	8 (10.3%)	28 (18.9%)	9 (7.4%)	35 (8.7%)	30 (11.7%)	41 (11.1%)	23 (23.0%)	14 (5.2%)	346 (12.2%)
Severe	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.3%)	0 (0%)	2 (0.7%)	7 (0.2%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	121 (71.2%)	0 (0%)	0 (0%)	14 (17.9%)	3 (2.0%)	0 (0%)	0 (0%)	4 (1.6%)	5 (1.3%)	1 (1.0%)	95 (35.6%)	244 (8.6%)
Hepatic Impairment Status																	
Normal	171 (59.2%)	26 (51.0%)	9 (75.0%)	30 (75.0%)	144 (56.9%)	117 (68.8%)	0 (0%)	165 (91.2%)	63 (80.8%)	115 (77.7%)	69 (56.6%)	191 (47.3%)	208 (80.9%)	170 (45.8%)	77 (77.0%)	213 (79.8%)	1768 (62.5%)
Mild	118 (40.8%)	25 (49.0%)	3 (25.0%)	10 (25.0%)	105 (41.5%)	52 (30.6%)	0 (0%)	16 (8.8%)	14 (17.9%)	33 (22.3%)	52 (42.6%)	208 (51.5%)	49 (19.1%)	194 (52.3%)	22 (22.0%)	47 (17.6%)	948 (33.5%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)	3 (0.8%)	1 (1.0%)	6 (2.2%)	14 (0.5%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	2 (0.1%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.2%)	1 (0.6%)	86 (100%)	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)	2 (0.5%)	0 (0%)	4 (1.1%)	0 (0%)	0 (0%)	97 (3.4%)
ECOG Status																	
0	180 (62.3%)	31 (60.8%)	3 (25.0%)	21 (52.5%)	146 (57.7%)	83 (48.8%)	54 (62.8%)	42 (23.2%)	28 (35.9%)	47 (31.8%)	72 (59.0%)	226 (55.9%)	152 (59.1%)	199 (53.6%)	43 (43.0%)	126 (47.2%)	1453 (51.4%)
1	109 (37.7%)	20 (39.2%)	9 (75.0%)	19 (47.5%)	106 (41.9%)	87 (51.2%)	31 (36.0%)	139 (76.8%)	50 (64.1%)	101 (68.2%)	50 (41.0%)	177 (43.8%)	105 (40.9%)	172 (46.4%)	56 (56.0%)	140 (52.4%)	1371 (48.5%)

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Table 36 Categorical Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	1 (1.0%)	1 (0.4%)	5 (0.2%)
IHC Class																	
0	30 (10.4%)	12 (23.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	37 (37.0%)	30 (11.2%)	109 (3.9%)
1	67 (23.2%)	22 (43.1%)	0 (0%)	7 (17.5%)	2 (0.8%)	22 (12.9%)	18 (20.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	214 (57.7%)	6 (6.0%)	25 (9.4%)	383 (13.5%)
2	61 (21.1%)	9 (17.6%)	1 (8.3%)	11 (27.5%)	38 (15.0%)	49 (28.8%)	28 (32.6%)	63 (34.8%)	10 (12.8%)	0 (0%)	24 (19.7%)	80 (19.8%)	25 (9.7%)	157 (42.3%)	20 (20.0%)	125 (46.8%)	701 (24.8%)
3	99 (34.3%)	4 (7.8%)	11 (91.7%)	18 (45.0%)	213 (84.2%)	97 (57.1%)	40 (46.5%)	27 (14.9%)	67 (85.9%)	0 (0%)	98 (80.3%)	324 (80.2%)	231 (89.9%)	0 (0%)	10 (10.0%)	75 (28.1%)	1314 (46.4%)
Unknown	32 (11.1%)	4 (7.8%)	0 (0%)	4 (10.0%)	0 (0%)	2 (1.2%)	0 (0%)	91 (50.3%)	1 (1.3%)	148 (100%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	27 (27.0%)	12 (4.5%)	322 (11.4%)
HER2-status																	
Negative	68 (23.5%)	47 (92.2%)	0 (0%)	0 (0%)	2 (0.8%)	27 (15.9%)	29 (33.7%)	3 (1.7%)	0 (0%)	0 (0%)	5 (4.1%)	6 (1.5%)	0 (0%)	370 (99.7%)	48 (48.0%)	145 (54.3%)	750 (26.5%)
Positive	186 (64.4%)	4 (7.8%)	0 (0%)	0 (0%)	251 (99.2%)	124 (72.9%)	57 (66.3%)	0 (0%)	77 (98.7%)	0 (0%)	69 (56.6%)	398 (98.5%)	231 (89.9%)	0 (0%)	14 (14.0%)	78 (29.2%)	1489 (52.6%)
Mutant	11 (3.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	91 (50.3%)	0 (0%)	148 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	250 (8.8%)
Over expressing	7 (2.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	41 (22.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	48 (1.7%)

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Table 36 Categorical Covariates at Baseline

	J101 (N=289)	J102 (N=51)	A103 (N=12)	A104 (N=40)	U201 (N=253)	J202 (N=170)	J203 (N=86)	U204 (N=181)	U205 (N=78)	U206 (N=148)	U207 (N=122)	U301 (N=404)	U302 (N=257)	U303 (N=371)	DP01 (N=100)	DP02 (N=267)	Overall (N=2829)
Unknown	17 (5.9%)	0 (0%)	12 (100%)	40 (100%)	0 (0%)	19 (11.2%)	0 (0%)	46 (25.4%)	1 (1.3%)	0 (0%)	48 (39.3%)	0 (0%)	26 (10.1%)	1 (0.3%)	38 (38.0%)	44 (16.5%)	292 (10.3%)

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Applicant – Table 37 **Final Model**

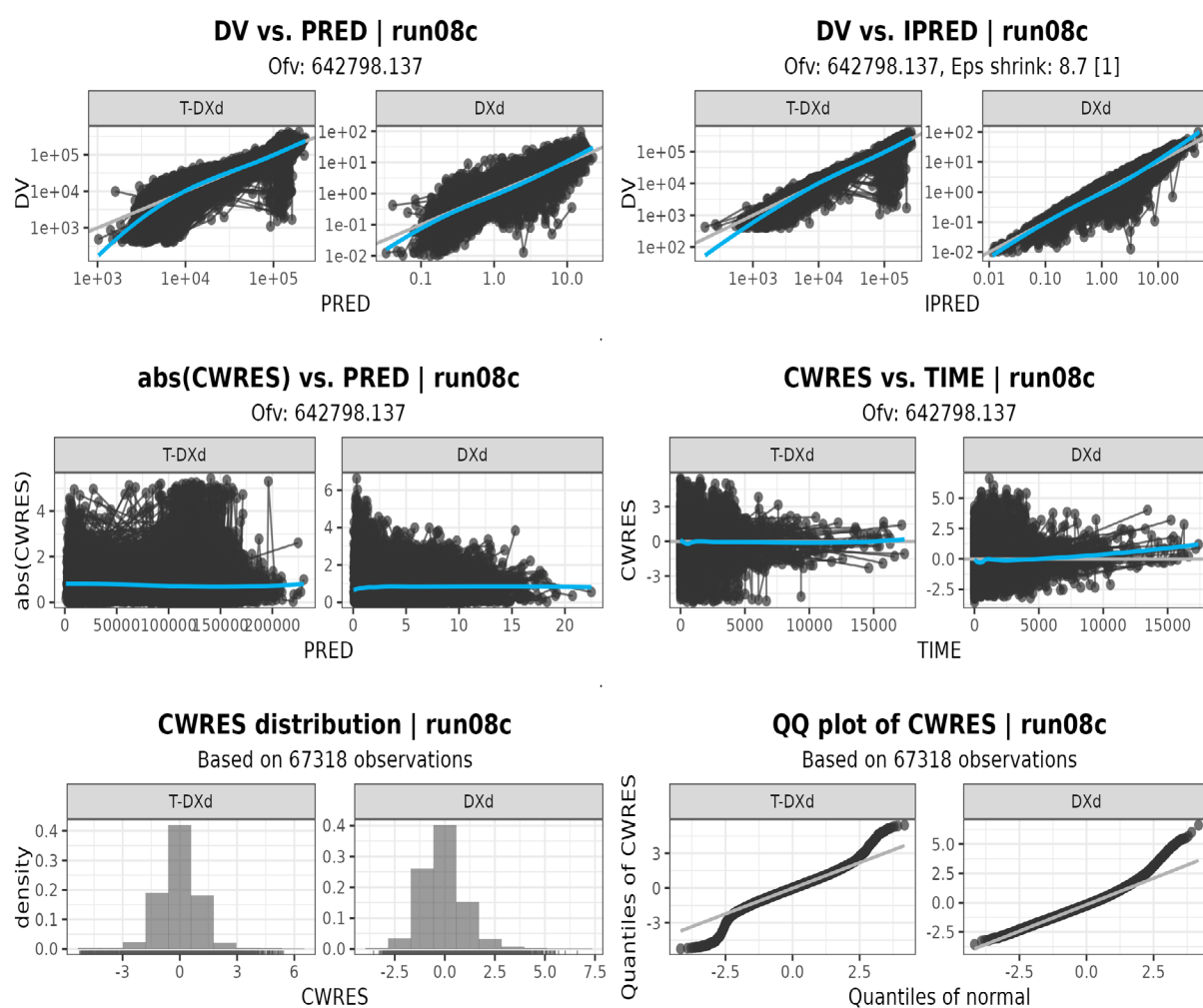
LABEL	VALUE	SE	RSE	FIXED
CL(TH1)	18.9	-	-	TRUE
V1(TH2)	2881	-	-	TRUE
Q(TH3)	8.04	-	-	TRUE
V2(TH4)	5852	-	-	TRUE
SIGPROP(TH5)	0.172	-	-	TRUE
SIGADD(TH6)	1020	-	-	TRUE
7CLBALB1	-0.478	-	-	TRUE
8 CLJGRP1	-0.0965	-	-	TRUE
9 CLSEX1	0	-	-	TRUE
10 CLBTSBL	0.0667	-	-	TRUE
11 CLBWT1	0.424	-	-	TRUE
12 V1SEX1	0.112	-	-	TRUE
13 V1BWT1	0.462	-	-	TRUE
14 V2JGRP1	-0.187	-	-	TRUE
15 CLPOP1 GC	0.12230	-	-	TRUE
16 CLPOP2 NSCLC	0	-	-	TRUE
17 CLPOP2 CRC	0.156	-	-	TRUE
18 VPOP1 GC	0.0783	-	-	TRUE
19 VPOP2 NSCLC	-0.0646	-	-	TRUE
20 VPOP4 CRC	0.0256	-	-	TRUE
CLPAY(TH21)	17.9	0.413	0.0230	FALSE
KREL(TH22)	0.0164	0.00034	0.0209	FALSE
FPC1 deconjugation fraction at CYCLE>1(TH23)	0.719	0.00572	0.0079	FALSE
FPC2 deconjugation fraction power cycle effect(TH24)	-0.141	0.00379	0.0269	FALSE
PSIGPROP(TH25)	-0.308	0.000922	0.00300	FALSE
PSIGADD(TH26)	0	-	-	TRUE

Applicant – Table 37 Final Model

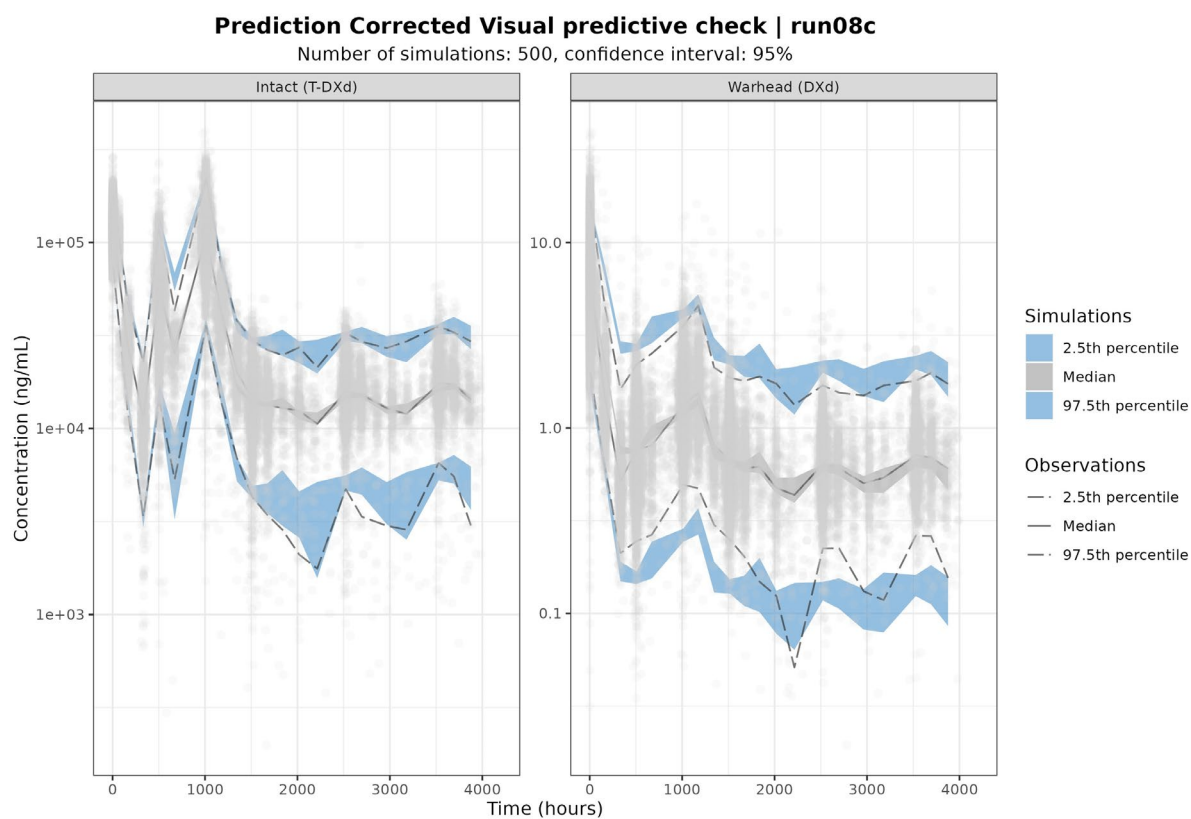
LABEL	VALUE	SE	RSE	FIXED
RITONVR effect on CLPAY(TH27)	-0.118	0.0175	0.149	FALSE
ITRACNZL effect on CLPAY(TH28)	-0.110	0.021	0.196300	FALSE
CLPAYAST1(TH29)	-0.186	0.0168	0.090170	FALSE
CLPAYTBIL1(TH30)	-0.15150	0.0157	0.103	FALSE
CLPAYWGTB1(TH31)	0.305	0.0396	0.129	FALSE
V3AGE1(TH32)	0.505	0.0513	0.102	FALSE
V3FORM1(TH33)	0.338	0.0521	0.154	FALSE
V3FORM2(TH34)	0	-	-	TRUE
GC V3PAYPOPTYP(TH35)	0	-	-	TRUE
NSCLC V3PAYPOPTYP (TH36)	-0.382	0.0197	0.0514	FALSE
CRC V3PAYPOPTYP (TH37)	-0.127	0.0487	0.393	FALSE
Others V3PAYPOPTYP (TH38)	-0.222	0.0303	0.137	FALSE
GC CLPAYPOPTYP(TH39)	-0.108	0.0255	0.236	FALSE
NSCLC CLPAYPOPTYP (TH40)	-0.233	0.0185	0.0795	FALSE
CRC CLPAYPOPTYP (TH41)	-0.232	0.0259	0.111	FALSE
Others CLPAYPOPTYP (TH42)	-0.283	0.0205	0.072	FALSE
V3Asian non-Jap (TH41)	0	-	-	TRUE
V3non-Asian (TH42)	-0.144	0.0199	0.138	FALSE
IIV_CL	0.255	-	-	TRUE
CL_V1_correlation	0.549	-	-	TRUE
IIV_V1	0.156	-	-	TRUE
IIV_Q	0.292	-	-	TRUE
IIV_V2	0.652	-	-	TRUE

