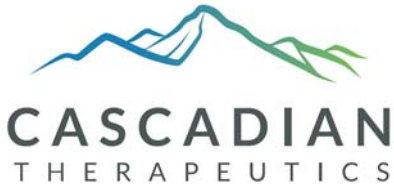

Please REMOVE and send to Sponsor.

Clinical Study Protocol

Signature Page

Protocol Number:	ONT-380-004
Protocol Title:	Phase 1b, open-label study to assess the safety and tolerability of tucatinib (ONT-380) combined with ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1)
Investigational Product:	Tucatinib (ONT-380)
Amendment No.	8 (16-MAY-2017)
Previous Version:	Original (22-AUG-2013), Amendment 1 (03-OCT-2013), Amendment 2 (17-OCT-2013), Amendment 3 (17-JAN-2014), Amendment 4 (25-JUN-2014), Amendment 5 (11-SEP-2014), Amendment 6 (18-MAR-2015), Amendment 7 (06-JUL-2016)

By signing this protocol, the investigator agrees to conduct the clinical trial in accordance with this protocol, generally accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, regulations, requirements, and guidelines (including all foreign laws and governmental requirements as applicable) relating to the conduct of the clinical trial. In addition, the investigator agrees to provide the sponsor with such information and certifications as the sponsor shall reasonably request from time to time regarding direct and indirect financial interests and other arrangements between sponsor and investigator, to allow the sponsor to submit complete and accurate certification and disclosure statements as required by FDA regulations.

The sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the clinical trial is conducted and data are generated, documented, and reported in compliance with this protocol, accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, regulations, requirements, and guidelines (including all foreign laws and governmental requirements as applicable) relating to the conduct of the clinical trial.

Principal Investigator's Signature	**Print Name**	**Date**

Site Address and Telephone

Please KEEP with protocol.

Clinical Study Protocol

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Principal Investigator's Signature	**Print Name**	**Date**

Site Address and Telephone

Clinical Study Protocol
Effective Date: 16-MAY-2017

Protocol Number:	ONT-380-004
Protocol Title:	A Phase 1b, open-label study to assess the safety and tolerability of ONT-380 combined with ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1)
Investigational Product:	Tucatinib (ONT-380)
Amendment No.	8 (16-MAY-2017)
Previous Version:	Original (22-AUG-2013) Amendment 1 (03-OCT-2013) Amendment 2 (17-OCT-2013) Amendment 3 (17-JAN-2014) Amendment 4 (25-JUN-2014) Amendment 5 (11-SEP-2014) Amendment 6 (18-MAR-2015) Amendment 7 (06-JUL-2016)
Indication:	HER2-positive Metastatic Breast Cancer
Sponsor:	Cascadian Therapeutics, Inc. 2601 4th Avenue, Suite 500 Seattle, WA 98121
Sponsor Monitor:	Luke Walker, MD Senior Vice President, Clinical Development Office: 206-801-2912 Fax: 206-801-2101
Serious Adverse Event Reports:	Cascadian Therapeutics, Inc. Fax: 1-206-801-2127

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Protocol Synopsis

Protocol Number: ONT-380-004 **Version:** Amendment 8 (16-MAY-2017) **Phase:** 1b	**Product Name:** Tucatinib (ONT-380) **Sponsor:** Cascadian Therapeutics, Inc. 2601 4th Avenue, Suite 500 Seattle, WA 98121

Protocol Title

A Phase 1b, open-label study to assess the safety and tolerability of tucatinib (ONT-380) combined with ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1)

Study Objectives

Primary:

- Determine the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) of tucatinib (ONT-380) to be given in combination with the approved dose of T-DM1.

Secondary:

- Evaluate the safety of tucatinib given at the MTD/RP2D in combination with T-DM1.
- Evaluate the preliminary anti-tumor activity of tucatinib given in combination with T-DM1.

Exploratory:

- Assess HER2 mutations and the presence of other potential biomarkers of response in archived tumor biopsy specimens.
- Examine the effects of combination therapy on the pharmacokinetics (PK) of tucatinib and T-DM1.
- Evaluate the effect of tucatinib in combination with T-DM1 on central nervous system (CNS) metastases.

Study Population

Patients with progressive HER2+ metastatic breast cancer who have previously received trastuzumab and a taxane, separately or in combination. Patients must have received prior therapy with trastuzumab and a

taxane for metastatic disease.

Inclusion Criteria

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

1) HER2+ metastatic breast cancer, documented as HER2+ by fluorescence *in situ* hybridization (FISH) and/or 3+ staining by immunohistochemistry (IHC).

2) History of prior therapy with trastuzumab and a taxane, separately or in combination. For patients in dose escalation and MTD expansion cohorts, prior therapy with trastuzumab and a taxane must have been for metastatic disease. For patients in CNS disease expansion cohorts, trastuzumab and taxane (together or separately) may have been given at any time prior to study enrollment as part of neoadjuvant therapy, adjuvant therapy, or therapy for metastatic disease.

3) ≥ 18 years at time of consent.

4) If female and of child-bearing potential, has negative pregnancy test within 14 days prior to treatment.

5) If a sexually active male or a sexually active female of child-bearing potential, agrees to use dual (two concurrent) forms of medically accepted contraception from the time of consent until 6 months after the last dose of either tucatinib or T-DM1, whichever is longer.

6) Signed an informed consent document that has been approved by an institutional review board or independent ethics committee (IRB/IEC).

7) Must have target or non-target lesions as per RECIST 1.1.

8) All toxicity related to prior cancer therapies must have resolved to ≤ Grade 1, with the following exceptions: alopecia; neuropathy, which must have to resolved to ≤ Grade 2; and congestive heart failure (CHF), which must have been ≤ Grade 1 in severity and must have resolved completely.

9) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.

10) In the opinion of the Investigator, life expectancy > 6 months.

11) Adequate hematologic function as defined by:

    a) Hemoglobin ≥ 9 g/dL

    b) Absolute neutrophil count (ANC) ≥ 1000 cells/µL

    c) Platelets ≥ 100,000/µL

12) Adequate hepatic function as defined by the following:

a) Total bilirubin ≤ 1.5 X upper limit of normal (ULN)

b) Transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT] and alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT]) ≤ 1.5 X ULN (< 2.5 X ULN if liver metastases are present)

13) INR and aPTT ≤ 1.5 X ULN unless on medication known to alter INR and aPTT.

14) Calculated creatinine clearance ≥ 60 mL/min.

15) Left ventricular ejection fraction (LVEF) must be within institutional limits of normal as assessed by echocardiogram or multigated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study drug.

Exclusion Criteria

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

1) Medical, social, or psychosocial factors that, in the opinion of the Investigator, could impact safety or compliance with study procedures.

2) Patient is breastfeeding.

3) Patient was treated with any experimental agent within 14 days or five half-lives of study treatment, whichever is greater.

4) Patient was treated with trastuzumab or other antibody-based therapy within three weeks of starting study treatment or with chemotherapy or hormonal cancer therapy within two weeks of starting study treatment.

5) Patient had prior exposure to a cumulative dose of doxorubicin that exceeded 360 mg/m^2 or its equivalent..

6) Previous treatment with T-DM1 at any time; or previous treatment with any small molecule HER2 inhibitors including (but not limited to) lapatinib, neratinib, or afatinib within the last 4 weeks prior to initiation of study therapy.

7) CNS disease:

a) Patients with leptomeningeal disease are excluded.

b) Dose escalation and MTD/RP2D expansion cohort: Patients with symptomatic CNS metastases are excluded. Patients with treated CNS metastases or untreated asymptomatic CNS metastases not requiring immediate local therapy may be eligible. Enrollment of patients with metastases must be approved by the study medical monitor.

c) Optional CNS disease expansion cohort: Patients with asymptomatic untreated CNS metastases not needing immediate local therapy or patients with progressive CNS disease following local therapy may be eligible with medical monitor approval.

8) History of allergic reactions to compounds of similar chemical or biological composition to T-DM1 or tucatinib, except for a history of Grade 1 or Grade 2 Infusion Related Reaction to trastuzumab which has been successfully managed.

9) Patients with uncorrectable electrolyte abnormalities.

10) Known to be HIV positive. HIV testing is not required for those patients who are not known to be positive.

11) Known carrier of Hepatitis B and / or Hepatitis C (whether active disease or not).

12) Known liver disease, autoimmune hepatitis, or sclerosing cholangitis,

13) Inability to swallow pills or any significant gastrointestinal diseases, which would preclude adequate absorption of oral medications.

14) Use of a strong CYP3A4 inhibitor within three elimination half-lives of the inhibitor prior to the start of study treatment. (See Appendix E).

15) Use of a strong CYP2C8 inducer or inhibitor within three elimination half-lives of the inducer or inhibitor prior to the start of study treatment. (See Appendix F).

16) Radiotherapy within 14 days of study treatment; patient must have recovered from acute effects of radiotherapy to baseline.

17) Known impaired cardiac function or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, congestive heart failure and uncontrolled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).

18) Myocardial infarction or unstable angina within 6 months prior to the first dose of study drug.

