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| **Protocol Number:** | C4251006/SGNTUC-025 |
| **Version:** | Amendment 03; 16-Oct-2024 |
| **Protocol Title:** | A Single Arm, Open Label Phase 2 Study of Tucatinib in Combination with Trastuzumab Deruxtecan in Subjects with Previously Treated Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer |
| **Investigational Product:** | PF-07265792 (Tucatinib) |
| **Brief Title:** | A study of tucatinib plus trastuzumab deruxtecan in HER2+ breast cancer |
| **Phase:** | 2 |
| **IND Number:** | 119421 |
| **sponsor:** | Seagen Inc., a wholly owned subsidiary of Pfizer<br>21823 30th Drive SE<br>Bothell, WA 98021, USA |

**Document History**

| Document | Version Date |
|---|---|
| Original | 10-Jun-2020 |
| Amendment 1 | 16-Oct-2020 |
| Amendment 2 | 03-Dec-2021 |
| Amendment 3 | 16-Oct-2024 |

## Protocol Amendment Summary of Changes Table

## Amendment 03 (DD-Oct-2024)

**Overall Rationale for the Amendment:** The primary purpose of this amendment is to incorporate a long-term extension phase and to align with the Pfizer protocol template and standard operating procedures.

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| **Substantial Modification(s)** | | |
| Added that participants still receiving clinical benefit and remaining on study treatment as of Amendment 3 may continue to receive study intervention during the LTEP. | To allow participants who are still receiving clinical benefit to remain on treatment. | Synopsis (Post-safety Lead-in, Duration of Treatment)<br>Section 3.1 Summary of Study Design |
| Added: "During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care." | To clarify collection of efficacy assessments during the LTEP. | Synopsis (Efficacy Assessments), Section 7.2 Response/Efficacy Assessments |
| Clarified that only pregnancies and SAEs will be collected by the sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential. | Clarification of data collection during LTEP. | Synopsis (Safety Assessments), Section 7.7 Safety Assessments |
| Added: "As of Amendment 3, all participants still on study who are not entering the LTEP will have a last visit/contact. The study will end when the last LTEP participant has had their last visit/contact. The sponsor will provide continued access to study intervention during the LTEP for any participant who is still on tucatinib with or without T-DXd and receiving clinical benefit based on the investigator's assessment." | Defined end of study for participants entering LTEP. | Section 3.1.4 End of Study |
| Updated definition of women of childbearing and non-childbearing potential. | To align with Pfizer's Protocol Template. | Section 4.4 Childbearing Potential |
| Added that for participants continuing to LTEP, data will only be documented in the participant's medical record. | Clarification of data collection during LTEP. | Section 4.5 Removal of Participants from Therapy or Assessment |
| Language revised to have overdose reported to Safety only when associated with an SAE. | To align with Pfizer's safety reporting process. | Section 5.4.4, 5.3.4 Overdose |
| Added that treatment administration data will no longer be collected during the LTEP. | Clarification of data collection during LTEP. | Section 5.8 Treatment Compliance |

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| Added LTEP for participants still receiving clinical benefit and remaining on treatment with tucatinib with or without T-DXd. Only pregnancies and SAEs will be collected by the sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential. | LTEP added to allow participants still receiving clinical benefit to remain on study treatment and clarification of data collection during the LTEP. | Section 6.7 Long-term Extension Phase (LTEP), Appendix I |
| Added that pregnancy testing will continue every 3 weeks for participants of child-bearing potential during the LTEP | To clarify that pregnancy testing per protocol specified frequency will continue during the LTEP. | Section 6.3.5 Cycle 3 and Beyond, Day 1 (–1 day to +3 days) |
| Clarified that during the LTEP, brain metastases evaluations will be performed per institutional guidelines and investigator-determined usual and customary clinical care. | To clarify that brain metastases evaluations will be conducted during the LTEP. | Section 7.2.1 Evaluation of Brain Metastases |
| Clarified that during the LTEP, only AESIs that meet SAE criteria will be reported to Pfizer Safety using PSSA only and will not be recorded within the CRF. | Clarification of data collection during LTEP. | Section 7.7.1.1 Definitions/Adverse Events of Special Interest |
| Clarified that during the LTEP, pregnancies and SAEs will be reported to the sponsor. | Guidance on steps to following when recording safety data during the LTEP. | Section 7.7.1.2 Procedures for Eliciting and Recording Adverse Events/Recording Serious Events |
| Added section indicating lack of efficacy as reportable event to Pfizer Safety only if associated with an SAE. | To support Study transition to Pfizer Pharmacovigilance processes and systems. | Section 7.7.1.2 subsection Lack of Efficacy |
| Clarified that during the LTEP, pregnancy reporting should continue and will be collected per guideline outlined under EDP. | Guidance for data collection of pregnancies that occur during the LTEP. | Section 7.7.5 Pregnancy Testing |
| Added the following text: “During the LTEP, ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.” | Guidance regarding ECG assessments during the LTEP. | 7.7.7.2 Electrocardiogram |
| Added the following text: “During the LTEP, cardiac assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.” | Guidance regarding cardiac function assessments during the LTEP. | Section 7.7.7.1 MUGA or ECHO |
| Added the following text: “During the LTEP, ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.” | Guidance regarding ECG assessments during the LTEP. | Section 7.7.7.2 Electrocardiogram |

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| Added text to indicate CRFs will not be collected during LTEP | eCRFs will not be collected in the LTEP. | Section 8.2 Accuracy and Reliability of Data |
| Added text to indicate data collection needed during LTEP. | Guidance for data collection during LTEP. | Section 8.3 Data Management Procedures |
| Added LTEP | Column added to indicate assessments to be done during the LTEP. | Appendix A. Schedule of Events |
| Added footnote "v": "During the LTEP, safety and efficacy assessments that include determination of disease progression will be performed per institutional guidelines and investigator-determined usual and customary clinical care." | Guidance for data collection during LTEP. | Appendix A. Schedule of Events |
| Added footnote "w": "Only SAEs and pregnancy will be collected by the sponsor" | Guidance for data collection during LTEP. | Appendix A. Schedule of Events |
| **Non-Substantial Modification(s)** | | |
| Added Pfizer sponsor's name and logo | Alignment with Pfizer document format and requirements. | Title page |
| Removed Medical Monitor's name and contact information | The medical monitor's name and contact information is personal identifiable information | Title page |
| Removal of Investigator's agreement and the investigator's signature. | The investigator's agreement and signature is personal identifiable information. | Page 2 (no Section number) |
| Pfizer Product Number added to the Seagen number. Throughout the rest of the protocol, Seagen product number replaced by Pfizer product number. | Alignment with Pfizer document format and requirements. | Title Page<br>Synopsis<br>Footer |
| Added ClinicalTrials.gov number | Alignment with Pfizer document format and requirements. | Synopsis |
| Contraception and barrier guidance updated | To align with Pfizer's Protocol Template. | Section 4.3 Contraception |
| Added that the withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow up. | To align with Pfizer's Protocol Template. | Section 4.5.1 Discontinuation of Study Treatment |

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| Added: "If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly. If the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected except for publicly available information as appropriately directed in accordance with local law. The sponsor may retain and continue to use any data collected before such withdrawal of consent." | To align with Pfizer's Protocol Template | Section 4.5.2 Participant Withdrawal from Study |
| Added tabular presentation of study interventions | To align with Pfizer's protocol template | Section 5.1 Treatments Administered |
| An SRSD was indicated for each IMP and NIMP/AxMP | To support study transition to Pfizer Pharmacovigilance processes and systems | Section 5.1 Treatments Administered |
| Details on storage temperature recording, temperature excursion management, product complaint reporting, IMP preparation and destruction added. | To align with Pfizer's Protocol Template. | Section 5.2 Preparation, Handling, Storage, and Accountability |
| Added section to augment existing study intervention information as it relates to preparation and dispensing | To align with Pfizer's Protocol Template. | Sections 5.3.8, 5.4.7 Preparation and Dispensing |
| Added that complications that occur during hospitalization are AEs. Clarified that the term disabling/incapacitating does not include experiences of relatively minor medical significance. | To further define the definitions of hospitalization and disabling/incapacitating | Section 7.7.1.1 Definitions |
| Revised language regarding exposure during pregnancy and added information on environmental and occupational exposure. | To support study transition to Pfizer Pharmacovigilance processes and systems. | Section 7.7.1.2 subsections Environmental Exposure, Exposure During Pregnancy and Occupational Exposure |
| Added that if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.<br>Safety reporting period clarified in case a participant begins a new anticancer therapy. | To support study transition to Pfizer Pharmacovigilance processes and systems. | Section 7.7.1.3 Reporting Period for Adverse Events and Serious Adverse Events |
| Pfizer Safety added as new destination of safety reporting.<br>PSSA added as electronic tool for reporting. | To support study transition to Pfizer | Section 7.7.1.4 Serious Adverse |

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| | Pharmacovigilance processes and systems. | Events Require Immediate Reporting |
| Clarified that local laboratory testing will be performed per institutional guidelines and investigator-determined usual and customary care. | Consistency with updates made in the document. | Section 7.7.3 Clinical Laboratory Tests |
| Added guidance on pregnancy testing | To align with Pfizer's Protocol Template. | Section 7.7.5 Pregnancy Testing |
| Added language requiring a protocol amendment incorporating any major modifications of the primary endpoint definitions or their analyses in the SAP. | To align with Pfizer's Protocol Template. | Section 9.3 Statistical and Analytical Plans |
| Section retitled from "Informed Consent, Ethical Review, and Regulatory Considerations" to "Regulatory, Ethical, and Study Oversight Considerations" and text was updated with required Pfizer protocol template language. Numerous subsections were added (appropriate to this study) consistent with Pfizer template language and sections that were obsolete from prior version of this document were removed. Sections that were not obsolete were kept and integrated in appropriately. | To support study transition to Pfizer processes and to align with required Pfizer protocol template language. | Section 10 Regulatory, Ethical, and Study Oversight Considerations |
| Removal of Investigator's agreement and the investigator's signature. | The investigator's agreement and signature is personal identifiable information. | Appendix J from prior amendment |
| AE definition, AE/SAE recording/reporting requirements and procedures | To support study transition to Pfizer Pharmacovigilance processes and systems. | Appendix J Adverse Events: Definitions and Procedures for Recording and Reporting |
| Replaced "package insert" with "product label" | Provide more informational terminology of product label. | Throughout document |
| The term "subject" has been updated to "participant" when referring to an individual who has consented to participate in the clinical study.<br>The term "Subject" has been updated to "patient" when used to describe the wider population beyond the trial.<br>The term "study drug" has been updated to "study intervention". | Alignment with Pfizer document format and requirements. | Throughout protocol |
| Minor editorial modifications in the text, which are not provided in this summary of changes, were made for additional clarity. | Minor updates and clarifications. | Throughout protocol |

# PROTOCOL SYNOPSIS

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|---|---|
| **Protocol Number**<br>C4251006/SGNTUC-025<br>**Version**<br>Amendment 03; 15-Oct-2024<br>**Phase**<br>2 | **Product Name**<br>PF-07265792 (Tucatinib)<br>**sponsor**<br>Seagen Inc., a wholly owned subsidiary of Pfizer<br>21823 30th Drive SE<br>Bothell, WA 98021, USA |

**Protocol Title**

A Single Arm, Open Label Phase 2 Study of Tucatinib in Combination with Trastuzumab Deruxtecan in Subjects with Previously Treated Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer

**Regulatory Agency Identification Numbers:**

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|---|---|
| **US IND Number:** | 119421 |
| **ClinicalTrials.gov ID:** | NCT04539938 |
| **Protocol Number:** | C4251006 (SGNTUC-025) |
| **Phase:** | 2 |

**Study Objectives and Endpoints**

| **Primary Objective** | **Corresponding Primary Endpoint** |
|---|---|
| • To determine the antitumor activity of tucatinib given in combination with trastuzumab deruxtecan (T-DXd) as measured by confirmed objective response rate (cORR) according to investigator (INV) assessment | • cORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 according to INV assessment |
| **Secondary Objectives** | **Corresponding Secondary Endpoints** |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd as measured by progression-free survival (PFS) according to INV assessment | • PFS per RECIST v1.1 according to INV assessment |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd as measured by duration of response (DOR) according to INV assessment | • DOR per RECIST v1.1 according to INV assessment |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd as measured by disease control rate (DCR) according to INV assessment | • DCR per RECIST v1.1 according to INV assessment |
| • To assess overall survival (OS) in participants treated with tucatinib given in combination with T-DXd | • OS |

| | |
|---|---|
| • To assess the safety and tolerability of tucatinib given in combination with T-DXd | • Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and lab abnormalities<br>• Frequency of dose modifications and treatment discontinuations<br>• Other relevant safety variables |
| **Exploratory Objectives** | **Corresponding Exploratory Endpoints** |
| *Efficacy* | |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd according to independent central review (ICR) assessment | • cORR per RECIST v1.1 according to ICR assessment<br>• PFS per RECIST v1.1 according to ICR assessment<br>• DOR per RECIST v1.1 according to ICR assessment<br>• DCR per RECIST v1.1 according to ICR assessment |
| *Pharmacokinetic* | |
| • To evaluate the pharmacokinetics (PK) of tucatinib | • Plasma concentrations of tucatinib |
| *Biomarker* | |
| • To explore correlations between blood-based or tissue biomarkers and clinical outcomes | • Potential biomarkers of response, resistance, or toxicity from blood-based or tumor samples |
| *Patient Reported Outcomes* | |
| • To assess patient-reported outcomes (PROs) associated with tucatinib given in combination with T-DXd | • Change from baseline in PRO assessments of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) |

**Study Population**

Participants with previously treated unresectable locally advanced/metastatic (LA/M) human epidermal growth factor receptor positive (HER2+) breast cancer who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab).

Participants must meet the following criteria to be eligible for the study:

***Inclusion Criteria***

1. Have confirmed HER2+ breast cancer, as defined by the current American Society of Clinical Oncology – College of American Pathologists (ASCO/CAP) guidelines, previously determined at a Clinical Laboratory Improvements Amendments (CLIA)-certified or International Organization for Standardization (ISO)-accredited laboratory.

2. History of prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab)

3. Have disease progression of unresectable LA/M breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy

4. Have measurable disease assessable by RECIST v1.1

5. Be at least 18 years of age at time of consent

6. Have Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1

7. Have a life expectancy of at least 6 months, in the opinion of the investigator

8. Have adequate hepatic function as defined by the following:

    a. Total bilirubin ≤1.5 x upper limit of normal (ULN). Exception: Participants with known history of Gilbert's Syndrome who have a direct bilirubin ≤1.5 x ULN in addition to a normal AST and ALT are eligible.

    b. Transaminases (AST and ALT) ≤3 x ULN (≤5 x ULN if liver metastases are present)

9. Have adequate baseline hematologic parameters as defined by:

    a. Absolute neutrophil count (ANC) ≥1.5 x $10^3$/µL

    b. Platelet count ≥100 x $10^3$/µL

    c. Hemoglobin ≥9 g/dL

    d. In participants transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support

10. Estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 $m^2$ using the Modification of Diet in Renal Disease (MDRD) study equation

11. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5 x ULN, unless on medication known to alter INR and PTT/aPTT.

12. Have left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study treatment

13. For participants of childbearing potential (Section 4.4), the following stipulations apply.

    a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to starting study treatment. A participant with a false positive result and documented verification that the participant is not pregnant is eligible for participation.

    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study intervention

    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study intervention

    d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix I) starting at the time of informed consent and

continuing throughout the study and for at least 7 months after the final dose of study intervention administration.

14. For participants who can father children, the following stipulations apply:

    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 4 months after the final study intervention

    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix I) starting at time of informed consent and continuing throughout the study and for at least 4 months after the final dose of study intervention

    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options (as defined in Appendix I) starting at time of informed consent and continuing throughout the study and for at least 4 months after the final dose of study intervention administration

15. Participant must provide signed informed consent per a consent document that has been approved by an institutional review board or independent ethics committee (IRB/IEC) prior to initiation of any study-related tests or procedures that are not part of standard of care for the patient's disease

16. Participants must be willing and able to comply with study procedures

***CNS Inclusion – Based on medical history and screening contrast brain magnetic resonance imaging (MRI), participants with a history of brain metastases must have one of the following***

17. Untreated brain metastases not needing immediate local therapy. For participants with untreated CNS lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment

18. Previously treated brain metastases

    a. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator

    b. Participants treated with CNS local therapy for newly identified or previously treated progressing lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if all of the following criteria are met:

        i. Time since whole brain radiation therapy (WBRT) is ≥14 days prior to first dose of study treatment, time since SRS is ≥7 days prior to first dose of study treatment, or time since surgical resection is ≥28 days

        ii. Other sites of measurable disease by RECIST v1.1 are present

    c. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

***Exclusion Criteria***

Participants will be excluded from the study for any of the following reasons:

1. Have previously been treated with:

a. Lapatinib or neratinib within 12 months of starting study treatment (except in cases where lapatinib or neratinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity)

b. Tucatinib or enrolled on a tucatinib clinical trial

c. Any investigational HER2/EGFR or HER2 TKI (eg, afatinib) at any time previously

d. T-DXd or another ADC consisting of an exatecan derivative

2. History of exposure to the following cumulative doses of anthracyclines:

a. Doxorubicin >360 mg/m$^2$

b. Epirubicin >720 mg/m$^2$

c. Mitoxantrone >120 mg/m$^2$

d. Idarubicin >90 mg/m$^2$

e. Liposomal doxorubicin (eg, Doxil, Caelyx, Myocet) >550 mg/m$^2$

3. History of allergic reactions to trastuzumab or compounds chemically or biologically similar to tucatinib or T-DXd, except for Grade 1 or 2 infusion-related- reactions (IRRs) to trastuzumab that were successfully managed, or known allergy to one of the excipients in the study interventions

4. Have received treatment with:

a. Any systemic anti-cancer therapy (including hormonal therapy) or experimental agent ≤21 days of first dose of study treatment or are currently participating in another interventional clinical trial. An exception for the washout of hormonal therapies is gonadotropin releasing hormone (GnRH) agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications

b. Treatment with non-CNS radiation ≤7 days prior to first dose of study treatment

c. Major surgery within <28 days of first dose of study treatment

5. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:

- Alopecia
- Neuropathy, which must have resolved to ≤ Grade 2
- Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
- Anemia, which must have resolved to ≤ Grade 2

6. Have clinically significant cardiopulmonary disease such as:

- Ventricular arrhythmia requiring therapy
- Symptomatic hypertension or uncontrolled hypertension as determined by investigator
- Any history of symptomatic CHF
- Severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy

- Hypoxia requiring supplementary oxygen therapy
- Have had a history of ILD/pneumonitis (eg, interstitial pneumonia, pneumonitis, pulmonary fibrosis, or radiation pneumonitis) that required systemic corticosteroids, or has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening

7. Have known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment

8. Known to be positive for hepatitis B by surface antigen expression. Known to be positive for hepatitis C infection. Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks

9. Presence of known chronic liver disease

10. Participants known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:

    - CD4+ T-cell count of <350 cells/μL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks

11. Active or uncontrolled clinically serious infection

12. Are pregnant, breastfeeding, or planning a pregnancy

13. Have inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications

14. Have used a strong cytochrome P450 (CYP) 2C8 inhibitor within 5 elimination half-lives of the inhibitor, or have used a strong CYP3A4 or moderate/strong CYP2C8 inducer within 5 days prior to first dose of study treatment.

15. Unable for any reason to undergo contrast MRI of the brain

16. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures

17. History of malignancy other than breast cancer within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (eg, 5-year OS of ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

***CNS Exclusion*** – Based on medical history and screening contrast brain MRI, participants must not have any of the following (listed in criteria 18–22):

18. Any untreated brain lesions >2.0 cm in size, unless discussed with medical monitor and approval for enrollment is given

19. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or equivalent). However, participants on a chronic stable dose of ≤2 mg total

daily dose of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor

20. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to participant (eg, brain stem lesions). Participants who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria 18b

21. Known or suspected leptomeningeal disease (LMD) as documented by the investigator

22. Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases

23. Have ongoing ≥ Grade 2 diarrhea of any etiology

**Number of Planned Participants**

Approximately 60 to 70 participants will be enrolled in the study to ensure about 60 participants will be treated at the Safety Monitoring Committee (SMC) recommended dose.

**Study Design**

This is a single arm, open-label, multi-center phase 2 trial designed to assess the safety and efficacy of tucatinib in combination with T-DXd for the treatment of participants with previously treated unresectable LA/M HER2+ breast cancer with or without brain metastases, who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab).

A SMC will continuously monitor participants for AEs, serious adverse events (SAEs), dose modifications, and laboratory abnormalities throughout the course of the study.

**Safety Lead-in**

Ten participants will be enrolled, irrespective of cohort, in the safety lead-in portion of the study and receive tucatinib 300 mg orally twice daily (PO BID) and T-DXd 5.4 mg/kg via intravenous (IV) infusion on Day 1 of each of 21-day cycle. The participants enrolled in the safety lead-in will undergo the same efficacy, PK, and biomarker analyses as all other participants with the exception of an additional PK assessment performed at Cycle 1 Day 12. Once 10 participants are enrolled in the safety lead-in, enrollment will be paused until all participants have been followed for at least 1 cycle and a comprehensive review of the safety profile by the SMC has occurred. The SMC will make recommendations regarding continuing with enrollment if the safety and tolerability of the regimen is acceptable. If clinically significant safety events are observed at any point during the safety lead-in, enrollment will be paused until relatedness has been determined, and review by the SMC has occurred. Based on the totality of the safety data, the SMC may recommend proceeding with enrollment, evaluation of alternative dosing, or not proceeding with further enrollment. The SMC may also recommend expanding the safety lead-in to enroll up to approximately 10 additional participants with continued monitoring for safety by the SMC.

**Post-safety Lead-in**

Following the safety lead-in, enrollment will continue until approximately 60 response-evaluable participants have been enrolled at the SMC recommended dose. There will be 2 cohorts in the study, 1 for participants without brain metastases (Cohort A) and 1 for participants with a history of brain metastases (Cohort B), with approximately 30 participants enrolled into each cohort. All participants, including those in the safety lead-in, treated at the SMC recommended dose, will be included in the efficacy analysis. Additional optional cohorts evaluating the combination of tucatinib and T-DXd in earlier treatment lines for breast cancer, such as the

first-line metastatic setting or neoadjuvant/adjuvant setting, may be added. Optional cohorts may also be opened in other malignancies, such as non-small cell lung cancer, urothelial cancer, gastric/gastroesophageal junction cancer, and colorectal cancer.