Applicant – Table 37 Final Model

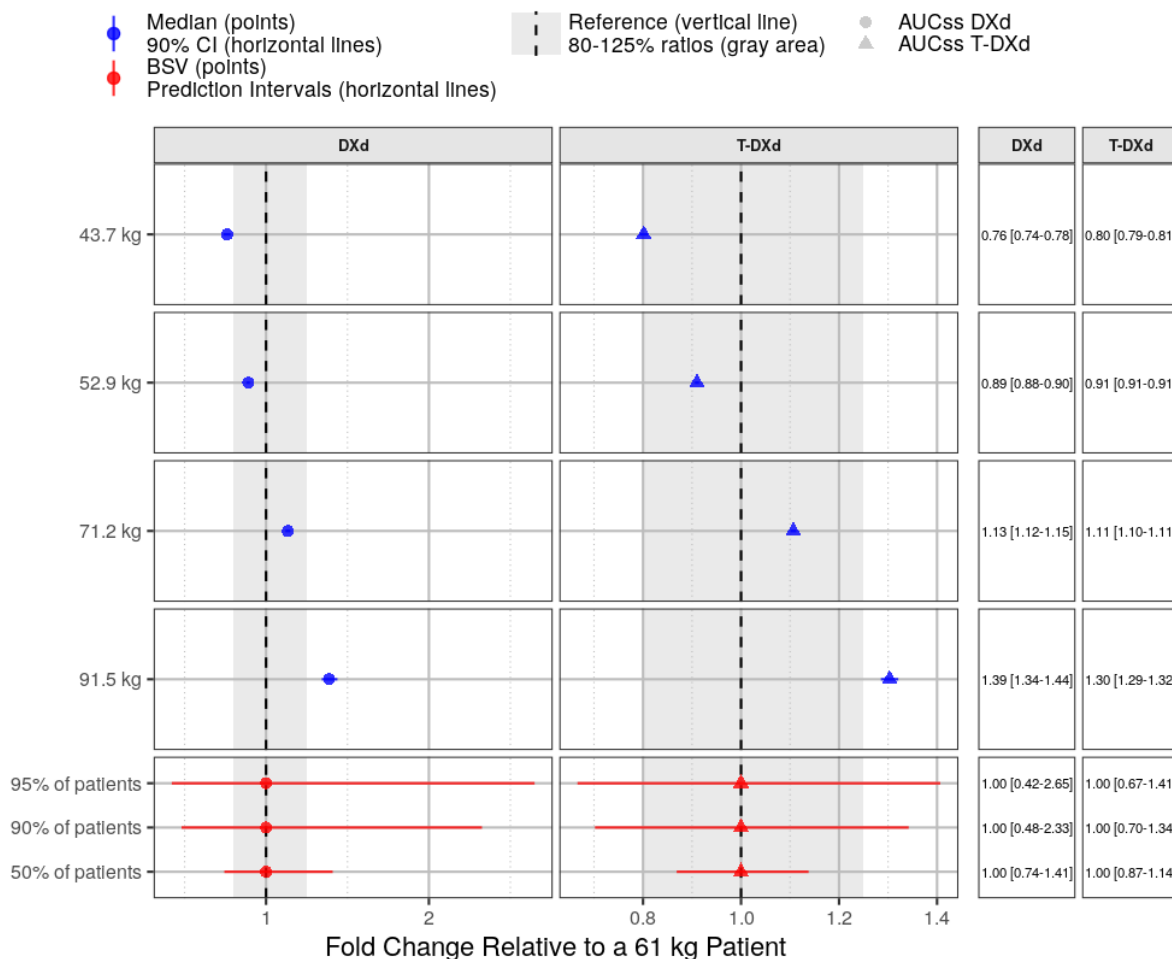
LABEL	VALUE	SE	RSE	FIXED
IIV_CLPAY	0.313	0.0090	0.0289	FALSE
IIV_V3	0.483	0.0091	0.0188	FALSE
IIV_KREL	0.298	0.0100	0.0335	FALSE
IIV_FPC1	0.769	0.0227	0.0295	FALSE

Applicant – Figure 3 Goodness-of-fit Plots for the Final Population PK Model

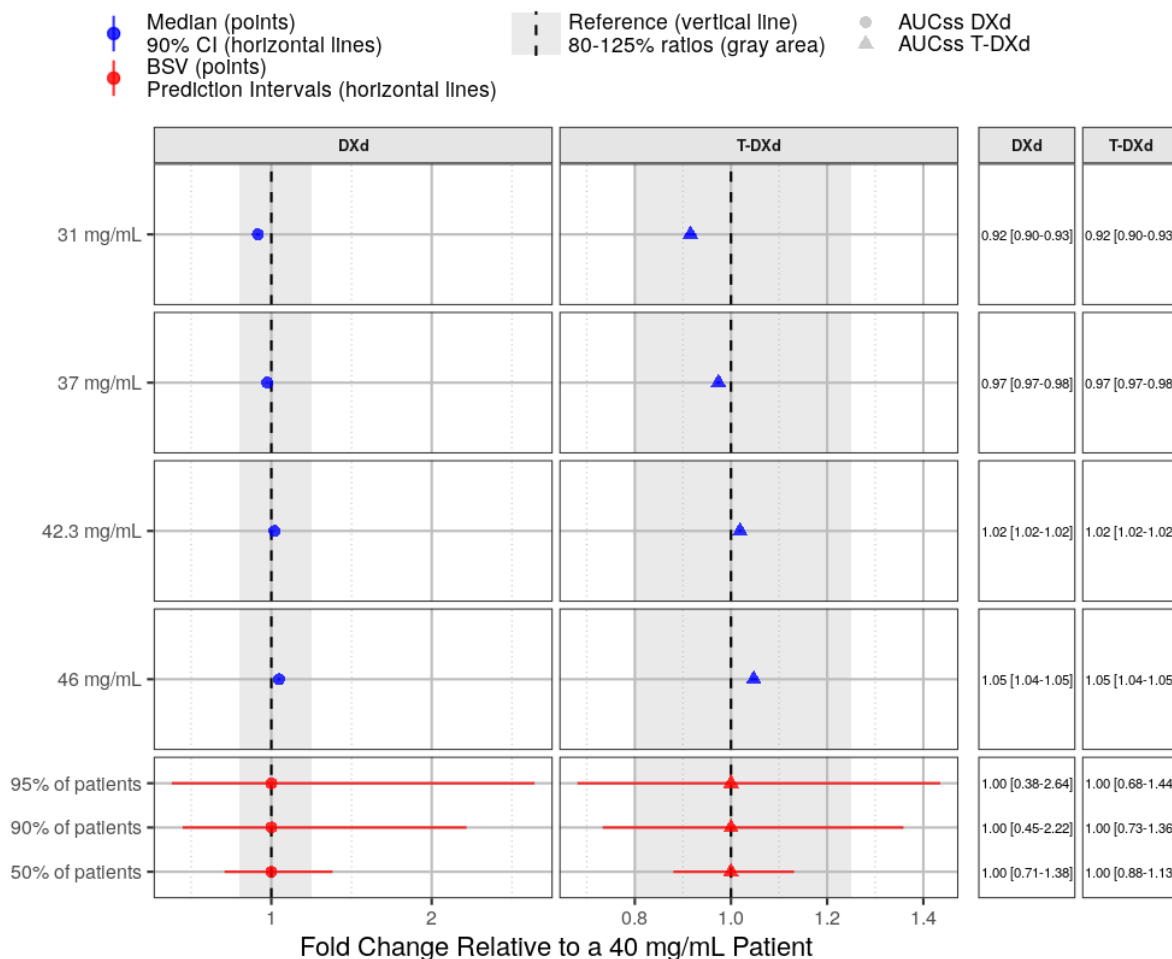
Applicant – Figure 4 VPC of Final Population PK Model, Stratified by Dose



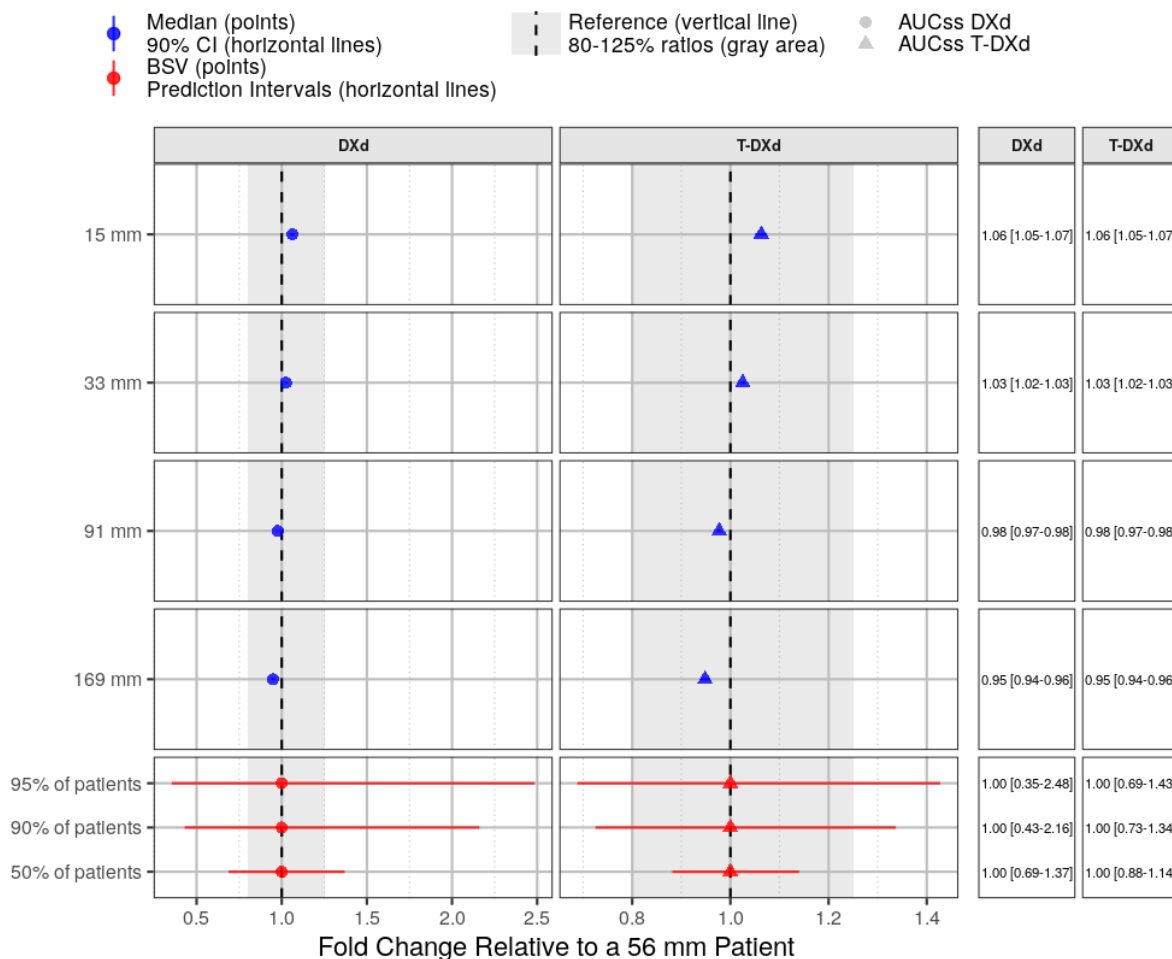
Applicant – Figure 5 Impact of Body Weight on Exposure to T-DXd and DXd



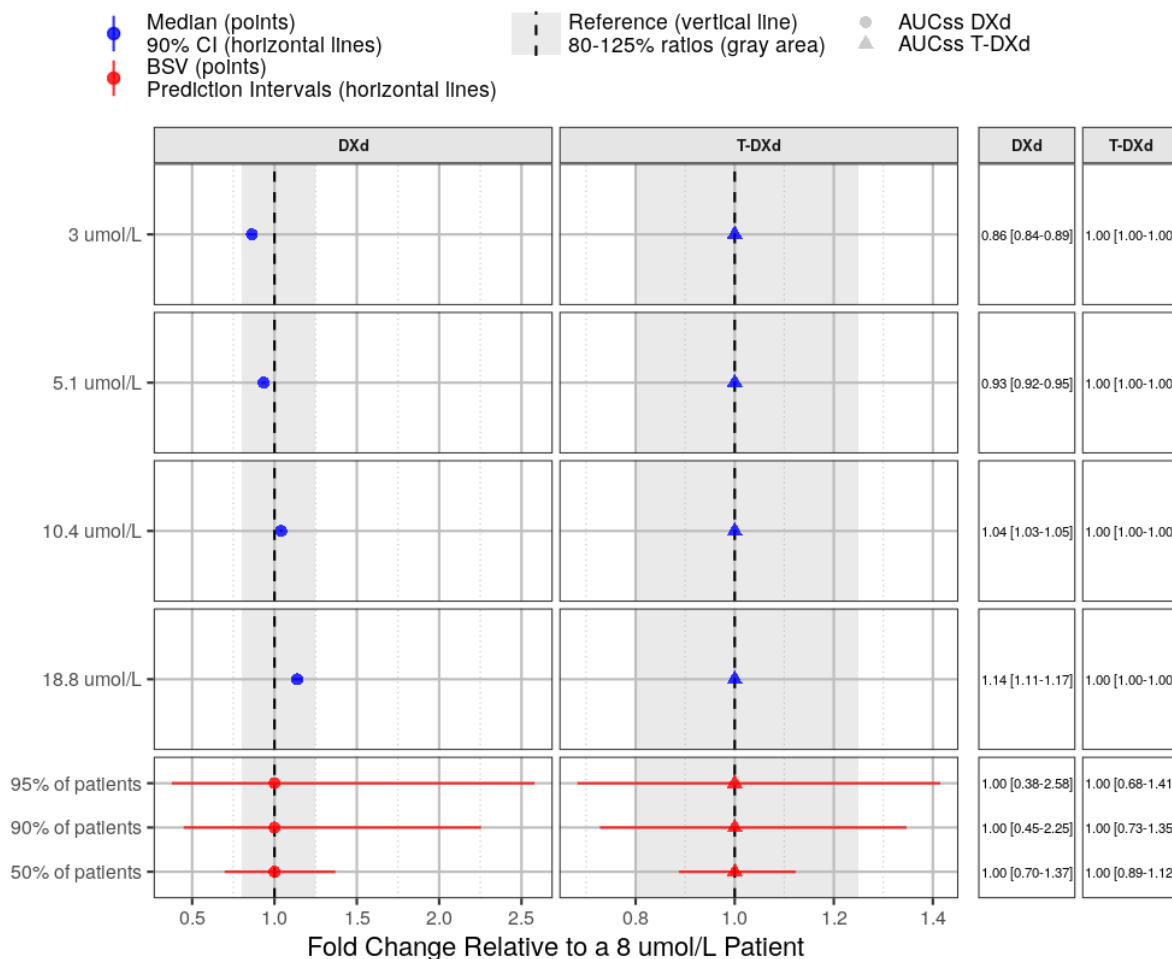
Applicant – Figure 6 Impact of Albumin Level on Exposure to T-DXd and DXd



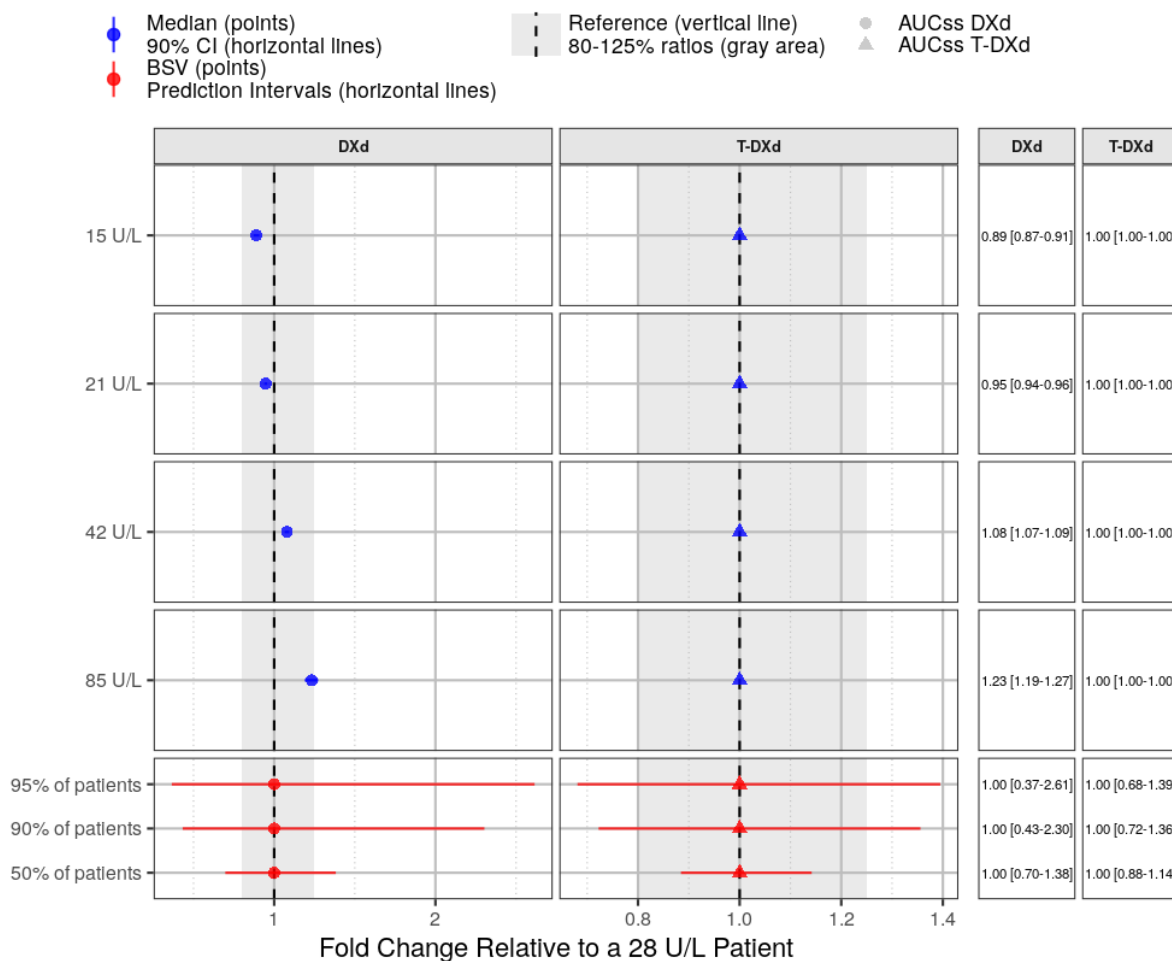
Applicant – Figure 7 Impact of Baseline Tumor Size on Exposure to T-DXd and DXd