Study Design and Number of Planned Patients

This is a Phase 1b, open-label study to assess the safety, tolerability, and MTD or recommended Phase 2 dose of tucatinib combined with ado-trastuzumab emtansine (T-DM1). The study will use a 3+3 dose escalation design to evaluate up to four dose levels of tucatinib in order to determine the MTD/RP2D to be given with the approved dose of T-DM1. Three to six evaluable patients will be enrolled in each cohort in the dose escalation phase. A Safety Monitoring Committee (SMC) comprising the Investigators and Cascadian Therapeutics personnel, including the study medical monitor will meet and review safety data after each cohort is enrolled and/or approximately once every 3 months unless otherwise agreed upon, and

on an ad hoc basis as needed. At least 6 evaluable patients are to be treated at a dose level in order for an MTD/RP2D to be declared. Once an MTD/RP2D is declared, up to 24 additional evaluable patients will be in enrolled in an MTD/RP2D expansion cohort for a total of up to 30 evaluable patients to be treated at the MTD/RP2D. An additional optional cohort of up to 15 evaluable patients with either untreated, asymptomatic CNS metastases not needing immediate local therapy or progressive CNS metastasis following local therapy may also be enrolled and treated at the MTD/RP2D. Up to 63 evaluable patients may be treated in this study.
Following approval of Amendment 8, patients who are on study treatment may continue to receive study drug.

Test Product, Dose, and Mode of Administration

All treatments will be given on a 21-day cycle. Tucatinib will be administered twice daily. The first cohort will receive a tucatinib dose of 300 mg PO BID + T-DM1 3.6 mg/kg intravenously (IV) every 21 days. If the first dose level is tolerated (i.e., 0 of 3 or < 2 of 6 evaluable patients experience DLT), it will be followed by a second cohort of tucatinib administered at 350 mg PO BID + T-DM1 3.6 mg/kg IV every 21 days. If the second dose level is tolerated (i.e., 0 of 3 or < 2 of 6 evaluable patients experience DLT), it may be followed by a third cohort of tucatinib administered at 400 mg PO BID + T-DM1 3.6 mg/kg IV every 21 days. If the first dose is not tolerated, the SMC may recommend evaluating another cohort at a lower dose of tucatinib.

Duration of Treatment

Patients will be assessed for progression every 6 weeks initially, and then every 9 weeks after 6 cycles. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal of consent.

Efficacy Assessments

Efficacy will be measured by contrast computer tomography (CT) and/or contrast magnetic resonance imaging (MRI) of the body done at baseline, every 2 cycles through Cycle 6, and then every 3 cycles. All known sites of disease will be assessed at time of restaging. Additional imaging, such as nuclear bone scans, may also be done as appropriate at the discretion of the Investigator. Imaging will be assessed per RECIST 1.1 by the Investigator. Patients with CNS disease may also be assessed by modified CNS RECIST 1.1 criteria or Volumetric Response Criteria (See Appendix G). Contrast brain MRI images for patients with CNS metastases may be collected for additional independent review. However, all treatment decisions will be made on the basis of local review of radiologic imaging. Following approval of Amendment 8, patients on study treatment will be assessed for efficacy based upon institutional policy without protocol mandated efficacy time points.

Safety Assessments

Safety assessments will include surveillance and documentation of adverse events (AEs) (including dose-limiting toxicities [DLTs]), laboratory assessments, physical exam findings, and cardiac assessments.

Following approval of Amendment 8, patients on study treatment will be assessed for safety based upon institutional policy. Only serious adverse events (SAEs) and adverse events of interest (AOIs) will be collected by the Sponsor.

Statistical Methods

The total sample size will depend upon the number of patients required to reach the MTD/RP2D of the combination of tucatinib and T-DM1 and the number of expansion cohorts enrolled. The study may enroll up to 63 evaluable patients in up to 4 dose escalation cohorts using a standard 3+3 dose escalation design and up to two expansion cohorts. Both tumor responses and analysis of biomarkers will be summarized descriptively.

Endpoints

Primary:

- Incidence and severity of AEs

Secondary:

- Incidence and severity of clinical lab abnormalities
- Frequency of dose reductions in tucatinib
- Frequency of dose reductions in T-DM1
- Objective response rate (ORR)
- Duration of response
- Disease control rate (best response of complete response [CR], partial response [PR], or stable disease [SD])
- Clinical benefit rate (CBR) (SD for ≥ 6 months, PR, or CR)
- Progression-free survival (PFS)

Exploratory:

- Assess HER2 mutations and the presence of other potential biomarkers of response in archived tumor biopsy specimens
- Plasma concentrations of tucatinib and its metabolite

- Serum concentrations of T-DM1 and its metabolites
- CNS response rate

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Appendices: Schedules of Events and Criteria

1 INTRODUCTION

1.1 HER2+ Breast Cancer

Breast cancer is the most common form of cancer in women worldwide, and the second leading cause of cancer-related death in the United States. [1-2] Approximately 20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2).[3] HER2 is a trans-membrane 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, although the introduction of HER2 targeted therapies has led to ongoing improvements in clinical outcomes.[4]

HER2 belongs to a family of four related receptor tyrosine kinases, which also include HER1 (also referred to as epidermal growth factor receptor [EGFR]), HER3, and HER4. These are single-pass transmembrane glycoprotein receptors containing an extracellular ligand binding region and an intracellular signaling domain. In addition, all receptors contain an intracellular active tyrosine kinase domain with the exception of HER3, whose kinase domain does not exhibit enzymatic activity. The activation process is initiated by ligand binding to the extracellular domain of the receptor by one of a number of different hormones such as EGF, TGF, and the neuregulins. Upon ligand binding, homo- or heterodimerization is induced, which results in the activation of the tyrosine kinase domains and phosphorylation of tyrosines on the intracellular signaling domains. As no known ligand for HER2 has been described and HER3 lacks an active kinase domain, these receptors heterodimerize to elicit a response, and it has been demonstrated that HER2 is typically the preferred dimerization partner for the other HER family receptors. Receptor activation initiates several different signaling cascades including the Ras/Raf/MEK/MAPK, PI3K/AKT, Src, and STAT pathways. These signaling pathways lead to both cell proliferation and cell survival through inhibition of apoptosis.[5-10]

HER2 targeted therapy using either antibody-based therapy or a small molecule tyrosine kinase inhibitor (TKI) has led to significant and ongoing improvements in disease-free survival (DFS), progression-free survival (PFS), and OS in both the adjuvant and metastatic settings.[11-14] Trastuzumab (HERCEPTIN®), a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, was the first anti-HER2 agent approved by the FDA for use in the treatment of HER2+ breast cancer, and remains the backbone of treatment in this setting in the adjuvant setting and first-line metastatic setting, usually in combination with a taxane. The approval of trastuzumab was followed by the approval of lapatinib (TYKERB®), a small molecule TKI that targets both HER2 and EGFR. Lapatinib is approved for use in combination with capecitabine (XELODA®) in patients

with metastatic disease who have progressed following prior trastuzumab and taxane therapy, or in combination with letrozole (FEMARA®) in patients with ER+/PR+ metastatic disease. Pertuzumab (PERJETA®), another antibody-based therapy which binds to HER2 at a site different than trastuzumab, has also been approved for use in combination with trastuzumab and paclitaxel (TAXOL®) as first-line therapy for patients with metastatic disease.

Ado-trastuzumab emtansine (KADCYLA®, also known as trastuzumab emtansine or T-DM1) is the most recently approved anti-HER2 agent. T-DM1 is an antibody-drug conjugate composed of trastuzumab, a thioether linker, and a derivative of the antimitotic agent maytansine. T-DM1 was approved by the United States Food and Drug Administration (FDA) in February 2013 for patients with HER2+ metastatic breast cancer who previously received trastuzumab and a taxane, either separately or in combination, as treatment for either metastatic disease or as adjuvant therapy. For patients who received treatment as adjuvant therapy, disease recurrence must have occurred during or within six months of completing treatment. FDA approval was based on the Phase 3 EMILIA study, which enrolled 978 patients with HER2+ metastatic breast cancer who were randomly assigned to treatment with T-DM1 or the combination of capecitabine plus lapatinib. With a median duration of follow-up of 19 months, T-DM1 resulted in: a reduction in the risk of disease progression compared to capecitabine plus lapatinib (median PFS 10 versus [vs.] 6 months [mon], respectively); a reduction in mortality compared to capecitabine plus lapatinib (median OS, 31 vs. 25 mon); a clinically significant improvement in the objective response rate (ORR) (44 vs. 31%); and lower rate of serious (Grade 3/4) toxicity overall (41 vs. 57%, including diarrhea [2 vs. 21%], palmar plantar erythrodysesthesia [0 vs. 16%], and vomiting [0.8 vs. 5%]).[12] Further studies investigating the use of T-DM1in the first-line setting in combination with pertuzumab, as well as in the adjuvant setting, are ongoing.