The incidence of diarrhea, though predominantly low grade, has resulted in dose modifications of tucatinib, and prophylactic antidiarrheals have been recommended by the SMC. Antidiarrheal prophylaxis will be administered for the first 42 days of study treatment. After this initial 42-day period, participants may continue on antidiarrheal prophylaxis or be switched to symptomatic treatment of diarrhea, at the investigator's discretion. Symptomatic management of treatment-induced diarrhea should be based on established guidelines (Benson et al, 2004; Bossi et al, 2018).

The primary endpoint of the study is confirmed ORR by investigator. Radiographic efficacy assessments will be made by the investigator, according to RECIST v1.1, with confirmation required ≥4 weeks from the first documentation of response. In addition, images will be collected by an ICR facility for possible future analysis.

Secondary efficacy endpoints include DOR, PFS, DCR, and OS.

As of Amendment 3, the objectives of the study have been achieved. Therefore, the decision has been made to close the study. For participants in long-term follow-up, a last visit or contact will occur prior to the participant's discontinuation from participation in the study. Any participant on treatment with tucatinib with or without T-DXd will transition to the long-term extension phase (LTEP) of the study. The sponsor will provide continued access to study intervention during the LTEP for any participant who is still on tucatinib with or without T-DXd and receiving clinical benefit based on the investigator's assessment. Once post-study access to study treatment is available, participants will have a last visit or contact prior to discontinuation from the study.

**Investigational Products, Dose, and Mode of Administration**

Participants will receive tucatinib and T-DXd in combination at the following doses:

- Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle.
- T-DXd 5.4 mg/kg IV on Day 1 of each 21-day cycle.

**Duration of Treatment**

Participants may continue on study treatment until progressive disease (PD), unacceptable toxicity, investigator or participant decision to discontinue, or study closure. All efforts should be made to continue treatment until unequivocal evidence of radiographic progression, per RECIST v1.1, occurs.

Participants assessed as having isolated progression in the CNS per RECIST v1.1, may be eligible to continue on study treatment for clinical benefit after undergoing local therapy to CNS disease, with approval from the medical monitor.

As of Amendment 3, participants still receiving clinical benefit based on the investigator's assessment and remaining on treatment with tucatinib with or without T-DXd may continue receiving study intervention during the LTEP until post-study access to study treatment is available.

**Efficacy Assessments**

Disease response per RECIST v1.1 will be assessed by the investigator. Response assessments will include measurement of all known sites of unresectable LA/M disease (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast computed tomography (CT), at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose delays. Positron emission tomography (PET)/CT (if high quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other known sites of disease (eg, photography for skin lesions, nuclear bone scan imaging for bone lesions). For each participant, the same imaging modality as used at baseline should be used throughout the study.

Contrast MRI of the brain will be required on this same schedule only in those participants with prior history of brain metastases or brain metastases found on screening MRI. Additional contrast MRIs of the brain may also be performed in participants without known brain metastases if there is clinical suspicion of new brain lesions.

Participants who discontinue study treatment for reasons other than documented PD will continue to have disease assessments every 9 weeks (±1 week) until the occurrence of disease progression per RECIST v1.1, death, withdrawal of consent or study closure.

Follow-up for survival and subsequent anti-cancer therapy will occur approximately every 3 months and continue until death, withdrawal of consent, lost to follow-up, or study closure.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

**Pharmacokinetic Assessments**

PK assessments of trough levels of tucatinib drug levels will be performed on Day 1 of Cycles 2, 3, and 6 prior to administration of tucatinib. On Day 1 of Cycles 2 and 3, PK assessments of peak levels of tucatinib will be performed 2 hours (±15 minutes) after administration of tucatinib. For safety lead-in participants only, an additional post-tucatinib dose pharmacokinetic assessment will be performed on Cycle 1 Day 12.

**Biomarker Assessments**

Blood samples will be collected at screening, Cycle 3 Day 1 (predose), and at end of treatment (EOT) to assess exploratory biomarkers in relation to response, resistance, or toxicity. Biomarker assessments may include an exploratory assessment of HER2 mutations or other genetic alterations as potential biomarkers of response. Additional exploratory analyses on archival tissue including but not limited to immunohistochemistry (IHC) and next generation sequencing (NGS) analysis may be performed to interrogate biomarkers that are associated with tumor growth, survival, and resistance to targeted therapeutics. This assessment may enable the correlation of additional biomarkers with treatment outcome and may ultimately guide or refine participant selection strategies to better match tucatinib regimens with tumor phenotype/genotype in the future.

**Safety Assessments**

Participants will be assessed throughout the study for safety. Safety assessments including physical exam and collection of AEs and laboratory abnormalities will be performed at a minimum of once every 3 weeks throughout study treatment and 30 days after the last dose of study interventions. Laboratory assessments will be performed locally. During Cycle 1, an in-person safety assessment will be performed on Days 1 and 12. During Cycle 2, an in-person safety assessment will be performed on Day 1 and liver function tests (LFTs) will be collected on Cycle 2 Day 12. An in-person safety assessment will then be performed on Day 1 of each cycle throughout the remainder of the study or as clinically indicated. Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation irrespective of dose delays or interruption, and 30 days after the last dose of study interventions (unless done within 12 weeks prior to the EOT visit).

Participants will be monitored for signs and symptoms of ILD/pneumonitis. In cases where ILD/pneumonitis is suspected, treatment with T-DXd will be interrupted, and the participant will undergo evaluation including radiographic imaging. Pulmonary consultation should also be considered. Dose modification or discontinuation of T-DXd for cases of ILD/pneumonitis will be made as per product label.

Only pregnancies and SAEs will be collected by the sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential.

**Patient-Reported Outcomes**

PROs will be explored with the EQ-5D-5L instrument. EQ-5D-5L will be administered prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment at: Cycle 1 Day 1 (C1D1), C2D1, C3D1, C4D1, every 2 cycles starting at Cycle 6 thereafter, until treatment discontinuation, PD, death, unacceptable toxicity, withdrawal of consent or study closure, and at the EOT visit.

**Statistical Methods**

Safety and efficacy will be assessed using descriptive statistics, including the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

The primary endpoint, cORR per investigator, is defined as the proportion of participants with confirmed complete response (CR) or partial response (PR), per RECIST v1.1. The 2-sided 95% exact confidence interval (CI) using Clopper-Pearson method will be calculated for the response rates.

For illustrative purposes, a summary of the expected 95% CIs for the overall study (N=60) and by cohort (N=30) is presented below, which shows reasonable precision for the estimation.

| Number of participants | Number of Responses | ORR | 95% exact CI |
|---|---|---|---|
| 60 | 40 | 66.7% | (53.3%, 78.3%) |
| | 42 | 70.0% | (56.8%, 81.2%) |
| | 44 | 73.3% | (60.3%, 83.9%) |
| | 46 | 76.7% | (64.0%, 86.6%) |
| | 48 | 80.0% | (67.7%, 89.2%) |
| | 50 | 83.3% | (71.5%, 91.7%) |
| | 52 | 86.7% | (75.4%, 94.1%) |
| 30 | 20 | 66.7% | (47.2%, 82.7%) |
| | 22 | 73.3% | (54.1%, 87.7%) |
| | 24 | 80.0% | (61.4%, 92.3%) |
| | 26 | 86.7% | (69.3%, 96.2%) |

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## APPENDICES

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ADC | antibody-drug conjugate |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| BAP | biomarker analysis plan |
| β-hCG | beta human chorionic gonadotropin |
| BID | twice daily |
| CAP | College of American Pathologists |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CHF | congestive heart failure |
| CI | confidence interval |
| CLIA | Clinical Laboratory Improvements Amendments |
| CNS | central nervous system |
| cORR | confirmed objective response rate |
| CR | complete response |
| CRF | case report form |
| CSR | clinical study report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DCR | disease control rate |
| DILI | drug-induced liver injury |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| eCRF | electronic CRF |

| | |
|---|---|
| EDB | exposure during breastfeeding |
| EDP | exposure during pregnancy |
| eGFR | estimated glomerular filtration rate |
| EGRF | epidermal growth factor receptor |
| EOT | end of treatment |
| EQ-5D-5L | European Quality of Life 5-Dimension 5-Level |
| FDA | U.S. Food and Drug Administration |
| GCP | Good Clinical Practice |
| HER2 | human epidermal growth factor receptor |
| HR | hazard ratio |
| IB | investigator's brochure |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICR | independent central review |
| IEC | independent ethics committee |
| IHC | immunohistochemistry |
| ILD | interstitial lung disease |
| IMP | investigational medicinal product |
| INR | international normalized ratio |
| INV | investigator |
| IP | investigational product |
| IRB | institutional review board |
| IRR | infusion-related reaction |
| ISO | International Organization for Standardization |
| IV | intravenous |
| LA/M | locally advanced/metastatic |
| LFT | liver function test |
| LTEP | long-term extension phase |
| LVEF | Left ventricular ejection fraction |
| MBC | metastatic breast cancer |
| MDRD | Modification of Diet in Renal Disease [study] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MQI | medically qualified individual |

| | |
|---|---|
| MRI | magnetic resonance imaging |
| MUGA | multiple-gated acquisition scan |
| NCI | National Cancer Institute |
| NGS | Next Generation Sequencing |
| ORR | Objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PET | positron emission tomography |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| PK | pharmacokinetics |
| PO | orally |
| PR | partial response |
| PRO | patient-reported outcome |
| PSSA | Pfizer's SAE submission assistant |
| PTT | partial thromboplastin time |
| QoL | quality of life |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SMC | Safety Monitoring Committee |
| SoE | schedule of events |
| SRS | stereotactic radiosurgery |
| SRSD | Single Reference Safety Document |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T-DM1 | ado-trastuzumab emtansine |
| T-DXd | trastuzumab deruxtecan |
| TEAE | treatment-emergent adverse event |
| T-Ex | trastuzumab conjugated with exatecan moiety |
| TKI | tyrosine kinase inhibitor |
| ULN | upper limit of normal |
| VAS | visual analog scale |

| | |
|---|---|
| WBRT | whole brain radiation therapy |
| WOCBP | woman of childbearing potential |

# 1. INTRODUCTION

## 1.1. HER2+ Breast Cancer

Breast cancer is the most common form and leading cause of cancer-related death in women worldwide (Bray et al, 2018). In 2020, the estimated number of women that will be newly diagnosed with breast cancer in the United States is 276,480, and there will be 42,170 breast cancer-related deaths (Siegel et al, 2020). Approximately 15% to 20% of all breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) (Owens et al, 2004; Giordano et al, 2014; American Cancer Society (ACS), 2018). HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Tumors that overexpress HER2 are more aggressive and historically have been associated with poorer overall survival (OS) compared to HER2 negative cancers (Slamon et al, 1987).

## 1.2. Treatment of HER2+ Breast Cancer

The introduction of HER2-targeted therapies has led to significant and meaningful improvements in disease-free survival, progression-free survival (PFS), and OS in both the neoadjuvant/adjuvant and metastatic settings (Slamon et al, 2001; Geyer et al, 2006; Baselga et al, 2012; Verma et al, 2012).

### 1.2.1. Trastuzumab, Pertuzumab, and T-DM1

Trastuzumab, a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, was the first anti-HER2 agent approved by regulatory authorities for use in the treatment of HER2+ breast cancer and remains the backbone of treatment in the perioperative and metastatic setting, usually in combination with a taxane (Slamon et al, 2001; Vogel et al, 2002).

The development of trastuzumab has been followed by the approval of multiple anti-HER2 agents for the management of HER2+ breast cancer. Pertuzumab, a monoclonal antibody that binds to the HER2 receptor at a site different from trastuzumab, in combination with trastuzumab and a taxane is the current standard of care in the first-line metastatic setting based on data from the CLEOPATRA study (Swain et al, 2015). In addition, pertuzumab is approved for the neoadjuvant treatment of patients with early stage breast cancer (either greater than 2 cm in diameter or node positive) and adjuvant treatment of patients with HER2+ early breast cancer at high risk of recurrence (Gianni et al, 2016; von Minckwitz et al, 2017); (PERJETA® Prescribing Information, Genentech, Inc., Dec 2018).

Ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate (ADC) composed of trastuzumab, a thioether linker, and a derivative of the antimitotic agent maytansine, was approved for the treatment of patients with HER2+ metastatic breast cancer (MBC) who previously received trastuzumab and a taxane (prior therapy for metastatic disease, or development of recurrence during or within 6 months of completing adjuvant therapy), and is the current standard of care in the second-line metastatic setting (Verma et al, 2012) (KADCYLA® Prescribing Information, Genentech, Inc., Dec 2018). More recently, T-DM1 showed superior efficacy relative to trastuzumab in the adjuvant therapy management of participants who had less than a pathological complete remission to neoadjuvant

trastuzumab-based therapy in the KATHERINE study (von Minckwitz et al, 2014; von Minckwitz et al, 2019).

### 1.2.2. Lapatinib and Neratinib

Lapatinib and neratinib are HER2 targeting tyrosine kinase inhibitors (TKIs) that have also been approved for the treatment of HER2+ breast cancer. Lapatinib targets both the HER2 receptor and the epidermal growth factor receptor (EGFR) and was approved in combination with capecitabine in patients with metastatic disease who have progressed following prior trastuzumab, anthracycline, and taxane therapy (Geyer et al, 2006) (TYKERB® Prescribing Information, Novartis Pharmaceuticals Corp., Dec 2018). Lapatinib has also been approved in combination with letrozole in postmenopausal patients with hormone receptor positive metastatic disease(Schwartzberg et al, 2010). Neratinib, a pan-Erb inhibitor, was approved for the extended adjuvant treatment of patients with high-risk early stage HER2+ breast cancer, to follow adjuvant trastuzumab-based therapy (Chan et al, 2016). Neratinib is also approved in combination with capecitabine for treatment in the metastatic setting in breast cancer patients who have received 2 or more prior anti-HER2 based regimens. However, lapatinib and neratinib have been associated with toxicities including diarrhea and rash that are likely associated with EGFR inhibition. As an example, over 40% of participants in the neratinib adjuvant ExteNET study experienced Grade ≥3 diarrhea, and antidiarrheal prophylaxis is now recommended with neratinib use (NERLYNX® Prescribing Information, Puma Biotechnology, Inc., Jun 2018). Despite these advances, the toxicities associated with lapatinib and neratinib limit their ability to combine with other HER2-directed or cytotoxic agents.

### 1.2.3. Tucatinib

Tucatinib is an orally (PO)-available, reversible HER2 small molecule TKI. Two key features of tucatinib are its potency and selectivity for HER2 compared to the closely related kinase EGFR. Tucatinib is a potent inhibitor of HER2 in vitro, and in cellular signaling assays is >1000-fold more selective for HER2 compared to EGFR. The selectivity of tucatinib for HER2 reduces the potential for EGFR-related side effects, such as skin rash and gastrointestinal toxicity. This unique feature also differentiates tucatinib from other HER2 targeting TKIs, such as lapatinib and neratinib, which inhibit both HER2 and EGFR with similar potency and are associated with the aforementioned side effects associated with EGFR inhibition. Furthermore, the limited toxicity associated with tucatinib allows for the potential for combination with other agents.

Recently, based on results from the HER2CLIMB study, tucatinib was approved in the US under the trade name TUKYSA, in combination with trastuzumab and capecitabine, for treatment of adult patients with advanced unresectable or metastatic HER2+ breast cancer, including patients with brain metastases, who have received 1 or more prior anti-HER2-based regimens in the metastatic setting (TUKYSA Prescribing Information, Seattle Genetics, Apr 2020). In HER2CLIMB, the addition of tucatinib to trastuzumab and capecitabine was found to be superior to trastuzumab and capecitabine alone, with a 46% reduction in the risk of disease progression or death (hazard ratio [HR]=0.54 [95% confidence interval {CI}: 0.42, 0.71]; p<0.00001) in participants previously treated

with trastuzumab, pertuzumab, and T-DM1 (Murthy et al, 2020). The trial also met the 2 key secondary endpoints at interim analysis. The tucatinib arm demonstrated an improvement in OS, with a 34% reduction in the risk of death (HR=0.66 [95% CI: 0.50, 0.88]; p=0.0048) compared to trastuzumab and capecitabine alone. For patients with brain metastases at baseline, the tucatinib arm also demonstrated superior PFS, with a 52% reduction in the risk of disease progression or death compared to those who received trastuzumab and capecitabine alone (HR=0.48 [95% CI: 0.34, 0.69]; p<0.00001). Lastly, treatment with tucatinib in combination with trastuzumab and capecitabine in these participants resulted in a significantly higher confirmed objective response rate (cORR) (40.6% [95% CI: 35.3, 46.0]) vs. participants treated in the control arm (22.8% [95% CI: 16.7, 29.8]; P=0.00008).

Tucatinib in combination with trastuzumab and capecitabine was generally well tolerated with a manageable safety profile. The most frequent adverse events (AEs) in the tucatinib arm included diarrhea, palmar-plantar erythrodysesthesia syndrome (PPE), nausea, fatigue, and vomiting. Grade 3 or greater AEs in the tucatinib arm compared to the control arm included diarrhea (12.9% vs. 8.6%), increased aspartate aminotransferase (AST) (4.5% vs. 0.5%), increased alanine aminotransferase (ALT) (5.4% vs. 0.5%) and increased bilirubin (0.7% vs. 2.5%). There was no requirement for prophylactic antidiarrheals. AEs leading to discontinuations were infrequent in both the tucatinib arm and the control arm (5.7% and 3.0%).

Clinical trials are ongoing to examine the safety and efficacy of tucatinib when combined with other HER2-directed therapies. A complete summary of the clinical and nonclinical data for tucatinib and its study in human participants is provided in the Investigator's Brochure.

### 1.2.4. Trastuzumab deruxtecan

T-DXd is an ADC comprised of a humanized IgG1 antibody directed at HER2 (fam-trastuzumab), the topoisomerase I inhibitor, Dxd, and a cleavable tetrapeptide linker. T-DXd targets HER2 at the cell surface and, upon binding to HER2, is internalized. Intracellularly, the tetrapeptide linker is cleaved by lysosomal cathepsins, releasing Dxd, a derivative of exatecan. Dxd inhibits topoisomerase I resulting in antitumor activity (Modi et al, 2020).

Trastuzumab deruxtecan was granted accelerated approval in the US under the trade name ENHERTU for treatment of adult patients with unresectable or metastatic HER2+ breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting, based upon data from the DESTINY-Breast01 study (ENHERTU Prescribing Information, Daiichi Sankyo, Dec 2019). In the phase 2 single arm study, treatment with T-DXd resulted in a cORR of 60.9% (95% CI: 53.4, 68.0) in participants with metastatic HER2+ breast cancer previously treated with T-DM1 (Modi et al, 2020). In contrast to the HER2CLIMB study, patients with active brain metastases were excluded; however, the study did enroll participants with treated brain metastases. In DESTINY-Breast03, a randomized phase 3 study, participants with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane received either T-DXd or TDM1. The median PFS was not reached for T-DXd vs 6.8 months for T-DM1 (HR 0.28 [95% CI, 0.22, 0.37]). The confirmed ORR for T-DXd was 79.1% (95% CI, 74.3, 84.4) (Cortés et al, 2021).

Common AEs for T-DXd in the DESTINY-Breast01 study were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, diarrhea, cough, and thrombocytopenia. The most common Grade ≥3 AEs were neutropenia (20.7%), anemia (8.7%), and nausea (7.6%) (Modi et al, 2020). The safety profile of T-DXd in the DESTINY-Breast03 study was consistent with what was reported in the DESTINY-Breast01 study. In DESTINY-Breast03, similar rates of any grade and Grade ≥3 drug-related treatment-emergent adverse events were reported in the two treatment arms. Treatment with T-DXd may result in severe or fatal interstitial lung disease (ILD), including pneumonitis. In studies of T-DXd for MBC, 9% of patients experienced ILD and/or pneumonitis; 2.6% of which had fatal outcomes due to ILD and/or pneumonitis (ENHERTU Prescribing Information, Daiichi Sankyo, Dec 2019). In DESTINY-Breast03, drug-related ILD and/or pneumonitis was reported in 10.5% of participants treated with T-DXd; none of which reported Grade 4 or Grade 5 ILD and/or pneumonitis events.

### 1.3. Brain Metastases in HER2+ Breast Cancer

The advances over the past 2 decades in the development of novel therapeutics for HER2+ breast cancer have resulted in better control of systemic disease. Because of this significant improvement, patients live longer (as demonstrated by increases in PFS and OS) and more patients are developing brain metastases. Clinical trials suggest that there is an increased risk of first relapse occurring in the central nervous system (CNS) in participants who have received trastuzumab-based adjuvant therapy (Clayton et al, 2004; Olson et al, 2013a; Olson et al, 2013b), and up to 50% of HER2+ participants with metastatic disease will develop CNS metastases at some point during the course of the disease (Clayton et al, 2004; Goldhirsch et al, 2013; Pestalozzi et al, 2013). The increasing prevalence of CNS metastases in participants with HER2+ breast cancer may be due to several factors (Lin et al, 2004). First, HER2+ breast cancer appears to display a special tropism for the CNS tissue. Second, with better control of non-CNS disease, participants may be living longer, allowing CNS metastases to become more of a critical clinical issue. Finally, the CNS may represent a sanctuary site for HER2+ disease, as large molecules such as trastuzumab and pertuzumab do not penetrate the blood-brain barrier to any meaningful extent at approved doses. The evidence suggests that drug blood-brain barrier permeability is most likely a function of not only P-glycoprotein expression but also the interplay of molecule size, charge, lipophilicity, tumor neovasculature anatomy, and plasma protein binding (Gerstner & Fine, 2007).