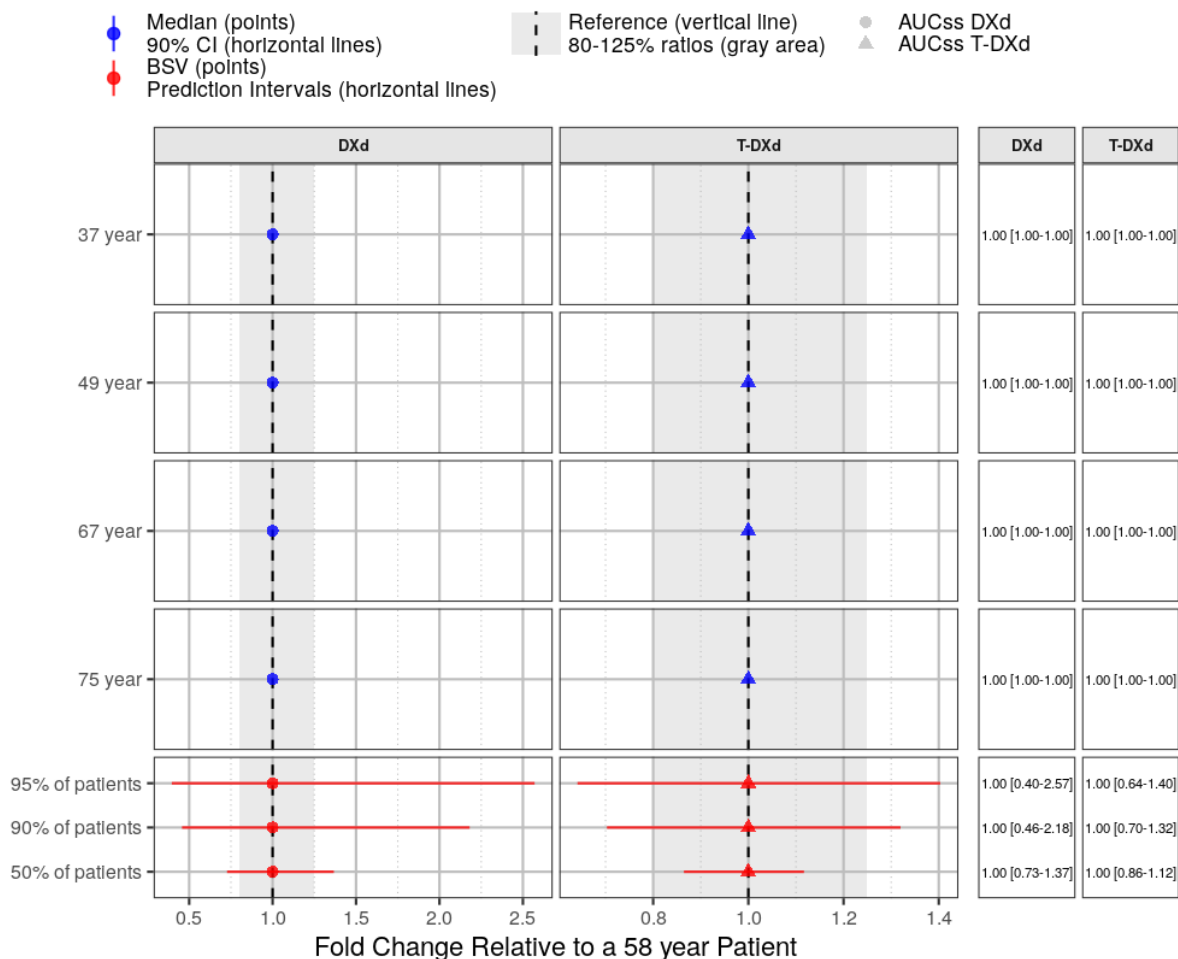
Applicant – Figure 8 Impact of Baseline Bilirubin Level on Exposure to T-DXd and DXd



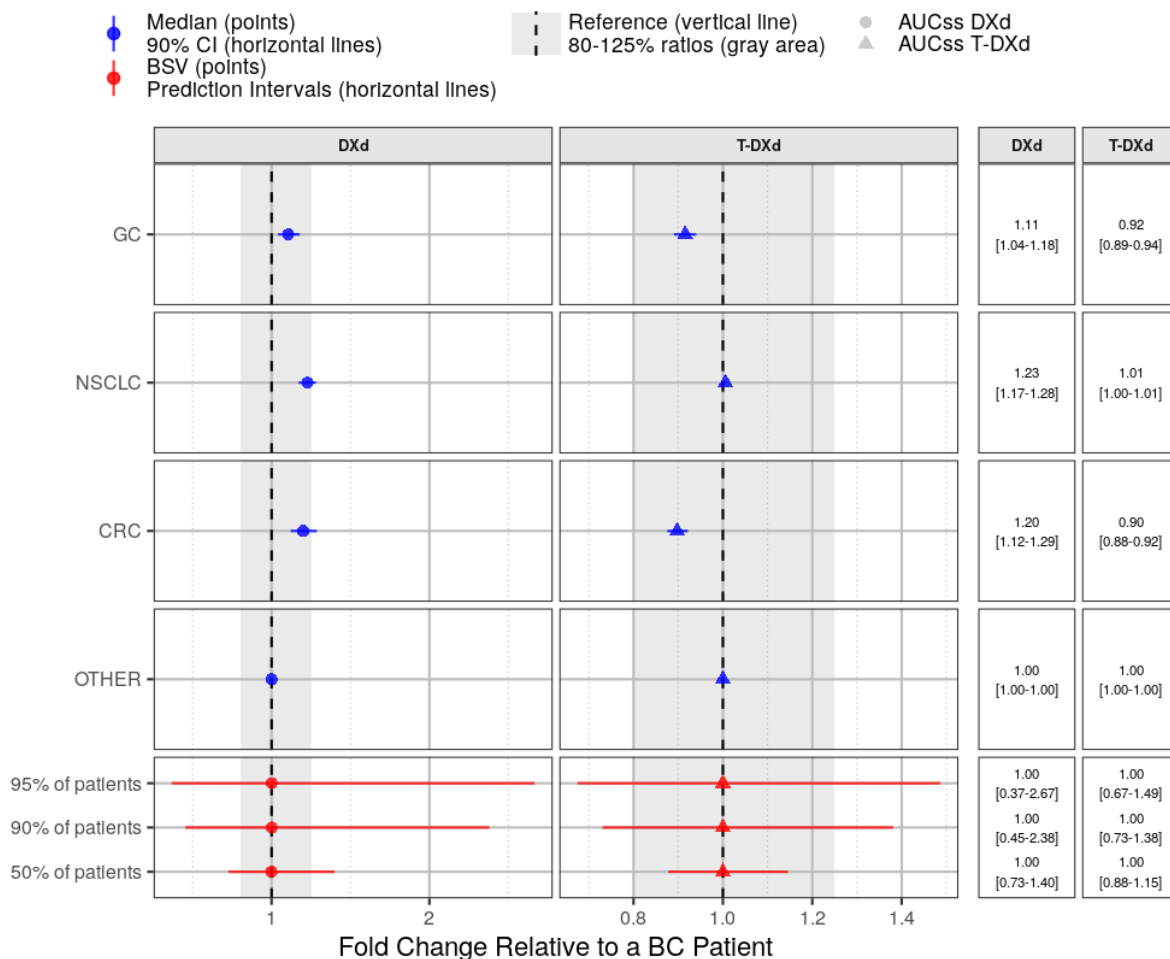
Trastuzumab deruxtecan (T-DXd, DS-8201a)

Applicant – Figure 9 Impact of Baseline Aspartate Transferase Level on Exposure to T-DXd and DXd

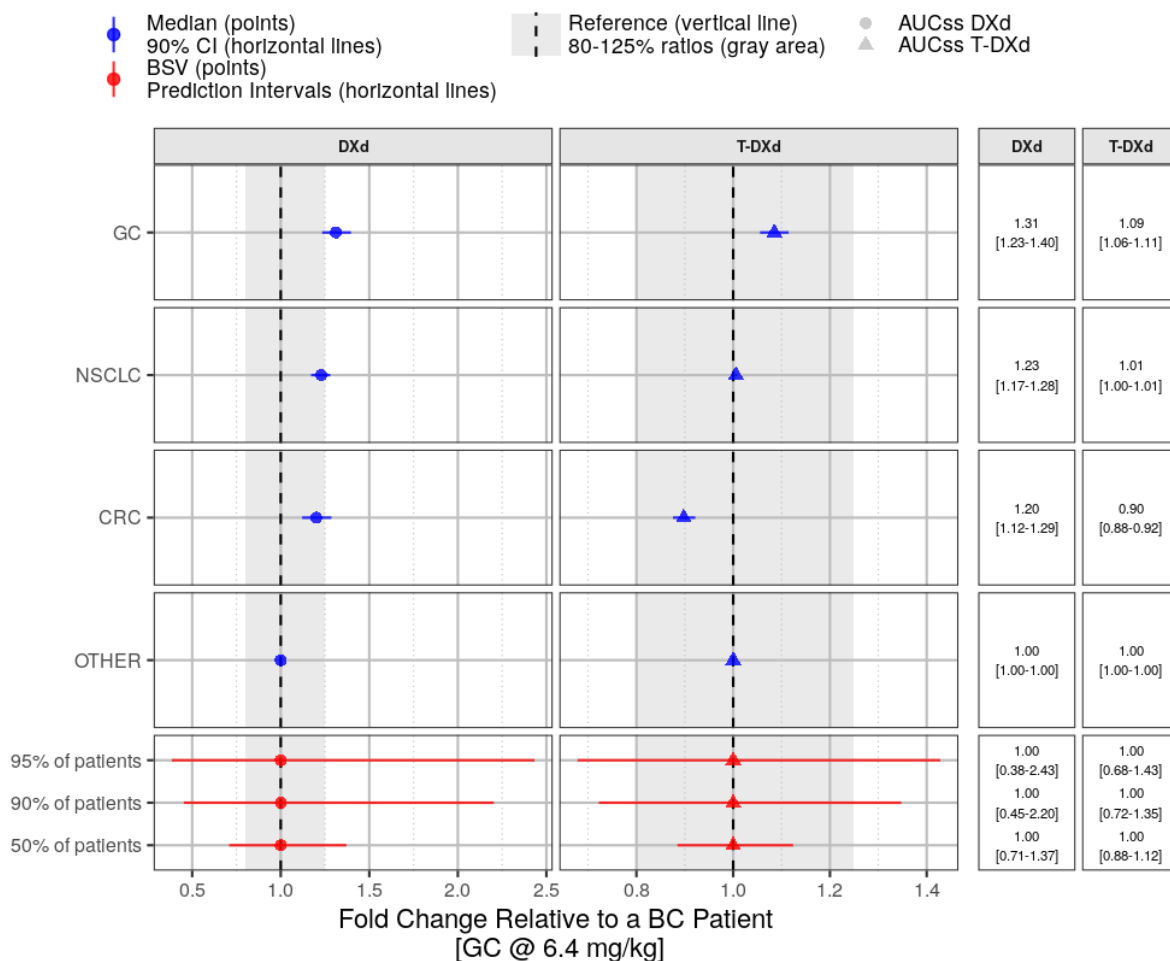
Applicant – Figure 10 Impact of Age on Exposure to T-DXd and DXd



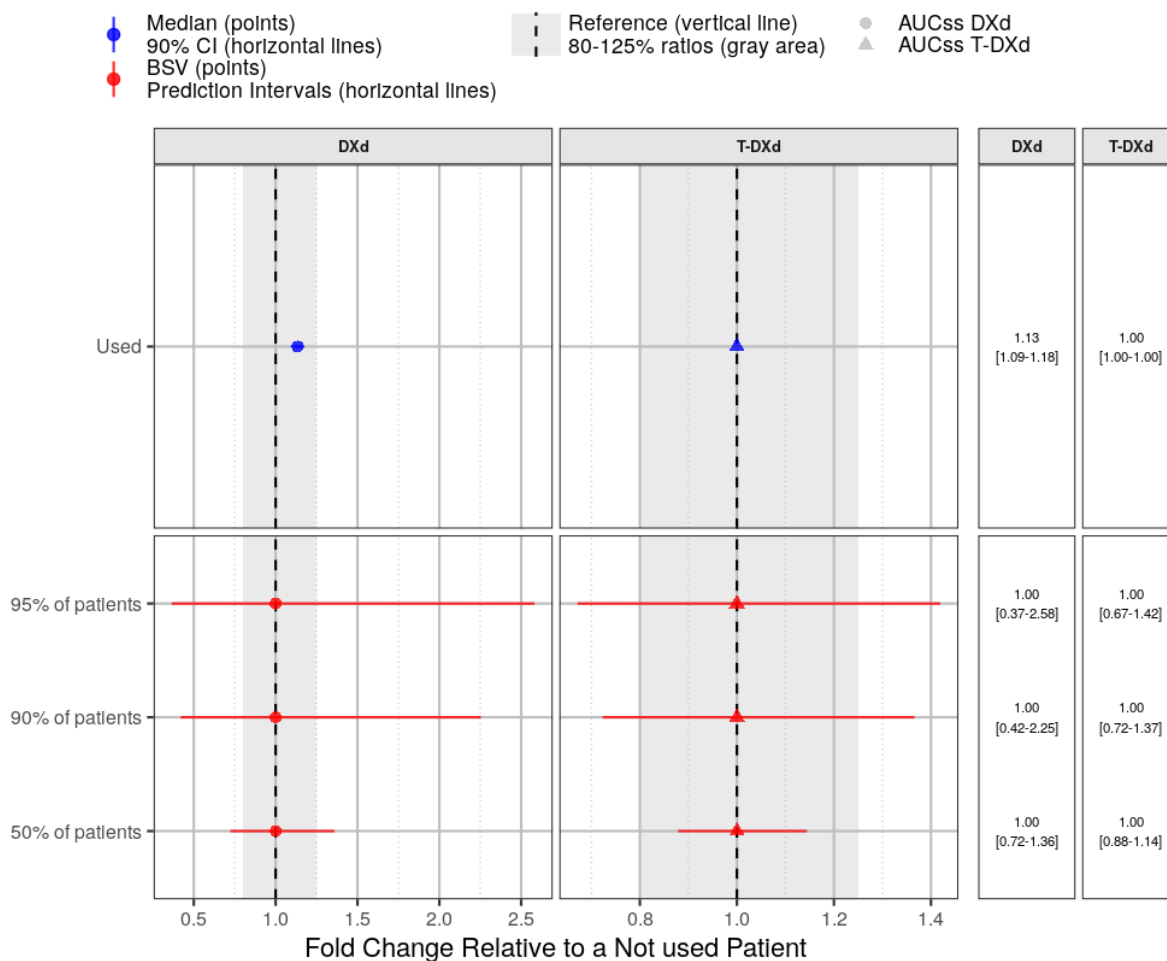
Applicant – Figure 11 Impact of Tumor Type on Exposure to T-DXd and DXd