1.1.1 Ongoing Medical Need in HER2+ Breast Cancer

Despite the improvements in outcomes for HER2+ breast cancer, up to a quarter of all patients treated with anti-HER2 therapy in the adjuvant setting relapse, and essentially all patients in the metastatic setting ultimately progress, including those treated with the newest agents such as T-DM1. Treatment failures may result from primary or acquired resistance to HER2 blockade. Potential mechanisms of resistance to trastuzumab-based therapy may include increased dimerization with other HER2 family members, cross-talk with insulin-like growth factor-1 receptor[15], expression of a truncated form of HER2 (p95HER2) which lacks the extracellular trastuzumab binding domain[16], and changes in expression of surface glycopeptides such as MUC4 which may block access to the trastuzumab binding site. Other mechanisms of resistance may include increased

signaling through non-HER family growth factor receptors, increased signaling through the PI3K pathway either due to kinase activating mutations or PTEN deficiency, or increased activation of Rac1, a GTPase that affects trastuzumab-mediated endocytosis of the HER2 receptor.[17–18]

There is increasing evidence that dual targeting of HER2, either through combination of two different HER2 targeted antibodies such as trastuzumab and pertuzumab, or through use of an antibody-based therapy such as trastuzumab and a TKI, can lead to further improvements in efficacy.[13, 19] In particular, combination of a small molecule TKI with an antibody-based therapy may be effective. This combination may help overcome resistance to antibody-mediated inhibition through utilization of an alternative mechanism of receptor inhibition, as well as through inhibition of the p95 form of HER2. A small molecule HER2 inhibitor with good brain penetration may also be better able to prevent or treat CNS metastases than an antibody-based therapy.

Lapatinib, a dual EGFR/HER2 oral TKI, has been shown to have increased activity in combination with trastuzumab compared to lapatinib alone, even when given to patients who have previously progressed on prior trastuzumab-based therapy.[20–21] Use of lapatinib, however, has been limited by the anti-EGFR/HER1 activity of the drug, which results in toxicities such as rash, diarrhea, and fatigue. There is therefore a need for a more selective small molecule inhibitor of HER2 which could be combined with other anti-HER2 therapies to improve clinical outcomes.

Perhaps the greatest unmet medical need in the post-trastuzumab era is treatment and prevention of central nervous system (CNS) metastases. Recent data suggest that the incidence of first relapse occurring in the CNS is increasing in patients who have received trastuzumab-based adjuvant therapy,[22] and approximately 30% of HER2+ patients with metastatic disease will develop CNS metastases.[23] The increasing prevalence of CNS metastases in HER2+ breast cancer patients may be due to several factors. First, HER2+ breast cancer appears to display tropism for the CNS. Second, with better control of non-CNS disease, patients may be living longer allowing CNS metastases to become more of a critical clinical issue. Finally, and perhaps most importantly, the CNS may represent a sanctuary site for HER2+ disease as large molecules such as trastuzumab do not penetrate the blood-brain barrier.[24]

Treatment options for CNS metastases are limited. There is currently no specific treatment regimen approved for CNS disease. Treatment of CNS metastases currently consists of use of whole brain or stereotactic radiation. Patients may also receive chemotherapy alone, or capecitabine and lapatinib, although response rates are generally modest as described below.

Use of a small molecule HER2 inhibitor such as lapatinib offers a theoretically attractive approach to the treatment of CNS disease. However, results with single-agent lapatinib have been disappointing, with response rates below 10%. Response rates for lapatinib and capecitabine have been variable, in part due to differences in patient populations studied and methodology used to assess response. Of note, several of these studies use volumetric response rather than RECIST to measure response. Response rates using the former method tend be higher than those using the latter. Use of lapatinib/capecitabine is limited, due to concerns regarding toxicity and limited efficacy. A summary of studies looking at capecitabine and lapatinib is presented in Table 1. New approaches to treat CNS disease are therefore needed.

Table 1 Studies Evaluating Capecitabine and Lapatinib in CNS Metastases

Study	Patient Population	Treatment	Results	Comments
Phase 2 Multicenter; single arm **Lin et al., JCO 2008[25]**	39 patients with CNS progression after WBRT or SRS (n=37) or no prior radiation and asymptomatic (n=2). All patients with prior trastuzumab.	Single-agent lapatinib 750 mg BID.	1 PR (3%) by RECIST; 3 pts with at least 30% volumetric reduction; 10 pts (8%) with 10–30% volumetric reduction.	Differences in information from RECIST criteria vs. volumetric measures led to changes in measurement of response in subsequent studies.
Phase 2 Multicenter; extension phase available at progression. **Lin et al., CCR 2009[26]**	242 patients with CNS progression after WBRT or SRS and prior exposure to trastuzumab. 50 patients continued onto combination therapy with capecitabine at the time of CNS progression on single agent lapatinib.	Single-agent lapatinib 750 mg BID -OR- Combination lapatinib 1250 mg qd +capecitabine 1000 mg/m^2 bid 14 of 21 days.	Single agent: 19 pts (8%) with at least 50% volumetric reduction. Combination: 11 pts (22%) with at least 50% volumetric reduction.	Combination activity reported was in patients with known CNS progression on single agent lapatinib.
Phase 2 Multicenter Open label randomized **Lin et al., J Neurooncol, 2011[27]**	22 patients with CNS progression after WBRT or SRS and prior exposure to trastuzumab.	Randomized to: Lapatinib 1250 mg qd +capecitabine 1000mg/m^2 bid (n=13) -OR- Lapatinib 1250 mg qd + topotecan 3.2 mg/m^2 d1, 8, 15 of 28 d cycle (n=9).	In lapatinib+ capecitabine combination arm, 5 pts (38%) with at least 50% volumetric reduction.	Initially planned to enroll 110 patients. Study terminated early due to lack of efficacy and excess toxicity in topotecan arm.
Phase 2 Multicenter single arm **Bachelot et al., The Lancet, 2013[28]**	45 patients never previously treated with WBRT or SRS.	Lapatinib 1250 mg qd +capecitabine 1000 mg/m^2 BID.	29 pts (64%) with at least 50% volumetric reduction.	Difference in patients' exposure to cranial irradiation makes results difficult to compare to studies listed above. Three pts had never been exposed to trastuzumab; 14 pts had never received trastuzumab for metastatic disease.

Abbreviations: central nervous system (CNS); twice daily (BID); patients (pts); Response Evaluation Criteria in Solid Tumors (RECIST); Stereotactic Radiosurgery (SRS); Whole Brain Radiation Therapy (WBRT).

1.2 Tucatinib: Product Description and Mechanism for Action

Tucatinib (previously known as ONT-380 and ARRY-380) is an oral, potent, HER2-specific tyrosine kinase inhibitor that is being developed by Cascadian Therapeutics, Inc. as a novel treatment for HER2+ breast cancer. Unlike other small molecule inhibitors of HER2 that are currently either approved or in development for treatment of HER2+ breast cancer, including lapatinib, neratinib, and afatinib (GILOTRIF™), all of which are dual inhibitors of both EGFR and HER2, tucatinib selectively inhibits HER2. This enables tucatinib to provide potent inhibition of HER2 while avoiding many of the side effects associated with dual inhibitors, including frequent occurrence of severe skin rash and gastrointestinal (GI) toxicity. In nonclinical studies, tucatinib has also demonstrated superior activity to lapatinib in animal models of CNS metastases.

1.3 Preclinical Studies

For full details of preclinical studies of tucatinib, please refer to the Investigator's Brochure.

In preclinical studies, tucatinib is a nanomolar inhibitor of HER2, with only minimal activity relative to EGFR. Tucatinib demonstrated similar potency against HER2 as the dual HER2/EGFR inhibitor neratinib, and superior potency relative to lapatinib. Tucatinib also significantly inhibited phosphorylation of truncated HER2 (p110/p95) that is thought to be associated with trastuzumab resistance in HER2+ breast cancer (Table 2).

Table 2 HER2 and HER1 Inhibition

	HER2 IC_{50} (nM)	**HER1 (EGFR) IC_{50} (nM)**	**Truncated HER2 IC_{50} (nM)**
Tucatinib	8	4000	7
Neratinib	7	8	Not tested
Lapatinib	49	31	25

Numerous *in vivo* pharmacology studies have demonstrated significant tumor growth inhibitory activity of tucatinib as a single agent, as well as in combination with standard-of-care (SOC) therapies, in tumor-bearing animals. Tucatinib demonstrated synergistic activity when combined with docetaxel (TAXOTERE®) or trastuzumab, including complete responses as shown in Figure 1 and Figure 2.