Treatment for brain metastases usually includes either surgical resection, radiosurgery, and/or whole brain radiotherapy in addition to continuation of systemic anti-HER2 therapy. Unfortunately, these treatments often result in significant neurologic toxicities, which may impair quality of life (QoL). Stereotactic radiosurgery (SRS) has been increasingly used to avoid the neurologic toxicities of whole-brain radiotherapy, but the trade-off for this decrease in toxicity has been inferior control of distant brain relapse outside of the radiation fields (Chang et al, 2009; Brown et al, 2016; Kaidar-Person et al, 2016).

Breast cancer patients with HER2+ brain metastases have a worse prognosis relative to those without CNS disease. In population-based registries of HER2+ MBC enrolled at diagnosis, evidence of brain metastases leads to a shortened survival relative to participants without brain metastases (Brufsky et al, 2011). Among the 377 participants with brain metastases,

median OS from the date of initial MBC diagnosis was 26.3 months (range: 1.0 to 60.9 months) compared to 44.6 months (range: 0.5 to 59.7 months) in the 635 participants who did not have CNS metastases (Brufsky et al, 2011).

Taken together, HER2-targeting regimens that distribute into the brain are needed. Until the recent regulatory approval of tucatinib in combination with trastuzumab and capecitabine, which includes patients with brain metastases, no systemic agents had been shown to demonstrate benefit in this patient population. Moreover, breast cancer patients with brain metastases have historically been excluded from clinical trials. Development of novel combinations for this patient population remains an important medical need, and addressing this need will require including these participants in clinical trials.

### 1.4. Rationale for Combination of Tucatinib with Trastuzumab deruxtecan

Treatment failures in HER2+ breast cancer may result from primary or acquired resistance to HER2 blockade (Lu et al, 2001; Nahta & Esteva, 2006; Scaltriti et al, 2007; Pohlmann et al, 2009). There is evidence that dual targeting of HER2, in particular when further combining with a cytotoxic agent, can lead to further improvements in efficacy in patients with MBC (Swain et al, 2015; Murthy et al, 2020). Therefore, the combination of tucatinib with T-DXd may result in further improvement on the efficacy seen with either agent, potentially through overcoming or delaying the development of resistance through dual HER2 blockade.

#### 1.4.1. Preclinical

Pre-clinical data have shown that the combination of tucatinib with a HER2 directed ADC comprised of trastuzumab conjugated with exatecan moieties (T-Ex) results in improved anti-tumor activity in HER2+ breast cancer models. In HER2+ tumor-derived cell lines, tucatinib in combination with T-Ex can result in additive or synergistic activity (data not shown). In addition, the combination of tucatinib and T-Ex resulted in more effective tumor reduction than either drug individually in the BT-474 cell line-derived xenograft model and in 2 HER2+ patient-derived (PDX) breast cancer models (Kulukian et al, 2020).

#### 1.4.2. Rationale for Study

Significant progress has been made in the management of HER2+ breast cancer over the past 2 decades, with regulatory approval of multiple HER2-targeting agents. Recently, both tucatinib (in combination with trastuzumab and capecitabine) and T-DXd were approved by the US FDA for the treatment of patients with HER2+ MBC who have received prior HER2-directed therapy in the metastatic setting. However, despite these advances, metastatic disease remains incurable, and patients will eventually progress on currently available therapies. Although tucatinib (in combination with trastuzumab and capecitabine) and T-DXd have demonstrated clinically meaningful improvements in efficacy for patients with MBC, better outcomes may be achieved by combining the 2 agents. This is particularly important in patients with brain metastases where the prognosis remains worse when compared to patients without brain metastases. Gastrointestinal adverse events such as nausea and/or diarrhea have been observed as an overlapping toxicity with these 2 agents. Additionally, tucatinib is associated with increases in liver transaminases (AST and ALT), and T-DXd is associated with decreased blood counts (eg, neutropenia and anemia) and

ILD/pneumonitis. Thus, the intent of this phase 2 single arm study is to assess the safety and preliminary efficacy of the combination of tucatinib and T-DXd in participants with HER2+ MBC, with and without brain metastases.

## 2. OBJECTIVES

This study will evaluate the safety and efficacy of tucatinib in combination with T-DXd in participants with unresectable locally advanced/metastatic (LA/M) HER2+ breast cancer, with and without brain metastases, who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab). Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

**Table 1: Study Objectives and corresponding endpoints**

| **Primary Objective** | **Corresponding Primary Endpoint** |
|---|---|
| • To determine the antitumor activity of tucatinib given in combination with T-DXd as measured by confirmed objective response rate (cORR) according to investigator (INV) assessment | • cORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 according to INV assessment |
| **Secondary Objectives** | **Corresponding Secondary Endpoints** |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd as measured by progression-free survival (PFS) according to INV assessment | • PFS per RECIST v1.1 according to INV assessment |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd as measured by duration of response (DOR) according to INV assessment | • DOR per RECIST v1.1 according to INV assessment |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd as measured by disease control rate (DCR) according to INV assessment | • DCR per RECIST v1.1 according to INV assessment |
| • To assess overall survival (OS) in participants treated with tucatinib given in combination with T-DXd | • OS |
| • To assess the safety and tolerability of tucatinib given in combination with T-DXd | • Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and lab abnormalities<br>• Frequency of dose modifications and treatment discontinuations<br>• Other relevant safety variables |
| **Exploratory Objectives** | **Corresponding Exploratory Endpoints** |
| *Efficacy* | |
| • To evaluate the antitumor activity of tucatinib given in combination with T-DXd according to independent central review (ICR) assessment | • cORR per RECIST v1.1 according to ICR assessment |

**Table 1: Study Objectives and corresponding endpoints**

| | |
|---|---|
| | • PFS per RECIST v1.1 according to ICR assessment<br>• DOR per RECIST v1.1 according to ICR assessment<br>• DCR per RECIST v1.1 according to ICR assessment |
| *Pharmacokinetic* | |
| • To evaluate the pharmacokinetics (PK) of tucatinib | • Plasma concentrations of tucatinib |
| *Biomarker* | |
| • To explore correlations between blood-based or tissue biomarkers and clinical outcomes | • Potential biomarkers of response, resistance, or toxicity from blood-based or tumor samples |
| *Patient Reported Outcomes* | |
| • To assess patient-reported outcomes (PROs) associated with tucatinib given in combination with T-DXd | • Change from baseline in PRO assessments of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) |

# 3. INVESTIGATIONAL PLAN

## 3.1. Summary of Study Design

This is a single arm, open-label, multi-center phase 2 trial designed to assess the safety and efficacy of tucatinib in combination with T-DXd for the treatment of participants with previously treated unresectable LA/M HER2+ breast cancer with or without brain metastases who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab).

A Safety Monitoring Committee (SMC) will monitor participants for AEs, serious adverse events (SAEs), dose modifications, and laboratory abnormalities throughout the course of the study.

As of Amendment 3, the objectives of the study have been achieved. Therefore, the decision has been made to close the study. For participants in long- term follow-up, a last visit or contact will occur prior to the participant's discontinuation from the study. Any participant on treatment with tucatinib with or without T-DXd will transition to the LTEP of the study. The sponsor will provide continued access to study intervention during the LTEP for any participant who is still on tucatinib with or without T-DXd and receiving clinical benefit based on the investigator's assessment. Once post-study access to study treatment is available, participant will have a last visit or contact prior to discontinuation from the study.

### Safety Lead-in

Ten participants will be enrolled, irrespective of cohort, in the safety lead-in portion of the study and receive tucatinib 300 mg PO twice daily (BID) and T-DXd 5.4 mg/kg via

intravenous (IV) infusion on Day 1 of each of 21-day cycle. The participants enrolled in the safety lead-in will undergo the same efficacy, PK, and biomarker analyses as all other participants with the exception of an additional PK assessment performed at Cycle 1, Day 12. Once 10 participants are enrolled in the safety lead-in, enrollment will be paused until all participants have been followed for at least 1 cycle and a comprehensive review of the safety profile by the SMC has occurred. The SMC will make recommendations regarding continuing with enrollment if the safety and tolerability of the regimen is acceptable. If clinically significant safety events are observed at any point during the safety lead-in, enrollment will be paused until relatedness has been determined, and review by the SMC has occurred. Based on the totality of the safety data, the SMC may recommend proceeding with enrollment, evaluation of alternative dosing, or not proceeding with further enrollment. The SMC may also recommend expanding the safety lead-in to enroll up to approximately 10 additional participants with continued monitoring for safety by the SMC.

**Post-safety Lead-in**

Following the safety lead-in, enrollment will continue until approximately 60 response-evaluable participants have been enrolled at the SMC recommended dose. There will be 2 cohorts in the study, 1 for participants without brain metastases (Cohort A) and 1 for participants with a history of brain metastases (Cohort B), with approximately 30 participants enrolled into each cohort. All participants, including those in the safety lead-in, treated at the SMC recommended dose, will be included in the efficacy analysis. Additional optional cohorts evaluating the combination of tucatinib and T-DXd in earlier treatment lines for breast cancer, such as the first-line metastatic setting or neoadjuvant/adjuvant setting, may be added. Optional cohorts may also be opened in other malignancies, such as non-small cell lung cancer, urothelial cancer, gastric/gastroesophageal junction cancer, and colorectal cancer.

The incidence of diarrhea, though predominantly low grade, has resulted in dose modifications of tucatinib, and prophylactic antidiarrheals have been recommended by the SMC. Antidiarrheal prophylaxis will be required for all participants following protocol amendment 2. Antidiarrheal prophylaxis will be administered for the first 42 days of study treatment. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis or be switched to symptomatic treatment of diarrhea, at the investigator's discretion. Symptomatic management of treatment-induced diarrhea should be based on established guidelines (Benson et al, 2004; Bossi et al, 2018).

The primary endpoint of the study is cORR by investigator. Radiographic efficacy assessments will be made by the investigator, according to RECIST v1.1, with confirmation required ≥4 weeks from the first documentation of response. In addition, images will be collected by an ICR facility for possible future analysis.

Secondary efficacy endpoints include DOR, PFS, DCR, and OS.

### 3.1.1. Clinically Significant Safety Events

Clinically significant safety events will be AEs or laboratory abnormalities that occur during the safety lead-in portion that are related to tucatinib or T-DXd, and that are considered sufficiently important to merit a pause of enrollment during the safety lead-in for determination of relatedness and review by the SMC. Events for which there is an alternative clinical explanation (eg, clearly related to an intercurrent illness or disease progression), will not be considered clinically significant safety events. The severity of AEs and laboratory abnormalities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The relationship of AEs to study interventions will be determined by the investigator.

Occurrence of a clinically significant safety event will result in a pause in enrollment while the SMC evaluates the events and determines whether to proceed with the study. Participants who experience a clinically significant safety event may continue on study treatment if treatment discontinuation is not required by protocol dose modification criteria and the investigator believes it to be in the participant's best interest. Participants may resume treatment at a lower dose (eg, the next lower dose level of tucatinib and/or a reduced dose of T-DXd) following recovery of the AE to ≤ Grade 1 or the baseline grade.

### 3.1.2. Safety Monitoring Committee

The SMC will be responsible for monitoring the safety of participants in the study at regular intervals. In particular, the SMC will evaluate clinically significant safety events and other safety data in the safety lead-in stage; PK data may also be evaluated, if available. The SMC will review data on deaths, study treatment and study intervention discontinuations, dose reductions, AEs, SAEs, laboratory abnormalities, and PK data on a regular basis. The SMC will make recommendations to the sponsor regarding the conduct of the study, including changes to dosing and administration schedule, and make recommendations concerning study continuation as planned, protocol amendment, or early discontinuation of the study for excessive toxicity.

An SMC Charter will outline the committee’s composition, members’ roles and responsibilities, and describe SMC procedures. The sponsor will provide a copy of each SMC recommendation to the investigators.

### 3.1.3. Stopping Criteria

Reasons for prematurely terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants, either through a safety review by the sponsor or the SMC.
- Participant enrollment is unsatisfactory.

### 3.1.4. End of Study

As of Amendment 3, all participants still in the study who are not entering the LTEP will have a last visit/contact. The study will end when the last LTEP participant has had their last

visit/contact. The sponsor will provide continued access to study intervention during the LTEP for any participant who is still on tucatinib with or without T-DXd and receiving clinical benefit based on the investigator's assessment.

### 3.1.5. Method of Assigning Participants to Treatment Groups

This is an open-label, single arm study.

### 3.1.6. Rationale for Selection of Doses

Selection of the tucatinib dosing at 300 mg PO BID for the current study was based upon the recommended phase 2 dose (RP2D) derived from 2 phase 1b studies in HER2+ MBC that evaluated tucatinib in combination with T-DM1 (ONT-380-004), or capecitabine and trastuzumab (ONT-380-005). Moreover, in the pivotal HER2CLIMB study, the combination of tucatinib 300 mg PO BID with trastuzumab and capecitabine was found to be well tolerated with a manageable safety profile. The single-agent approved dose for T-DXd for HER2+ MBC is 5.4 mg/kg IV every 3 weeks. Importantly, no major overlapping toxicities between tucatinib and T-DXd are expected based on the individual agent safety profiles. Therefore, the proposed starting dose for each agent in this study is tucatinib 300 mg PO BID and trastuzumab 5.4 mg/kg IV every 3 weeks.

### 3.1.7. Blinding and Unblinding

This is an open-label, single arm study.

## 4. STUDY POPULATION

This study will enroll participants with previously treated unresectable LA/M HER2+ breast cancer who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab).

Participants must meet all of the enrollment criteria outlined in Section 4.1 and Section 4.2 to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

### 4.1. Inclusion Criteria

Participants must meet the following criteria to be eligible for the study:

1. Have confirmed HER2+ breast cancer, as defined by the current American Society of Clinical Oncology – College of American Pathologists (ASCO/CAP) guidelines, previously determined at a Clinical Laboratory Improvements Amendments (CLIA)-certified or International Organization for Standardization (ISO)-accredited laboratory.
2. History of prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab)

3. Have disease progression of unresectable LA/M breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
4. Have measurable disease assessable by RECIST v1.1
5. Be at least 18 years of age at time of consent
6. Have Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
7. Have a life expectancy of at least 6 months, in the opinion of the investigator
8. Have adequate hepatic function as defined by the following:
   a. Total bilirubin ≤1.5 x upper limit of normal (ULN). Exception: Participants with known history of Gilbert's Syndrome who have a direct bilirubin ≤1.5 x ULN in addition to a normal AST and ALT are eligible.
   b. Transaminases (AST and ALT) ≤3 x ULN (≤5 x ULN if liver metastases are present)
9. Have adequate baseline hematologic parameters as defined by:
   a. Absolute neutrophil count (ANC) ≥1.5 x $10^3$/μL
   b. Platelet count ≥100 x $10^3$/μL
   c. Hemoglobin ≥9 g/dL
   d. In participants transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support
10. Estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 $m^2$ using the Modification of Diet in Renal Disease (MDRD) study equation
11. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5 x ULN, unless on medication known to alter INR and PTT/aPTT.
12. Have left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study treatment
13. For participants of childbearing potential (Section 4.4), the following stipulations apply.
    a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to starting study treatment. A participant with a false positive result and documented verification that the participant is not pregnant is eligible for participation.
    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study intervention
    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study intervention

d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix I) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention administration.

14. For participants who can father children, the following stipulations apply:

a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 4 months after the final study intervention

b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix I) starting at time of informed consent and continuing throughout the study and for at least 4 months after the final dose of study intervention

c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options (as defined in Appendix I) starting at time of informed consent and continuing throughout the study and for at least 4 months after the final dose of study intervention administration

15. Participant must provide signed informed consent per a consent document that has been approved by an institutional review board or independent ethics committee (IRB/IEC) prior to initiation of any study-related tests or procedures that are not part of standard of care for the patient's disease

16. Participants must be willing and able to comply with study procedures

***CNS Inclusion*** – Based on medical history and screening contrast brain magnetic resonance imaging (MRI), participants with a history of brain metastases must have **one** of the following

17. Untreated brain metastases not needing immediate local therapy. For participants with untreated CNS lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment

18. Previously treated brain metastases

a. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator

b. Participants treated with CNS local therapy for newly identified or previously treated progressing lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if all of the following criteria are met:

i. Time since whole brain radiation therapy (WBRT) is ≥14 days prior to first dose of study treatment, time since SRS is ≥7 days prior to first dose of study treatment, or time since surgical resection is ≥28 days

ii. Other sites of measurable disease by RECIST v1.1 are present

c. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

### 4.2. Exclusion Criteria

Participants will be excluded from the study for any of the following reasons:

1. Have previously been treated with:
   a. Lapatinib or neratinib within 12 months of starting study treatment (except in cases where lapatinib or neratinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity)
   b. Tucatinib or enrolled on a tucatinib clinical trial
   c. Any investigational HER2/EGFR or HER2 TKI (eg, afatinib) at any time previously
   d. T-DXd or another ADC consisting of an exatecan derivative
2. History of exposure to the following cumulative doses of anthracyclines:
   a. Doxorubicin >360 mg/m$^2$
   b. Epirubicin >720 mg/m$^2$
   c. Mitoxantrone >120 mg/m$^2$
   d. Idarubicin >90 mg/m$^2$
   e. Liposomal doxorubicin (eg, Doxil, Caelyx, Myocet) >550 mg/m$^2$
3. History of allergic reactions to trastuzumab or compounds chemically or biologically similar to tucatinib or T-DXd, except for Grade 1 or 2 infusion-related reactions (IRRs) to trastuzumab that were successfully managed, or known allergy to one of the excipients in the study interventions
4. Have received treatment with:
   a. Any systemic anti-cancer therapy (including hormonal therapy) or experimental agent ≤21 days of first dose of study treatment or are currently participating in another interventional clinical trial. An exception for the washout of hormonal therapies is gonadotropin releasing hormone (GnRH) agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
   b. Treatment with non-CNS radiation ≤7 days prior to first dose of study treatment
   c. Major surgery within <28 days of first dose of study treatment
5. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
   - Alopecia
   - Neuropathy, which must have resolved to ≤ Grade 2
   - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely

- Anemia, which must have resolved to ≤ Grade 2

6. Have clinically significant cardiopulmonary disease such as:
   - Ventricular arrhythmia requiring therapy
   - Symptomatic hypertension or uncontrolled hypertension as determined by investigator
   - Any history of symptomatic CHF
   - Severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy
   - Hypoxia requiring supplementary oxygen therapy
   - Have had a history of ILD/pneumonitis (eg, interstitial pneumonia, pneumonitis, pulmonary fibrosis, or radiation pneumonitis) that required systemic corticosteroids, or has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
7. Have known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
8. Known to be positive for hepatitis B by surface antigen expression. Known to be positive for hepatitis C infection. Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks
9. Presence of known chronic liver disease
10. Participants known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:
    - CD4+ T-cell count of <350 cells/µL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks
11. Active or uncontrolled clinically serious infection
12. Are pregnant, breastfeeding, or planning a pregnancy
13. Have inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications
14. Have used a strong cytochrome P450 (CYP) 2C8 inhibitor within 5 elimination half-lives of the inhibitor, or have used a strong CYP3A4 or moderate/strong CYP2C8 inducer within 5 days prior to first dose of study treatment.
15. Unable for any reason to undergo contrast MRI of the brain
16. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures

17. History of malignancy other than breast cancer within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (eg, 5-year OS of ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

***CNS Exclusion*** – Based on medical history and screening contrast brain MRI, participants must not have any of the following (listed in criteria 18–22):

18. Any untreated brain lesions >2.0 cm in size, unless discussed with medical monitor and approval for enrollment is given
19. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or equivalent). However, participants on a chronic stable dose of ≤2 mg total daily dose of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor
20. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to participant (eg, brain stem lesions). Participants who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria 18b
21. Known or suspected leptomeningeal disease (LMD) as documented by the investigator
22. Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases
23. Have ongoing ≥ Grade 2 diarrhea of any etiology

### 4.3. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is using an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix I) and will confirm that the participant has been instructed in its consistent and correct use.

At time points indicated in the SoE, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 2 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

### 4.4. Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

Premenopausal with 1 of the following conditions:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator judgment will determine childbearing status and study eligibility.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

### 4.5. Removal of Participants from Therapy or Assessment

Pfizer or their designee must be notified if a participant is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the participant's medical records and electronic case report form (eCRF). For participants continuing to LTEP, data will only be documented in the participant's medical record.

#### 4.5.1. Discontinuation of Study Treatment

A participant's study treatment may be discontinued for any of the following reasons:

- Progressive disease (PD; per RECIST v1.1)
- AE
- Pregnancy or begins breastfeeding while on trial
- Investigator decision due to clinical progression
- Investigator decision, other
- Participant decision, non-AE
  Note: Ensure that participants who decide to stop treatment **because of an AE** are not included in this rationale.
- Study termination by sponsor
- Other, non-AE

Participants who discontinue study treatment without documented radiographic progression will undergo follow-up disease assessments approximately every 9 weeks (±1 week) until disease progression is documented as per RECIST v1.1.

In the absence of progression, participants who discontinue T-DXd may continue receiving tucatinib alone. Participants who discontinue tucatinib may continue to receive T-DXd alone.

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent from any further contact with them or persons previously authorized by the participant to provide this information. A participant also may choose to withdraw consent from procedures and visits but remain on study for follow-up and further data collection through phone contact, review medical records, public records, or other public platforms. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow up. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

#### 4.5.1.1. Continuing on Study for Isolated CNS Progression

If a participant is found to have isolated progression in the CNS per RECIST v1.1 (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and does not have progression of disease outside the CNS, the participant may be eligible to continue on study treatment after completion of local treatment (radiotherapy or surgery) of any progressive brain/dural metastases to allow for clinical benefit. Local treatment must be completed prior to the participant's next response assessment time point. Participants may continue on study treatment for clinical benefit after this PFS event in the CNS; however, this requires discussion with and documented approval from the study medical monitor. Participants may continue treatment until either systemic progression or a second isolated CNS progression. The participant may continue on study provided the following criteria are met and the participant continues to receive clinical benefit:

- The participant is not experiencing any worsening of cancer-related symptoms or signs indicating clinically significant progression of disease. Participants who are clinically deteriorating (eg, have a decline in ECOG PS, symptomatic rapid disease progression requiring urgent medical intervention) and unlikely to receive further benefit from continued treatment should discontinue study treatment
- The participant is tolerating study intervention
- Review and concurrence by the medical monitor
- Participant has no evidence of unequivocal systemic progression
- Participant has not had a previous isolated CNS progression while on study

Study treatment may be held up to 6 weeks to allow local CNS therapy. Longer holds must be discussed and approved by the medical monitor. Interruption and re-initiation of study treatment is described in Section 5.5.