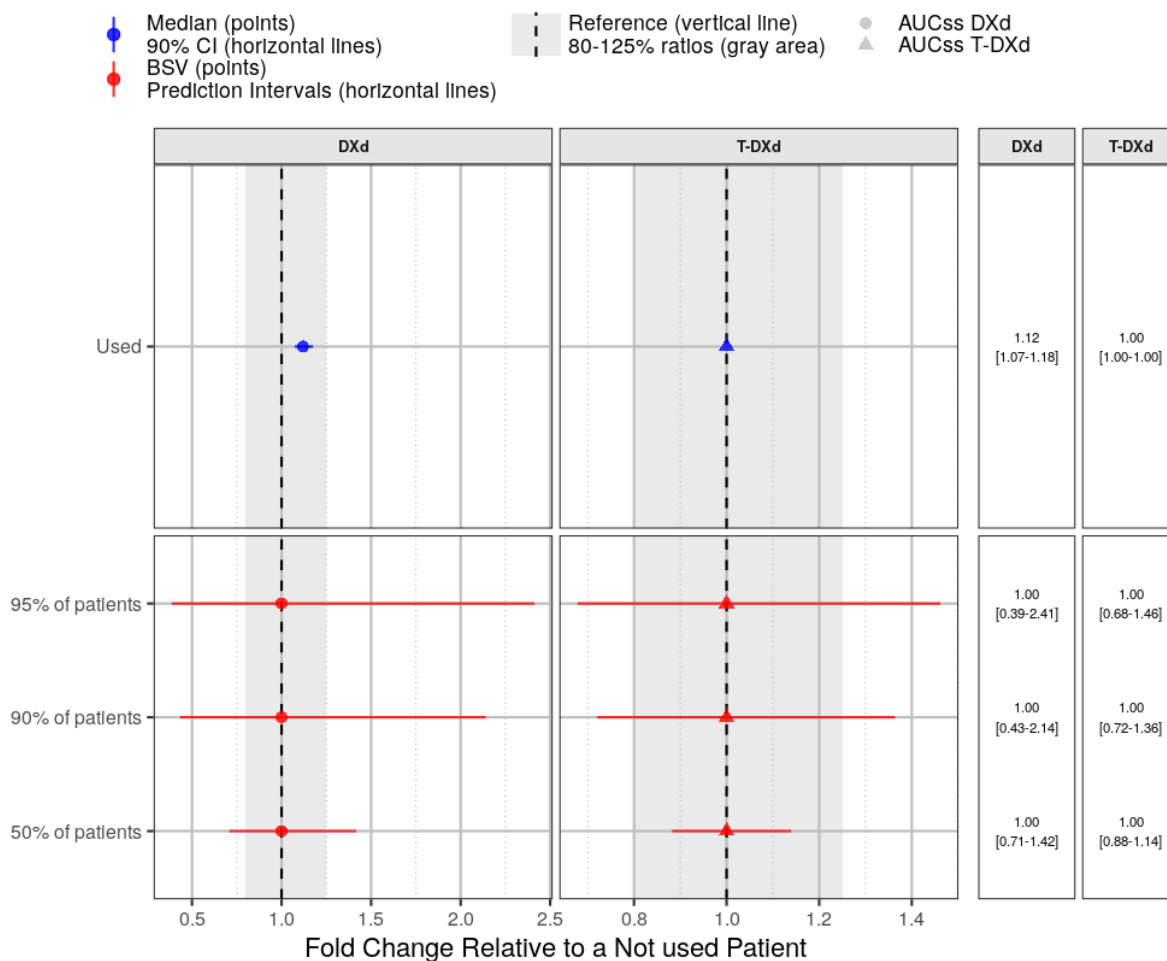
Applicant – Figure 12 Impact of Tumor Type on Exposure to T-DXd and DXd when GC Patients are Dosed at 6.4 mg/kg



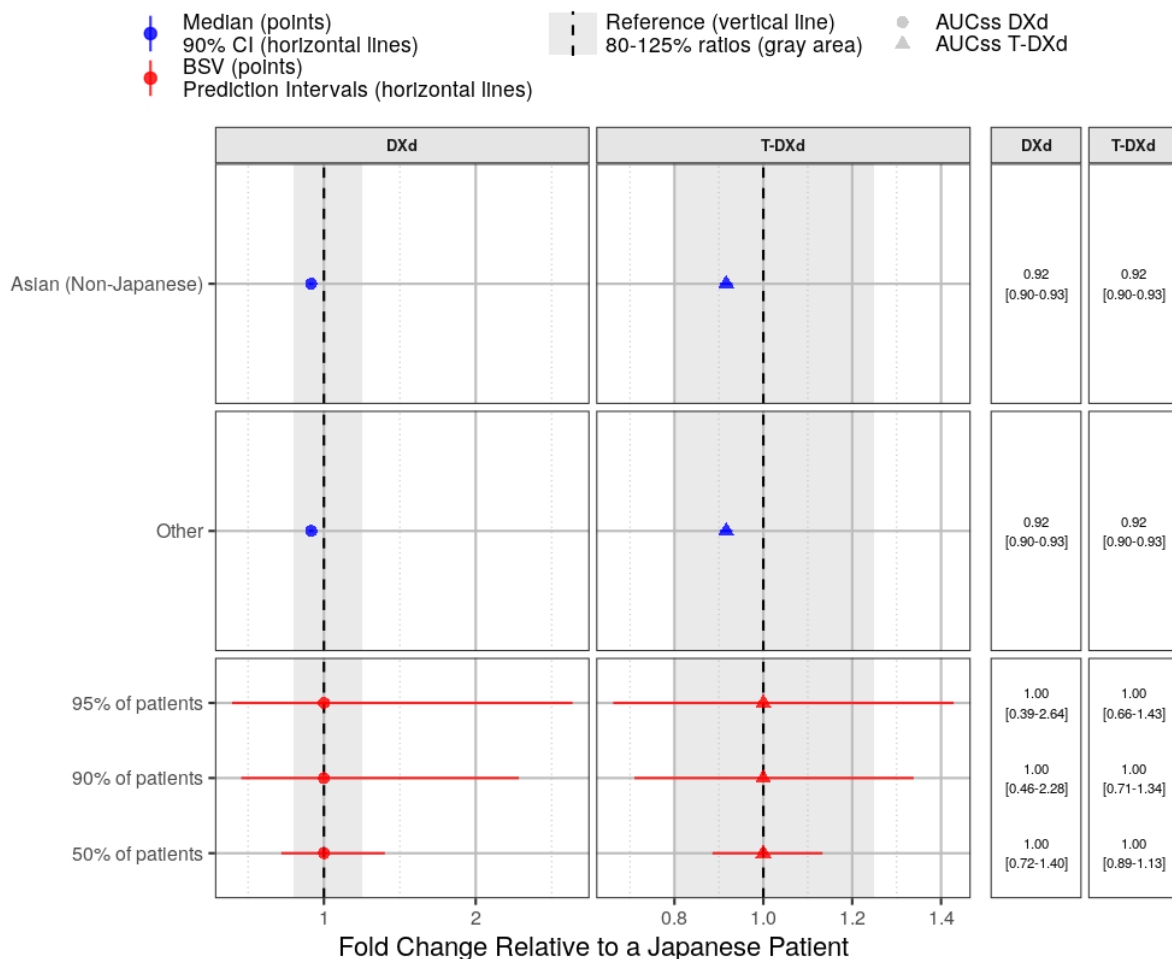
Applicant – Figure 13 Impact of Coadministration with Ritonavir on Exposure to T-DXd and DXd



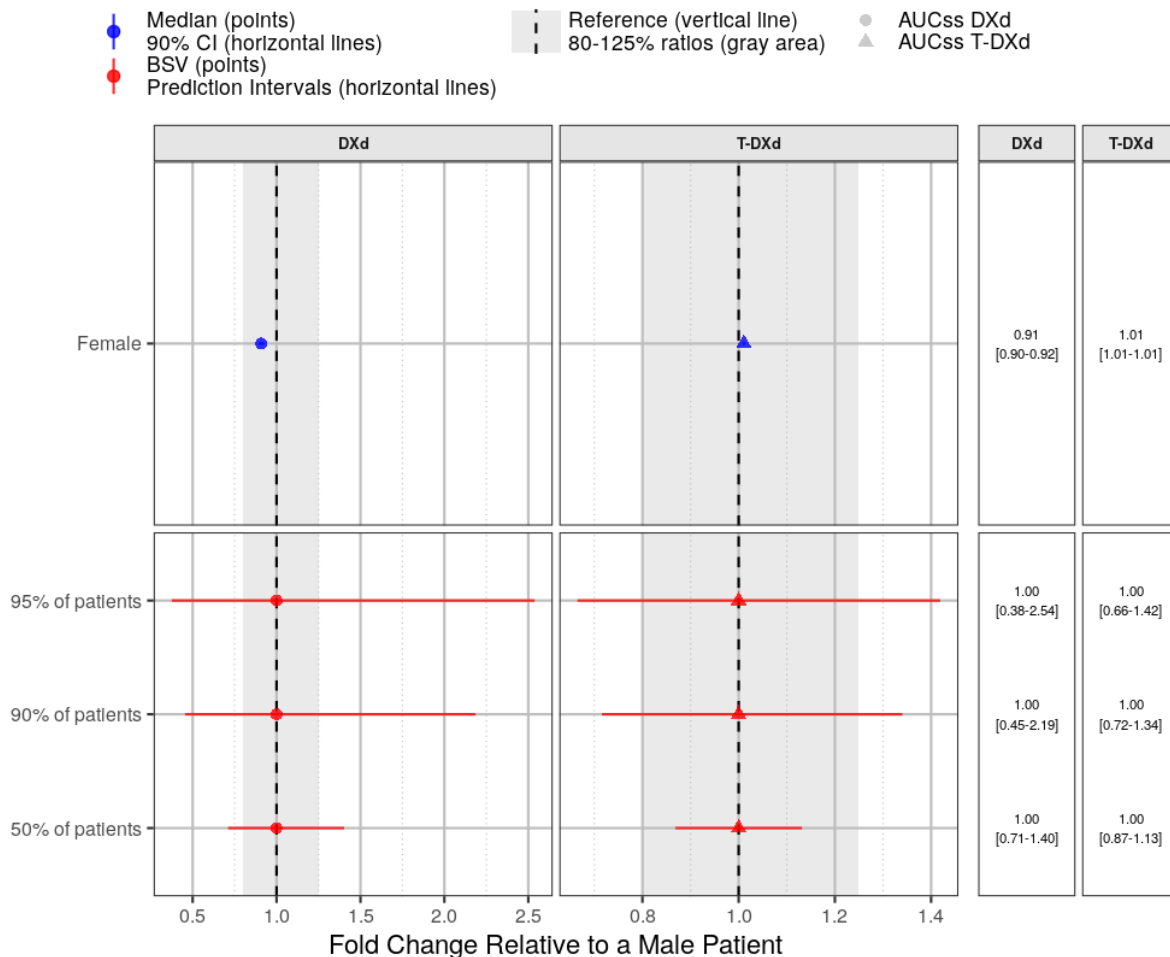
Applicant – Figure 14 Impact of Coadministration with Itraconazole on Exposure to T-DXd and DXd



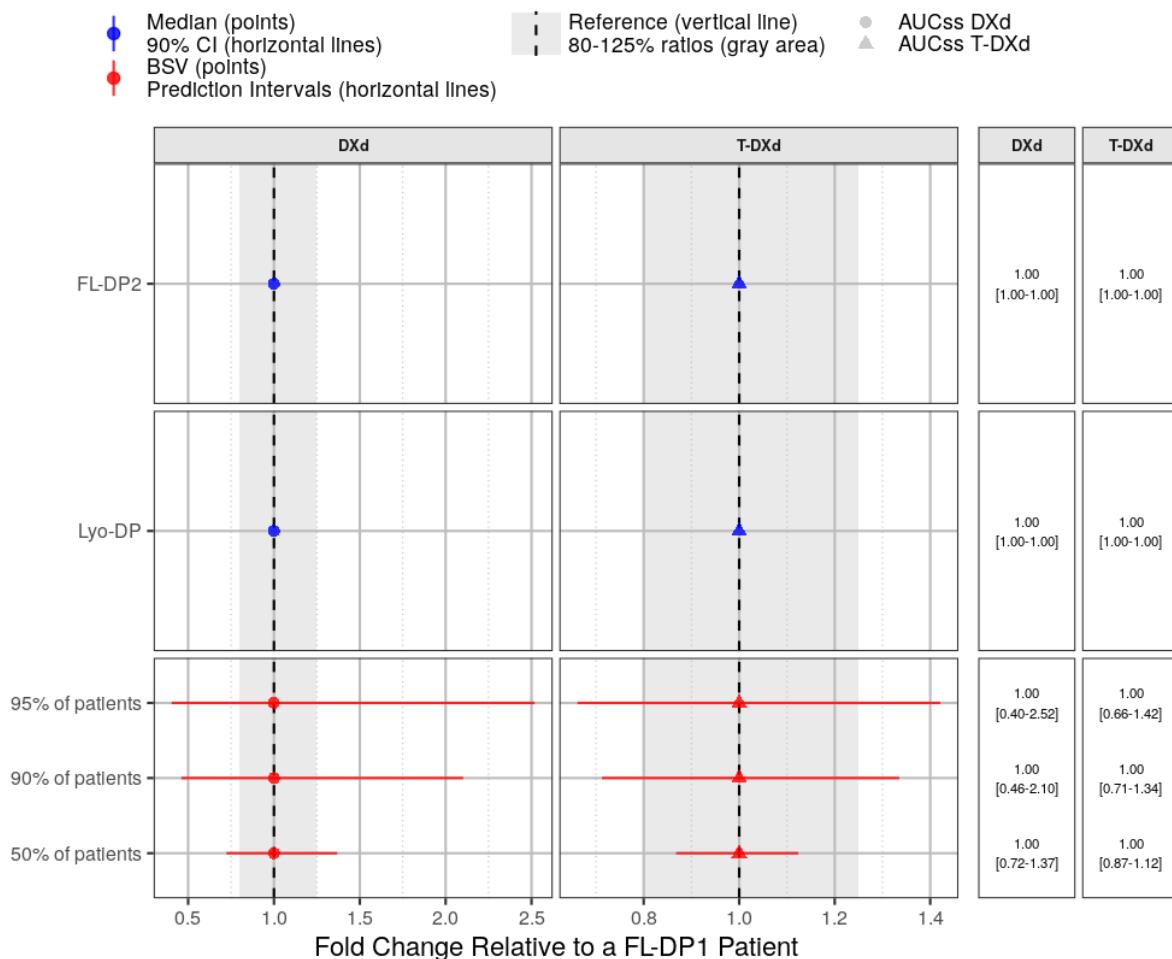
Applicant – Figure 15 Impact of Ethnicity on Exposure to T-DXd and DXd



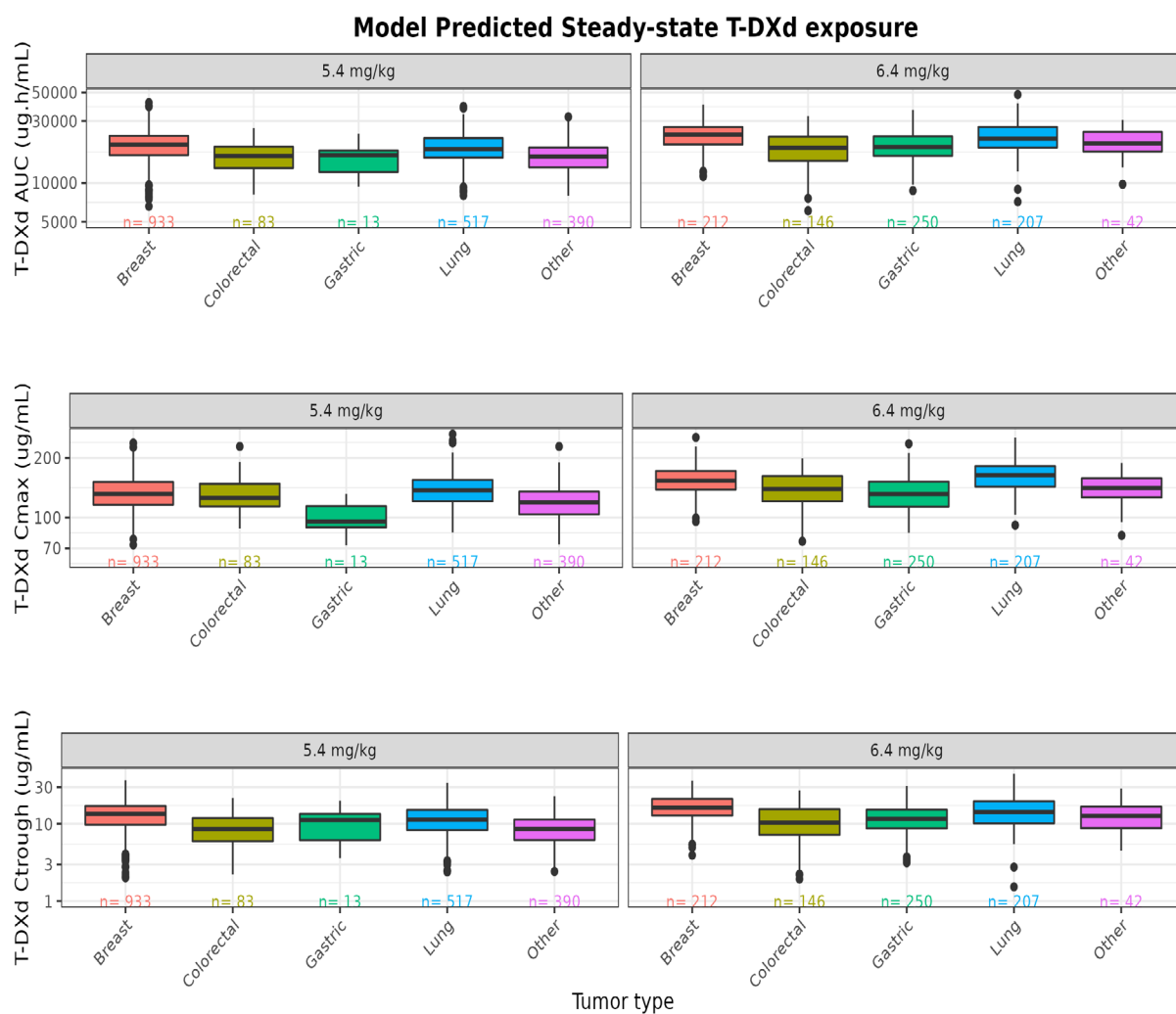
Applicant – Figure 16 Impact of Sex on Exposure to T-DXd and DXd