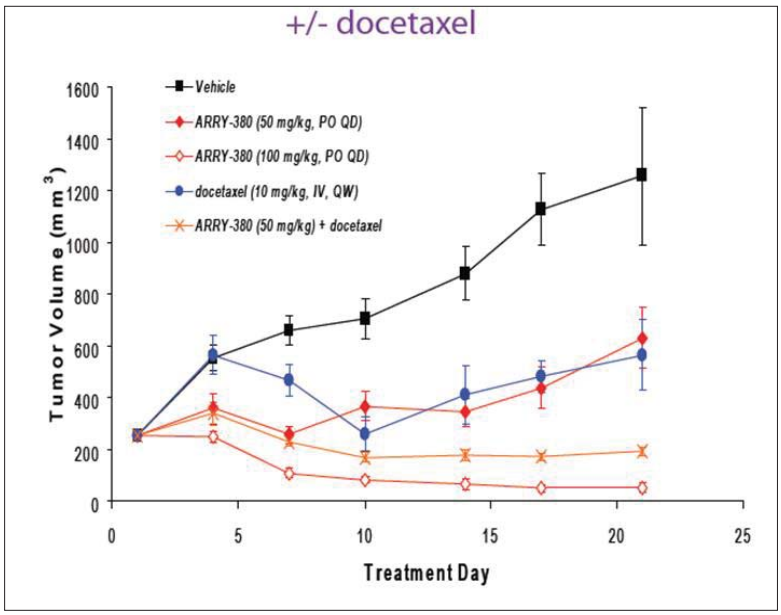

Figure 1 Effect of Treatment with Tucatinib (± Docetaxel) on BT-474 HER2+ Breast Cancer Model

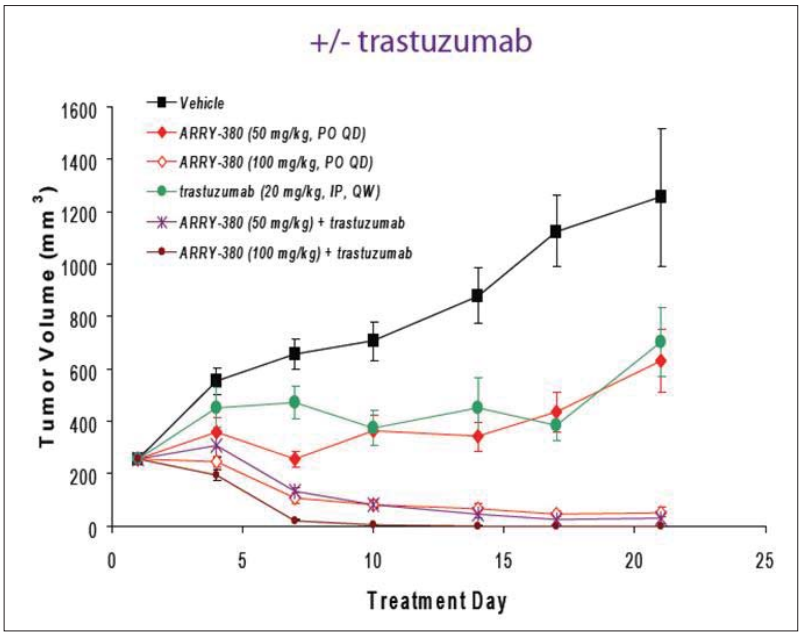

Figure 2 Effect of Treatment with Tucatinib (± Trastuzumab) on BT-474 HER2+ Breast Cancer Models

Tucatinib also demonstrated superior activity compared to neratinib and lapatinib in models of intracranial disease as shown in Figure 3. This improved CNS activity may be due both to better brain penetration as well as to the conversion of the parent drug to an active metabolite with a long brain residence time (Figure 3).

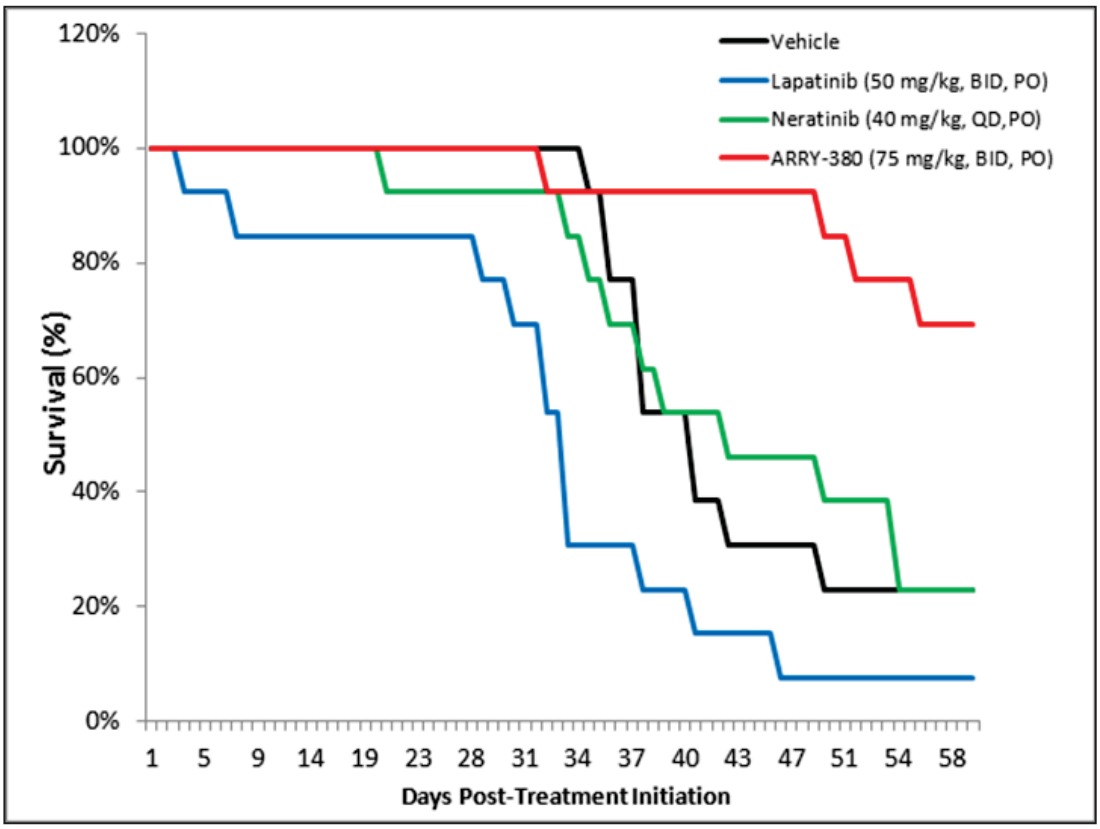

Figure 3 BT-474 HER2+ Breast Carcinoma: Intracranial Tumor Implantations

1.4 Summary of Clinical Data for Tucatinib

Tucatinib has been investigated in three clinical studies, including two completed Phase 1 formulation studies in healthy subjects (clinical studies ARRAY-380-102 and ARRAY-380-103) and a Phase 1 single-agent, dose escalation study with an expansion cohort in HER2+ breast cancer patients (clinical study ARRAY-380-101) at the MTD. Information regarding the studies in healthy subjects is noted in Table 3, while information regarding the Phase 1 dose escalation study is noted in more detail below in section 1.4.1.

Table 3 Summary of Clinical Studies using Tucatinib

Study ID	Design/Objective	Treatment	Population/ Enrollment	Status/Results
ARRAY-380-101	Single-agent, open-label, dose-escalation study to identify the MTD of ARRY-380 capsules and to assess safety, PK and preliminary efficacy	Dose-escalation phase: 25 to 800 mg PO BID in 28-day cycles Expansion phase: 600 mg PO BID in 28-day cycles	HER2+ (IHC 3+ and/or FISH + cancers) metastatic breast cancer. 50 patients enrolled, including 31 at doses ≥ 600 mg	Completed. MTD 600 mg PO BID Among 35 patients evaluable for efficacy, 5 patients with PR (14%), 18 patients with SD (51%)
ARRAY-380-102	Open-label, single-dose fixed-sequence, 4-period cross over study to evaluate the PK, relative bioavailability, and safety of 4 ONT-380 formulations in healthy subjects	Single 300 mg PO dose of tucatinib in 4 treatment formulations: 1. Capsules (PIC) 2. Micronized PIC 3. Aqueous suspension 4. Captisol®/apple juice solution	14 healthy subjects	Completed. The relative bioavailability of ARRY-380 (AUC and C_{max}) was higher following the micronized PIC and aqueous suspension formulations, and lower following the 20% Captisol®/apple juice solution compared to the control capsule (PIC formulation)
ARRAY-380-103	Open-label, single-dose fixed-sequence, 4-period cross over study to evaluate the PK, relative bioavailability, potential food effect, omeprazole drug interaction, and safety of	Single 300 mg PO dose of tucatinib in each of 4 treatment periods: 1. Capsules (PIC) 2. Tablets (fasted) 3. Tablets (fed) 4. Tablets (fasted) following omeprazole 40 mg x 5 days	12 healthy subjects	Completed. Tucatnib metabolism was not affected by formulation, food, or gastric pH. Tablet and capsule had similar bioavailability. Higher drug

Study ID	Design/Objective	Treatment	Population/ Enrollment	Status/Results
	tucatinib PO capsules and tablets in healthy subjects			exposure was observed with the tablet formulation in fed state.
ARRAY-380-104X (Investigator Sponsored Trial, Dana Farber Cancer Institute)	Phase I dose-escalation trial of ARRY-380 in combination with trastuzumab in participants with brain metastases from HER2+ breast cancer	Dose escalation phase: ARRY-380 (ONT-380) 450–600 mg BID, or 750–1200 mg daily; plus trastuzumab 6 mg/kg IV (after one initial loading dose of 8mg/kg IV) q 21 days	HER2+ (IHC 3+ and/or FISH + cancers) metastatic breast cancer with CNS metastases. Planned enrollment 50 patients.	Ongoing

Abbreviations: fluorescence in situ hybridization (FISH); immunohistochemistry (IHC); intravenous (IV); twice daily (BID); maximum tolerated dose (MTD); powder in capsule (PIC); oral (PO); pharmacokinetics (PK); partial response (PR); stable disease (SD).