### 4.5.2. Participant Withdrawal from Study

Reasons for discontinuation from the study may include:

- Death
- Participant withdrawal of consent
- Lost to follow-up
- Study termination by sponsor
- Other

A participant may withdraw from the study at any time at their own request. If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly. If the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected except for publicly available information as appropriately directed in accordance with local law. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

## 5. TREATMENTS

### 5.1. Treatments Administered

Participants will receive tucatinib and T-DXd in combination at the following doses:

- Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle.
- T-DXd 5.4 mg/kg IV on Day 1 of each 21-day cycle.

Study interventions are all prespecified IMPs and NIMPs intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to tucatinib and T-DXd.

Study interventions are outlined in Table 2.

**Table 2: Study Interventions**

| Intervention Name | Tucatinib | T-DXd |
|---|---|---|
| **Type** | Drug | Biologic |
| **Use** | Experimental | Experimental |
| **IMP or NIMP/AxMP** | IMP | NIMP |
| **Dose Formulation** | Film-coated Tablet | Lyophilized powder for solution for injection |
| **Unit Dose Strength(s)** | 50 and 150 mg | 100 mg |
| **Dosage Level(s)** | 300 mg BID | 5.4 mg/kg |

| | | |
|---|---|---|
| **Route of Administration** | Oral | IV |
| **Sourcing** | Provided centrally by the sponsor or designee. | Locally sourced by site. |
| **Packaging and Labeling** | Each bottle of tucatinib will be labeled in compliance with applicable regulatory requirements. | Each vial will be labeled as required per country requirement |
| **Single Reference Safety Document (SRSD)** | IB | USPI |
| **Current/Former Name(s) or Alias(es)** | TUKYSA; tucatinib; PF-07265792; ONT-380; ARRY-380 | Enhertu; fam-trastuzumab deruxtecan-nxki |

## 5.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the Pharmacy Instructions/IP manual.

5. Any storage conditions stated in the single reference safety document (SRSD) will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention. See the Pharmacy instructions/IP manual for storage conditions of the study intervention.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution, (where applicable) or authorized site staff is responsible for study intervention accountability,

reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records) such as the study drug accountability log. All centrally sourced study interventions will be accounted for using a study intervention accountability form/record. All unused tucatinib that is taken home by the participant must be returned to the investigator by the participant. Returned tucatinib must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Instructions/IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

### 5.3. Study Intervention (Tucatinib)

Tucatinib is a kinase inhibitor that selectively inhibits HER2 and displays limited activity against the related kinase EGFR.

Tucatinib is supplied as coated yellow oval-shaped tablets (150 mg) or round tablets (50 mg) for oral administration.

Detailed information describing the preparation, administration, and storage of tucatinib is located in the Pharmacy Instructions.

#### 5.3.1. Description

Tucatinib is a potent, selective, adenosine triphosphate (ATP)-competitive small-molecule inhibitor of the receptor tyrosine kinase HER2.

Chemical Name:
N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine.

Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150-mg dosage strength and a coated yellow round tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate CCI [redacted] of tucatinib in CCI [redacted], which is then combined with the pharmaceutical excipients (copovidone, crospovidone, sodium chloride, potassium chloride, sodium bicarbonate, colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose) and compressed into tablets.

#### 5.3.2. Method of Procurement

Tucatinib will be provided by the sponsor.

### 5.3.3. Dose and Administration

Tucatinib will be administered PO BID and may be taken with or without food. Dose modifications of tucatinib are described in Section 5.5.1. Participants will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, participants will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

Participants will be instructed to take tucatinib twice each day (once in the morning, and once in the evening) approximately 8 to 12 hours between doses in the same calendar day. It is recommended that if a participant misses a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the participant should not take the missed dose but should wait and take the next regularly scheduled dose. Tucatinib may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose.

Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will also be provided to study participants and will include the minimum times between doses, dosing in relation to meals, and instructions for missed doses. Participant compliance with study intervention dosing instructions will be assessed with the use of study intervention accountability. Participant diaries may also be used to assess compliance.

### 5.3.4. Overdose

In the event of an overdose of tucatinib, defined as any dose greater than the prescribed dose, study personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tucatinib.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of tucatinib administered, participant weight) and AEs, if any.

Overdose is reportable to Pfizer Safety only when associated with an SAE.

### 5.3.5. Storage and Handling

Tablets of tucatinib are packaged in round, high-density polyethylene bottles containing a desiccant, with an induction sealed liner and child-resistant plastic closure cap. Bottles of tucatinib tablets are to be stored under refrigeration at 2 to 8°C in a secure, access-limited location.

The tablets are coated with a non-hazardous film to prevent any exposure to the active pharmaceutical ingredient during routine handling. Avoid breaking or crushing tablets. In the

event the tablets are broken or crushed, wash hands and exposed skin thoroughly with soap and water.

Refer to the Pharmacy Instructions for more information.

#### 5.3.6. Packaging and Labeling

Each bottle of tucatinib will be labeled in compliance with applicable regulatory requirements.

#### 5.3.7. Study intervention Accountability

Tucatinib used during the course of the study should be handled according to the Pharmacy Instructions. Tucatinib is to be tracked and documented from the time of receipt at the site, through participant dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty bottles, should be tracked.

The sponsor or designee will conduct drug accountability monitoring during the course of the study. All used and unused bottles of tucatinib should be handled according to the sponsor's instructions.

#### 5.3.8. Preparation and Dispensing

Detailed drug preparation instructions are provided in the Pharmacy Binder.

A qualified staff member will dispense tucatinib in the bottles provided, in quantities appropriate according to the SoE. The participant/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

### 5.4. Combination Study intervention (T-DXd)

#### 5.4.1. Description

T-DXd is an ADC consisting of a HER2-directed antibody, a topoisomerase inhibitor, and a tetrapeptide linker which is indicated, as a single agent, for treatment of patients with locally advanced unresectable or metastatic HER2+ breast cancer.

#### 5.4.2. Method of Procurement

T-DXd is commercially available and details regarding sourcing of T-DXd may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

#### 5.4.3. Dose, Preparation, and Administration

T-DXd (5.4 mg/kg) will be given as an IV infusion once every 21 days (Day 1 of each 21-day cycle). T-DXd should be prepared and administered per instructions in the ENHERTU product label. T-DXd will be administered IV per institutional guidelines, under the direction of the investigator.

Protocol-defined visits and cycle numbering will be determined by T-DXd dosing date, allowing for dose holds or delays with T-DXd. Dose modifications of T-DXd are described in Section 5.5.2.

### 5.4.4. Overdose

For this trial, an overdose will be defined as any dose at least 10% greater than the prescribed dose of T-DXd. In the event of an overdose, study personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of T-DXd. In the event of overdose, participants should be observed, and appropriate supportive care should be given, if required.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of T-DXd administered, participant weight) and AEs, if any.

Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

### 5.4.5. Storage and Handling

T-DXd should be stored according to the product label.

### 5.4.6. Study intervention Accountability

Site will also be required to provide accountability for administration of T-DXd for entry into the eCRF.

### 5.4.7. Preparation and Dispensing

See the T-DXd product label for instructions on how to prepare T-DXd for administration. T-DXd should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

## 5.5. Dose Modifications

Tucatinib and T-DXd dose reduction recommendations are described in Table 3 and Table 4, respectively.

Guidelines for dose modification recommendations (including dose holds, dose reduction, or discontinuation of drug) in response to potential AEs are described in the tables in Section 5.5.3. Dose reductions or treatment interruption/discontinuation for reasons other than those described in Section 5.5.3 may be made by the investigator if it is deemed in the best interest of participant safety. Whenever possible, these decisions should first be discussed with the study medical monitor.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to tucatinib and T-DXd. An AE may be considered related to tucatinib alone, T-DXd alone, to both drugs, or to neither. In the event that the relationship is unclear, discussion should be held with the study medical monitor, to discuss which study intervention(s) should be held and/or modified.

Doses held for toxicity will not be replaced. Tucatinib or T-DXd should be discontinued if a delay greater than 6 weeks is required due to treatment-related toxicity, unless a longer delay is approved by the study medical monitor.

In the event of isolated progression in the CNS, study treatment may be held up to 6 weeks to allow local CNS therapy (Section 4.5.1.1). Tucatinib and T-DXd are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib and T-DXd is unknown. Study treatment may be reinitiated ≥7 days after completion of SRS, ≥14 days after WBRT, and ≥28 days after surgical resection. Plans for holding and reinitiating study interventions before and after local therapy will require discussion with, and documented approval from, the medical monitor.

Protocol-defined visits and cycle numbering will be determined by T-DXd dosing, allowing for dose holds or delays with T-DXd. In the event T-DXd is discontinued but study treatment with tucatinib continues, protocol-defined visits and cycle numbering will proceed using a 21-day cycle regardless of dose holds or delays for tucatinib.

### 5.5.1. Tucatinib Dose Reductions

Up to 3 dose reductions of tucatinib are allowed (Table 3); fewer dose reduction levels may be available if alternative tucatinib doses or schedules are adopted, following SMC recommendation. Participants who would require a dose reduction to below 150 mg BID should discontinue treatment with tucatinib. Dose reductions of larger intervals than those described in Table 3 may be made at the discretion of the investigator, but dose reductions to below 150 mg BID are not allowed.

Tucatinib dose should not be re-escalated after a dose reduction is made.

**Table 3: Recommended tucatinib dose reduction**

| Dose Reduction Schedule | Tucatinib Dose Level[a] |
|---|---|
| Starting dose | 300 mg PO BID |
| 1st dose reduction | 250 mg PO BID |
| 2nd dose reduction | 200 mg PO BID |
| 3rd dose reduction | 150 mg PO BID |
| Requirement for further dose reduction | Discontinue treatment |

a Dose reductions of greater intervals than those recommended in this table (ie, more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator. However, tucatinib may not be dose reduced below 150 mg BID.

### 5.5.2. Trastuzumab Deruxtecan Dose Reductions

Up to 2 dose reductions of T-DXd will be allowed.

T-DXd dose should not be re-escalated after a dose reduction is made as shown in Table 4.

**Table 4: Recommended T-DXd dose reduction**

| Dose Reduction Schedule | T-DXd Dose Level |
|---|---|
| Starting dose | 5.4 mg/kg IV |
| 1st dose reduction | 4.4 mg/kg IV |
| 2nd dose reduction | 3.2 mg/kg IV |
| 3rd dose reduction | Discontinue treatment |

### 5.5.3. Dose Modifications for Adverse Events

#### 5.5.3.1. General Guidelines

General dose modification guidelines for tucatinib and T-DXd are provided in Table 5 for clinical AEs.

Separate dose modification guidelines are provided for AEs of hepatotoxicity (Table 6), ILD/pneumonitis (Table 7), neutropenia and febrile neutropenia (Table 8), and LVEF decrease (Table 9).

**Table 5: Dose modifications for clinical adverse events related to either tucatinib or T-DXd**

| | Tucatinib | T-DXd |
|---|---|---|
| Clinical adverse event | Related to tucatinib | Related to T-DXd |
| Grade 3 AEs other than Grade 3 fatigue lasting ≤3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Reduce to next lowest dose level. |
| Grade 3 nausea and/or vomiting WITHOUT maximal use of antiemetics | Hold until severity ≤ Grade 1 or pretreatment level.<br>Initiate appropriate therapy.<br>Restart without dose reduction. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Initiate appropriate therapy.<br>Restart without dose reduction. |
| Grade 3 nausea and/or vomiting WITH maximal use of antiemetics | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. |
| Grade 3 diarrhea WITHOUT maximal use of antidiarrheals | Hold until severity ≤ Grade 1 or pretreatment level.<br>Initiate appropriate therapy.<br>Restart without dose reduction. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Initiate appropriate therapy.<br>Restart without dose reduction. |
| Grade 3 diarrhea WITH maximal use of antidiarrheals | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. |

**Table 5: Dose modifications for clinical adverse events related to either tucatinib or T-DXd**

| | Tucatinib | T-DXd |
|---|---|---|
| Clinical adverse event | Related to tucatinib | Related to T-DXd |
| Grade 2 diarrhea with concomitant Grade 2 nausea and/or vomiting, both related to study intervention WITHOUT maximal use of antidiarrheals and/or antiemetics | Hold until severity ≤ Grade 1 or pretreatment level of either the Grade 2 nausea/vomiting or diarrhea.<br>Initiate appropriate therapy.<br>Restart without dose reduction. | Hold until severity ≤ Grade 1 or pretreatment level of either the Grade 2 nausea/vomiting or diarrhea.<br>Initiate appropriate therapy.<br>Restart without dose reduction. |
| Grade 2 diarrhea with concomitant Grade 2 nausea and/or vomiting, both related to study intervention WITH maximal use of antidiarrheals and/or antiemetics | Hold until severity ≤ Grade 1 or pretreatment level of either the Grade 2 nausea/vomiting or diarrhea.<br>Restart at next lowest dose level. | Hold until severity ≤ Grade 1 or pretreatment level of either the Grade 2 nausea/vomiting or diarrhea.<br>Restart at next lowest dose level. |
| Grade 3 rash WITHOUT maximal use of topical corticosteroids or anti-infectives | Hold until severity ≤ Grade 1 or pretreatment level.<br>Initiate appropriate therapy.<br>Restart without dose reduction. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Initiate appropriate therapy.<br>Restart without dose reduction. |
| Grade 3 rash WITH maximal use of topical corticosteroids or anti-infectives | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. | Hold until severity ≤ Grade 1 or pretreatment level.<br>Restart at next lowest dose level. |
| Grade 4 AEs | Permanently discontinue | Permanently discontinue |

Tucatinib or T-DXd should be discontinued if a delay greater than 6 weeks is required due to treatment-related toxicity, unless a longer delay is approved by the study medical monitor.
a.No dose modifications are required for alopecia

### 5.5.3.2. Hepatotoxicity

Dose modification is required in the case of liver function abnormalities, regardless of relationship to tucatinib and T-DXd as outlined in Table 6.

For participants with documented Gilbert's disease, contact the medical monitor for guidance regarding dose modifications.

**Table 6: Dose modification guidelines for liver function abnormalities**

| | Tucatinib | T-DXd |
|---|---|---|
| ALT or<br>AST<br>(>3 – ≤5 x ULN) | Dose modification not required. | Dose modification not required. |

**Table 6: Dose modification guidelines for liver function abnormalities**

| | Tucatinib | T-DXd |
|---|---|---|
| Bilirubin (>1.5 – ≤3 x ULN) | Hold until recovery to (≤1.5 x ULN).<br>Then resume tucatinib at the same dose level. | Dose modification not required. |
| ALT or AST (>5 – ≤20 x ULN) | Hold until recovery to (≤3 x ULN) or until return to pre-treatment level in participants with known liver metastasis.<br>Then resume tucatinib at the next lower dose level. | Hold until recovery to (≤3 x ULN) or until return to pre-treatment level in participants with known liver metastasis.<br>Then resume at the same dose level. |
| Bilirubin (>3 – ≤10 x ULN) | Hold until recovery to (≤1.5 x ULN).<br>Then resume tucatinib at the next lower dose level. | Hold until recovery to(≤1.5 x ULN).<br>Then resume T-DXd at the next lower dose level. |
| ALT or AST (>20 x ULN)<br>OR<br>Bilirubin (>10 x ULN) | Permanently discontinue. | Permanently discontinue. |
| ALT or AST >3 x ULN<br>AND<br>Bilirubin >2 x ULN | Permanently discontinue. | Permanently discontinue. |

Source: TUKYSA Prescribing Information, Seattle Genetics, Inc., Apr, 2020; ENHERTU Prescribing Information Daiichi Sankyo, Inc., Dec 2019.

### 5.5.3.3. Interstitial Lung Disease/Pneumonitis

Dose modifications are required for ILD/pneumonitis, regardless of relationship to T-DXd (Table 7).

Dose modification of tucatinib is not required for ILD/pneumonitis.

**Table 7: Dose modification guidelines for interstitial lung disease/pneumonitis**

| | **T-DXd** |
|---|---|
| Asymptomatic ILD/pneumonitis (Grade 1) | Interrupt until resolved to Grade 0, then:<br>if resolved in 28 days or less from date of onset, maintain dose,<br>if resolved in greater than 28 days from date of onset, reduce dose 1 level (see Table 4)<br>consider corticosteroid treatment as soon as ILD/pneumonitis is suspected |
| Symptomatic ILD/pneumonitis (Grade 2 or greater) | Permanently discontinue |

| | |
|---|---|
| | Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected |

Source: ENHERTU Prescribing Information Daiichi Sankyo, Inc., Dec 2019

#### 5.5.3.4. Neutropenia and Febrile Neutropenia

Dose modifications are required for neutropenia or febrile neutropenia, regardless of relationship to T-DXd (Table 8).

Dose modification of tucatinib is not required for neutropenia or febrile neutropenia.

**Table 8: Dose modification guidelines for neutropenia and febrile neutropenia**

| | **T-DXd** |
|---|---|
| Grade 3 neutropenia (less than 1.0 to 0.5 x $10^9$/L) | Interrupt until resolved to Grade 2 or less, then maintain dose. |
| Grade 4 neutropenia (less than 0.5 x $10^9$/L) | Interrupt until resolved to Grade 2 or less. Reduce dose by 1 level (see Table 4). |
| Febrile Neutropenia (Absolute neutrophil count of less than 1.0 x $10^9$/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than 1 hour) | Interrupt until resolved. Reduced dose by 1 level (see Table 4). |

Source: ENHERTU Prescribing Information Daiichi Sankyo, Inc., Dec 2019.

#### 5.5.3.5. Left Ventricular Ejection Fraction Decrease

Dose modification guidelines for LVEF decrease, regardless of relationship to T-DXd, are provided in Table 9.

Dose modification of tucatinib is not required for LVEF decrease.

**Table 9: Dose modification guidelines for left ventricular ejection fraction decrease**

| | | T-DXd |
|---|---|---|
| LVEF greater than 45% and absolute decrease from baseline is 10% to 20% | | Dose modification not required |
| LVEF 40% to 45% | And absolute decrease from baseline is less than 10% | • Dose modification not required<br>• Repeat LVEF assessment within 3 weeks |
| | And absolute decrease from baseline is 10% to 20% | • Interrupt treatment<br>• Repeat LVEF assessment within 3 weeks.<br>• If LVEF has not recovered to within 10% of baseline, permanently discontinue treatment<br>• If LVEF recovers to within 10% from baseline, resume treatment at the same dose. |

**Table 9: Dose modification guidelines for left ventricular ejection fraction decrease**

| | |
|---|---|
| LVEF less than 40% or absolute decrease from baseline is greater than 20% | • Interrupt treatment<br>• Repeat LVEF assessment within 3 weeks.<br>• If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue treatment |
| Symptomatic congestive heart failure (CHF) | • Permanently discontinue treatment |

Source: ENHERTU Prescribing Information Daiichi Sankyo, Inc., Dec 2019.

### 5.6. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent through the safety reporting period.

Any planned surgery (major or minor) not directly related to cancer that occurs on study requires consultation with the sponsor medical monitor. Participants are required to suspend study treatment 3 to 7 days prior to surgery and depending upon the nature of the surgery resume study treatment 3 to 21 days postoperatively. For emergency surgeries, contact medical monitor as soon as feasible to discuss resumption of study treatment postoperatively.

#### 5.6.1. Required Concomitant Therapy

In participants following protocol amendment 2, loperamide 4 mg 3 times daily (Days 1 to 14) during Cycle 1 followed by 4 mg 2 times daily (Day 15 through Day 42) is to be given.

- Titrate above initial loperamide dosing schedule for a goal of 1–2 bowel movements per day.
- Antidiarrheal prophylaxis should be held in situations where use is contraindicated (eg, bacterial enterocolitis), until resolution of the contraindication.
- If either tucatinib or T-DXd is discontinued during the first 42 days of treatment, antidiarrheal prophylaxis is no longer required.

#### 5.6.2. Allowed Concomitant Therapy

Participants may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. However, efforts should be made to maintain stable doses of concomitant medications during the course of study treatment.

- During study treatment, participants may receive supportive care to include bisphosphonates, denosumab, antibiotics, hematologic support, pain management, antacids, and laxatives.

- Supportive care medications such as antidiarrheals and antiemetics are permitted.
    - Antidiarrheals for symptomatic or prophylactic use are permitted at the discretion of the investigator.
        - Participants who enroll while use of primary prophylactic antidiarrheals is implemented as a required concomitant therapy may continue on prophylactic use or be switched to symptomatic use, per investigator assessment, following Day 42 of therapy.
        - Symptomatic management of treatment-induced diarrhea should be based on established guidelines (Benson et al, 2004; Bossi et al, 2018).
    - Antiemetic prophylaxis prior to Day 1 infusions of T-DXd at each cycle should be administered per established guidelines (Hesketh et al, 2020).
    - Symptomatic treatment of nausea and vomiting may be used per standard of care.
- Thoracentesis or paracentesis may be performed, if needed for comfort.
- If surgery or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor), these concomitant procedures are permitted for non-target non-CNS lesions only in situations where other disease remains assessable by RECIST v1.1. These interventions should be avoided if clinically feasible until after the second response assessment. The medical monitor should be consulted prior to the intervention occurring.
- Corticosteroids
    - Participants requiring systemic corticosteroids for control of CNS metastases at a dose >2 mg of dexamethasone (or equivalent) on the first day of study treatment are not eligible to begin study treatment and should not be enrolled until doses <2 mg can be achieved.
    - After initiation of study treatment, corticosteroids may be initiated for control of CNS symptoms.
    - Systemic corticosteroids for control of other comorbidities (eg, asthma or auto-immune diseases) or premedication for contrast use in computed tomography (CT) or MRI scans are permitted.
- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.
- Routine prophylaxis with vaccines (without live virus) are permitted during the study.