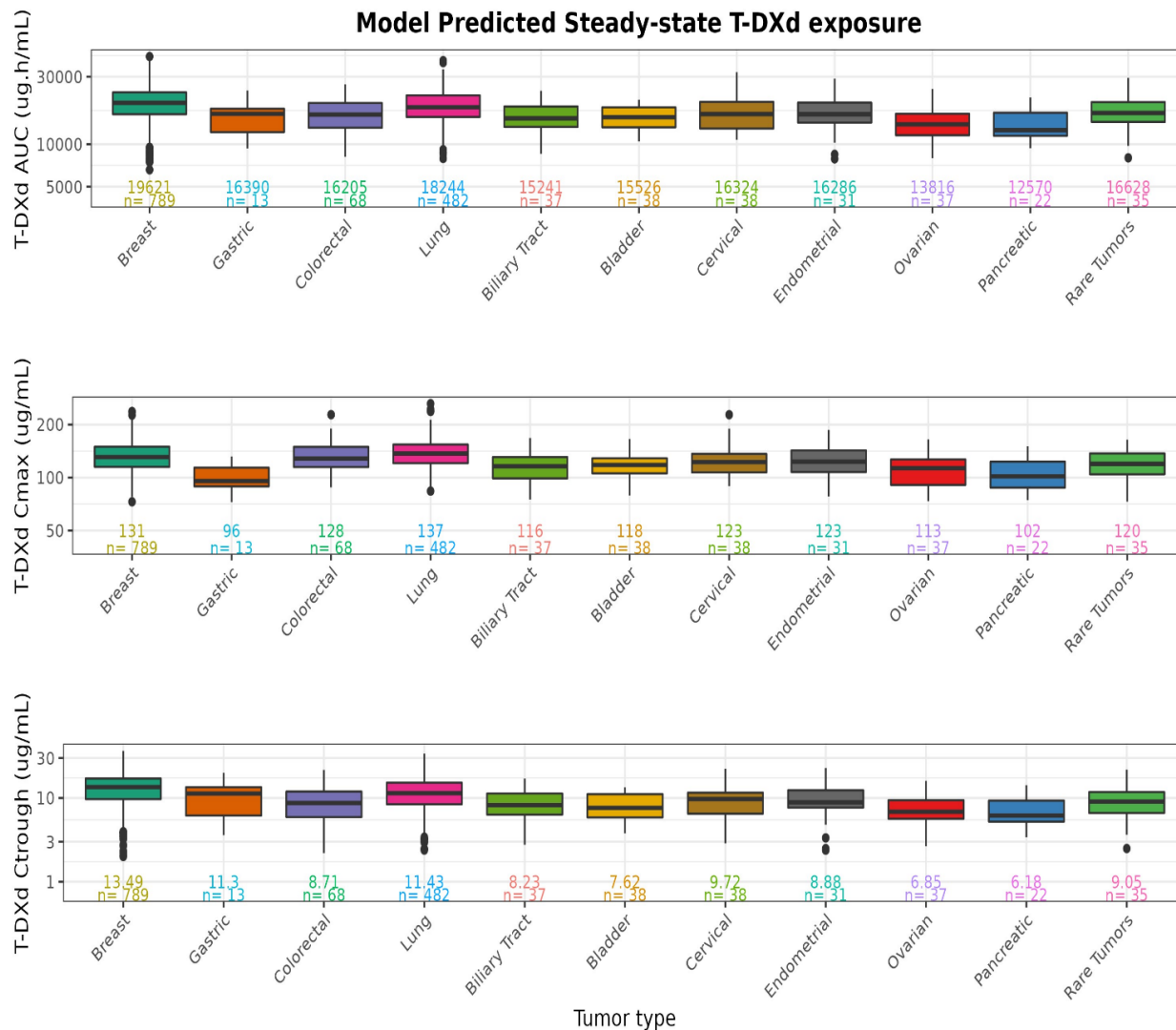
Applicant – Figure 17 Impact of Formulation on Exposure to T-DXd and DXd



Applicant – Figure 18 Steady State T-DXd Exposures by Tumor Type



Applicant – Figure 19 Model Predicted T-DXd Steady State Exposures in Tumor Types Contained in Study DP-02, when Compared to Breast, Gastric, Colorectal and Lung Tumors, Following IV Administration at 5.4 mg/kg



The FDA's Assessment:

The Applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. Note that the summary of IHC class and HER2 status in Applicant – Table 36 was not updated according to the classification change recommended by the clinical

team. However, it has no impact on the results of popPK analysis.

19.4.1.3. PPK Review Issues

The FDA's Assessment:

None.

19.4.1.4. Reviewer's Independent Analysis

The FDA's Assessment:

This reviewer verified the Applicant's analysis in general.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The Applicant's exposure response analyses on efficacy are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	The objectives were to carry out exposure-efficacy and exposure safety analysis on data from IHC3+ patients from studies U204, U207 and DP-02.
Study Included	Data from 3 trials were pooled to inform a tumor agnostic indication in IHC3+ patients not earlier submitted
Endpoint	Primary: ORR Secondary: OS
No. of Patients (total, and with individual PK)	In total, 236 subjects received IV doses of T-DXd at target doses of 5.4 or 6.4 mg/kg, and 236 samples were included in the each of the analysis data sets.

Population Characteristics (Applicant – Table 38, Applicant – Table 39)	General	Age median 62 (23-85) Weight median 68.3 (37-124) 113 (47.9%) male 123 (52.1%) female	
	Pediatrics (if any)	Not applicable	
Dose(s) Included		5.4 mg/kg and 6.4 mg/kg	
Exposure Metrics Explored (range)		steady-state exposure metrics for both T-DXd and DXd (AUC, Cmax and Ctrough)	
Covariates Evaluated		sex, weight, height, baseline albumin level, baseline tumor size, baseline bilirubin, baseline aspartate transferase, baseline creatinine clearance, ECOG status and IHC class	
Final Model Parameters		Summary	Acceptability [FDA's comments]
Model Structure		The final model for ORR can be represented by the following equation: logit(Prob ORR) = -2.221 + (0.06879* BALB)	Acceptable BALB: Baseline Albumin
Model Parameter Estimates		A summary of the models tested, and their fit criteria can be seen in Applicant – Table 40.	Acceptable
Model Evaluation		A summary of the models tested, and their fit criteria can be seen in Applicant – Table 40.	Acceptable
Covariates and Clinical Relevance		The addition of demographic covariates into the logistic regression model meant that the effect of Cmax,ss on the ORR was no longer significant in any	Acceptable

	of the models tested. The covariate model with the most significant p-value (and lowest AIC) was shown to contain only baseline albumin level as a predictor of ORR (p=0.0233)	
Simulation for Specific Population	Not applicable	
Visualization of E-R relationships	Applicant – Figure 20	Acceptable
Overall Clinical Relevance for ER	There was no notable relationship between any exposure metric for T-DXd or DXd and either ORR or OS Any relationship between exposure metrics for T-DXd or DXd and ORR/OS was likely confounded by markers of disease condition, eg baseline albumin level. Baseline albumin level was shown to be a predictor of ORR.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	

Applicant – Table 38 Continuous Covariates at Baseline

	DP-02 (N=111)	U204 (N=27)	U207 (N=98)	Overall (N=236)
Baseline age (year)				
Mean (SD)	61.7 (12.7)	59.1 (10.6)	58.0 (12.6)	59.8 (12.5)
Median [Min, Max]	64.0 [23.0, 85.0]	61.0 [31.0, 74.0]	59.0 [25.0, 80.0]	62.0 [23.0, 85.0]
Baseline weight (kg)				

Applicant – Table 38 Continuous Covariates at Baseline

	DP-02 (N=111)	U204 (N=27)	U207 (N=98)	Overall (N=236)
Mean (SD)	68.5 (16.1)	75.1 (12.5)	66.2 (14.5)	68.3 (15.3)
Median [Min, Max]	68.0 [37.0, 124]	75.5 [51.5, 104]	65.8 [39.9, 107]	68.0 [37.0, 124]
Baseline height (cm)				
Mean (SD)	165 (9.53)	170 (8.55)	167 (10.5)	167 (9.95)
Median [Min, Max]	165 [147, 187]	170 [154, 187]	168 [144, 198]	166 [144, 198]
Baseline Body Mass Index (kg/m²)				
Mean (SD)	25.2 (5.78)	25.8 (3.51)	23.5 (4.21)	24.6 (5.01)
Median [Min, Max]	24.7 [13.9, 41.1]	26.0 [20.5, 33.3]	23.4 [15.8, 37.0]	23.9 [13.9, 41.1]
Baseline Body Surface Area (m²)				
Mean (SD)	1.75 (0.208)	1.86 (0.181)	1.74 (0.210)	1.76 (0.209)
Median [Min, Max]	1.75 [1.31, 2.36]	1.85 [1.48, 2.24]	1.74 [1.33, 2.31]	1.76 [1.31, 2.36]
Baseline Tumor Size (mm)				
Mean (SD)	74.2 (54.9)	76.8 (43.8)	95.7 (60.6)	83.4 (57.0)
Median [Min, Max]	63.0 [11.0, 342]	68.0 [13.0, 168]	77.5 [10.0, 242]	68.5 [10.0, 342]
Baseline Creatinine Clearance (mL/min)				
Mean (SD)	83.7 (31.1)	88.3 (24.8)	96.5 (30.1)	89.5 (30.5)
Median [Min, Max]	80.1 [29.9, 197]	80.5 [45.8, 142]	93.4 [44.3, 207]	85.1 [29.9, 207]
Baseline Albumin (g/L)				
Mean (SD)	39.4 (4.35)	39.9 (4.93)	38.2 (4.54)	38.9 (4.53)
Median [Min, Max]	39.0 [28.0, 49.0]	41.0 [28.0, 49.0]	38.0 [26.7, 49.0]	39.0 [26.7, 49.0]
Baseline Bilirubin (umol/L)				
Mean (SD)	9.25 (7.75)	6.02 (2.95)	11.0 (8.16)	9.63 (7.68)
Median [Min, Max]	7.20 [3.00, 58.5]	6.00 [1.50, 15.0]	9.72 [2.37, 73.5]	8.00 [1.50, 73.5]

Applicant – Table 39 Categorical Covariates at Baseline

	DP-02 (N=111)	U204 (N=27)	U207 (N=98)	Overall (N=236)
Sex				
Female	66 (59.5%)	9 (33.3%)	48 (49.0%)	123 (52.1%)
Male	45 (40.5%)	18 (66.7%)	50 (51.0%)	113 (47.9%)

Applicant – Table 39 Categorical Covariates at Baseline

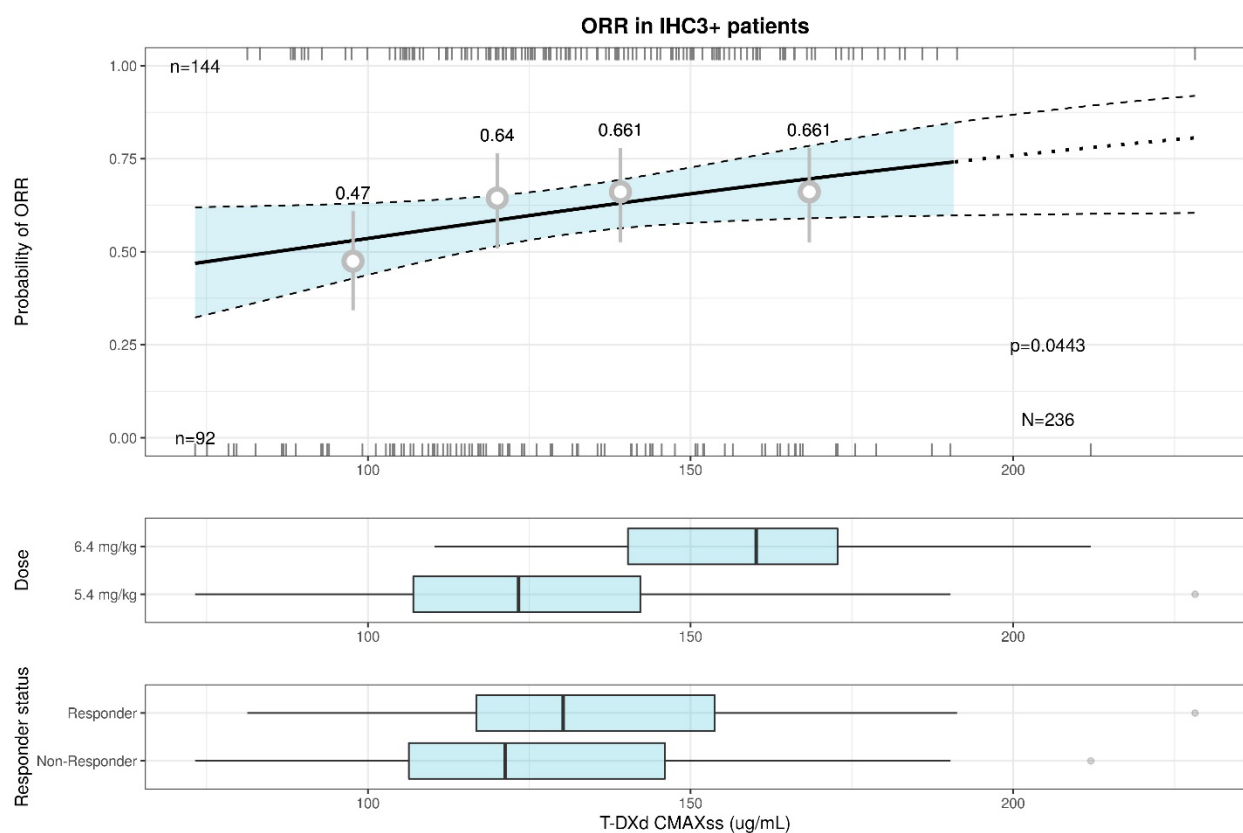
	DP-02 (N=111)	U204 (N=27)	U207 (N=98)	Overall (N=236)
Tumor type				
Biliary Tract Cancer	22 (19.8%)	0 (0%)	0 (0%)	22 (9.3%)
Bladder Cancer	27 (24.3%)	0 (0%)	0 (0%)	27 (11.4%)
Cervical Cancer	10 (9.0%)	0 (0%)	0 (0%)	10 (4.2%)
Endometrial Cancer	16 (14.4%)	0 (0%)	0 (0%)	16 (6.8%)
Ovarian Cancer	15 (13.5%)	0 (0%)	0 (0%)	15 (6.4%)
Pancreatic Cancer	5 (4.5%)	0 (0%)	0 (0%)	5 (2.1%)
Rare Tumors	16 (14.4%)	0 (0%)	0 (0%)	16 (6.8%)
Lung Cancer	0 (0%)	27 (100%)	0 (0%)	27 (11.4%)
Colorectal Cancer	0 (0%)	0 (0%)	98 (100%)	98 (41.5%)
ECOG Status				
ECOG 0	54 (48.6%)	5 (18.5%)	58 (59.2%)	117 (49.6%)
ECOG 1	57 (51.4%)	22 (81.5%)	40 (40.8%)	119 (50.4%)
IHC Class				
IHC 3	111 (100%)	27 (100%)	98 (100%)	236 (100%)