1.4.1 Phase 1 Single-Agent Study (ARRAY-380-101)

Tucatinib has been studied in a single-agent Phase 1 dose escalation study with an MTD expansion cohort conducted at four sites in the US and Canada. Tucatinib was administered as an active pharmaceutical ingredient (API) in capsule on a BID dosing schedule. The study was open-label, and originally designed to enroll patients with advanced solid tumors believed to express HER2. The protocol was later amended to allow only patients with documented HER2+ immunohistochemistry [IHC] 3+ and/or fluorescence *in situ* hybridization [FISH] + cancers. A total of seven patients with a diagnosis other than breast cancer were enrolled in the first four dose levels. This study was designed to identify the MTD and to assess the safety, pharmacokinetic (PK), and preliminary efficacy of tucatinib capsules with doses ranging from 25 to 800 mg administered orally BID. Capsules were administered without respect to food on all days in all cycles, with the exception of Cycle 1 Day 1 when subjects were given a single dose of tucatinib in a fasted state. The study is complete, with a total of 33 patients treated in the dose-escalation phase, and 17 additional patients with HER2+ metastatic breast cancer in the expansion cohort. Thirty one patients received doses at or above the MTD of 600 mg BID. The RP2D was 600 mg BID.

1.4.1.1 Patient Characteristics

The median age of patients treated was 58.0 yrs (36–77), with a median ECOG status of 1 (0–2). Patients were heavily pre-treated, with a median number of five prior treatment

regimens. All of the patients with a diagnosis of breast cancer had received prior trastuzumab, and 88% of these patients had received prior lapatinib.

1.4.1.2 Dose Escalation and Determination of Maximum Tolerated Dose

A total of 33 patients were enrolled and treated in the dose escalation phase of the study at the following dose levels: 25 mg BID (n=3), 50 mg BID (n=3), 100 mg BID (n=3), 200 mg BID (n=3), 300 mg BID (n=3), 500 mg BID (n=4), 650/600 mg BID (n=10) and 800 mg BID (n=4). In the 650/600 mg BID cohort, the first three patients were treated at 650 mg BID. The dose-escalation proceeded to 800 mg BID, which was deemed a non-tolerated dose due to the occurrence of DLT in two of four patients treated at that level, each of whom experienced Grade 3 liver transaminase elevation, which reversed upon interruption of therapy. Both of these patients were able to resume treatment at the next lowest dose level.

The 650 mg BID dose cohort was then modified to 600 mg due to lack of availability of 25 mg capsules and an additional seven patients were treated at 600 mg BID. Based on DLTs observed at the 800 mg BID dose level and a review of safety data, the MTD was determined to be 600 mg BID. Seventeen additional patients were enrolled in the expansion phase of the study.

1.4.1.3 Adverse Events

Forty-nine of 50 patients (98%) reported at least one AE. Treatment-emergent AEs occurring in ≥ 20% of patients, regardless of relationship to study drug, were nausea (56%); diarrhea (52%); fatigue (48%); vomiting (40%); rash (24%); and constipation, cough and pain in extremity (20% each). Grade 3 treatment-emergent AEs were reported by 21 of 50 patients (42%) and those occurring in > 1 patient included anemia and cellulitis (6% each); and abdominal pain, hypokalemia, increased ALT, increased AST, musculoskeletal chest pain and vomiting (4% each). Grade 4 treatment-emergent AEs were reported by 4 of 50 patients (8%) and included asthenia, diabetes insipidus, hypercalcemia and sepsis (2% each). Among patients treated at the MTD (n=27), the most common AEs were diarrhea, nausea, fatigue, vomiting, rash, and ALT/AST increase. Of these events, the majority of were Grade 1 in severity. Grade 2 events included diarrhea (n=3); nausea (n=5), vomiting (n=2), fatigue (n=8), and ALT/AST elevation (n=2), while Grade 3 events included one event each of diarrhea (of one day duration), erythematous rash, and ALT/AST elevation.

Table 4 Treatment-emergent Adverse Events by Preferred Term and Severity Reported in Patients (Study ARRAY-380-101), Regardless of Relationship to Drug

	Dose cohorts of ARRY-380											
	< 600 mg BID (N=19) n(%)			600–650 mg BID (N=27) n(%)			800 mg BID (N=4) n(%)			Any Dose (N=50) n(%)		
Preferred Term	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Nausea	11 (57.9)	0 (0)	0 (0)	15 (55.6)	0 (0)	0 (0)	2 (50.0)	1 (25.0)	0 (0)	28 (56.0)	1 (2.0)	0 (0)
Diarrhea	5 (26.3)	0 (0)	0 (0)	18 (66.7)	1 (3.7)	0 (0)	3 (75.0)	0 (0)	0 (0)	26 (52.0)	1 (2.0)	0 (0)
Fatigue	11 (57.9)	1 (5.3)	0 (0)	12 (44.4)	0 (0)	0 (0)	2 (50.0)	0 (0)	0 (0)	25 (50.0)	1 (2.0)	0 (0)
Vomiting	8 (42.1)	2 (10.5)	0 (0)	10 (37.0)	0 (0)	0 (0)	2 (50.0)	0 (0)	0 (0)	20 (40.0)	2 (4.0)	0 (0)
Rash[a]	7 (36.9)	0 (0)	0 (0)	4 (14.8)	1 (3.7)	0 (0)	1 (25.0)	0 (0)	0 (0)	12 (24.0)	1 (2.0)	0 (0)
Increased AST	1 (5.3)	0 (0)	0 (0)	3 (11.1)	0 (0)	0 (0)	2 (50.0)	2 (50.0)	0 (0)	6 (12.0)	2 (4.0)	0 (0)
Increased ALT	1 (5.3)	0 (0)	0 (0)	3 (11.1)	1 (3.7)	0 (0)	2 (50.0)	1 (25.0)	0 (0)	6 (12.0)	2 (4.0)	0 (0)

Abbreviations: alanine aminotransferase (ALT); aspartate aminotransferase (AST); twice daily (BID).

a. "Rash" includes event terms rash, maculopapular rash, skin exfoliation, dermatitis acneiform, and pruritic rash.

1.4.1.4 Efficacy Results

Among the 35 patients evaluable for efficacy at any dose level (defined as having measurable disease and at least one follow-up scan), best response per RECIST was PR in 5 patients (14%), SD in 18 patients (51%) and progressive disease (PD) in 12 patients (34%) (Table 5). Tumor shrinkage was seen in both skin and visceral lesions, including liver metastases.

Table 5 RECIST Response by Dose Level

	Dose cohorts of ARRY-380								
Best Response	**25mg n=2**	**50mg n=1**	**100mg n=3**	**200mg n=3**	**300mg n=3**	**500mg n=2**	**600/650mg n=18**	**800mg n=3**	**Total n=35**
PR	0	0	0	0	1	0	3	1	5
SD	0	1	1	2	2	1	10	1	18
PD	2	0	2	1	0	1	5	1	12

Abbreviations: partial response (PR); progressive disease (PD); stable disease (SD).

Among patients treated at doses of ≥ 600 mg BID with measurable disease at baseline, the clinical benefit rate (PR + SD ≥ 6 months) was 27% (6/22), including three PRs and three SDs. One additional patient without measurable disease at baseline had SD for ≥ 6 months. In the three patients with partial response, the duration of response was 8 weeks (n=1) and 28 weeks (n=2). All three of these patients had received prior trastuzumab, and two had also received prior lapatinib.

Figure 4 illustrates the change in the sum of longest diameter per RECIST in patients treated at ≥ 600 mg BID with measurable disease and evaluable follow-up scans.