### 5.6.3. Prohibited Concomitant Therapy

The following therapies are prohibited during the study (unless otherwise noted):

- Investigational drugs and devices

- Anti-cancer therapy, including but not limited to chemotherapy and hormonal therapy
- Radiation therapy, except for palliative radiotherapy at focal non-CNS sites which are not considered target lesions per RECIST v1.1, which may be given after consultation with the medical monitor, provided that there remain other sites of disease assessable by RECIST v1.1
- Vaccination with live vaccines
- Strong CYP2C8 inhibitors are prohibited within 5 elimination half-lives of the inhibitor. Moderate/strong inducers of CYP2C8 are prohibited within 5 days prior to the first dose of study treatment, as concomitant medications during study treatment, and within 1 week of discontinuation of tucatinib treatment. Moderate inhibitors of CYP2C8 should be used with caution. For additional information, including drug elimination half-lives of strong inhibitor, moderate inhibitors, and moderate inducers, see Appendix B
- Strong inducers of CYP3A4 are prohibited within 5 days prior to first dose of study treatment, as concomitant medications during study treatment, and within 1 week of discontinuation of study treatment. For additional information including drug elimination half-lives of strong inducers, see Appendix C
- Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment (Appendix D). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information
- Concomitant use of tucatinib with digoxin, a P-glycoprotein (P-gp) substrate, which increases digoxin concentrations and may increase the risk for digoxin-related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dose adjustment recommendations due to drug interactions

## 5.7. Management of Treatment-emergent Adverse Events

### 5.7.1. Infusion-related Reaction and its Management

An IRR is characterized by an adverse reaction to the infusion of pharmacological or biological substances. IRRs occur within 24 hours of infusion and may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension (Kang & Saif, 2007).

IRRs with T-DXd were observed (2.6% of patients); the infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms. T-DXd should be discontinued

permanently in the case of severe infusion reactions. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs.

Any IRR related to T-DXd should be managed according to the product label and/or institutional standard of care. Premedication for IRRs is allowed at the investigator's discretion

The severity of IRRs should be graded according to NCI CTCAE, version 5.0, guidelines.

### 5.7.2. Allergic/Hypersensitivity Reaction

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE version 5.0). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of T-DXd. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs, ie, a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension.

### 5.7.3. Anaphylaxis

Anaphylaxis is a severe, life threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death (NCI CTCAE, version 5.0 and (Rosello et al, 2017).

If anaphylaxis occurs, administration of T-DXd should be immediately and permanently discontinued.

### 5.7.4. Management of Treatment-associated Diarrhea

- Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. If an alternate cause of diarrhea is suspected and/or identified, treat accordingly.
- In participants enrolled during which primary antidiarrheal prophylaxis is implemented, please refer to Section 5.5.1 for dosing guidance.
    - Antidiarrheal prophylaxis should be held in situations where use is contraindicated (eg, bacterial enterocolitis), until resolution of the contraindication.
- In participants receiving antidiarrheals for symptomatic control (not prophylactically) of treatment-associated diarrhea:
    - **Early Detection:** Instruct participants to report diarrhea on the first symptom/sign of diarrhea.
    - **Early Intervention:**

- Provide participants with prescription for loperamide and instruct them to start treatment as soon as first unformed stool occurs.
- The recommended dose of loperamide is 4mg at first unformed stool, followed by 2mg every 2 to 4 hours until diarrhea free (maximum 16 mg/day).
- Instruct participants to call site if diarrhea persists >48 hours or there is an increase of >7 stools per day over baseline (Grade 3 Diarrhea per CTCAE v5.0).
- Instruct participants to seek medical attention if unable to maintain oral hydration due to diarrhea, particularly in the presence of concomitant emesis.
- Instruct participants to seek medical attention if unable to maintain oral hydration. Intervention with IV fluids and electrolyte replacement should be considered as clinically indicated.

### 5.8. Treatment Compliance

Study intervention administration will be documented in source documents and the CRF.

The pharmacist or designee will record the number of tucatinib tablets dispensed to each individual participant, and the number of tablets returned to the clinic at the end of each cycle. Tucatinib compliance may also be assessed on a participant-by-participant basis using participant diaries.

Data regarding the administration and dose of T-DXd will also be collected by the site after each cycle. Dose modifications and interruptions of both study interventions will be documented in the source documents and the CRF. Following implementation of Amendment 3 and entry of remaining on-treatment participants into the LTEP, treatment administration data will no longer be collected in CRFs. Refer to Section 8.3 for further detail on LTEP data collection requirements.

## 6. STUDY ACTIVITIES

### 6.1. Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.7.1.3). Any study protocol-related AE (defined in Section 7.7.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, liver function tests [LFTs], complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.7.3], physical exam, weight, and ECOG PS) may be performed within 1 day prior to administration of study intervention. The results from all relevant clinical assessments must be reviewed prior to dosing.

The participants enrolled in the safety lead-in will undergo the same efficacy, PK, and biomarker analyses as all other participants enrolled in the study, with the exception of an additional PK assessment performed at Cycle 1 Day 12.

Tumor biopsies performed while the participant is on study should be made available to the sponsor, if feasible (see Section 7.4).

Participants still receiving clinical benefit and remaining on tucatinib with or without T-DXd as of Amendment 3 may continue receiving study intervention during the LTEP. During this phase of the study, only pregnancies and SAEs will be collected by the sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

A schedule of events is provided in 11. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

**6.2. Screening Visit (Days –28 to 1)**

- Informed consent*
- Documentation of AEs
- Study eligibility per inclusion/exclusion criteria
- Documentation of concomitant medications
- Documentation of baseline medical conditions
- Documentation of disease history
- Height
- Vital signs (blood pressure, heart rate, temperature, respiration rate, and pulse oximetry), including weight
- Physical examination
- ECOG PS
- Blood samples for laboratory testing (as listed in Section 7.7.3)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - Coagulation panel
- For participants of childbearing potential, serum or urine pregnancy test within 7 days of first study treatment (a positive urine test must be confirmed with a serum pregnancy test).
- Blood samples for hepatitis screening: Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B core (anti-HBc), and antibodies to Hepatitis C (anti-HCV). (If positive, additional testing may be required after discussion with medical monitor.)*
- Electrocardiogram (ECG)

- ECHO or MUGA; note that whichever testing modality is chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.*
- Contrast CT (preferred), positron emission tomography (PET)/CT (if high quality CT scan included) or MRI scan as appropriate to document sites of extracranial disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis. Additional appropriate imaging of any other known sites of disease (eg, photography for skin lesions, nuclear bone scan imaging for bone lesions) may also be obtained at the investigator's discretion. For each participant, the same assessment modalities used at screening/baseline should be used throughout the study.
- Contrast MRI scan of the brain for all participants for assessment of brain tumor burden; CT of the brain will not be allowed, and participants with known contraindications to undergoing contrast MRI imaging will be excluded from the study*
- For participants with brain metastases discovered during screening or a history of brain metastases, confirm relevant MRI brain reports and CNS treatment records can be obtained.
- Blood sample for biomarker analysis*
- Collection of archived tumor samples for biomarker analysis. If tumor blocks are not available, slides may be submitted after discussion with and approval from the medical monitor

*For participants who have unsuspected brain metastases discovered at screening and go on to receive immediate local therapy to the CNS, certain screening evaluations may not need to be repeated outside the 28-day screening window with medical monitor approval. This includes the following: Informed consent, ECHO/MUGA, hepatitis screening, and biomarker sampling. All other safety labs and assessments will need to be repeated if outside the 28-day window for these participants. An additional contrast MRI brain scan following local therapy will not be required prior to starting study treatment if radiation treatment was given. A postoperative contrast MRI brain scan is required prior to starting study treatment if surgical resection was performed.

### 6.3. Treatment Period (21-day cycles)

#### 6.3.1. Cycle 1 Day 1

- Documentation of AEs
- Documentation of concomitant medications
- Vital signs (blood pressure, heart rate, temperature, respiration rate, and pulse oximetry), including weight
- Physical examination
- ECOG PS

- Blood samples for laboratory testing (results must be reviewed and eligibility confirmed prior to first dose):
    - CBC with differential
    - Serum chemistry
    - LFTs
- Completion of the EQ-5D-5L quality of life questionnaire (to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment)
- Dispense tucatinib and administer the first dose of tucatinib‡
- Administer T-DXd (administered IV on Day 1 of the 21-day cycle)‡
- Beginning with the first dose of tucatinib in participants following protocol amendment 2, loperamide 4 mg 3 times daily (Days 1 to 14) during Cycle 1 followed by 4 mg twice daily (Day 15 through Day 42) is to be given
- Collect blood samples for PK (predose)

‡Drugs may be administered in any order and can be given simultaneously.

**6.3.2. Cycle 1 Day 12 (±3 days)**

- Documentation of AEs
- Documentation of concomitant medications
- Vital signs (blood pressure, heart rate, temperature, respiration rate, and pulse oximetry), including weight
- Physical examination
- ECOG PS
- Blood samples for laboratory testing:
    - CBC with differential
    - Serum chemistry
    - LFTs
- Collect blood samples for PK (for safety lead-in participants only). Record time of tucatinib dose and blood draw

**6.3.3. Cycle 2 Day 1 (–1 day to +3 days)**

- Documentation of AEs
- Documentation of concomitant medications, including the dosing regimen of antidiarrheals taken in the previous cycle
- Vital signs (blood pressure, heart rate, temperature, respiration rate, and pulse oximetry), including weight

- Physical examination
- ECOG PS
- Blood samples for laboratory testing:
  - CBC with differential
  - Serum chemistry
  - LFTs
- For participants of childbearing potential, a serum or urine pregnancy test (a positive urine test must be confirmed with a serum pregnancy test)
- Completion of the EQ-5D-5L quality of life questionnaire (to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment)
- Dispense tucatinib and administer the first dose. On Day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle.†
- Administer T-DXd (administered IV on Day 1 of the 21-day cycle)†
- Collect blood samples for PK (pre-tucatinib dose and 2 hours [±15 minutes] post-tucatinib dose)

†At Cycle 2 Day 1, tucatinib should be administered onsite before T-DXd; participants should remain onsite for 2 hours (±15 minutes) after tucatinib administration to coordinate peak PK sampling times.

**6.3.4. Cycle 2 Day 12 (±3 days)**

- Blood samples for LFTs

**6.3.5. Cycle 3 and Beyond, Day 1 (–1 day to +3 days)**

- Documentation of AEs
- Documentation of concomitant medications, including the dosing regimen of antidiarrheals taken in the previous cycle
- Vital signs (blood pressure, heart rate, temperature, respiration rate, and pulse oximetry), including weight
- Physical examination
- ECOG PS
- Blood samples for laboratory testing:
  - CBC with differential
  - Serum chemistry
  - LFTs

- For participants of childbearing potential, a serum or urine pregnancy test performed at each cycle (a positive urine test must be confirmed with a serum pregnancy test). Pregnancy testing will be performed every 3 weeks for participants of child-bearing potential receiving study treatment during the LTEP and will follow Section 6.4 after last dose of study treatment.
- Blood sample for biomarker analysis (at C3D1 only, predose)
- Completion of the EQ-5D-5L quality of life questionnaire (to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment for Cycle 3 and Cycle 4 and every 2 cycles starting at Cycle 6 through the end of treatment [EOT])
- Dispense and administer the first dose of tucatinib (On Day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle).†
- Administer T-DXd (administered IV on Day 1 of each 21-day cycle)†
- Blood samples for PK (through Cycle 6 only: Pre-tucatinib dose at Cycles 3 and 6, and 2 hours (±15 minutes) post-tucatinib dose at Cycle 3 only)

†Tucatinib should be administered before T-DXd onsite at Cycle 3 and Cycle 6; for Cycle 3, participants should remain onsite for 2 hours (±15 minutes) after tucatinib administration to coordinate peak PK sampling times. For all other cycles, study interventions may be given in any order and can be given simultaneously.

### 6.3.6. Every 6 Weeks (–7 days) as Determined by Cycle 1 Day 1, Through Week 24, then Every 9 Weeks (–7 days) Through End of Treatment

- Contrast CT (preferred), PET/CT (if high quality CT scan included) or MRI scan as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.
- Contrast MRI of the brain (only in participants with brain metastases at baseline)
    - If cycles are delayed for any reason continue with initial scan schedule as determined by the date of Cycle 1 Day 1 visit.
- If an interim unscheduled visit assessment is performed, scans should continue to be done on schedule, with scheduling determined by the date of Cycle 1 Day 1. In cases of medical contraindication for repeat scans, contact the medical monitor to discuss as, in some instances, assessments done at an unscheduled time point may not need to be repeated if medically contraindicated as approved by the medical monitor.

### 6.3.7. Every 12 Weeks (–7 days) as Determined by Cycle 1 Day 1

- ECHO or MUGA, using the same cardiac testing modality performed in Screening/Baseline

- If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment.

**6.4. End of Treatment Visit (30 to 37 days after last dose of study treatment)**

- Documentation of AEs
- Documentation of concomitant medications, including the dosing regimen of antidiarrheals taken in the previous cycle
- Vital signs (blood pressure, heart rate, temperature, respiration rate, and pulse oximetry), including weight
- Physical examination
- ECOG PS
- Blood samples for laboratory testing:
  - CBC with differential
  - Serum chemistry
  - LFTs
  - Coagulation panel
- For participants of childbearing potential, a serum or urine pregnancy test (if not done in the last 30 days) a positive urine test must be confirmed with a serum pregnancy test.
- For persons of childbearing potential (for 7 months after the last dose of study treatment; see Section 7.7.5):
  - Remind participant that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment.
  - Testing may be performed at home. If performed at home, site staff will contact the participant monthly to confirm testing was performed and obtain pregnancy test results.
- Blood sample for biomarker analysis
- Completion of the EQ-5D-5L quality of life questionnaire (to be completed prior to evaluation by study personnel [physical examination, review of AEs])
- Only in participants who discontinue study treatment for reasons other than radiographic disease progression: Contrast CT (preferred); PET/CT (if high quality CT scan included), and/or non-brain MRI scan may be done as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated. Not required if imaging was performed within 30 days of discontinuing study treatment.

- Only in participants with a history of brain metastases who discontinue study treatment for reasons other than radiographic disease progression: Contrast MRI of the brain. Not required if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study.
- ECHO or MUGA, using the same cardiac testing modality performed in Screening/Baseline. Not required if ECHO/MUGA was done within the previous 12 weeks (excluding the Screening/Baseline assessment).

### 6.5. Follow-up

Participants who discontinue study treatment will remain on study for follow-up until withdrawal from the study. If a participant discontinues study treatment, every attempt should be made to follow the participant until death or administrative study closure.

#### 6.5.1. Follow-up until Disease Progression (at least every 9 weeks ±1 week)

For participants who discontinue study treatment prior to disease progression (per RECIST v1.1), the following assessments must be obtained every 9 weeks (±1 week) starting from the date of the last imaging scan, until investigator-assessed disease progression (per RECIST v1.1), death, withdrawal of consent, or study closure.

- Contrast CT (preferred), PET/CT (if high quality CT scan included) or MRI scan as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.
- Contrast MRI of the brain (only in participants with brain metastases at baseline)

#### 6.5.2. Long Term Follow-up (every 90 Days ±14 days)

Starting 90 days (±14 days) from the EOT Visit and continuing every 90 days (±14 days) until death, withdrawal of consent, lost to follow-up, or study closure, the following must be performed:

- Participant contact or in-person assessment of OS and/or disease recurrence, as well as collection of information regarding any additional anti-cancer therapies administered after completion of study treatment. Review of medical records, public records, or other public platforms only as appropriately directed in accordance with local law may be used to obtain this information if reasonable efforts to contact the participant are unsuccessful (see 11).
- For persons of childbearing potential (for 7 months after the last dose of study treatment; see Section 7.7.5):
    - Remind participant that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment
    - Testing may be performed at home. If performed at home, site staff will contact the participant monthly to confirm testing was performed and obtain pregnancy test results.

- More frequent long-term follow-up may be conducted as needed for OS event tracking

### 6.6. End of Study/End of Follow-up

The date the participant met criteria for study discontinuation and the reason for study discontinuation will be recorded.

### 6.7. Long-term Extension Phase (LTEP)

As of Amendment 3, participants still receiving clinical benefit and remaining on tucatinib with or without T-DXd may continue receiving study treatment during the LTEP. During this phase of the study, only pregnancies and SAEs will be collected by the sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential.

## 7. STUDY ASSESSMENTS

### 7.1. Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only participants who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Participants must have confirmed HER2+ breast cancer, as determined at a CLIA-certified or ISO-accredited local laboratory. HER2 positivity will be defined by the current ASCO/CAP guidelines. Participant medical history includes a thorough review of significant past medical history, current conditions, any prior treatment and response to prior treatment for the participant's breast cancer, and any concomitant medications.

All measurable and evaluable lesions will be assessed and documented at Screening/Baseline (see Section 7.2). A contrast MRI of the brain will be performed to evaluate for the presence of brain metastases (see Section 7.2.1). Participants with brain metastases at study entry may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 7.1.1.

A physical examination including height (Section 7.7.4), vital signs and weight (Section 7.7.2), ECOG PS (Appendix E), clinical laboratory testing (Section 7.7.3), Contrast CT, PET/CT, or MRI (Section 6.3.6), ECHO/MUGA (Section 6.3.7), ECG (Section 7.7.7.2), hepatitis B and C screening (11), biomarker evaluation (Section 7.4), and pregnancy testing (Section 7.7.5) will be done at Screening/Baseline (see 11).

#### 7.1.1. Treatment for Brain Metastases Prior to Study Entry

Participants with brain metastases at study entry may be eligible for study participation if they meet the eligibility criteria described in Sections 4.1 and 4.2. In order to minimize the risk of symptomatic cerebral edema in participants with brain metastases in this study, participants with high-risk metastases, including those requiring immediate local therapy, those with rapidly progressing lesions, those requiring corticosteroids at the start of the study (>2 mg of dexamethasone or equivalent per day) for control of CNS symptoms, and those with larger untreated lesions, are excluded from the trial. However, if these participants are

amenable to immediate CNS-directed therapy with either surgery or radiation, they may undergo local therapy and then be eligible for the trial.

Immediate local therapy to the CNS may delay the screening process beyond the 28-day screening window, in which case the requirement for a repeat contrast MRI after completion of local therapy and prior to starting study treatment is as follows:

- For participants who receive brain radiotherapy during the screening period, the original baseline contrast brain MRI will serve as the baseline for comparison for further response assessments.
- For participants who undergo surgical resection of brain metastases during the screening period, a postoperative contrast brain MRI will be performed and will serve as the baseline for comparison for further response assessments.
- For participants with brain metastases discovered during screening or a history of brain metastases, relevant MRI brain reports and CNS treatment records should be obtained and available for CRF source verification.

### 7.2. Response/Efficacy Assessments

Radiographic scans and additional imaging assessments (if applicable) will be performed at protocol-specified time points outlined in Section 6 and 11, or if disease progression is suspected. Efficacy assessments will be made at each time point according to RECIST v1.1 (Eisenhauer et al, 2009; Schwartz et al, 2016) by the investigator.

All known sites of metastatic or locally advanced unresectable disease should be assessed by radiographic imaging at Screening/Baseline to document sites of disease and overall tumor burden. Imaging, preferably by high quality spiral contrast CT scan (with oral and/or IV contrast), should include the chest, abdomen, and pelvis, at a minimum; PET/CT (if high quality CT scan is included) and/or MRI scan may also be done as appropriate. If a CT scan with contrast is contraindicated (ie, in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed instead, with MRI scans of the abdomen and pelvis (if an MRI is not feasible, a non-contrast CT scan is acceptable). At the investigator's discretion, other appropriate imaging (eg, photography for skin lesions, nuclear bone scan imaging for bone lesions) should be used to assess additional known sites of measurable disease. The same imaging modalities employed in Screening/Baseline should be used for all subsequent response assessments during study treatment and in the follow-up period, unless otherwise clinically indicated. If any other radiographic or assessment exam, including pathology from any on-study biopsies or procedures, is conducted per standard of care, the assessment information will be collected in the CRF.

In the event of equivocal progression, for example a new lesion which is small in size (defined as an equivocal new lesion) and no imminent threat to participant safety, all efforts should be made to continue the participant with study treatment until unequivocal progression is documented. Demonstration of an unequivocal new lesion constitutes disease progression.

Participants' clinical data must be available for CRF source verification. In addition, images will be collected by an ICR facility for possible future analysis. Copies of tumor images must

be made available for review by the sponsor (or its designee) upon request. All imaging will be submitted or uploaded to the ICR facility as soon as reasonably possible (eg, within approximately 2 weeks) following the date of assessment. Refer to the Study Manual for instructions on collecting and submitting tumor imaging studies to the ICR facility.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

### 7.2.1. Evaluation of Brain Metastases

Contrast MRI scan of the brain will be performed for all participants at Screening/Baseline to assess tumor burden in the brain and/or dura and identify participants with brain metastases at baseline. CT of the brain will not be allowed, and participants with known contraindications to undergoing contrast MRI imaging will be excluded from the study. Participants are considered to have brain metastases at baseline with any of the following:

- Any history of brain metastases
- Any brain metastases at baseline
- Brain lesions of equivocal significance at baseline

Only participants with documented brain metastases at baseline, as defined above, will continue to have follow-up contrast MRIs of the brain on the same schedule as non-CNS response assessments (Section 6 and 11). Contrast MRIs of the brain may also be performed in participants without known brain metastases if there is clinical suspicion of new brain lesions. All participants with a history of brain metastases who discontinue study treatment for reasons other than radiographic disease progression will have an additional contrast MRI of the brain at the EOT visit, unless one has been performed within 30 days of discontinuing study treatment or if progression in the brain has already been documented while on the study.

In participants with baseline brain lesions, at least 1 brain lesion should be included in the baseline RECIST lesion selection as either a target or non-target lesion. As an exception, however, when unsuspected brain metastases are discovered at screening and immediate CNS-directed therapy is administered, treated lesions should not be selected as target lesions but as non-target lesions for the purpose of disease assessment by RECIST v1.1.

All brain imaging will be collected by an ICR facility for possible future analysis. Copies of brain imaging must be made available for review by the sponsor (or its designee), upon request. Images will be submitted or uploaded to the ICR facility as soon as reasonably possible (eg, within approximately 2 weeks) following the date of assessment. Refer to the Study Manual for instructions on collecting and submitting brain imaging studies to the ICR facility.