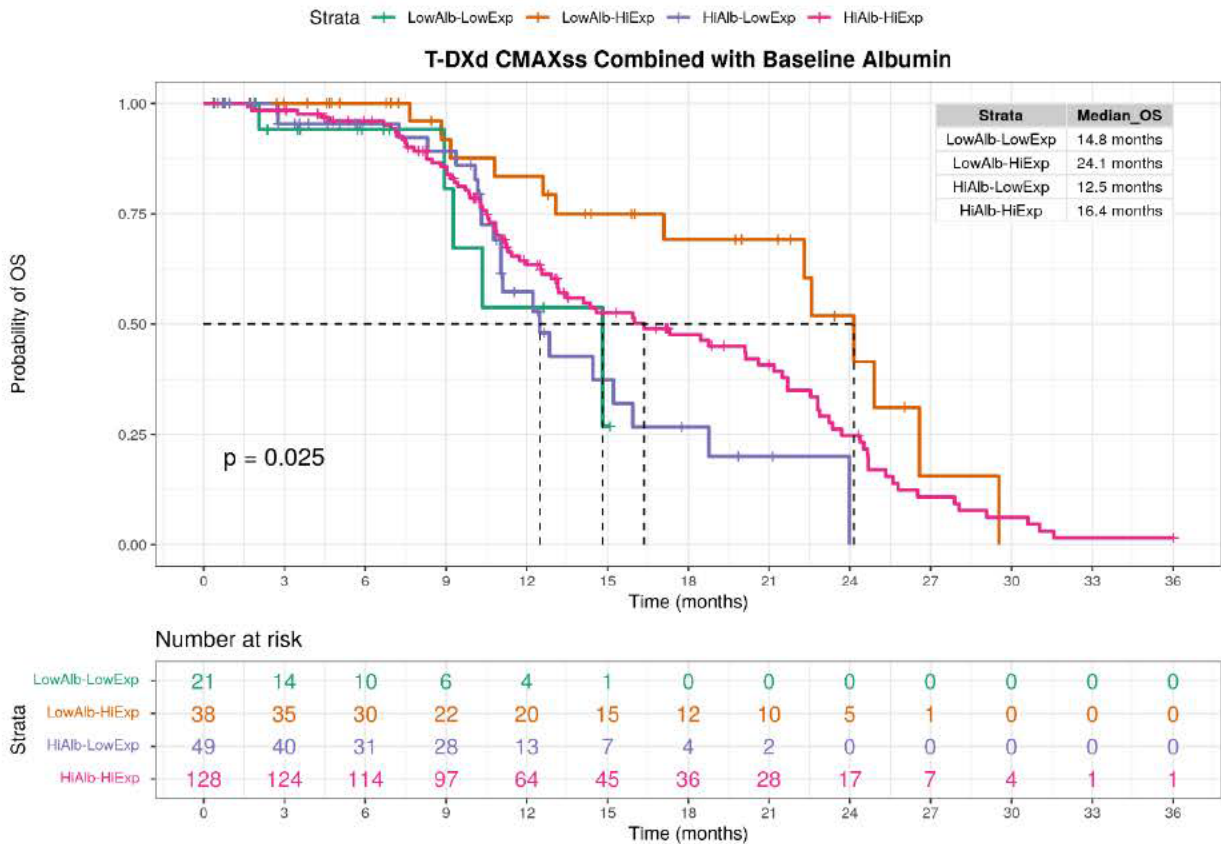
Applicant – Table 40 Logistic Regression Models Tested in Exposure-Efficacy Modelling

Model	Exposure metric	Covariates added	Variable	Coefficient	P.Value	AIC
1	T-DXd CMAXSS	None	(Intercept)	-0.8588	0.1926	315.44
			I(CMAXSS_TOTAL)	0.01002	0.0443	
2	T-DXd CMAXSS	AGE+SEX+ ECOG+BALB+ BTSBL+BBILI+ BCRCL+BAST+ BALT	(Intercept)	-1.55	0.4871	317.964
			I(CMAXSS_TOTAL)	0.003386	0.5459	
			AGE	0.01007	0.5009	
			SEXMale	-0.426	0.1444	
			ECOG1	-0.5659	0.04843	
			BALB	0.04168	0.2535	
			BTSBL	-0.00379	0.165	
			BBILI	-0.01852	0.3738	
			BCRCL	0.005536	0.3469	
			BAST	0.003534	0.668	
			BALT	-0.01002	0.1958	
3	T-DXd CMAXSS	AGE+BWT+ECOG+BALB+BT SBL+ BBILI+BCRCL+ BAST+BALT	(Intercept)	-1.938	0.3826	318.788
			I(CMAXSS_TOTAL)	0.001874	0.7531	
			AGE	0.002727	0.8562	
			BWT	0.01303	0.2543	
			ECOG1	-0.5498	0.05425	
			BALB	0.04797	0.1846	
			BTSBL	-0.00362	0.1879	
			BBILI	-0.01983	0.3386	
			BCRCL	0.001622	0.7973	
			BAST	0.005691	0.4917	
			BALT	-0.01195	0.1372	
4	T-DXd CMAXSS	BALB+BTSBL	(Intercept)	-2.017	0.1763	313.017
			I(CMAXSS_TOTAL)	0.007608	0.1385	
			BALB	0.04623	0.1547	
			BTSBL	-0.00379	0.1399	

Applicant – Table 40 Logistic Regression Models Tested in Exposure-Efficacy Modelling

Model	Exposure metric	Covariates added	Variable	Coefficient	P.Value	AIC
5	None	BALB	(Intercept)	-2.221	0.0598	314.319
			BALB	0.06879	0.02326	
6	T-DXd CMASS	BALB	(Intercept)	-3.113	0.01668	313.226
			I(CMASS_TOTAL)	0.008805	0.08205	
			BALB	0.06218	0.04248	
7	T-DXd CMASS	BWT+BALB+ BTSBL	(Intercept)	-2.352	0.09496	309.913
			BWT	0.01622	0.08236	
			BALB	0.05864	0.05955	
			BTSBL	-0.01007	0.09256	

Applicant – Figure 20 T-DXd Cmax at Steady-State v ORR in IHC3+ Patients



19.4.2.3. ER (safety) Executive Summary

The FDA’s Assessment:

The Applicant’s exposure response analyses on safety are considered acceptable for the purpose of supporting analyses objectives. The Applicant’s analyses were verified by the FDA reviewer, with no significant discordance identified.

19.4.2.4. ER (safety) Assessment Summary

The Applicant’s Position:

General Information

Goal of ER analysis		The objective was to carry out exposure-safety analysis on data from IHC3+ patients from studies U204, U207 and DP-02.
Study Included		Data from 3 trials were pooled to inform a tumor agnostic indication in IHC3+ patients not earlier submitted.
Population Included		Patients from studies U204, U207 and DP-02.
Endpoint		Interstitial Lung Disease (including pneumonitis), classified as any grade (ILD) and Grade 3 or higher (ILD G3+).
No. of Patients (total, and with individual PK)		In total, 236 subjects received IV doses of T-DXd at target doses of 5.4 or 6.4 mg/kg, and 236 samples were included in the each of the analysis data sets.
Population Characteristics (Applicant – Table 38, Applicant – Table 39)	General	Age median 62 (23-85) Weight median 68.3 (37-124) 113 (47.9%) male 123 (52.1%) female
	Organ impairment	Not applicable
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	Not applicable
Dose(s) Included		5.4 mg/kg and 6.4 mg/kg
Exposure Metrics Explored (range)		Steady-state exposure metrics for both T-DXd and DXd (AUC, Cmax and Ctrough)
Covariates Evaluated		No assessment was carried out for ILD G3+ since only 5 events were available in the patient population as per Modelling analysis plan.
Final Model Parameters		Summary Acceptability [FDA's comments]

Model Structure	The final equation for the logistic model to any Grade ILD was given by: $\text{logit(Prob any Grade ILD)} = -1.3 - 1.7 \times \text{AGE}/62 + 0.2 \times \text{REGIONEUROPE} + 0.2 \times \text{REGIONJAPAN} + 0.1 \times \text{REGIONUSA} - 1.5 \times \text{REGIONOTHER} + 1.3 \times \text{AUCSS_TOTAL} / 16798965 \text{ (ng/mL)}$	Note that the final equation listed is different from the best model from the model selection (See Applicant-Table 31) with respect to transformation of AUCSS_TOTAL and age. In addition, the coefficients of the model parameters cannot be fully verified. This model was considered as a sensitivity analysis.
Model Parameter Estimates	A summary of the models tested, and their fit criteria can be seen in Applicant – Table 41.	Acceptable
Model Evaluation	A summary of the models tested, and their fit criteria can be seen in Applicant – Table 41.	Acceptable
Covariates and Clinical Relevance	Any relationship between exposure metrics for T-DXd or DXd and ILD was likely confounded by markers of disease condition, eg baseline albumin level. Age and ethnicity region were shown to have potential impact on the incidence rate of ILD of any grade.	Acceptable
Simulation for Specific Population	Not applicable	

Visualization of E-R relationships	Applicant – Figure 21	Serve as sensitivity analysis
Overall Clinical Relevance for ER	A relationship between incidence of any grade ILD and the steady-state AUC of T-DXd was noted ($p = 0.02875$). Due to low incidence rate of Grade 3+ ILD events ($n = 5$) no relationship between any exposure metric for T-DXd or DXd and ILD G3+ was explored. Any relationship between exposure metrics for T-DXd or DXd and ILD was likely confounded by markers of disease condition, eg baseline albumin level. Age and ethnicity region were shown to have potential impact on the incidence rate of ILD of any grade.	See previous comment on the final model.
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	

Applicant – Table 41 Logistic Regression Models Tested in Exposure-Safety Modelling for ILD of any grade

Mode l	Exposure metric	Covariates added	Variable	Coefficient	p-value	AIC
1	AUCSS_TOTAL	BALB+ BWT+ AGE+ BCRCL+ OXYSAT+ AUCSS_TOTA	(Intercept)	-21.316	0.993	214.140
			BALB	0.028	0.638	
			BWT	0.026	0.184	
			AGE	-0.059	0.014	

L+ REGION+ ECOG+ RACE+ LUNGMET+ TTYPE	BCRCL	-0.021	0.072
	OXYSAT	-0.170	0.068
	AUCSS_TOTAL	1.322	0.132
	REGIONEUROPE	0.701	0.578
	REGIONJAPAN	1.730	0.251
	REGIONOTHER	0.121	0.946
	REGIONUSA	0.812	0.506
	ECOG1	-0.312	0.499
	RACE1	17.256	0.994
	RACE2	17.727	0.994
	RACE3	17.679	0.994
	RACE9	1.594	1.000
	LUNGMET0	-2.282	0.033
	LUNGMET1	-2.733	0.067
	TTYPECohort 2: Bladder Cancer	-1.099	0.172
	TTYPECohort 3: Cervical Cancer	-1.313	0.232
	TTYPECohort 4: Endometrial Cancer	-1.438	0.159
	TTYPECohort 5: Ovarian Cancer	-1.330	0.186
	TTYPECohort 6: Pancreatic Cancer	-16.568	0.992
	TTYPECohort 7: Rare Tumors	-0.119	0.891
	TTYPEColorectal Cancer	-1.895	0.225

2	AUCSS_TOTAL	BALB+ BWT+ AGE+ BCRCL+ OXYSAT+ AUCSS_TOTAL+ REGION+ ECOG+ RACE+ LUNGMET	(Intercept)	-27.181	0.992	206.310
			BALB	0.025	0.657	
			BWT	0.030	0.107	
			AGE	-0.049	0.024	
			BCRCL	-0.017	0.121	
			OXYSAT	-0.129	0.175	
			AUCSS_TOTAL	1.346	0.112	
			REGIONEUROPE	0.205	0.862	
			REGIONJAPAN	0.594	0.375	
			REGIONOTHER	-1.105	0.255	
			REGIONUSA	0.481	0.671	
			ECOG1	-0.147	0.739	
			RACE1	17.051	0.995	
			RACE2	16.843	0.995	
			RACE3	17.305	0.995	
			RACE9	1.596	1.000	
			LUNGMET0	-1.214	0.163	
			LUNGMET1	-1.331	0.263	

3	AUCSS_TOTAL	BALB+ BWT+ AGE+ BCRCL+ OXYSAT+ AUCSS_TOTAL+ REGION+ ECOG+ LUNG MET	(Intercept)	-11.265	0.453	201.850
			BALB	0.014	0.799	
			BWT	0.022	0.191	
			AGE	-0.050	0.022	
			BCRCL	-0.016	0.135	
			OXYSAT	-0.132	0.162	
			AUCSS_TOTAL	1.502	0.072	
			REGIONEUROPE	-0.079	0.900	
			REGIONJAPAN	0.502	0.449	
			REGIONOTHER	-1.456	0.045	
			REGIONUSA	0.142	0.835	
			ECOG1	-0.144	0.738	
			LUNG MET0	-1.183	0.167	
			LUNG MET1	-1.251	0.283	
4	AUCSS_TOTAL	BWT+ AGE+ BCRCL+ OXYSAT+ AUCSS_TOTAL+ REGION+ ECOG+ LUNG MET	(Intercept)	-12.060	0.410	199.920

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

			BWT	0.022	0.195	
			AGE	-0.052	0.012	
			BCRCL	-0.016	0.124	
			OXYSAT	-0.127	0.169	
			AUCSS_TOTAL	1.566	0.049	
			REGIONEUROPE	-0.076	0.904	
			REGIONJAPAN	0.458	0.474	
			REGIONOTHER	-1.478	0.041	
			REGIONUSA	0.128	0.850	
			ECOG1	-0.152	0.723	
			LUNGMET0	-1.188	0.164	
			LUNGMET1	-1.197	0.296	
5	AUCSS_TOTAL	BWT+ AGE+ BCRCL+ OXYSAT+ AUCSS_TOTAL+ REGION+ LUNGMET	(Intercept)	-12.965	0.368	198.050
			BWT	0.022	0.193	
			AGE	-0.052	0.011	
			BCRCL	-0.017	0.121	
			OXYSAT	-0.124	0.179	
			AUCSS_TOTAL	1.600	0.042	
			REGIONEUROPE	-0.118	0.847	
			REGIONJAPAN	0.470	0.462	
			REGIONOTHER	-1.503	0.037	
			REGIONUSA	0.136	0.841	
			LUNGMET0	-1.238	0.140	

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

Trastuzumab deruxtecan (T-DXd, DS-8201a)

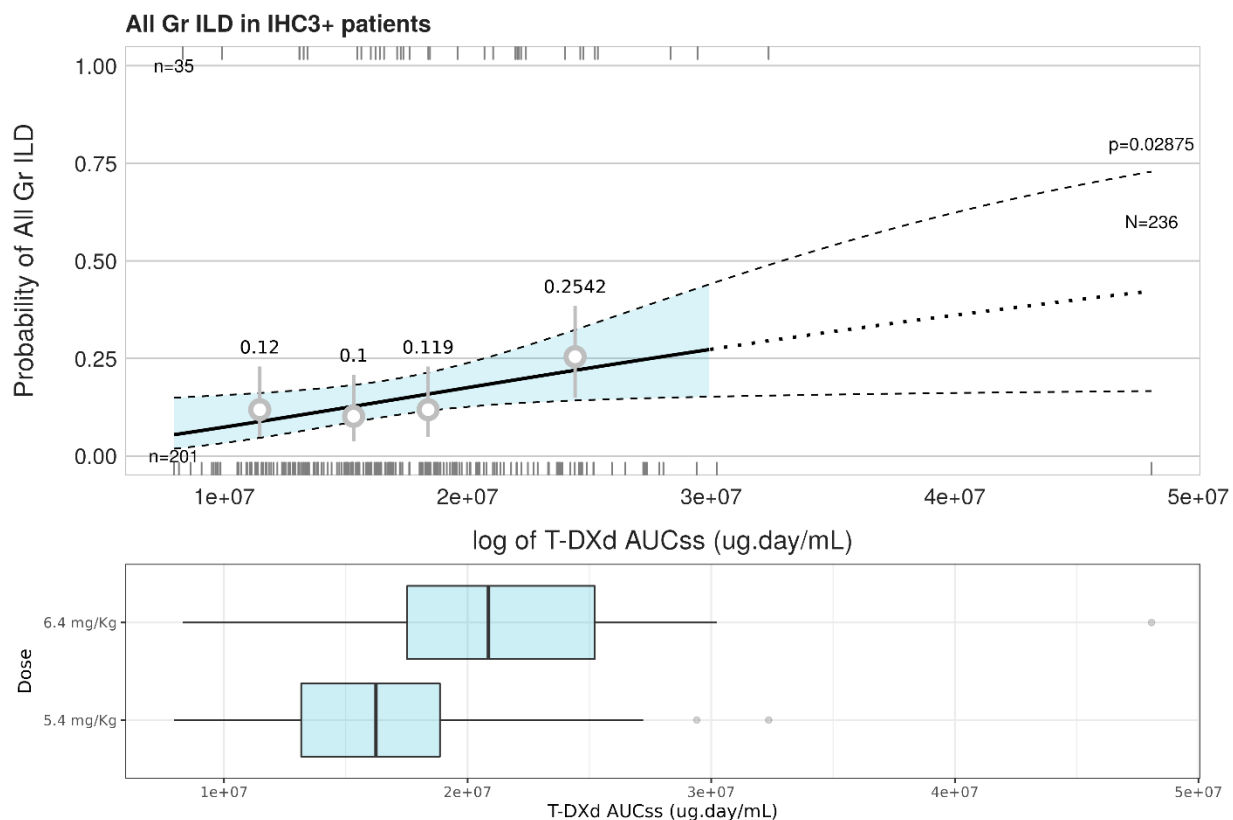
			LUNGMET1	-1.238	0.277	
6	AUCSS_TOTAL	BWT+ AGE+ BCRCL+ AUCSS_TOTAL+ REGION+ LUNGMET	(Intercept)	-24.054	0.056	197.550
			BWT	0.024	0.156	
			AGE	-0.050	0.014	
			BCRCL	-0.017	0.116	
			AUCSS_TOTAL	1.524	0.052	
			REGIONEUROPE	-0.108	0.860	
			REGIONJAPAN	0.509	0.422	
			REGIONOTHER	-1.439	0.044	
			REGIONUSA	0.123	0.856	
			LUNGMET0	-1.119	0.176	
			LUNGMET1	-1.191	0.303	
7	AUCSS_TOTAL	BWT+ AGE+ BCRCL+ AUCSS_TOTAL+ REGION	(Intercept)	-21.067	0.081	196.710
			BWT	0.022	0.182	
			AGE	-0.045	0.021	
			BCRCL	-0.015	0.146	
			AUCSS_TOTAL	1.324	0.077	
			REGIONEUROPE	-0.330	0.583	
			REGIONJAPAN	0.414	0.509	
			REGIONOTHER	-1.400	0.049	