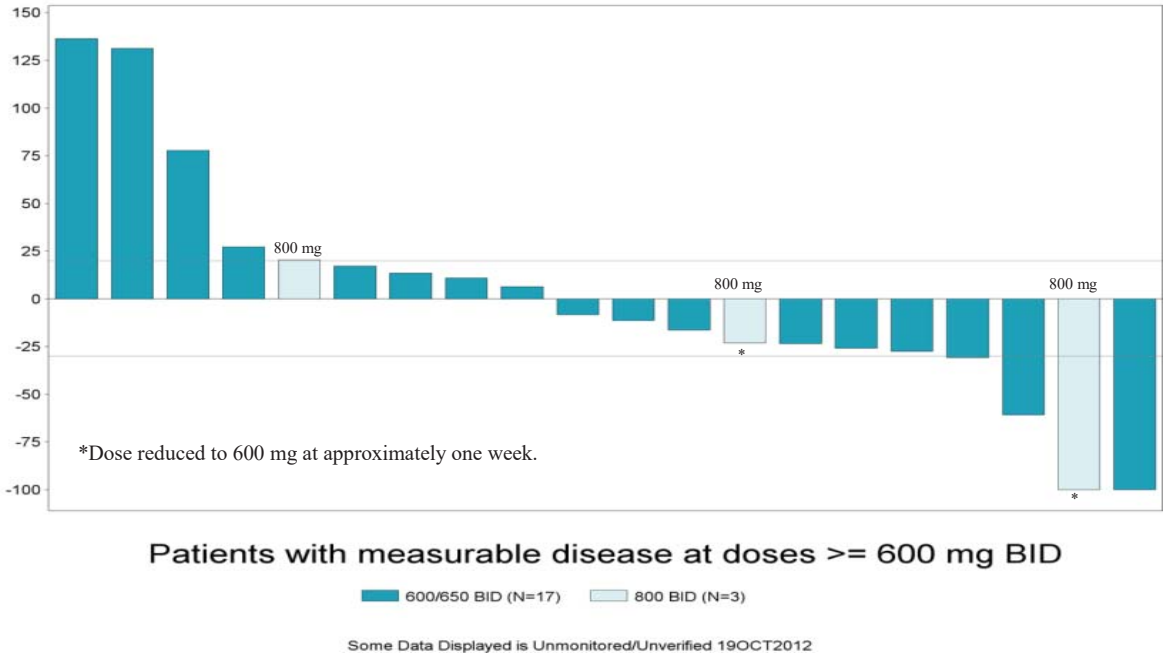

Figure 4 Change in Measurable Disease (Study ARRAY-380-101)

1.4.2 Clinical Pharmacokinetic Results

The PK of tucatinib have been investigated in a Phase 1 single-agent dose escalation study with MTD expansion cohort in HER2+ breast cancer patients (Study ARRAY-380-101). Preliminary PK analysis demonstrated that dose-proportional behavior was observed over the evaluated range. When dosed at the MTD, tucatinib levels were maintained at or above the predicted IC_{90} at steady state. Moderate variability was seen in C_{max} and AUC, all of which was considered typical of an orally administered drug. No evidence of drug accumulation or reduction was noted after repeated dosing. PK samples were drawn on Cycle 1 Day 1 in a fasting state. All other PK samples were collected irrespective of food intake.

The PK of tucatinib have also been investigated in two Phase 1 formulation studies (Studies ARRAY-380-102 and ARRAY-380-103) in healthy subjects. Results indicated that there was no clinically significant difference in the drug exposure (C_{max} and AUC) between the tablet formulation and powder in capsule (PIC) formulation. A major metabolite, a hydroxylated product of tucatinib, was also evaluated in these studies and results showed little difference in the metabolite to parent ratios for all formulations. In the fed state, the tablet formulation showed an increase in AUC of nearly 50%, with an increase in the time to C_{max} (T_{max}) of approximately 2.3 hours while the C_{max} remained relatively unchanged compared to the PIC. Therefore, the observed increase in drug exposure is probably due to the delay in absorption leading to an apparent increase in

AUC. The median apparent half-life of the drug ranged between 5–6 hours and between 7–8 hours for the hydroxylated metabolite. Overall, there was no significant difference in drug exposure in the fasting state between the tablet formulation and PIC formulation. However, the intersubject variability improved with the tablet formulation. Based on the results from these formulation studies, the tablet formulation will be utilized in this study and in future clinical studies.

1.4.3 Summary of Tucatinib

Overall, tucatinib was well tolerated and demonstrated single-agent anti-tumor activity, including partial responses in patients who had progressed after two prior HER2-directed therapies. Notably, toxicities associated with dual EGFR/HER2 inhibitors were uncommon, with Grade 3 diarrhea and rash reported in only 1 patient each. Based upon the preclinical and clinical profile observed to date, tucatinib may be able to address some of the unmet needs in the treatment of HER2+ breast cancer, particularly with regard to combination approaches with other HER2 agents.

1.5 Ado-trastuzumab Emtansine (T-DM1)

As described above, T-DM1 is a HER2-targeted antibody and microtubule inhibitor conjugate indicated for the treatment of patients with HER2+ metastatic breast cancer who previously received trastuzumab and a taxane, either separately or in combination.

1.5.1 Efficacy of T-DM1

The efficacy of T-DM1 was evaluated in a randomized, multicenter, open-label study of 991 patients with HER2+, unresectable locally advanced or metastatic breast cancer. Details of this Phase 3 study, which showed an improvement in OS and PFS compared to capecitabine and lapatinib, are noted above in section 1.1.

In addition, there is increasing anecdotal evidence that T-DM1 may have some activity in the CNS with decrease in size of CNS metastases noted in some patients.[29–30] In the EMILIA study of T-DM1 vs. lapatinib plus capecitabine, patients with CNS metastasis at baseline treated with T-DM1 had a median OS of 26.8 months, compared to 12.9 months for similar patients treated with capecitabine plus lapatinib.[31]

1.5.2 Safety of T-DM1

The most common (frequency ≥ 25%) AEs seen in patients treated with T-DM1 in clinical studies have been fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. The most common ≥ Grade 3 adverse drug reactions (frequency > 2%) were thrombocytopenia, increased

transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue (KADCYLA® package insert).

Patients treated with T-DM1 are at increased risk of developing left ventricular dysfunction. A decrease of left ventricular ejection fraction (LVEF) to < 40% has been observed in patients treated with T-DM1. In a randomized study, left ventricular dysfunction occurred in 1.8% of patients in the T-DM1-treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group.[12]

Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity, or peripheral neuropathy may require temporary interruption, dose reduction, or treatment discontinuation of T-DM1 as per guidelines provided in the package insert as well as in Table 10.

1.5.3 Purpose of the Study

While the use of directed anti-HER2 therapy has greatly improved the outlook for patients with HER2+ breast cancer, patients with metastatic disease ultimately relapse, including those treated with T-DM1. This treatment failure may result from development of resistance to HER2 blockade; resistance which may be overcome by a dual approach to HER2 inhibition. This study, combining T-DM1 and tucatinib, allows the exploration of a combination which will provide dual inhibition of HER2, potentially improving upon the efficacy of T-DM1 by overcoming or delaying the development of resistance. Furthermore, the greater selectivity of tucatinib compared to other oral anti-HER2 agents offers the potential to provide dual HER2 blockade with fewer toxicities than currently available agents.

In addition, emerging anecdotal and retrospective data on the use of T-DM1, along with preclinical studies of tucatinib, suggest that both of these drugs have the potential for activity in the CNS. This study will explore the possibility that this combination may be effective against CNS metastases in HER2+ breast cancer, an area of continued medical need.

In the following sections, the term “study drug” will refer to tucatinib and / or T-DM1.

2 OBJECTIVES

2.1 Primary Objective

- Determine the MTD/RP2D of tucatinib to be given in combination with the approved dose of T-DM1.

2.2 Secondary Objectives

- Evaluate the safety of tucatinib given at the MTD/RP2D in combination with T-DM1.
- Evaluate the preliminary anti-tumor activity of tucatinib given in combination with T-DM1.

2.3 Exploratory Objectives

- Assess HER2 mutations and the presence of other potential biomarkers of response in archived tumor biopsy specimens
- Examine the effects of combination therapy on the PK of tucatinib and T-DM1.
- Evaluate the effect of tucatinib in combination with T-DM1 on CNS metastases

2.4 Endpoints

2.4.1 Primary Endpoint

- Incidence and severity of AEs

2.4.2 Secondary Endpoints

- Incidence and severity of clinical lab abnormalities
- Frequency of dose reductions in tucatinib
- Frequency of dose reductions in T-DM1
- Objective response rate (ORR)
- Duration of response
- Disease control rate (DCR) (best response of complete response CR, PR, or SD)
- Clinical benefit rate (CBR) (SD for ≥ 6 months, PR, or CR)
- Progression-free survival (PFS)

2.4.3 Exploratory Endpoints

- Assess HER2 mutations and the presence of other potential biomarkers of response in archived tumor biopsy specimens
- Plasma concentrations of tucatinib and its metabolite
- Serum concentrations of T-DM1 and its metabolites
- CNS response rate

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a Phase 1b, open-label study to assess the safety, tolerability, and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of tucatinib to be given with the approved dose of T-DM1 (Figure 5). The study will use a 3+3 dose escalation design to evaluate up to four dose levels of tucatinib in order to determine the MTD/RP2D. Three to six evaluable patients will be enrolled in each cohort in the dose escalation phase. Safety will be monitored throughout the study by the study Safety Monitoring Committee (SMC) comprising the Investigators and Cascadian Therapeutics personnel, including the study medical monitor. The SMC will meet and review safety data after each cohort is enrolled and/or approximately once every 3 months unless otherwise agreed upon, and on an ad hoc basis as needed. Additional details will be provided in the SMC Guidelines.

At least six evaluable patients are to be treated at a dose level for an MTD/RP2D to be declared. Once an MTD/RP2D is declared, up to 24 additional evaluable patients will be enrolled in an MTD/RP2D expansion cohort for a total of up to 30 evaluable patients to be treated at the MTD/RP2D. The MTD/RP2D will be based upon review of all available safety and PK data, including data from outside of the DLT evaluation period. In addition to the MTD/RP2D expansion cohort, an optional additional cohort of up to 15 evaluable patients with either untreated, asymptomatic CNS metastases not needing immediate local therapy or progressive CNS metastasis following local therapy may be enrolled and treated at the MTD/RP2D.