During the LTEP, brain metastases evaluations will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

### 7.2.2. Isolated Progression in the Brain

In participants with isolated progression in the brain per RECIST v1.1 (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and

does not have progression of disease outside the CNS, the participant may be eligible to continue on study treatment after completion of local treatment (radiotherapy or surgery) to the brain/dural metastases to allow for clinical benefit with medical monitor approval. This approach approximates standard clinical practice in this clinical scenario.

Because the primary endpoint of the study is cORR, every effort should be made to avoid radiation or surgery to target lesions in the brain in the absence of PD by RECIST v1.1 unless clinically necessary in the opinion of the investigator and approval of the medical monitor. Target lesions, once treated with local CNS therapy, cannot be adequately assessed for subsequent response to systemic therapy. Because of this, if a participant continues on study therapy after local CNS treatment to a target lesion, special consideration must be given for evaluation of the treated target lesion and the impact on the overall RECIST v1.1 assessment.

Following CNS-directed therapy for isolated CNS disease progression, RECIST v1.1 criteria would continue to measure CNS target lesions(s) if previously identified and used in the overall estimation of the sum of diameters measuring total disease burden. However, following treatment, measurement of the treated CNS target lesion(s) would use the immediate pre-CNS treatment measurement. If a subsequent decrease in the size of a treated CNS lesion post-treatment is seen, the immediate pre-CNS treatment longest diameter would be used for RECIST measurement. Should a treated CNS lesion enlarge following CNS-directed therapy that was identified as a target lesion, the new and larger longest diameter is to be used for RECIST measurement.

Additionally, treatment changes which may mimic progression will be taken into account, and participants with possible “pseudo-progression” should continue on study until unequivocal evidence of radiographic or clinical progression is present. In the absence of clear evidence of PD (per RECIST v1.1), development of CNS symptoms or radiographic changes thought to pose potential immediate risk to participant, all efforts should be made to continue treatment until unequivocal evidence of radiographic progression occurs, as defined in RECIST v1.1.

After discontinuing study treatment, participants may receive further care as determined by their physician.

### 7.3. Pharmacokinetic Assessments

Blood samples will be collected in all participants at baseline, predose, and at 2 hours (±15 minutes) post-dose of tucatinib per the sample collection schedule provided in Table 10.

The steady state PK of tucatinib will be assessed through the sparse sampling of the peak and trough levels from Cycle 2 to Cycle 6. PK assessment of trough levels will be performed on all participants on Day 1 of Cycles 2, 3, and 6 prior to drug administration and peak level assessment will be on Day 1 of Cycles 2 and 3 at 2 hours (±15 minutes) post-tucatinib dose. PK samples should continue to be collected on schedule regardless of dose holds or interruptions. The time of tucatinib administration and PK collection will be recorded by the site.

For safety lead-in participants only, an additional pharmacokinetic assessment will be performed at an unspecified time on Cycle 1 Day 12. The time of the tucatinib administration on the morning of the visit will be recorded by the participant. Participants will be called the

evening before the visit and reminded to record the time of dose. The exact time of the PK sample will also be recorded by the site.

**Table 10: Pharmacokinetic sample collection time points**

| Cycle | Day | Plasma Sample | Serum Sample | Time point |
|---|---|---|---|---|
| 1 | 1 | X | X | 0 h (–2 h) prior to administration of tucatinib |
| | 12 | X | X | For safety lead-in participants only. Record time of dose and blood draw. |
| 2 | 1 | X | X | 0 h (–2 h) prior to administration of tucatinib |
| | | X | X | 2 h following administration of tucatinib |
| 3 | 1 | X | X | 0 h (–2 h) prior to administration of tucatinib |
| | | X | X | 2 h following administration of tucatinib |
| 6 | 1 | X | X | 0 h (–2 h) prior to administration of tucatinib |

### 7.4. Biomarker Studies

When available, archival tumor blocks are to be collected at screening. If tumor blocks are not available, slides may be submitted after discussion with and approval from the medical monitor. HER2 expression may be further evaluated by multiple methods including immunohistochemistry (IHC), in situ hybridization (ISH), tissue-based next generation sequencing (NGS), and cell-free DNA. Additionally, tumor biopsies performed while the participant is on study should be made available to the sponsor, if feasible. For example, if a biopsy on residual tumor is performed at the EOT or at progression, a sample will be collected (if residual tumor is available). Blood samples for biomarker assay will be drawn at screening, Cycle 3, Day 1 (predose), and at EOT.

Biomarker assessments may include an exploratory assessment of HER2 mutations or other mutations as potential biomarkers of response. Additional analyses including but not limited to IHC and NGS analysis may be performed to interrogate biomarkers that are associated with tumor growth, survival and resistance to targeted therapeutics. This assessment may enable the correlation of additional biomarkers with treatment outcome and may ultimately guide or refine participant selection strategies to better match tucatinib regimens with tumor phenotype/genotype in the future.

### 7.5. Biospecimen Repository

In the US only, for participants who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Pfizer and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of sensitivity and resistance mechanisms to targeted therapeutics, and the identification of biomarkers. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

### 7.6. Patient-reported Outcomes

Patient-reported outcome measures will be administered as specified in 11 and Section 6 using the EQ-5D-5L instrument. During study treatment, these questionnaires must be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days.

#### 7.6.1. EQ-5D-5L – Utility Measurement

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group for use as a generic, preference-based measure of health-related quality of life (HR-QoL) outcomes that can be used in a wide range of health conditions and treatments (van Agt et al, 1994). The EQ-5D-5L consists of a descriptive system questionnaire and the EuroQoL (EQ) visual analog scale (VAS; Appendix H).

The descriptive system questionnaire assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The scores on these 5 dimensions can be presented as a health profile or the digits for the 5 dimensions can be converted to a 5-digit number that describes the participant's health state. The recall time frame for the descriptive system is the day in which the questionnaire is administered. The EQ VAS records the participant's self-rated health status on a vertical VAS ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) and can be used as a quantitative measure of health outcome that reflects the participant's own judgment.

### 7.7. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs (including clinically significant safety events) identified during the safety lead-in stage and SAEs identified during the safety lead-in or study activity assessment phase, physical examination findings, vital signs including weight, concomitant medication, pregnancy testing, and laboratory tests. Participants will be monitored for signs and symptoms of ILD/pneumonitis. In cases where ILD/pneumonitis is suspected, treatment with T-DXd will be interrupted, and the participant will undergo evaluation including radiographic imaging. Pulmonary consultation should also be considered. Dose modification or discontinuation of T-DXd for cases of ILD/pneumonitis will be made as per product label. Assessment of cardiac ejection fraction will be performed using MUGA scan or ECHO.

Only pregnancies and SAEs will be collected by the sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential.

Safety will be monitored over the course of the study by the SMC as described in Sections 3.1 and 9.3.1.9.

### 7.7.1. Adverse Events

#### 7.7.1.1. Definitions

**Adverse Event**

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 that increase in CTCAE grade should be recorded.
- Medical conditions present or ongoing predose on study Day 1 that worsen in severity, increase in frequency, become related to study intervention, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study intervention) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.7.1.3). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record “anemia” rather than “low hemoglobin”).
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**Serious Adverse Events**

An AE should be classified as an SAE if it meets one of the following criteria:

| | |
|---|---|
| Fatal: | AE resulted in death |
| Life threatening: | The AEs placed the participant at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe. |
| Hospitalization: | The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether |

| | |
|---|---|
| | "hospitalization" occurred or was necessary, the AE should be considered serious. |
| Disabling/ incapacitating: | An AE that resulted in a persistent or significant incapacity or substantial disruption of the participant's ability to conduct normal life functions.<br>This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| Congenital anomaly or birth defect: | An adverse outcome in a child or fetus of a participant exposed to the molecule or study treatment regimen before conception or during pregnancy. |
| Medically significant: | The AE did not meet any of the above criteria, but could have jeopardized the participant and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.1.2 for the definition of potential DILI.) |

**Adverse Event Severity**

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

**Relationship of the Adverse Event to Study Treatment**

The relationship of each AE to each study treatment (tucatinib or T-DXd) should be evaluated by the investigator using the following criteria:

| | |
|---|---|
| Related: | There is evidence to suggest a causal relationship between the drug and the AE, such as:<br>A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) |

| | |
|---|---|
| | One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture) |
| Unrelated: | Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible |

If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the PSSA and in accordance with the SAE reporting requirements.

**Adverse Events of Special Interest**

An adverse event of special interest (AESI) can be any serious or non-serious AE that is of scientific or medical concern as defined by the sponsor and specific to the program, for which ongoing monitoring and rapid communication to the sponsor may be appropriate.

During the LTEP, only AESIs that meet SAE criteria will be reported to the sponsor using the PSSA and will not be recorded within the CRF.

AESIs for this study are:

- Diarrhea
  - ≥Grade 3 diarrhea
  - Grade 2 diarrhea with concomitant Grade 2 nausea and/or vomiting
- Hepatotoxicity: Any of the following types of LFT elevations:
  - AST or ALT elevations that are >3 × ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2 ×ULN, except in participants with documented Gilbert's syndrome
  - AST or ALT elevations > 20 ×ULN
  - Bilirubin elevations > 10 ×ULN

  Measurement of direct and indirect bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology. The sponsor will subsequently determine whether the elevations are associated with other possible causes of aminotransferase elevation and hyperbilirubinemia, such as viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

- Interstitial lung disease (ILD)/pneumonitis

Participants should be advised to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Treating physicians should monitor participants for signs and symptoms of ILD/pneumonitis and promptly investigate for any evidence of ILD/pneumonitis. The evaluation of participants with suspected ILD/pneumonitis should include radiographic imaging.

See Section 5.5.3.3 for dose modification guidelines and Appendix F for ILD/pneumonitis evaluation and treatment guidelines. See Appendix G for potential conditions that can trigger potential ILD.

- Left Ventricular Ejection Fraction (LVEF) decrease

  The following 2 types of LVEF decrease are considered AESIs:

  - An asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment. Use the term "ejection fraction decreased" and severity Grades 2 to 4 to report asymptomatic LVEF decrease.
  - Symptomatic CHF. Use the term "heart failure" and severity Grades 2 to 5 to report symptomatic CHF.

#### 7.7.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during participant questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or reporting through the PSSA, as appropriate. Refer to Appendix J for guidance on recording/reporting AEs and SAEs.

During the LTEP, pregnancies and SAEs will be reported to the sponsor using the PSSA and will not be recorded within the CRF.

**Eliciting Adverse Events**

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

**Recording Adverse Events**

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

**Diagnosis vs. Signs or Symptoms**

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study intervention. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

**Recording Serious Adverse Events**

For SAEs, record the event(s) on the CRF and report to Pfizer Safety using the PSSA.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be reported to Pfizer Safety using the PSSA.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

**Progression of Underlying Malignancy**

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms “Disease Progression”, “Progression of Disease”, or “Malignant disease progression” and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

**Environmental Exposure, Exposure During Pregnancy, and Occupational Exposure**

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness. Refer to Table 12 in Appendix J for guidance on reporting/recording environmental exposure.

**Exposure During Pregnancy**

An EDP occurs if:

- A participant is found to be pregnant while receiving or after discontinuing study intervention.
- A participant who is receiving or has discontinued study intervention inseminates a partner.
- A nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
  - A family member or healthcare provider reports that they are pregnant after exposure to study intervention, for example, by ingestion or skin contact.
  - A family member or healthcare provider who has been exposed to the study intervention, for example, by ingestion or skin contact and then inseminates their partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy). Refer to Table 12 in Appendix J for guidance on reporting/recording EDP.

- If EDP occurs in a participant/participant's partner after the start of study intervention and until 7 months after the last dose of the last study intervention, the investigator must report this information to Pfizer Safety via PSSA, regardless of whether an SAE has occurred.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to their partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to their partner.

**Exposure During Breastfeeding**

An EDB occurs if:

- A participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a family member or healthcare provider who reports breastfeeding after having been exposed to study intervention by ingestion or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed PSSA is maintained in the investigator site file.

**Occupational Exposure**

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the PSSA regardless of whether there is an

associated SAE. Because the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA must be maintained in the investigator site file.

**Lack of Efficacy**

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety only if associated with an SAE.

**Potential Drug-induced Liver Injury**

Hy's Law can be used to estimate severity and the likelihood that a study intervention may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential DILI in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

***Definition***

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

   AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

***Reporting Requirements***

**Any potential Hy's Law case should be handled as a serious adverse event (SAE) and reported promptly to the sponsor.**

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

***Follow-up for Abnormal Laboratory Results Suggesting Potential DILI***

In general, an increase of serum ALT or AST to >3 x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study intervention.

#### 7.7.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 30 days after the last study treatment. However, all study protocol-related AEs are to be recorded from the time of informed consent.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the participant dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started. SAEs occurring during the safety reporting period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

#### 7.7.1.4. Serious Adverse Events Require Immediate Reporting

All SAEs occurring in a participant during the safety reporting period are reported to Pfizer Safety via the PSSA immediately upon awareness and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

For initial SAE reports, available case details are to be reported to Pfizer Safety using the PSSA. At a minimum, the following should be included:

- Participant number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

An investigator who receives suspected unexpected serious adverse reactions (SUSARs) or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

### 7.7.2. Vital Signs

Vital signs measures are to include weight, heart rate, blood pressure, temperature, respiratory rate, and pulse oximetry.

### 7.7.3. Clinical Laboratory Tests

Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessments will be performed to evaluate safety at scheduled time points (see 11) during the course of the study:

- The serum chemistry panel is to include the following tests: bicarbonate, blood urea nitrogen, calcium, creatinine, chloride, glucose, magnesium, phosphorus, potassium, and sodium
- LFTs include albumin, alkaline phosphatase, ALT, AST, total bilirubin (and both direct and indirect bilirubin when total bilirubin is >ULN), and total protein
- The CBC with differential is to include, but is not limited to, the following tests: white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- The coagulation panel is to include the following tests: international normalized ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)
- The eGFR should be calculated using the MDRD equation, with serum creatinine (Scr) reported in mg/dL.

  GFR (mL/min/1.73 $m^2$) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
- A serum or urine β-hCG pregnancy test for participants of childbearing potential

Following implementation of Amendment 3, local laboratory testing with the exception of pregnancy testing will be performed per institutional guidelines and investigator-determined usual and customary care. Pregnancy testing will be performed per the SoE.

### 7.7.4. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. For adult participants only, measurements of height obtained within the prior 12 months may be utilized.

### 7.7.5. Pregnancy Testing

For participants of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at the times listed in the SoE. A negative pregnancy result is required before the subject may receive study drug. Pregnancy tests will

also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study.

Participants with false positive results and documented verification that the participant is not pregnant are eligible for study participation. Similarly, participants with false positive results that develop during study treatment are allowed to continue treatment with documented verification that the participant is not pregnant.

After the last dose of study treatment, pregnancy tests will be performed once a month for 7 months. Participants may do monthly home pregnancy tests and report interim results at long term follow-up visits. Pregnancy tests may also be repeated as requested per IRB/IEC or if required by local regulations.

During the LTEP, pregnancy reporting should continue per protocol and pregnancy should be reported to the sponsor per guideline under EDP in Section 7.7.1.2.

### 7.7.6. Interstitial Lung Disease

ILD and pneumonitis, including fatal cases, have been reported with T-DXd in clinical studies. Evaluate participants with suspected ILD/pneumonitis by radiographic imaging. If a participant is suspected or diagnosed as having ILD, the investigator should consult with a pulmonologist as needed, and the participant will be treated appropriately. T-DXd dosing will be interrupted until drug induced pulmonary toxicity can be ruled out. Please see Section 5.5.3.3 for dose modification guidelines and Appendix F for ILD/pneumonitis evaluation and treatment guidelines. See Appendix G for potential conditions that can trigger potential ILD.

### 7.7.7. Cardiac Function

#### 7.7.7.1. MUGA or ECHO

Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter (as determined by the date of Cycle 1 Day 1), and at the EOT visit (if not done within the previous 12 weeks). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison. During the LTEP, cardiac function assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

#### 7.7.7.2. Electrocardiogram

ECGs will be performed at screening. To correct for heart rate, QT intervals should be calculated using the Fridericia formula (QTcF). During the LTEP, ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

### 7.8. Appropriateness of Measurements

Response will be assessed according to RECIST v1.1 (Eisenhauer et al, 2009; Schwartz et al, 2016) which are standardized criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are considered appropriate for disease management.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and clinical laboratory data will be graded using standardized criteria for oncology (NCI CTCAE version 5.0). The EQ-5D-5L is a validated instrument for use as a measure of HR-QoL.

# 8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

## 8.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of participants at the site, Pfizer or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/product label
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional review board/independent ethics committee (IRB/IEC) review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Pfizer representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study participants and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is

suitable for inspection by Pfizer or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

### 8.2. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.
- During the LTEP, data will no longer be collected in CRFs.

### 8.3. Data Management Procedures

Following implementation of Amendment 3 and entry of remaining on-treatment participants into the LTEP, data will no longer be collected in CRFs. Only pregnancies and SAEs will be collected by the sponsor during the LTEP, using the PSSA. See Section 7.7.1.2 for further details on SAE and AESI reporting requirements.

## 9. DATA ANALYSIS METHODS

### 9.1. Determination of Sample Size

Approximately 60 to 70 participants will be enrolled to ensure about 60 participants will be treated at the SMC recommended dose, with approximately 30 per cohort (HER2+ MBC with or without brain metastases). Participants are considered enrolled if they give informed consent and meet all eligibility criteria.

For illustrative purposes, Table 11 summarizes the expected 95% CIs for the overall study (N=60) and by cohort (N=30), which shows reasonable precision for the estimation.

**Table 11: Expected 95% CI for different number of responses**

| Number of participants | Number of Responses | ORR | 95% exact CI |
|---|---|---|---|
| 60 | 40 | 66.7% | (53.3%, 78.3%) |
| | 42 | 70.0% | (56.8%, 81.2%) |
| | 44 | 73.3% | (60.3%, 83.9%) |
| | 46 | 76.7% | (64.0%, 86.6%) |
| | 48 | 80.0% | (67.7%, 89.2%) |
| | 50 | 83.3% | (71.5%, 91.7%) |

**Table 11: Expected 95% CI for different number of responses**

| Number of participants | Number of Responses | ORR | 95% exact CI |
|---|---|---|---|
| | 52 | 86.7% | (75.4%, 94.1%) |
| 30 | 20 | 66.7% | (47.2%, 82.7%) |
| | 22 | 73.3% | (54.1%, 87.7%) |
| | 24 | 80.0% | (61.4%, 92.3%) |
| | 26 | 86.7% | (69.3%, 96.2%) |

## 9.2. Study Endpoint Definitions

### 9.2.1. Objective Response Rate

ORR is defined as the proportion of participants with confirmed complete response (CR) or partial response (PR), per RECIST v1.1. Participants who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments as described in Section 7.2 of the protocol will be counted as non-responders. ORR per investigator and per ICR are based on investigator response assessments and ICR response assessments, respectively.

### 9.2.2. Progression-free Survival

PFS is defined as the time from start of study treatment to first documentation of tumor progression (PD per RECIST v1.1), or to death due to any cause, whichever comes first. Participants without documentation of progression or death at the time of analysis will be censored at the date of the last disease assessment with an overall response of CR, PR, stable disease (SD) or non-CR/non-PD. If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of treatment initiation. PFS per investigator and per ICR are based on investigator response assessments and ICR response assessments, respectively.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, will be provided in the statistical analysis plan (SAP).

### 9.2.3. Duration of Response

DOR is defined as the time from first documentation of objective response (CR or PR, that is subsequently confirmed) to the first documentation of disease progression per RECIST v1.1 or death from any cause, whichever occurs earlier. Only participants with an objective response will be included in the analysis of DOR. DOR per investigator and per ICR are based on investigator response assessments and ICR response assessments, respectively.

### 9.2.4. Disease Control Rate

DCR is defined as the proportion of participants with confirmed CR, PR or stable disease (SD or non-CR/non-PD) according to RECIST v1.1. DCR per investigator and per ICR are based on investigator response assessments and ICR response assessments, respectively.

#### 9.2.5. Overall Survival

OS is defined as the time from treatment initiation to death due to any cause. For a participant who is not known to have died by the end of study follow-up, observation of OS is censored on the date the participant was last known to be alive (ie, the date of last contact). Participants lacking data beyond the day of treatment initiation will have their survival time censored on the date of treatment initiation (ie, OS duration of 1 day).

#### 9.2.6. Exploratory Endpoints

##### 9.2.6.1. Pharmacokinetic Analysis

PK parameters for tucatinib will be evaluated.

##### 9.2.6.2. Biomarker Analysis

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters may be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the SAP or biomarker analysis plan (BAP).

##### 9.2.6.3. Patient-reported Outcomes

Change from baseline in PRO assessments of the EQ-5D-5L.

### 9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in the protocol amendment.

#### 9.3.1. General Considerations

Tabular summaries will be presented by cohort, unless otherwise specified. In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data.

Unless otherwise specified, CIs will be calculated at 2-sided 95% level.

The 2-sided 95% exact CI using Clopper-Pearson method (Clopper & Pearson, 1934) will be calculated for the response rates where applicable (eg, ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett, 1994).

##### 9.3.1.1. Randomization and Blinding

This is a single arm and open-label study. Randomization and blinding will not be performed.

##### 9.3.1.2. Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

#### 9.3.1.3. Handling of Dropouts and Missing Data

With the exception of time-to-event endpoints, no imputation will be conducted for missing data unless otherwise specified in the SAP.

#### 9.3.1.4. Multi-center Studies

This study will be conducted at multiple study centers; however, it is not anticipated that site-to-site variation will be adjusted in the analyses.

#### 9.3.1.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed because only 1 primary endpoint will be estimated in this single arm study.

#### 9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date – start date +1 [in days]) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of study treatment unless otherwise specified in the SAP.

#### 9.3.1.7. Analysis Sets

The **all treated participants set** includes all participants who receive any amount of study intervention. The analyses of PFS, OS, and safety will be based on this analysis set.

The **response-evaluable analysis set** is defined as all participants with measurable disease who (1) had a baseline disease assessment, (2) received study treatment, and (3) had at least 1 post-baseline assessment or discontinued treatment due to PD, clinical progression, toxicity, or death. The analyses of ORR, DCR and DOR will use the response-evaluable analysis set.