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139)

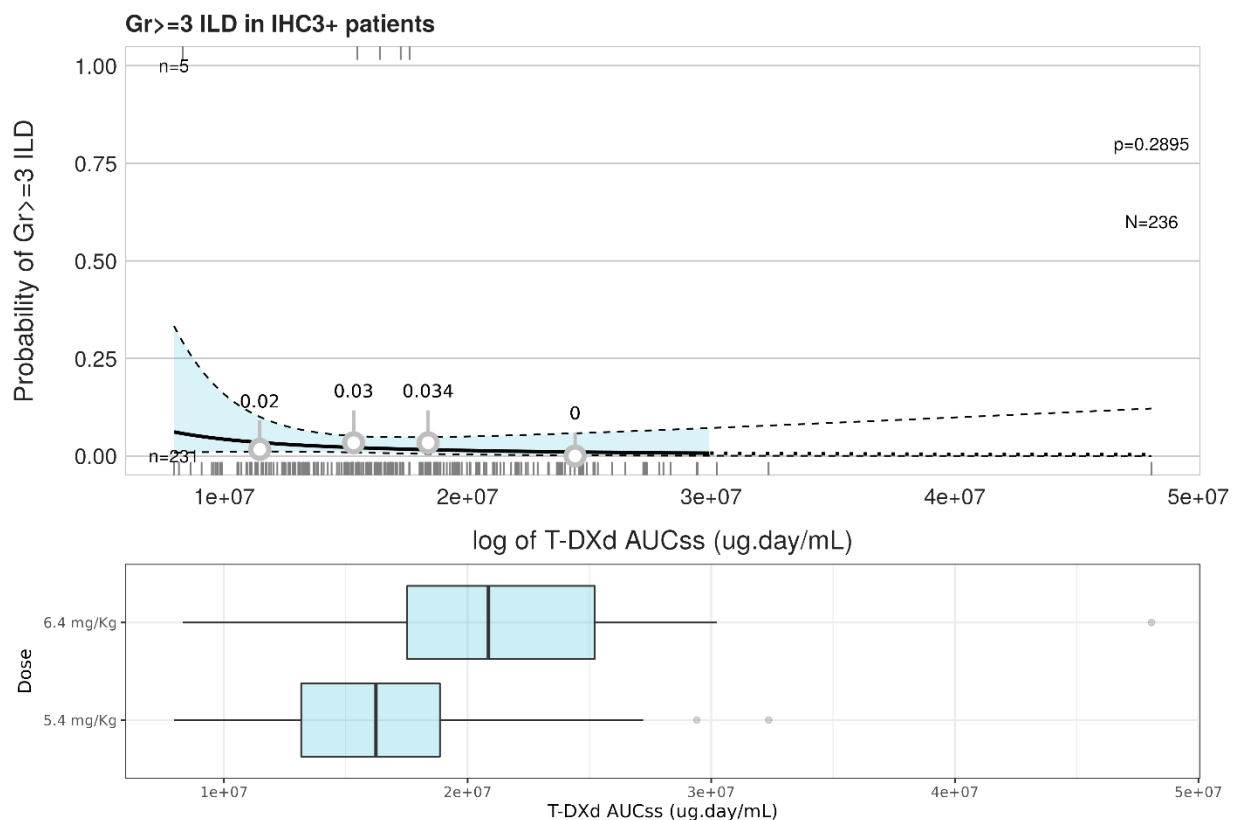
Trastuzumab deruxtecan (T-DXd, DS-8201a)

			REGIONUSA	-0.118	0.857	
8	AUCSS_TOTAL	AGE+ BCRCL+ AUCSS_TOTAL+ REGION	(Intercept)	-26.612	0.017	196.530
			AGE	-0.038	0.039	
			BCRCL	-0.008	0.360	
			AUCSS_TOTAL	1.682	0.015	
			REGIONEUROPE	-0.218	0.713	
			REGIONJAPAN	0.246	0.687	
			REGIONOTHER	-1.439	0.042	
			REGIONUSA	0.053	0.933	
9	AUCSS_TOTAL	AGE+ AUCSS_TOTAL+ REGION	(Intercept)	-25.595	0.020	195.410
			AGE	-0.028	0.063	
			AUCSS_TOTAL	1.548	0.020	
			REGIONEUROPE	-0.173	0.768	
			REGIONJAPAN	0.236	0.700	
			REGIONOTHER	-1.484	0.035	
			REGIONUSA	0.064	0.920	

Applicant – Figure 21 T-DXd AUC at Steady-State vs Incidence of ILD (Any Grade) in Patients with ICH 3+ Patients



Applicant – Figure 22 T-DXd AUC at Steady-State vs Incidence of $\geq$ Grade 3 ILD in Patients with ICH 3+ Patients



The FDA's Assessment:

The Applicant's analyses results are considered acceptable for the purpose of supporting analyses objectives.

19.4.2.5. ER Review Issues

See previous comments.

19.4.2.6. Reviewer's Independent Analysis

See previous comments.

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The E-R analysis for efficacy showed no notable relationship between any exposure metric for T-DXd or DXd and either ORR or OS. Results from the E-R analysis for safety demonstrated a relationship between incidence of any grade ILD and the steady-state AUC of T-DXd. No relationship between any exposure metric for T-DXd or DXd and ILD Grade ≥ 3 was performed due to low incidence rates (N=5). Overall, these analyses continue to support that T-DXd has a positive benefit-risk ratio in the patient population for which the indication is being sought.

The FDA's Assessment:

FDA agrees with the Applicant's position in general.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

N/A.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lily Leu	CDER/OTS/DCPI	Section: 6	Select one: ☒ Authored ☐ Approved
	Signature: Lily L. Leu -S Digitally signed by Lily L. Leu -S Date: 2024.04.03 08:34:43 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	CDER/OTS/DCPI	Section: 6 and 19	Select one: Authored ☒ Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2024.03.27 10:14:46 -04'00'			
Clinical Pharmacology Division Director	Atiqur Rahman	CDER/OTS/DCPI	Section: 6 and 19	Select one: Authored ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.03.27 10:49:04 -04'00'			
Pharmacometrics Reviewer	Junshan Qiu	CDER/OTS/DPM	Section: 19	Select one: ☒ Authored Approved
	Signature: Junshan Qiu -S Digitally signed by Junshan Qiu -S Date: 2024.03.26 15:12:52 -04'00'			
Pharmacometrics Team Leader	Jingyu Yu	CDER/OTS/DPM	Section: 6, 19	Select one: Authored ☒ Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S Date: 2024.03.26 15:18:16 -04'00'			
Clinical Reviewer (Efficacy)	Suparna Wedam	CDER/OOD/DO1	Sections: 1, 2, 3, 4, 7, 8, 13, 19	Select one: ☒ Authored Approved
	Signature: Suparna B. Wedam -S Digitally signed by Suparna B. Wedam Date: 2024.04.02 16:38:06 -04'00'			

Clinical Reviewer (Safety)	Asma Dilawari	CDER/OOD/DO1	Sections: 1, 2, 8, 11, 12, 13,19	Select one: ☒ Authored ☐ Approved
	Signature: Asma Dilawari -S Digitally signed by Asma Dilawari -S Date: 2024.03.27 08:58:11 -04'00'			
Statistical Reviewer	Zhou Feng	CDER/OTS/DBV	Section: 8.1, 8.3	Select one: ☒ Authored ☐ Approved
	Signature: Zhou Feng -S Digitally signed by Zhou Feng -S Date: 2024.03.27 09:47:42 -04'00'			
Statistical Team Leader	Xin Gao	CDER/OTS/DBV	Section: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature: Xin Gao -S Digitally signed by Xin Gao -S Date: 2024.04.02 16:54:12 -04'00'			
Acting Division Director (OB)	Shenghui Tang	CDER/OTS/DBV	Section: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang Date: 2024.04.03 11:25:52 -04'00'			
Associate Director for Labeling (ADL)	William Pierce	CDER/OOD	Section: 11, Prescribing Information, Patient Labeling	Select one: ☒ Authored ☒ Approved
	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S Date: 2024.04.02 17:27:25 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Preeti Narayan	CDER/OOD/DO1	Section: All	Select one: ☒ Authored ☒ Approved
	Signature: Preeti Narayan -S Digitally signed by Preeti Narayan -S Date: 2024.03.28 12:57:18 -04'00'			

Division Director	Laleh Amiri-Kordestani	CDER/DO1	Section: All	Select one: ☒ Authored ☒ Approved
	Signature:			

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/s/

PREETI NARAYAN
04/05/2024 01:58:04 PM

LALEH AMIRI KORDESTANI
04/05/2024 02:02:50 PM

Clinical Discipline Review Memo
Division of Oncology 1

BLA #	BLA 761139 S-28
Drug Name	ENHERTU (fam-trastuzumab deruxtecan-nxki; T-DXd)
Indication	ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options
Applicant	AstraZeneca
Dates	Submission date: 11/30/2023 PDUFA date: May 30, 2024
Review Priority	Priority Review
Recommendation on Regulatory Action	Accelerated Approval
Clinical Reviewer	Suparna Wedam (Efficacy Primary Review) Asma Dilawari (Safety Primary Review)
Team Leader/CDTL	Preeti Narayan (Secondary Review)
Regulatory Project Manager	Alice Lee

The primary clinical review (DO1) is complete and has been added to the sBLA Assessment Aid review document. The recommendation for this application is accelerated approval.

The clinical secondary review is also complete. The recommendation for this application is accelerated approval.

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/s/

ASMA A DILAWARI
04/02/2024 01:08:24 PM

SUPARNA B WEDAM
04/02/2024 03:30:03 PM

PREETI NARAYAN
04/02/2024 10:42:03 PM

CDTL Review Memo
Division of Oncology 1

BLA #	BLA 761139 S-28
Drug Name	ENHERTU (fam-trastuzumab deruxtecan-nxki; T-DXd)
Indication	ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options
Applicant	AstraZeneca
Dates	Submission date: November 30, 2023 PDUFA date: May 30, 2024
Review Priority	Priority Review
Recommendation on Regulatory Action	Accelerated Approval
Clinical Reviewer	Suparna Wedam (Efficacy Primary Review) Asma Dilawari (Safety Primary Review)
Team Leader/CDTL	Preeti Narayan (Secondary Review)
Regulatory Project Manager	Alice Lee

The clinical secondary review is also complete. The recommendation for this application is accelerated approval.

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/s/

PREETI NARAYAN
04/05/2024 01:45:24 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Assessment Aid (AA), which will be uploaded to DARRTS when it is finalized. Refer to the AA for details. From a clinical pharmacology perspective, this BLA supplement is approvable.

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/s/

LILY L LEU
04/03/2024 11:53:34 AM

HONG ZHAO
04/03/2024 12:51:56 PM

Statistical Review is complete, and has been added to the sBLA integrated review document. My recommendation for this application is accelerated approval.

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/s/

ZHOU FENG
03/27/2024 10:49:33 AM

XIN GAO
03/28/2024 12:56:32 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s028

PRODUCT QUALITY REVIEW(S)

Memorandum of Assessment

Submission Tracking Number (STN):	BLA 761139, supplement-28 (SN0290)
Subject:	PAS (Efficacy Supplement): treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.
Stamp Date:	November 30, 2023
Review Date:	March 12, 2022
Primary Assessor:	Jun Liu, CDER/OPQ/OPQA III/DPQA XV
Secondary Assessor:	Maria Gutierrez Lugo, CDER/OPQ/OBP/DBRR III
RBPM:	Kelly Ballard, CDER/OPQ/OPRO/DRBPMI/RBPMB2
Applicant:	Daiichi Sankyo, Inc
Product:	Enhertu (fam-trastuzumab deruxtecan-nxki)
Action Due Date:	April 05, 2024

I. SUMMARY BASIS OF RECOMMENDATION:

A. Recommendation:

I recommend approval of this supplement from an immunogenicity assay perspective. Overall, the assays used in the immunogenicity assessment were adequately validated and their performance during analysis of the clinical samples is acceptable. No approvability issues were identified with respect to the validation and performance of the immunogenicity assays. We defer to the clinical and clinical pharmacology review teams for assessment of the immunogenicity data and the adequacy of the changes to labeling.

II. ASSESSMENT

A. Product Introduction

Enhertu/fam-trastuzumab deruxtecan (also known as DS-8201a) is an antibody-drug conjugate (ADC) composed of a recombinant humanized anti-human epidermal growth factor receptor (anti-HER) 2 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) covalently conjugated to a topoisomerase 1 inhibitor drug-linker (D-L), MAAA-1162a. The mAb component, referred to as MAAL-9001, has the same amino acid sequence as trastuzumab and binds specifically to the human HER2 extracellular domain. The released drug, MAAA-1181a, inhibits topoisomerase I and leads to apoptosis of the target cells. Enhertu was approved on December 20, 2019 under the accelerated approval regulations, 21 CFR 601.41, for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

DS-8201a drug product (DP) is a single-use sterile lyophilized powder containing 100 mg of DS-8201a in a Type I amber glass vial sealed with a rubber stopper and flip-off crimp cap. Prior to use, DS-8201a DP is reconstituted with 5 mL of water for injection to provide a solution with a concentration of 20 mg/mL

DS-8201a in 25mM histidine buffer that contains 90 mg/mL sucrose and 0.03% (w/v) of polysorbate 80 at a pH of 5.5.

B. Scope of Changes

On December 20, 2019, Enhertu was approved under accelerated approval, for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. To date, Enhertu has been approved for treatment of:

- Adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimens either:
 - in the metastatic setting, or
 - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- Adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
- Adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

In the current submission Daiichi provided clinical study results to support treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

No CMC related changes were reported in the current submission.

Immunogenicity

Reviewer Comments: The changes to the immunogenicity labeling submitted in this supplement are based on an integrated immunogenicity assessment made across 13 clinical studies (refer to Table 7 of section 2.7.2 Summary of Clinical Pharmacology Studies) comprising patients with different solid tumors including unresectable or metastatic HER2-positive (IHC 3+) solid tumors. The patient populations used to support the indications approved are similar to the patient population included in the integrated immunogenicity assessment.

To date, two ADA assays for detection, confirmation, and titration of anti-DS-8201a antibodies were developed by (b) (4) and (b) (4) respectively, and two neutralization assays were also developed by the two companies, respectively. All clinical samples from the thirteen studies were analyzed using ADA and Nab assays validated at (b) (4) or (b) (4). Overall, the assays used to analyze the immunogenicity data in Section 12.6 of Supplement 28 labeling were adequately validated (Refer to the CMC review memos for assessment of the immunogenicity assay validation provided in the original BLA submission and PMC reports received in Seq. 0118 and Seq. 0149).

Environmental Assessment

Reviewer Comments: The applicant provided an environmental analysis for Enhertu in section 1.12.14 of the current submission. Enhertu is an ADC comprised of a monoclonal antibody (MAAL-9001) conjugated with a drug-linker (MAAA-1162a), where the released drug is DXd (MAAA-1181a). (b) (4)

[REDACTED]

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Jun
Liu

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Maria
Gutierrez Lugo

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s028

OTHER REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING MEMO

Date of Assessment:	May 10, 2024
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III
Through:	Jun Liu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761139 / S-28
Applicant:	Daiichi Sankyo, Inc.
Submission Date:	November 30, 2023
Product:	Enhertu (fam-trastuzumab deruxtecan-nxki)
Dosage form(s):	For injection
Strength and Container-Closure:	100 mg in single-dose vial
Purpose of assessment:	The Applicant submitted an efficacy supplement for addition of indication for treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options with addition of statement in section 2 to indicate that maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours.
Recommendations:	The prescribing information, medication guide, and carton labeling are acceptable from an OPQA III labeling perspective.