Patients will be seen for safety assessments at a minimum of once per week for the first two cycles and then once every three weeks or as otherwise specified. Assessment of cardiac function by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) will be performed at baseline and after every four cycles of treatment. Tumor assessments will be performed at baseline, every two cycles through Cycle 6 and then every three cycles. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal of consent.

Plasma and serum samples will be collected to allow for PK evaluation of tucatinib and T-DM1. During Cycle 1 only, tucatinib will be administered on Day 1 and T-DM1 on Day 2 to allow for collection of PK samples prior to exposure to T-DM1. Patients enrolled under Protocol Amendment 6 will not have PK samples collected.

HER2 status will be based upon reported results in the patient medical record. Results must have been obtained from a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory, as confirmed by the Investigator. If results are not available or are

not from a CLIA certified lab, archived biopsies or fresh biopsy must be obtained to evaluate HER2 status to document eligibility prior to enrollment. Archived tumor biopsies will be requested from all patients and assessed when available for potential biomarkers of response to tucatinib and T-DM1.

3.2 Dose Escalation Phase

After establishing eligibility, patients will be enrolled in the current dose cohort of tucatinib plus T-DM1. Initially, each dose cohort will enroll at least three patients. To account for potential patient discontinuation from the study prior to being evaluable for DLT (e.g., progressive disease), enrollment of up to three additional patients per cohort will be allowed (even in the absence of the need to expand the cohort based upon a DLT). Non-evaluable patients will be replaced.

The first dose level of tucatinib to be evaluated will be 300 mg orally (PO) twice daily (BID). If tucatinib is not tolerated at a dose level of 300 mg PO BID, the study SMC may recommend that lower doses of tucatinib be evaluated in combination with T-DM1. Three dose escalation cohorts are planned for evaluation in Phase 1, although intermediate, and/or additional cohorts may be studied at the recommendation of the SMC. Dose escalation may occur based upon the guidelines below.

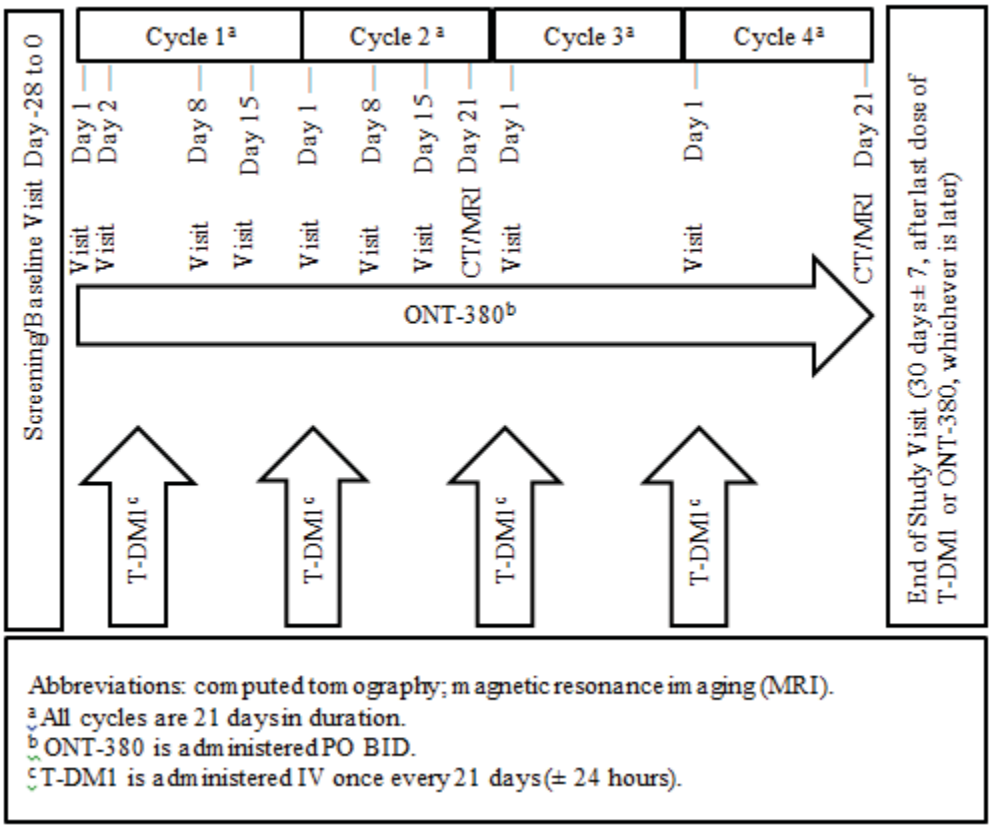

Figure 5 ONT-380-004 Study Schema

Table 6 Planned Dose Escalation Cohorts

Cohort	Tucatinib	T-DM1	Comment
1	300 mg PO BID	3.6 mg/kg IV q 21 days	If 300 mg not tolerated, SMC may consider evaluating lower dose of tucatinib
2	350 mg PO BID	3.6 mg/kg IV q 21 days	-
3	400 mg PO BID	3.6 mg/kg IV q 21 days	-
4	TBD PO BID	3.6 mg/kg IV q 21 days	Optional fourth cohort to evaluate dose lower than 300 mg of tucatinib or other dose level as recommended by SMC

Abbreviations: oral (PO); twice daily (BID); intravenous (IV); Safety Monitoring Committee (SMC).

Dose Escalation/Cohort Advancement Guidelines

Cohort advancement will be based on safety data during the first treatment cycle from cohorts of up to six evaluable patients. An SMC will be established to review patient data and make decisions regarding cohort advancement. The SMC will review patient data prior to advancing to the next dose cohort. For the purpose of the SMC review, a patient will be considered evaluable if s/he has received at least 75% of the planned dosing with tucatinib and T-DM1 during Cycle 1. If the reason for not receiving 75% or more of the planned doses is DLT, or if a patient has received a dose reduction, a patient will still be considered evaluable for this SMC review. Patients considered non-evaluable will be replaced.

The following guidelines will be followed for each dose cohort:

- If none of the first three patients experience DLT, then the cohort will be advanced;
- If one of the first three patients experiences DLT, then more patients will be added to that cohort to increase the cohort up to six patients at the same dose level;
- If no more than one patient of the first six patients treated experiences DLT, then the cohort will be advanced;
- If two or more patients within the first six patients treated within a cohort experience DLT, then this dose level will be considered not tolerated. The SMC may then either define the MTD/RP2D or recommend an alternative dose level or schedule of T-DM1 and tucatinib to be evaluated.

Patient accrual into any dose escalation cohort will be stopped as soon as two patients treated experience DLT. The study SMC will review all available safety data to determine if this dose should be declared not tolerated and if any further dose escalation should occur; and if an alternative dose or schedule should be evaluated. Once dose escalation has been halted, the SMC will convene to declare a MTD/RP2D for further study. A minimum of six evaluable patients need to be treated at a dose level in order for that dose to be declared the MTD/RP2D. While dose escalation decisions will be made based upon data from the first cycle of treatment for each patient within a given cohort, the SMC will also review safety data from patients receiving additional treatment cycles of tucatinib in combination with T-DM1.

After a dose has been declared to be the MTD/RP2D as defined by the SMC, any patient remaining on the study and being treated with a lower dose of tucatinib may, at the discretion of the Investigator and agreement of the Sponsor, be offered treatment at the new higher dose.

Definitions of Dose-Limiting Toxicities

DLTs, defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 (July 14, 2010), are events that occur following administration of T-DM1 and tucatinib combination therapy during Cycle 1, and meet the criteria described below. Events for which there is an alternative clinical explanation (e.g., clearly related to an intercurrent illness or disease progression) will not be considered DLT. The relationship of AEs to study drug treatment will be determined by the Investigator. Patients who experience a DLT may continue in the study at the discretion of the Investigator. Such patients may resume treatment at a lower dose (i.e., the dose level of tucatinib below that at which the DLT occurred) following recovery of the toxicity to no more than Grade 1 or the baseline level of severity.

DLT Criteria

Non-Hematologic

- Any non-hematologic AE ≥ Grade 3 in severity that is possibly, probably, or definitely related to tucatinib or the combination of tucatinib and T-DM1 treatment, with the following exceptions:
  - Grade 3 fatigue lasting ≤ 3 days
  - Grade 3 diarrhea, nausea, or vomiting without optimal use of anti-emetics or anti-diarrheals
  - Grade 3 rash without maximal use of corticosteroids or anti-infectives
  - Cerebral edema that occurs in patients with CNS metastases who are treated with systemic corticosteroids and have a return of all neurologic symptoms to baseline or ≤ Grade 1 within 5 days
- Greater than a two-week delay in the start of Cycle 2 due to unresolved toxicity related to tucatinib or the combination of tucatinib and T-DM1
- A dose reduction due to toxicity related to tucatinib or the combination of tucatinib and T-DM1
- Grade 4 hypokalemia
- Asymptomatic ≥ Grade 3 laboratory abnormalities(other than Grade 4 hypokalemia as above) will not in and of themselves be considered a DLT, except as described below. In the event that it is not clear if an adverse event or laboratory abnormality meets the criteria for a DLT, the study medical monitor should be contacted and the SMC consulted as needed.