Additional analysis sets of participants may be defined in the SAP.

#### 9.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. The subgroups and detailed methodology will be provided in the SAP.

#### 9.3.1.9. Timing of Analyses

A safety analysis will be undertaken by the SMC when the first 10 treated participants have been followed for at least 1 cycle (safety lead-in stage). The SMC will undertake similar analyses if alternative tucatinib and/or T-DXd dose levels or schedules are evaluated in additional safety lead-in stage(s). Once the safety lead-in stage is completed, the SMC will evaluate the safety of the study regimen throughout the remainder of the study.

The primary efficacy analysis will be then undertaken when approximately 60 response-evaluable participants have been treated at the SMC recommended dose and followed for at least 6 months.

### 9.3.2. Participant Disposition

An accounting of study participants by disposition will be tabulated and the number of participants in each analysis set will be summarized. Participants who discontinue study treatment and participants who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

### 9.3.3. Participant Characteristics

The following baseline characteristics will be summarized:

- Participant demographics
- Disease history
- Prior disease-related therapies
- Baseline disease characteristics

Concomitant medications, separately for medications taken prior to enrollment and while on study, will be listed and summarized.

Details will be provided in the SAP.

### 9.3.4. Exposure

Treatment administration will be summarized for the all treated analysis sets. Summary statistics for duration of therapy (weeks) and the number of cycles per participant will be presented. The number of dose reductions, holds, cycle delays, and doses skipped and dose intensity for each study intervention will be summarized.

Details will be provided in the SAP.

### 9.3.5. Efficacy Analyses

The efficacy analyses will be provided for all participants and by cohorts. Only participants who received the SMC recommended dose will be included in the main efficacy analyses. Efficacy from participants who did not receive the SMC recommended dose, if any, may be summarized separately.

#### 9.3.5.1. Primary Efficacy Analyses

The confirmed ORR per RECIST v1.1 according to investigator assessment will be summarized using the response-evaluable set. The point estimate of ORR and corresponding 95% CIs will be presented.

#### 9.3.5.2. Secondary Efficacy Analyses

DCR per RECIST v1.1 according to investigator assessment will be summarized using response-evaluable set. The point estimate of DCR and corresponding 95% CIs will be presented.

DOR per RECIST v1.1 according to investigator assessment will be estimated using response-evaluable set using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians will be calculated, where possible. The 95% CIs may also be calculated, as appropriate.

Time-to-event secondary efficacy endpoints, including PFS according to investigator assessment and OS will be estimated using the all treated participants set using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians will be calculated, where possible. The 95% CIs may also be calculated, as appropriate. Detailed methodology will be provided in the SAP.

#### 9.3.5.3. Exploratory Efficacy Analyses

cORR, PFS, DOR and DCR per RECIST v1.1 according to ICR assessment will also be analyzed, if the ICR assessments are available; discrepancies between the ICR and investigator's assessment may be summarized descriptively.

### 9.3.6. Pharmacokinetic Analyses

Individual (participant) plasma tucatinib concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will also be calculated. Additional exploratory PK analyses may be conducted. Exploratory analyses investigating the relationship between tucatinib exposure and efficacy and safety endpoints may be conducted.

### 9.3.7. Biomarker Analyses

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the SAP or BAP.

### 9.3.8. Patient-reported Outcomes Analyses

PRO assessments based on EQ-5D-5L will be using descriptive statistics. PRO scores will be analyzed descriptively. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment time point may be presented. Further investigation of missing patterns and details of imputation will be provided in the SAP. Additional statistical modeling for PRO measures may be performed separately as exploratory analyses.

### 9.3.9. Safety Analyses

Safety analyses will, in general, be conducted using the all treated participants set. Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in ECOG PS, and changes in cardiac ejection fraction results. AEs will be classified by System Organ Class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the NCI CTCAE criteria.

If there is more than 1 dosing level/schedule, the safety summaries will be provided by each dosing level/schedule.

#### 9.3.9.1. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will

be defined as treatment-emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by MedDRA, preferred term, severity, and relationship to study intervention. In the event of multiple occurrences of the same AE with the same preferred term in 1 participant, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study intervention will be summarized and listed in the same manner.

All collected AE data will be listed by cohort, study site, participant number, and cycle. Separately, all serious AEs and AESIs (see Section 7.7.1.1) will be analogously listed.

#### 9.3.9.2. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed. A separate listing of all on-study deaths will be presented.

#### 9.3.9.3. Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE version 5.0 and flagged when values are outside the normal reference range.

Changes from baseline in laboratory values (hematology, coagulation, serum chemistry, and liver function) will be summarized by study phase, treatment group and scheduled visit. Laboratory shift tables will also be provided by treatment group and scheduled visit. Abnormal values (relative to respective normal ranges) will be flagged in listings.

Additional analytical methods for a more thorough investigation of LFTs (including temporal/simultaneous summaries and figures) will be specified in the SAP.

#### 9.3.9.4. Other Safety Analyses

**Vital Signs and Physical Examinations**

The frequency and percentage of participants with post-baseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs.

**ECOG Performance Status**

ECOG performance status will be summarized for each scheduled visit. Shifts from baseline to the best and worst post-baseline score may be tabulated.

**Cardiac Ejection Fraction**

Cardiac ejection fraction data will be summarized and listed. Shift from baseline may be tabulated.

### 9.3.10. Interim Analyses

There is no formal interim analysis planned. The SMC will review available safety and PK data once the first 10 participants treated in the safety lead-in stage have been followed for at

least 1 cycle. If alternative tucatinib and/or T-DXd dose levels or schedules are evaluated, the SMC will undertake similar assessments in up to the first 10 participants.

# 10. REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, and all other applicable local regulations.

## 10.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

### 10.1.1. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

### 10.1.2. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in a secure location with access by study personnel only to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach,

the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

### 10.1.3. Committees Structure

Please see Section 3.1.2 for information on the safety monitoring committee.

### 10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results

are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

### 10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the Data Management Plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

### 10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A Source Document Identification Log (or equivalent) should be maintained with the Investigator Site File on site.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source record) that supports the information entered on the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

### 10.1.7. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

### 10.1.8. Study and Site Start and Closure

The study start date is the date of the first site activation.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

### 10.1.9. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator’s participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, “publication”) before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When appliable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

### 10.1.10. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

### 10.1.11. Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

## 10.2. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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## Appendix A. SCHEDULE OF EVENTS

| Study Procedure and Day | | Screening | Cycle 1 | | Cycle 2 | |
|---|---|---|---|---|---|---|
| | | Days –28 to 1 | Day 1 | Day 12 (±3 days) | Day 1 (–1 day to +3 days) | Day 12 (±3 days) |
| **Assessments** | Informed consent | X | | | | |
| | Document AEs | X | X | X | X | |
| | Document study eligibility | X | | | | |
| | Document concomitant meds[a] | X | X | X | X | |
| | Document baseline medical conditions | X | | | | |
| | Document disease history | X | | | | |
| | Height | X | | | | |
| | Vital signs (BP, heart rate, temp, resp rate, pulse oximetry), including weight[b] | X | X | X | X | |
| | Physical exam[b] | X | X | X | X | |
| | ECOG PS[b] | X | X | X | X | |
| | Labs[b,c] | X | X | X | X | X[d] |
| | Coagulation | X | | | | |
| | Pregnancy test[e] | X[f] | | | X | |
| | Hepatitis B and C screening | X[g] | | | | |
| | ECG | X | | | | |
| | ECHO/MUGA[h] | X | | | | |
| | CT, PET/CT, or MRI[h,i] | X | | | | |

| Study Procedure and Day | | Screening | Cycle 1 | | Cycle 2 | |
|---|---|---|---|---|---|---|
| | | Days –28 to 1 | Day 1 | Day 12 (±3 days) | Day 1 (–1 day to +3 days) | Day 12 (±3 days) |
| | Contrast MRI Brain | X | | | | |
| | Blood sample for biomarker evaluation | X | | | | |
| | Archived tumor sample for biomarker evaluation | X[j] | | | | |
| | EQ-5D-5L Questionnaire[k] | | X | | X | |
| **Study intervention** | Tucatinib[l] | | X | | X | |
| | T-DXd[m] | | X | | X[n] | |
| **PK** | Blood samples | | X[o] | X[p] | X[q] | |

a. Including concomitant procedures, hospitalizations, and a review of the dosing regimen of antidiarrheals taken in the previous cycle beginning with the first dose of tucatinib, participants following protocol amendment 2 are to receive loperamide (see Section 5.6.1).
b. Assessment to be done predose on days when study intervention(s) are administered. Predose assessments can be done within 1 day prior to study visit (with exception of vital signs). For Cycle 1 Day 1, lab results must be reviewed and eligibility confirmed prior to first dose of study treatment.
c. Blood samples for complete blood count with differential, serum chemistry, and liver function tests.
d. Only liver function tests are required at this visit.
e. Females of childbearing potential only: serum or urine pregnancy test. Pregnancy test to be performed each cycle prior to study treatment. A positive urine test must be confirmed with a serum pregnancy test.
f. Serum or urine pregnancy test within 7 days prior to treatment (required only for females of childbearing potential).
g. Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B core (anti-HBc), and antibodies to Hepatitis C (anti-HCV). If positive, additional testing may be required after discussion with medical monitor.
h. Use the same assessment modality throughout the study that was used at screening/baseline.
i. At minimum, scans must include chest, abdomen, and pelvis. Additional appropriate imaging of any other known sites of disease such as photography for skin lesions or nuclear bone scan imaging for bone lesions may also be obtained at the investigator's discretion. If bone imaging is collected, any RECIST appropriate imaging modality may be used.
j. If tumor blocks are not available, slides may be submitted after discussion with and approval from the medical monitor.
k. To be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of any study intervention .
l. Tucatinib is administered PO BID, on a 21-day cycle. On Day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle.
m. T-DXd is administered intravenously, once every 21 days.
n. Tucatinib should be administered prior to T-DXd on Day 1 for this cycle.

| Study Procedure and Day | Screening | Cycle 1 | | Cycle 2 | |
|---|---|---|---|---|---|
| | Days –28 to 1 | Day 1 | Day 12 (±3 days) | Day 1 (–1 day to +3 days) | Day 12 (±3 days) |

o. Predose
p. For safety lead-in participants only. After morning dose of tucatinib (record time of tucatinib dose and blood draw).
q. Predose and 2 hour (±15 min) post-dose.

| Study Procedure and Day | | Cycle 3 and Beyond | | End of Treatment Visit | Follow-up | LTEP |
|---|---|---|---|---|---|---|
| | | Day 1 (–1 day to +3 days) | CT/MRI and ECHO/MUGA Schedule | 30 Days (+7 days) After Last Dose of Study Treatment | 90 Days (±14 days) Following End of Treatment Visit and Continuing Every 90 Days[b] | |
| **Assessments** | Document AEs | X | | X | | X[v,w] |
| | Document concomitant meds[a] | X | | X | | X[v] |
| | Vital signs (BP, heart rate, temp, resp rate, and pulse oximetry), including weight[c] | X | | X | | X[v] |
| | Physical exam[c] | X | | X | | X[v] |
| | ECOG PS[c] | X | | X | | X[v] |
| | Labs[c,d] | X | | X | | X[v] |
| | Coagulation | | | X | | X[v] |
| | Pregnancy test | X[e] | | X[f] | X[f] | X[e,f] |
| | ECHO/MUGA[g] | | X[h] | X[i] | | X[v] |
| | CT, PET/CT, or MRI[g,j] | | X[k] | X[l] | X[m] | X[v] |
| | Contrast MRI Brain | | X[n] | X[o] | X[m] | X[v] |
| | Blood sample for biomarker evaluation | X[p] | | X | | |
| | EQ-5D-5L Questionnaire[q] | X | | X | | |
| | Participant contact/clinic visit | X | | X | X[r] | X[v] |

| Study Procedure and Day | | Cycle 3 and Beyond | | End of Treatment Visit | Follow-up | LTEP |
|---|---|---|---|---|---|---|
| | | Day 1 (–1 day to +3 days) | CT/MRI and ECHO/MUGA Schedule | 30 Days (+7 days) After Last Dose of Study Treatment | 90 Days (±14 days) Following End of Treatment Visit and Continuing Every 90 Days[b] | |
| **Study intervention** | Tucatinib[s] | X | | | | X |
| | T-DXd[t] | X | | | | X |
| **PK** | Blood samples | X[u] | | | | |

a. Including concomitant procedures, hospitalizations, and a review of the dosing regimen of antidiarrheals taken in the previous cycle. Beginning with the first dose of tucatinib, participants following protocol amendment 2 are to receive loperamide (see Section 5.6.1).
b. More frequent follow-up may be requested for OS event tracking. If an End Of Treatment Visit was not done, then long term follow-up should begin every 90 days (±14 days) starting from the date of the last dose of study treatment.
c. Assessment to be done predose on days when study intervention(s) are administered. Predose assessments can be done within 1 day prior to study visit (with the exception of vital signs).
d. Blood samples for complete blood count with differential, serum chemistry, and liver function tests.
e. Females of childbearing potential only: serum or urine pregnancy test. Pregnancy test to be performed each cycle prior to study treatment starting. A positive urine test must be confirmed with a serum pregnancy test.
f. Females of childbearing potential only: monthly pregnancy tests should be performed for 7 months after the last dose of study treatment. Participant will be asked to confirm that monthly pregnancy tests have been performed and have been negative. A pregnancy test should be performed at the End of Treatment Visit if not performed within the last 30 days. Confirmation of correct and consistent use of contraception and assessment of whether participant has changing reproductive needs.
g. Use the same assessment modality throughout the study that was used at screening/baseline.
h. Every 12 weeks (–7 days) as determined by the date of C1D1. If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment
i. If not done within the previous 12 weeks (excluding screening/baseline).
j. At minimum, scans must include chest, abdomen, and pelvis. Additional appropriate imaging of any other known sites of disease such as skin lesion photography or bone imaging may also be obtained at the investigator's discretion. If bone imaging is collected, any RECIST appropriate imaging modality may be used.
k. Schedule determined by the C1D1 date. Contrast CT (preferred), PET/CT (if high quality CT scan included) or MRI scans should be performed every 6 weeks (–7 days) through Week 24, then every 9 weeks (–7 days) through end of study intervention. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original C1D1 date as described in Section 6.3.6.
l. Only in participants who discontinue study treatment for reasons other than radiographic disease progression. Not required if performed within 30 days of discontinuing study treatment.
m. If study treatment is discontinued for reasons other than disease progression (per RECIST v1.1) or death, participants will continue to have follow-up for disease progression and scan data should be collected approximately every 9 weeks (±1 week) until the occurrence of disease progression per RECIST v1.1, death, withdrawal of consent, or study closure. Brain MRI only required for participants who have a history of brain metastases at baseline.

| Study Procedure and Day | Cycle 3 and Beyond | | End of Treatment Visit | Follow-up | LTEP |
|---|---|---|---|---|---|
| | Day 1 (–1 day to +3 days) | CT/MRI and ECHO/MUGA Schedule | 30 Days (+7 days) After Last Dose of Study Treatment | 90 Days (±14 days) Following End of Treatment Visit and Continuing Every 90 Days[b] | |

n. Schedule determined by the C1D1 date. Contrast MRI of the brain (only in participants with brain metastases at baseline) should be performed every 6 weeks (–7 days) through Week 24, then every 9 weeks (–7 days) through end of study intervention. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original C1D1 date as described in Section 6.3.6.
o. Only in participants who have a history of brain metastases who discontinue study treatment for reasons other than radiographic disease progression, except if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study.
p. At C3D1 only, predose.
q. To be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of any study intervention for Cycle 3 and 4 and every 2 cycles starting at Cycle 6 until treatment discontinuation, PD, death, unacceptable toxicity, withdrawal of consent or study closure, and at the End Of Treatment visit.
r. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to make phone/personal contact are unsuccessful.
s. Tucatinib is administered PO BID, on a 21-day cycle. On Day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle.
t. T-DXd is administered intravenously, D1 of each 21-day cycle.
u. PK samples will be taken at cycles 3 and 6 only. Tucatinib should be administered before T-DXd at Cycle 3 and Cycle 6; for Cycle 3, participants should remain onsite for 2 hours (±15 minutes) after tucatinib administration to coordinate peak PK sampling times. For all other cycles, study interventions may be given in any order and can be given simultaneously.
v. During the LTEP, safety and efficacy assessments that include determination of disease progression will be performed per institutional guidelines and investigator-determined usual and customary clinical care.
w. Only SAEs and pregnancy will be collected by the sponsor

## Appendix B. CYP2C8 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES

CYP2C8 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

| **Drug**[a,b] | **Elimination Half-life**[c] **(hours)** |
|---|---|
| **Strong Inhibitor** | |
| Gemfibrozil | 1–2 hours |
| **Moderate Inhibitors** | |
| Clopidogrel<br>Deferasirox<br>Teriflunomide | 6 hours<br>8–16 hours<br>18–19 days |
| **Moderate Inducer** | |
| Rifampin | 3–5 hours |

Note: Any additional strong inhibitors or inducers of CYP2C8 that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency).

b EMA. "Guideline on the investigation of drug interactions" http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

c Drug product label

## Appendix C. CYP3A4 INDUCERS AND THEIR ELIMINATION HALF-LIVES

Cytochrome P450 (CYP) 3A4 inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inducers with continued research.

| Drug[a,b] | Elimination Half-life[c] (hours, unless indicated otherwise) |
|---|---|
| **Strong Inducers** | |
| Apalutamide | 3 days[d] |
| Carbamazepine | 25–65 hours (single dose), 12–17 hours (repeat dose) |
| Enzalutamide | 5.8 days[e] |
| Mitotane | 18 to 159 days[f] |
| Phenytoin | 7–42 hours |
| Rifampin | 3–4 hours (single dose), 2–3 hours (repeat dose) |
| St. John's Wort | 9–43 hours[g] |

Note: Any additional CYP3A4 inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)

b EMA. Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Drug product label

d ERLEADA drug label 2018.

e XTANDI drug label 2018.

f LYSODREN drug label 2017.

g (Kerb et al, 1996)

## Appendix D. EXAMPLES OF CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

The following table provides examples of clinical substrates for CYP3A-mediated metabolism and is not intended to be an exhaustive list.

| **Sensitive (AUC increase ≥5-fold with strong index inhibitor)** | **Moderate Sensitive (AUC increase ≥2 to <5-fold with strong index inhibitor)** |
|---|---|
| alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[c], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[d], midazolam, naloxegol, nisoldipine, saquinavir[c], simvastatin[d], sirolimus, tacrolimus, tipranavir[c], triazolam, vardenafil | alprazolam, aprepitant, atorvastatin[a], colchicine, eliglustat[b], pimozide, rilpivirine, rivaroxaban, tadalafil |
| budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[c], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan | |

AUC=area under the concentration-time curve; CYP=cytochrome P450; DDI=drug-drug interaction; OATP1B1=organic anion transporting polypeptide 1B1.
Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.
a Listed based on pharmacogenetic studies.
b Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.
c Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
d Acid form is an OATP1B1 substrate
DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad et al, 2010).
Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

## Appendix E. ECOG PERFORMANCE STATUS SCALE

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

## Appendix F. RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF T-DXD INDUCED INTERSTITIAL LUNG DISEASE/PNEUMONITIS

| | Grade 1 | Grade 2 | Grade 3 or 4 |
|---|---|---|---|
| Work-up | If a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis<br>• Evaluations should include:<br>– High resolution CT<br>– Pulmonologist consultation (Infectious Disease consultation as clinically indicated)<br>– Blood culture and CBC. Other blood tests could be considered as needed<br>– Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible<br>– Pulmonary function tests and pulse oximetry<br>– Arterial blood gases if clinically indicated<br>– One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible<br>• If the AE is confirmed to have an etiology other than treatment-related ILD/pneumonitis, follow routine clinical practice<br>• If another etiology for the AE cannot be identified and it could be related to T-DXd, then follow the ILD/pneumonitis management guidance as outlined below<br>• All events of ILD/pneumonitis, regardless of severity or seriousness, should be followed until resolution | | |
| Dose modification | • The administration of T-DXd must be interrupted<br>• T-DXd can be restarted only if the event is fully resolved:<br>– If resolved in ≤28 days from day of onset, maintain dose.<br>– If resolved in >28 days from day of onset, reduce dose by 1 level<br>– However, if the event Grade 1 ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued | Permanently discontinue patient from T-DXd treatment | Permanently discontinue patient from T-DXd treatment |

| | Grade 1 | Grade 2 | Grade 3 or 4 |
|---|---|---|---|
| Toxicity management | • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry<br>• Consider follow-up imaging in 1 to 2 weeks (or as clinically indicated)<br>• Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks<br>• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines. (If the patient is asymptomatic, then they should still be considered as grade 1 even if steroid treatment is given) | • Promptly start systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks.<br>• Monitor symptoms closely<br>• Re-image as clinically indicated<br>• If worsening or no improvement in clinical or diagnostic observations in 5 days,<br>– Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)<br>– Re-consider additional workup for alternative etiologies as described above<br>– Escalate care as clinically indicated | • Hospitalization required<br>• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500 to 1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks<br>• Re-image as clinically indicated<br>• If still no improvement within 3 to 5 days,<br>– Re-consider additional workup for alternative etiologies as described above<br>– Consider other immunosuppressants and/or treat per local practice |

Source: (Modi et al, 2020) (supplementary appendix Table S6).