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices.

The proposed labeling changes included addition of a statement in section 2.4 Preparation and Administration of the prescribing information that reads "The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours. (b) (4)

" Same statement has been added to the carton labeling. The product quality reviewer confirmed that this statement is acceptable based on the data submitted in Module 3 Section P.2.6 Compatibility. Editorial edits have been suggested by the agency to relocate the added statement to Administration section for clarity and the applicant revised as requested. The revised prescribing information and carton labeling is acceptable from OPQA III labeling perspective.

In addition, the carton labeling contains potency statement, "No U.S. standard of potency." Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for fam-trastuzumab deruxtecan products (i.e., there is no specific test method described in regulation for fam-trastuzumab deruxtecan products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Enhertu because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling. In an Information Request (IR) dated March 5, 2024, we requested the applicant to remove the statement "No U.S. standard of potency" from the proposed carton labeling. The applicant revised as requested.

CONCLUSION

The prescribing information and medication guide submitted on April 9, 2024, and carton labeling submitted on March 13, 2024, were assessed and found to be acceptable (see Appendix A) from an OPQA III labeling perspective.

APPENDICES

Appendix A: Accepted Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on April 9, 2024)
<\\CDSESUB1\EVSPROD\bla761139\0324\m1\us\final-label-text-nonannotated-uspi-agnostic-dp-02.pdf>
- Medication Guide (submitted on April 9, 2024)
<\\CDSESUB1\EVSPROD\bla761139\0324\m1\us\final-medication-guide-nonannotated-usmg-agnostic-dp.pdf>

- Carton Labeling (submitted March 13, 2024)





Jennifer
Kim

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Jun
Liu

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: March 22, 2024

To: Alice Lee, Regulatory Project Manager, Division of Oncology I (DO1)
William Pierce, Associate Director for Labeling

From: Courtney Leach, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

NDA/BLA: 761139, S-028

Background:

In response to DO1's consult request dated December 11, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide and carton and container labeling for supplement 028 for ENHERTU®. This supplement is to update the original BLA 761139 with the new indication for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and have no satisfactory alternative treatment options.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 12, 2024, and our comments are provided below.

Medication Guide:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on March 18, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on March 14, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Courtney Leach at (301) 796-1044 or Courtney.Leach@fda.hhs.gov.

PI:

<u>Section(s)</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comments</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION: Adverse Reactions		We note that “stomatitis” is included in Table 15 at a rate of 20% (based on FDA’s analysis). This information is not included in the Adverse Reactions section of the HIGHLIGHTS. We recommend revising the HIGHLIGHTS to include “stomatitis.” Additionally, once the PI is finalized, We recommend updating the Adverse Reactions in the Highlights to ensure the listed reactions are consistent with section 6.1.
5.1 Interstitial Lung Disease/Pneumonitis 5.2 Neutropenia 5.3 Left Ventricular Dysfunction 6.1 Clinical Trials Experience	<u>“HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)”</u> (bolded emphasis added)	Should “HER2-Positive” be before Solid Tumors in each of these sub-sections? i.e., “. . . and HER2-Positive Solid Tumors (Including IHC 3+)” We defer to DO1 on whether that is an accurate representation of the solid tumors evaluated.
14.5 HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors	“DESTINY-PanTumor02 . . . (b) (4) (emphasis added) “DESTINY-Lung01 . . . (b) (4) (emphasis added) “DESTINY-CRC02 . . . (b) (4) (emphasis added)	(b) (4)

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 18, 2024

To: Alice Lee, PharmD
Senior Regulatory Project Manager
Division of Oncology I (DO1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, WOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Courtney Leach, PharmD, BCCCP, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ENHERTU (fam-trastuzumab deruxtecan-nxki)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761139

Supplement Number: S-028

Applicant: Daiichi Sankyo, Inc.

1 INTRODUCTION

On November 30, 2023, Daiichi Sankyo, Inc. submitted for the Agency's review the final submission package as part of the Real-Time Oncology Review (RTOR) for a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 761139/S-028 for ENHERTU (fam-trastuzumab deruxtecan-nxki) injection. With this supplement, the Applicant proposes a new indication for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology I (DO1) on December 11, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ENHERTU (fam-trastuzumab deruxtecan-nxki) injection.

2 MATERIAL REVIEWED

- Draft ENHERTU (fam-trastuzumab deruxtecan-nxki) injection MG received on November 30, 2023, and received by DMPP and OPDP on March 12, 2024.
- Draft ENHERTU (fam-trastuzumab deruxtecan-nxki) injection Prescribing Information (PI) received on November 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 12, 2024.
- Approved ENHERTU (fam-trastuzumab deruxtecan-nxki) injection labeling dated February 15, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

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- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

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LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 28, 2024
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761139/S-028
Product Name, Dosage Form, and Strength:	Enhertu (fam-trastuzumab deruxtecan-nxki) injection, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Daiichi Sankyo, Inc.
FDA Received Date:	November 30, 2023
TTT ID #:	2023-7448
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

Daiichi Sankyo, Inc. submitted a Efficacy Supplement for Enhertu (fam-trastuzumab deruxtecan-nxki) injection for the following indication:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

Subsequently, the Division of Oncology 1 (DO1) requested that we review the proposed Enhertu prescribing information (PI), Medication Guide, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Enhertu Medication Guide and carton labeling did not identify areas of vulnerability that may lead to medication errors.

The proposed prescribing information (PI) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division.

4 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

Table 1. Identified Issues and Recommendations for Division of Oncology 1 (DO1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The dosage and administration section did not provide the recommended dosage for “(b) (4) Solid Tumors” indication.	Not including this information will create a discrepancy between the dosage information in the Highlights of the PI and the Full PI.	Include the recommended dosage for “(b) (4) Solid Tumors” indication.
Full Prescribing Information – Section 2 Dosage and Administration, Section 2.4 Preparation and Administration			
1.	As currently stated under the “Administration” heading, “The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours. (b) (4)”	This information conflicts with the information provided under the “Dilution” heading, which states “If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours, protected from light.”	Clarify the discrepancy (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Enhertu received on November 30, 2023 from Daiichi Sankyo, Inc..

Table 2. Relevant Product Information for Enhertu	
Initial Approval Date	12/20/2019
Proper Name	fam-trastuzumab deruxtecan-nxki
Indication	Current indications: - adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either: - in the metastatic setting, or - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy. - adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. - adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. <i>Proposed indication:</i> <i>adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options</i>
Route of Administration	intravenous
Dosage Form	injection
Strength	100 mg/vial

Table 2. Relevant Product Information for Enhertu	
Dose and Frequency	Recommended Dosage for Metastatic Breast Cancer, Unresectable or Metastatic HER2-Mutant NSCLC, and (b) (4) <i>Unresectable or Metastatic Solid Tumors</i>: 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Recommended dosage for locally advanced or metastatic gastric cancer: 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
How Supplied	Carton of one 100 mg single-dose vial
Storage	Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of reconstitution. Do not freeze. Do not shake the reconstituted or diluted solution
Container Closure	Single-dose vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 26, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, Enhertu. Our search identified 1 previous review^a since the date of our last search on July 12, 2023, and we considered our previous recommendations to see if they are applicable for this current review.

^a Gao, T. Label and Labeling Review for Enhertu (BLA 761139/S-026). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Oct 6. TTT ID No.: 2023-4736.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Enhertu labels and labeling submitted by Daiichi Sankyo, Inc..

- Carton labeling received on November 30, 2023, available from <\\CDSESUB1\EVSPROD\bla761139\0290\m1\us\draft-enhertu-100-mg-carton.pdf>
- Prescribing Information (Image not shown) received on November 30, 2023, available from <\\CDSESUB1\EVSPROD\bla761139\0290\m1\us\annotated-draft-label-uspi-agnostic-dp-02.docx>
- Medication Guide (Image not shown) received on November 30, 2023, available from <\\CDSESUB1\EVSPROD\bla761139\0290\m1\us\annotated-draft-medication-guide-usmg-agnostic-dp-02-recon.docx>

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

F.2 Label and Labeling Images

Carton labeling

(b) (4)



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Clinical Inspection Summary

Date	02/27/2024
From	Regina Zopf, MD, Senior Medical Officer Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Asma Dilawari MD and Suparna Wedam, MD, Clinical Reviewers Preeti Narayan, MD, Clinical Team Leader Alice Lee, Regulatory Project Manager Division of Oncology 1 (DO1)
BLA #/Supplement #	761139/S-028
Applicant	Daiichi Sankyo, Inc.
Drug	Enhertu (fam-trastuzumab deruxtecan-nxki)
NME (Yes/No)	No
Therapeutic Classification	HER2-directed antibody and topoisomerase inhibitor conjugate
Proposed Indication	Treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options
Consultation Request Date	12/13/2023
Summary Goal Date	03/01/2024
Action Goal Date	03/11/2024
PDUFA Date	05/30/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Daiichi Sankyo, Inc. (DS), submitted clinical data from DESTINY Pan Tumor 02 Study (DP-02) to the Agency in support of a supplemental biologics license application (BLA 761139) for Enhertu for the proposed indication of treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment or who have no satisfactory alternative treatment options.

One clinical investigator (Dr. Meric-Bernstam) and the central imaging CRO, (b) (4) were inspected.

The inspections did not find significant concerns regarding the oversight of the clinical trials or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these

inspections, data generated by the inspected clinical investigator and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

Daiichi Sankyo, Inc., Inc. seeks approval for a supplemental biologics license application for Enhertu, A HER2-directed antibody drug conjugate (ADC), composed of composed of a humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab. Enhertu is currently approved for the treatment of unresectable or metastatic breast, non-small cell lung or gastric or locally advanced gastroesophageal cancers. In support of the supplemental BLA, the Applicant submitted clinical data from five phase 2 studies however, for purposes of inspection, one phase 2 study (DP-02) was selected for inspection. The following is a summary of the study protocol and key study information relevant to the clinical inspection.

Study Number DP-02:

This application relies on a phase 2, prospective, single-arm, multi-arm, multi-center, open-label study to evaluate the efficacy, tolerability, and safety of Enhertu for treatment of selected HER2-expressing solid tumors.

Study Status:

Study Initiation and Completion Dates: August 18, 2020 to ongoing

Interim Database Lock Date: July 3, 2023

Study Sites: 65 study centers globally across 15 countries.

Subject Enrollment and Completion Status:

- 268 subjects enrolled; 75 in Cohort of interest HER2-positive (IHC 3+)
- 267 received treatment (safety analysis set)
- 235 discontinued the study treatment (145 (54.3%) due to objective disease progression, 22 (8.2%) due to subjective disease progression)
- 83 (31.1%) remain in the study
- 30 (12.0%) remain in the ongoing study treatment

Study Design

Study Destiny-PanTumor-02 (DP-02) is an ongoing, open-label, multicenter, single-arm Phase II study to evaluate the antitumor activity and safety of ENHERTU for the treatment of selected HER2-expressing solid tumors. The treatment arm received ENHERTU 5.4 mg/kg injection administered once every 3 weeks. Eligible patients had locally advanced unresectable

or metastatic disease that had progressed following prior treatment or had no satisfactory alternative treatment options.

Objectives and Endpoints

The primary objective of the trial was to assess the efficacy of ENHERTU in patients with metastatic of unresectable tumors in selected HER2-expressing tumor types. The primary endpoint was Objective Response Rate (ORR) according to RECIST v1.1, as assessed by investigator and confirmed by ICR.

Secondary endpoints included:

- Safety
- tolerability duration of response
- disease control rate
- progression-free survival
- overall survival
- pharmacokinetics.

Exploratory analyses of the primary and secondary endpoints that were additional to the protocol-specified endpoints included:

- ORR
- duration of response
- disease control rate
- and progression-free survival by ICR (in overall population and by HER2 amplification and HER2 expression).

Study Conduct

Screening period:

- Day -28 to day -1: screening, HER2 status, tumor assessments (RECIST v1.1), serum tumor markers, high resolution Chest CT, ECHO or MUGA, concomitant medications, adverse events, laboratories (hematology, chemistry, coagulation, troponin), pregnancy test, ophthalmologic assessments, ECOG-Performance Score (PS), baseline data, concomitant medications and adverse events.

Treatment Period:

Treatment with ENHERTU was not to occur less than 19 days apart. With each treatment the following assessments were performed:

- Day 1: targeted physical examination, vital signs, ECOG-PS score and laboratory examinations, 12-lead ECG, pulse oximeter, pregnancy test, ENHERTU antidrug antibodies, optional blood sampling for biomarker and gene assessments.

- Day 8: Laboratories (chemistry and hematology), vital signs, concomitant medications and adverse events.
- Day 15: Laboratories (chemistry and hematology), vital signs, concomitant medications and adverse events.
- Treatment:
On-study tumor assessments of chest, abdomen, and pelvis occur every 6 weeks ($\pm$ 1 week) for the first 48 weeks after the date of first dose of IP and then every 12 weeks ($\pm$ 1 week) thereafter, until RECIST v1.1-defined radiological progression or until withdrawal of consent, regardless of any delays in dosing. Serum tumor markers were assessed every 6 weeks ($\pm$ 1 week) for the first 48 weeks relative to date of first dose of IP, then every 12 weeks ($\pm$ 1 week) thereafter and at end of treatment

RESULTS

1. Dr. Funda Meric-Bernstam (Site number 7801)

1515 Holcombe Blvd,
Houston, TX, 77030-4009 US

Inspection Dates: January 29, 2024 – February 1, 2024

This investigator was inspected as a routine PDUFA surveillance and data audit for Study DP-02. This was the first inspection of this clinical investigator.

Dr. Meric-Bernstam initiated DP-02 in September 2020 at Site 7801.

At the time of the inspection, the site had screened 40 subjects and enrolled and treated (b) (4) subjects. No subjects at this site completed the study and there were (b) (4) deaths. There were no discrepancies between the screening and enrollment logs and the data listings submitted to FDA.

All (b) (4) of the enrolled subjects' records were reviewed for inclusion/exclusion, protocol deviations, AEs, SAEs, IP accountability, investigator RECIST scores, concomitant medications, and observations and data on the condition of the subject throughout participation in the study.

Documents related to these outcomes were reviewed, including the following subject-related electronic source documents: EMR and eCRF. The audit trails were reviewed, and electronic source documents met the standards of being attributable, legible, contemporaneous, original, and accurate.

The informed consent forms were reviewed for all participants. Subjects were adequately informed about the purpose of the study inclusive with potential risks, benefits, as well as structure of the clinical study. All subjects received informed consent prior to screening and initiating study treatment.

Study-related documents were also reviewed and included: approved protocols; signed 1572s, financial disclosures, delegation log, screening/enrollment log; IRB approval for DP-02; and sponsor monitoring activities, all protocol amendments, administrative files, correspondence files, and master subject lists.

The primary efficacy endpoint data were reviewed and were verifiable. There were no over reporting or under reporting of AEs, SAEs, and deviations were reported according to the protocol.

The data generated by Dr. Meric-Bernstam's site are found to be acceptable in the support of the proposed indication of this supplemental BLA.

2. [REDACTED] (b) (4)

Inspection Date: [REDACTED] (b) (4)

[REDACTED] (b) (4) was inspected as a routine, pre-announced PDUFA inspection for Study DP-02. This firm underwent five BIMO inspections since 2018 all with no significant findings with the most recent prior inspection completed on [REDACTED] (b) (4).

The sponsor contracted [REDACTED] (b) (4) to provide medical imaging and Interactive Response Technology (IRT) services. [REDACTED] (b) (4)

Records reviewed at [REDACTED] (b) (4) included but were not limited to, organizational charts, financial disclosure forms, independent review charters, study protocols, source records related to radiology review and adjudication, the AstraZeneca RECIST 1.1 Independent Review Master Charter and Addendum.

All independent radiology reviews are maintained in [REDACTED] (b) (4). An independent review of tumor measurement data for 36 of 75 ICH 3+ subjects (1 from each of 36 sites among IHC 3+ subjects) were reviewed and compared to data listings. The endpoints were derived, and appropriate adjudication was performed as outlined in the charter and addendum. The Overall Response Assessment and Response Measurements by ICR were performed according to RECIST 1.1. All results were found to be consistent with the data listings.

The inspection found no compliance deficiencies in the performance of [REDACTED] (b) (4) central imaging review. Based on the results of the inspection, the imaging review data generated by [REDACTED] (b) (4) appear acceptable in support of the proposed indication in the BLA.

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