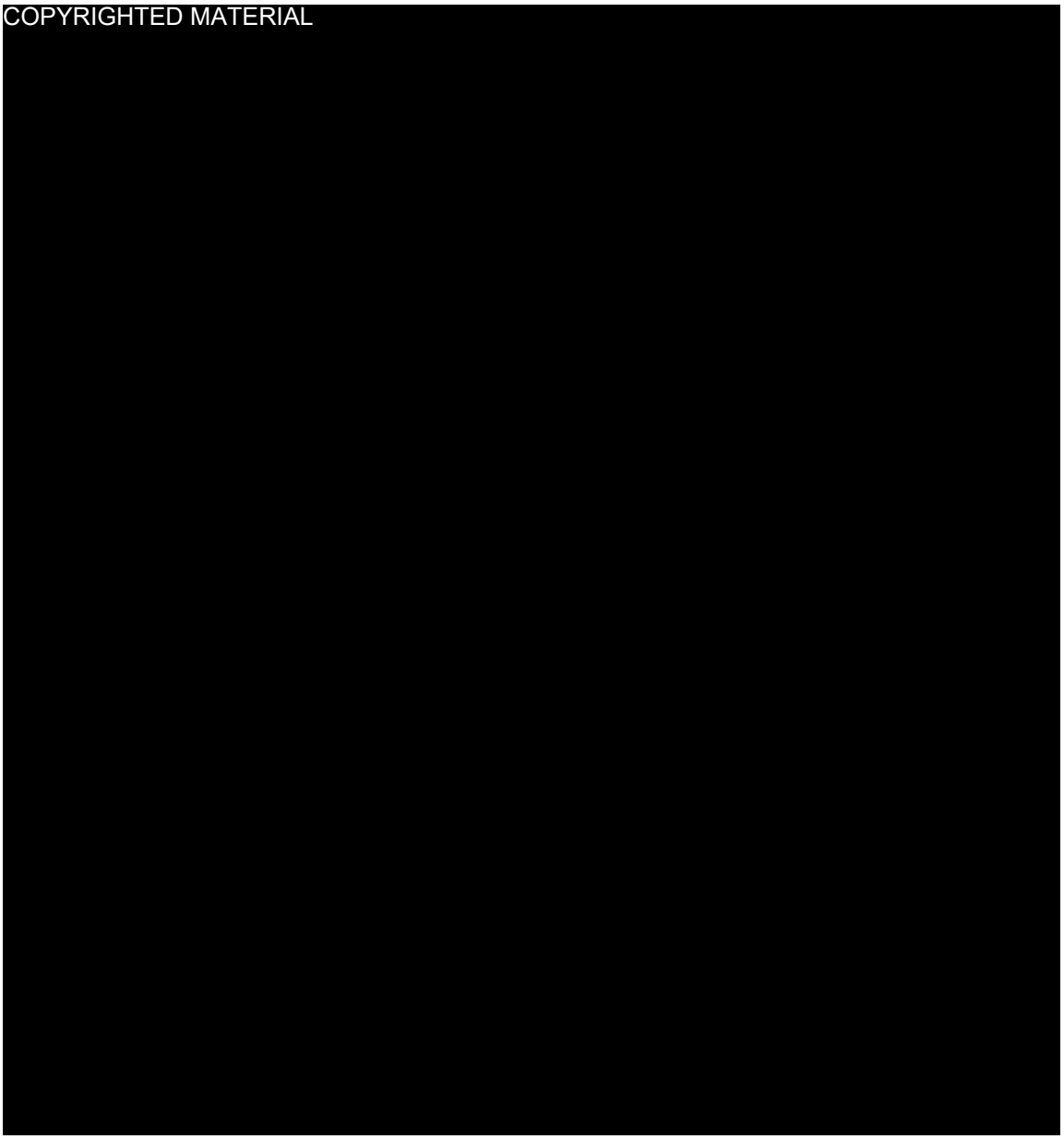
## Appendix G. POTENTIAL CONDITIONS THAT COULD TRIGGER CLINICAL EVALUATION FOR SUSPECTED INTERSTITIAL LUNG DISEASE

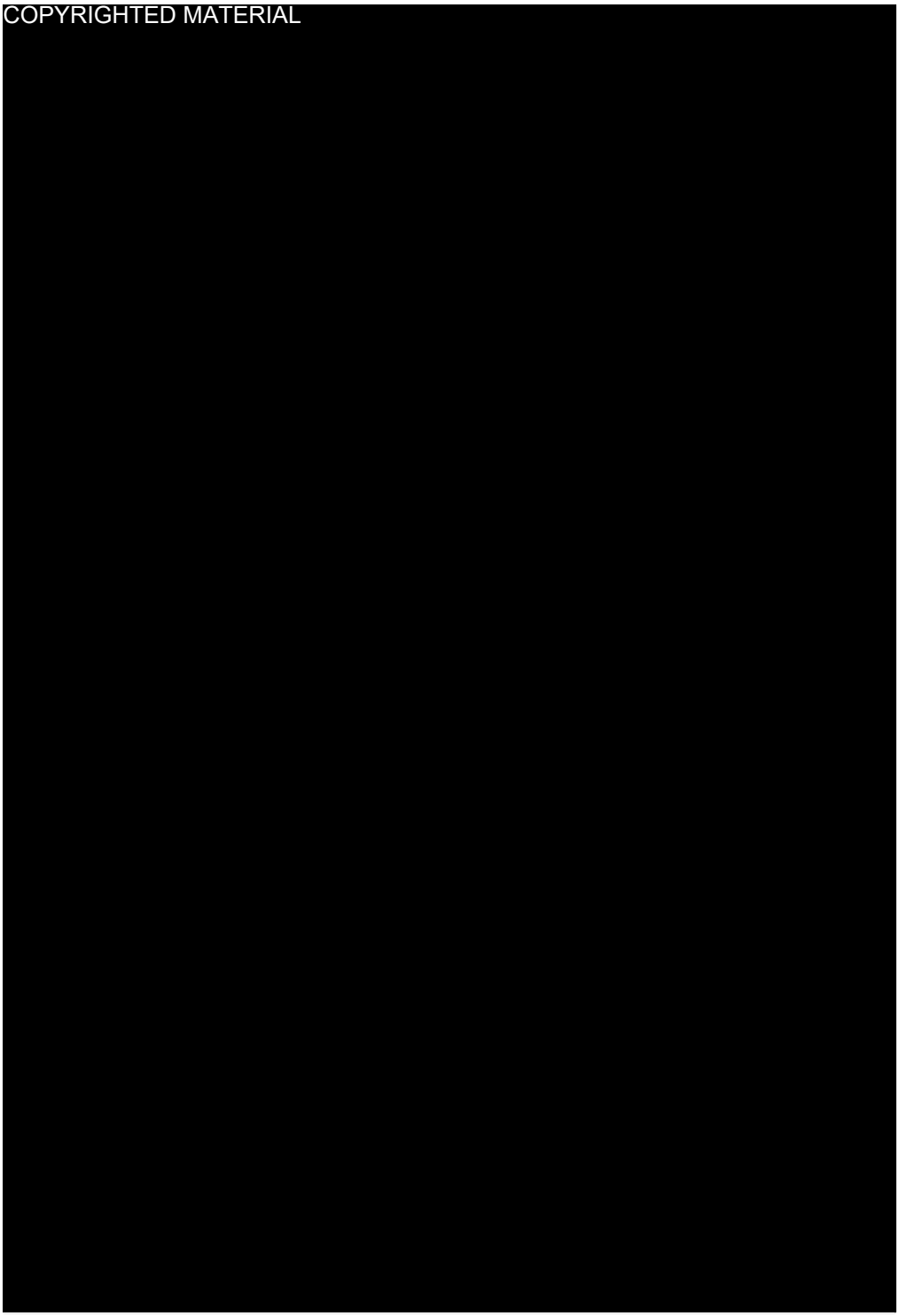
The table below provides examples and is not intended to be an exhaustive list of conditions that may potentially trigger suspected ILD.

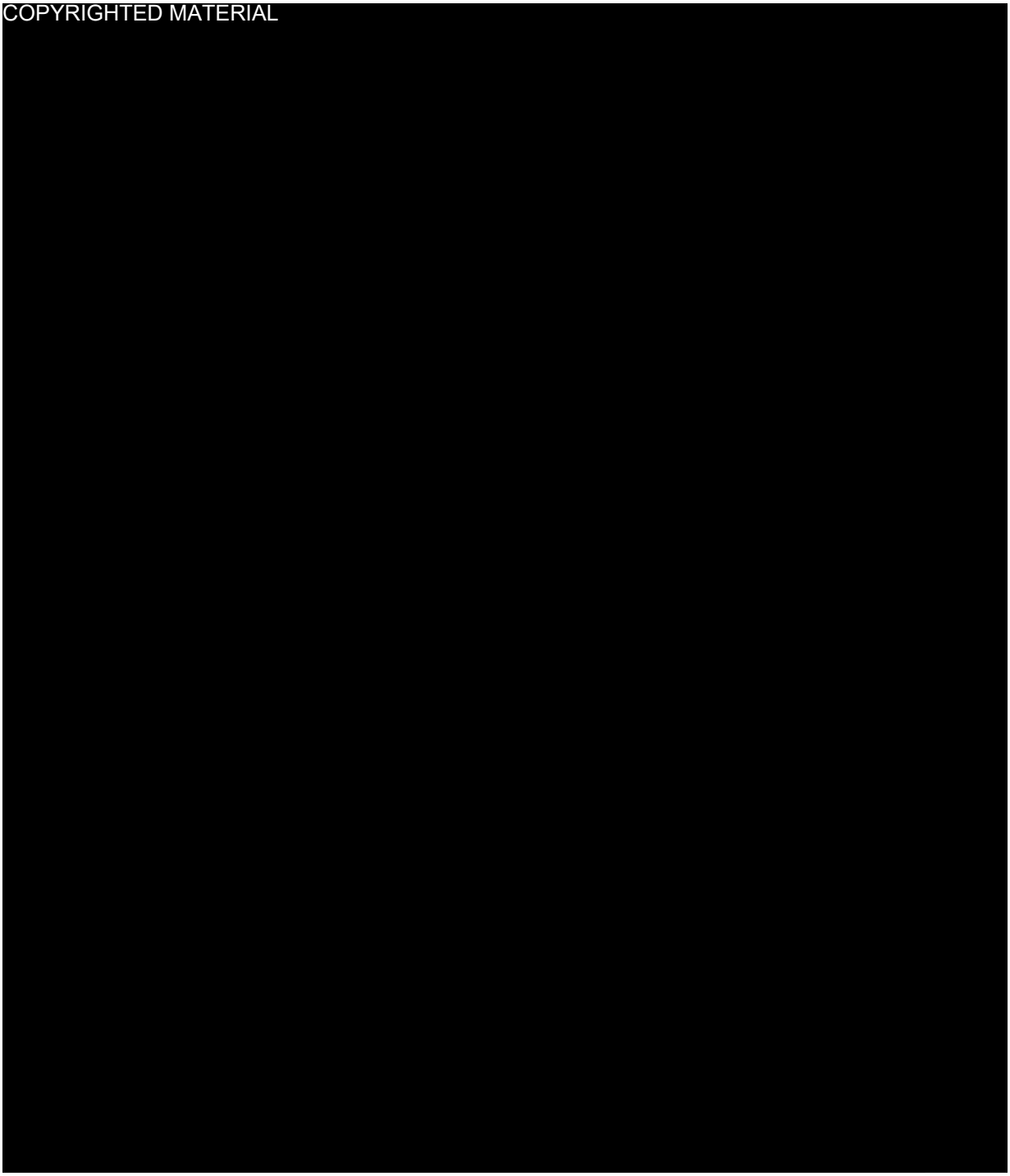
| | |
|---|---|
| • Acute interstitial pneumonitis<br>• Allergic eosinophilia<br>• Allergic granulomatous angiitis<br>• Alveolar lung disease<br>• Alveolar proteinosis<br>• Alveolitis<br>• Alveolitis allergic<br>• Alveolitis necrotizing<br>• Acute respiratory distress syndrome (ARDS)<br>• Bronchiolitis<br>• Diffuse alveolar damage<br>• Eosinophilia myalgia syndrome<br>• Eosinophilic pneumonia<br>• Eosinophilic pneumonia acute<br>• Eosinophilic pneumonia chronic<br>• Granulomatous pneumonitis<br>• Idiopathic pneumonia syndrome<br>• Idiopathic pulmonary fibrosis<br>• Interstitial lung disease | • Lung infiltration<br>• Necrotising bronchiolitis<br>• Obliterative bronchiolitis<br>• Organizing pneumonia<br>• Pneumonitis<br>• Progressive massive fibrosis<br>• Pulmonary fibrosis<br>• Pulmonary necrosis<br>• Pulmonary radiation injury<br>• Pulmonary sarcoidosis<br>• Pulmonary toxicity<br>• Pulmonary vasculitis<br>• Radiation alveolitis<br>• Radiation fibrosis - lung<br>• Radiation pneumonitis<br>• Restrictive pulmonary disease<br>• Rheumatoid lung<br>• Sarcoidosis<br>• Transfusion-related acute lung injury |

Source: (Modi et al, 2020) (supplemental material)

## Appendix H. EQ-5D-5L (SAMPLE QUESTIONNAIRE)







# Appendix I. GUIDANCE ON CONTRACEPTION

## Acceptable methods for highly effective birth control (preventing conception)

| **Participants who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):** |
|---|
| • Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated |
| • Intrauterine device with failure rate <1% |
| • Tubal ligation |
| • Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia) |
| • Barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b] |
| a See Section 4.4 for the definition of a person of childbearing potential. |
| b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception). |
| **Acceptable combinations of contraceptive methods:**<br>• Hormonal method and vasectomy<br>• Hormonal method and barrier method<br>• Intrauterine device and vasectomy<br>• Intrauterine device and barrier method<br>• Tubal ligation and vasectomy<br>• Tubal ligation and barrier method |

## Acceptable methods for preventing secondary exposure to seminal fluid

| |
|---|
| **Participants born male and who are sexually active with a pregnant person must use a male condom (even if the subject participant has had a vasectomy).**<br>**Participants born male and who are sexually active with a breastfeeding person must use a male condom (even if the subject participant has had a vasectomy). In addition, it is recommended that the breastfeeding partner use a highly effective female contraceptive method as listed in the section titled "Acceptable combinations of contraceptive methods".** |

**Unacceptable methods of contraception**

| | |
|---|---|
| • Periodic abstinence | • Spermicide only |
| • No method | • Progestin-only pills |
| • Withdrawal | • Concomitant use of female and male condoms |
| • Rhythm | • Barrier methods alone, including double-barrier methods |

For the purposes of this guidance, complete abstinence, if consistent with the participant's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 7 months for participants of childbearing potential and 4 months for participants who can father children after the final dose of study intervention; see Section 4.1).

# Appendix J. ADVERSE EVENTS: DEFINITIONS and PROCEDURES for RECORDING and REPORTING

## AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs via PSSA to Pfizer Safety throughout the safety reporting period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

**Table 12: Requirements for Recording AEs on the CRF and for Reporting SAEs via PSSA**

| Safety Event | Recorded on the CRF | Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| SAE | All | All |
| Nonserious AE | All | None |
| Exposure to the study intervention under study during pregnancy or breastfeeding | All AEs/SAEs associated with EDP or EDB<br>**Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured on the CRF | All instances of EDP are reported (whether or not there is an associated SAE)*<br>All instances of EDB are reported (whether or not there is an associated SAE) ** |
| Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB) | None. Exposure to a study non-participant is not collected on the CRF | The exposure (whether or not there is an associated AE or SAE) must be reported*** |

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety via PSSA.
**EDB** is reported to Pfizer Safety via PSSA, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via PSSA.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

**SAE Reporting to Pfizer Safety via an electronic DCT**

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (PSSA).

- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic DCT (PSSA) or paper form (as applicable) as soon as the data become available.

- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

**SAE Reporting to Pfizer Safety via the CT SAE Report Form**

- Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.

- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

## Appendix K. Summary of Changes for Prior Amendments

## SUMMARY OF CHANGES IN AMENDMENT 1

| Section(s) | Change | Rationale |
|---|---|---|
| **5.4.3.2** | Updated first statement in section to include trastuzumab deruxtecan.<br><br>Updated Table 5 dose modification guidelines for liver function abnormalities for trastuzumab deruxtecan as follows:<br><br>Bilirubin (>3 – ≤10 x ULN):<br>changed from "Dose modification not required." to "Hold until recovery to (≤1.5 x ULN). Then resume trastuzumab deruxtecan at the next lower dose level."<br><br>ALT or AST (>20 x ULN)<br>OR<br>Bilirubin (>10 x ULN):<br>Changed from "Dose modification not required." to "Permanently discontinue"<br><br>ALT or AST >3 x ULN<br>AND<br>Bilirubin >2 x ULN<br>Changed from "Dose modification not required." to "Permanently discontinue" | Modification based on FDA information request. |
| **Throughout protocol** | Updated Seattle Genetics, Inc. to Seagen Inc. in headers, body, and footers, as applicable. | Administrative, corporate name change |

## SUMMARY OF CHANGES IN AMENDMENT 2

| Section(s) | Change | Rationale |
|---|---|---|
| Synopsis Study Population, Synopsis Inclusion Criteria (IC), Synopsis Study Design, Section 2, Section 3.1, Section 4, and Section 4.1 | Updated text to indicate subjects who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab) are eligible for the study | To evaluate tucatinib in combination with T-DXd in earlier lines of therapy, given recent DESTINY-Breast03 data. |
| Synopsis IC and Section 4.1 | Updated text to include subjects with AST and ALT concentrations of ≤3 x ULN rather than ≤2.5 x ULN | Revised to align with CTCAE grading version 5.0 (Grade 1: >ULN - 3.0 x ULN [not 2.5 x ULN]) |
| Synopsis IC and Section 4.1 | Minor updates to contraception inclusion criteria (IC13 and IC14) | To ensure that appropriate barrier methods are used to avoid secondary exposure. |
| Synopsis Exclusion Criteria (EC) and Section 4.2 | Adjusted EC10 to indicate subjects with HIV are excluded if they meet any of the following criteria:<br>• CD4+ T-cell count of <350 cells/µL<br>• Detectable HIV viral load<br>• History of an opportunistic infection within the past 12 months<br>• On stable antiretroviral therapy for <4 weeks | Specify criteria for subjects with HIV. |
| Synopsis EC | Updated text to exclude subjects who have used a strong cytochrome P450 (CYP) 2C8 inhibitor within 5 rather than 3 elimination half-lives of the inhibitor | Consistency with current guidance |
| Synopsis EC and Section 4.2 | Added EC to exclude subjects with ongoing ≥Grade 2 diarrhea of any etiology at screening | To exclude subjects with increased risk of developing significant treatment-related adverse events |
| Synopsis Investigational Products, Dose, and Mode of Administration and Section 5.1 | Updated text related to dosing | Consistency with current guidance |
| Section 1.2.4 | Updated introductory text to include information about DESTINY-BREAST03 | Provide background on changes to subject eligibility |
| Synopsis Post-safety Lead-in, Section 3.1, and Section 6.3.1 | Addition of text related to management of diarrhea and risk mitigation approaches | To provide guidelines for management of diarrhea associated with treatment |

| Section(s) | Change | Rationale |
|---|---|---|
| Synopsis<br>Patient-Reported Outcomes, Section 6, and Appendix A | Updated text on patient-reported outcomes that EQ-5D-5L is to be administered before evaluation by study personnel | To clarify that EQ-5D-5L is to be administered before evaluation by study personnel |
| Section 5.4.3.1, Table 4 | Updated Table 4 to include more dose modification information for AEs related to nausea and/or vomiting and diarrhea. | Additional dose modification guidelines for management of gastrointestinal adverse events |
| Section 5.4.3.2, Table 5 | Updated to T-DXd dose modification for instances of ALT or AST (>5 – ≤20 x ULN) | Addition of dose modification guidance to ensure subject safety |
| Section 5.4.3.3, Table 6; Section 5.4.3.4, Table 7; and Section 5.4.3.5, Table 8 | Updated tables to remove tucatinib; since, no dose modifications are required | Tables updated to show that tucatinib dose modifications not required for ILD/pneumonitis or neutropenia and febrile neutropenia and for ejection fraction decrease |
| Section 5.5.1 | Added text about required concomitant therapy for subjects who enroll during the time antidiarrheal prophylaxis is implemented. | Provide guidance on antidiarrheal prophylaxis for subjects who enroll under protocol amendment 2 of the protocol. |
| Section 5.5.2 | Updated text about antidiarrheal and antiemetic supportive care medications<br><br>Updated text on premedication for contrast use in CT or MRI scans | Provide additional guidance for antidiarrheal and antiemetic prophylaxis<br><br>Provide additional guidance for allowed concomitant therapy in CT or MRI scans |
| Section 5.5.3 | Updated Prohibited Concomitant Therapy text | Provide additional guidance for prohibited concomitant use of CYP agents and digoxin |
| Section 5.6.4 | Added text for Management of Treatment-associated Diarrhea | Provide additional guidance for management of treatment-associated diarrhea |
| Section 6.3.1 | Added required concomitant antidiarrheal medication | Provide additional guidance for antidiarrheal medication |
| Section 6.3.3, Section 6.3.5, and Section 6.4 | Added text about reviewing the dosing regimen of antidiarrheals taken in the previous cycle | Consistency with updates to the schedule of events (SoE) |
| Section 7.2 | Added text allowing non-contrast CT scan if MRI is not feasible | Consistency with updates to other sections of the protocol |

| Section(s) | Change | Rationale |
|---|---|---|
| Section 7.7.1.1 | Added section on Overdose, Medication Error, and Abuse<br><br>Added Diarrhea as an AESI<br><br>Adverse Events of Special Interest text was updated | Define and provide guidance on overdose, medication error, and abuse<br><br>Consistency with risk mitigation strategies implemented in the protocol and stringent collection of diarrhea events in the database<br><br>Differentiate information around AST or ALT elevations and Bilirubin elevations. |
| Section 7.7.1.2, Pregnancy, Notification to Drug Safety | Update notification from 48 to 24 hours | Consistency with current guidance |
| Section 7.7.3 | Updated text for tests included in the CBC with differential | Clarify guidance |
| Appendix A | Updated footnote “a” to indicate that a review of the dosing regimen of antidiarrheals taken in the previous cycle should be done | Consistency with updates to SoE and Section 6 |
| Appendix B | List of CYP2C8 inhibitors updated | Clarify strong inhibitors and include moderate inhibitors |
| Appendix C | List of CYP3A4 inducers updated | List strong inducers |
| Appendix D | Minor wording changes | Clarify examples of substrates for CYP3A-mediated metabolism |
| Appendix I | Updated text on contraception: Modified the methods for preventing secondary exposure to seminal fluid to specify that they apply even if the subject has had a vasectomy and recommended that the breastfeeding partner use a highly effective female contraceptive method as listed in the appendix. | To ensure that appropriate barrier methods are used to avoid secondary exposure. |
| Throughout protocol | Editorial and Administrative Changes (formatting, updates to footers, etc.) | Administrative |