Hematologic

- Absolute neutrophil count (ANC) of Grade 3 or 4 with fever (fever must be present for the Grade 3 or 4 ANC to be considered a DLT, and is defined as a temperature of ≥ 38.5°C)
- ANC of < 500/μL for > 7 days
- Platelet count of < 25,000 cells/μL for > 7 days
- Grade 3 or 4 thrombocytopenia associated with significant bleeding
- Grade 4 anemia

Hepatic

- Grade ≥ 3 elevation of transaminases (ALT/SGPT or AST/SGOT) that is NOT thought to be due to disease progression or other medical illness
- Grade 3 or 4 elevation of bilirubin irrespective of transaminases that is NOT thought to be due to disease progression or other medical illness
- Any single instance of AST/ALT > 3 X ULN AND total bilirubin > 2 X ULN that is NOT thought to be due to disease progression or other medical illness

3.3 Expansion Phase

The dose of tucatinib for the expansion phase will be the MTD/RP2D determined in the dose-escalation phase. The dose of tucatinib will be adjusted or interrupted, as appropriate, based upon treatment modifications defined in section 5.1. Once an MTD/RP2D is declared, up to 24 additional evaluable patients will be enrolled in an MTD/RP2D expansion cohort for a total of up to 30 evaluable patients total to be treated at the MTD/RP2D. An additional optional cohort of up to 15 evaluable patients with untreated asymptomatic CNS metastases or progressive CNS metastases may also be enrolled and treated at the MTD/RP2D.

Patients enrolled in the expansion phase will be monitored for the occurrence of DLTs, as defined in section 3.2. If at any time, ≥ 33% or more patients treated at the same dose of tucatinib experience a DLT, enrollment in the expansion cohorts will be stopped for SMC review. The SMC will then review all data at this point to determine any further actions, including the evaluation of lower doses of tucatinib.

3.4 Long-Term Extension Phase

Patients still in the study as of Amendment 8 will be allowed to continue receiving study drug. During this phase of the study, safety and efficacy assessments that include determination of disease progression will be performed as per institutional guidelines and investigator-determined usual and customary clinical care. Only SAEs and AOIs will be collected by the Sponsor during the Long-Term Extension phase.

3.5 Rationale for Selection of Doses

Selection of the tucatinib dosing regimen for the current study was based upon the results of the Phase 1 dose-escalation study of single-agent tucatinib in patients with advanced solid tumors (ARRAY-380-101) as well as pharmacokinetic studies (ARRAY-380-102 and ARRAY-380-103). As the safety of tucatinib in combination with T-DM1 has not been previously studied, the starting dose of tucatinib will be 50% of the single-agent MTD. T-DM1 will be given at the full FDA approved dose of 3.6 mg IV q 21 days for single-agent use. This reduced starting dose also takes into account any possible increase in exposure to tucatinib in the fed state with the tablet formulation.

The combination of T-DM1 and tucatinib has not been previously evaluated in human patients. As there is potential for increased toxicity with combination, this Phase 1b study will evaluate the safety and tolerability of this combination in a limited number of patients, and to determine the MTD/RP2D for tucatinib to be taken forward in combination with T-DM1 for study in Phase 2 in a larger number of patients.

3.6 Potential Food Effects

The clinical study ARRAY-380-103 was conducted in healthy adult subjects to evaluate the oral bioavailability of tucatinib tablets relative to tucatinib capsules (both in the fasted state), to evaluate the oral bioavailability of tucatinib tablets after consumption of a high-fat meal relative to the fasted state, and also to evaluate the oral bioavailability of tucatinib tablets following daily oral administration of omeprazole for 5 days relative to tucatinib tablets in the fasted state. Pharmacokinetic results showed similar plasma concentration profiles for both tucatinib and its metabolite following capsule and tablet treatments and following the tablet treatment with or without omeprazole. However, in the fed state, total exposure of tucatinib after administration of the tablet formulation was approximately 48% to 49% higher, while the peak concentration (C_{max}) was less than 8% different. The time to C_{max} (T_{max}) was increased by approximately 2.3 hours for tucatinib tablets after oral administration in the fed state. Overall, the data suggest an increase in total drug exposure of tucatinib after oral administration of the tablet formulation in the presence of food. However, this increase is probably due to the delay in absorption leading to an apparent increase in AUC.

It is expected that by allowing patients to take tucatinib twice daily without regard to food, compliance will be increased. Although an increase in AUC was noted for tucatinib tablets in the food effects portion of ARRAY-380-103, it is not anticipated that co-administration of tucatinib tablets in the fed state will pose clinically significant risks. This is based on the finding that the PK of tucatinib tablets was not significantly different than that of tucatinib capsules administered in the fasting state, and that the MTD of 600 mg BID for tucatinib capsules was determined in a setting where tucatinib was

administered in a non-fasting state with the exception of Cycle 1 Day 1 in clinical study ARRAY-380-101. In order to minimize the risk to patients participating in this study, the starting dose of tucatinib will be 300 mg PO BID, 50% of the single agent MTD.

3.7 Potential Drug Interactions

Pharmacokinetic studies of T-DM1 in preclinical species and in humans have shown that T-DM1 is catabolized and degraded into its main components, trastuzumab and the small molecule toxin DM1.[32] DM1 has a very short half-life due to fast clearance and rapid metabolism into multiple metabolites. There was little free DM1 detected in plasma across the majority of time points with C_{max} in the low single-digit ng/mL concentration. *In vitro* studies indicate that DM1, the cytotoxic component of T-DM1, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. As per the package insert for T-DM1, concomitant use of strong CYP3A4 inhibitors with T-DM1 should be avoided due to the potential for an increase in DM1 exposure and toxicity. DM1 has also been shown to exhibit no inhibition or induction potential to CYP450, thus it is very unlikely that DM1 would pose any CYP450-dependent drug-drug interaction (DDI) with other small molecule drugs. Combination studies of T-DM1 have demonstrated that T-DM1 PK were not affected by taxanes (paclitaxel or docetaxel) and similarly, paclitaxel and docetaxel PK were not affected by T-DM1. Overall, the risk of DDI potential for T-DM1 catabolites is thought to be low.

In vitro experiments with MDR1 LLC PK1 cells indicated that tucatinib has high membrane permeability and is a P-gp substrate as well as an inhibitor of P-gp-mediated efflux of digoxin (IC_{50} value between 10 and 30 μM). *In vitro* metabolism studies have indicated that tucatinib is metabolized in human liver primarily by CYP2C8. To minimize the risk of potential DDI, concurrent use of strong CYP2C8 inhibitors and inducers will not be allowed. Tucatinib is a weak inhibitor of CYPs 2C19, 1A2, and 2D6 isoforms, and did show some moderate inhibition of CYPs 2C8, 2C9, and 3A4 with IC_{50} values from 9 to 17 μM, in addition to moderate inhibition of UGT1A1 at ~ 4 μM. Tucatinib was not a time-dependent inhibitor of CYP3A4 and did not significantly induce *in vitro* activity or messenger RNA (mRNA) of CYP3A4 or CYP1A2 in hepatocytes. The mean C_{max} of tucatinib at MTD was ~ 1.5 μM and well below the CYP inhibitory IC_{50} values. Overall, it is thought unlikely that tucatinib will pose a potential DDI risk with T-DM1.

While the risk of DDI is thought to be low, samples will be collected to allow for evaluation of combination therapy on the PK profile of tucatinib and T-DM1. While the PK of tucatinib tablets have been evaluated in healthy subjects, this is the first time that the PK will be evaluated in cancer patients. Therefore, samples to evaluate tucatinib PK will be collected on Cycle 1 Day 1 prior to administration of T-DM1 on Cycle 1 Day 2. Samples to evaluate the effects of combination therapy on the PK of both tucatinib and T-

DM1 will be collected at varying time points throughout Cycles 1–6 as outlined in section 6.

3.8 Potential Risks of Combination Therapy with Tucatinib and T-DM1

Adverse events with T-DM1 have been predominately mild in severity and transient, with the most common AEs reported being fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. Other less common but more serious events, which have occurred with administration of T-DM1 include drug-induced hepatotoxicity, interstitial lung disease, infusion-related reactions, and left ventricular dysfunction. T-DM1 is also known to cause embryo-fetal death and birth defects. The most common AEs reported to date in patients treated at the MTD of tucatinib include nausea, diarrhea, rash, fatigue, increased ALT, increased AST, and vomiting, the majority of which have been Grade 1 or 2 in severity. The effects of tucatinib on fetal development are not known.

Based on the safety profiles observed to date for T-DM1 and tucatinib, the most likely potential overlapping toxicities are nausea and elevation of liver transaminases. While decreased left ventricular function and interstitial lung disease have not been reported for tucatinib, they have been seen with other small molecule HER2 inhibitors, and an increase in incidence or severity may be seen in combination with T-DM1. Patients participating in this study will be closely monitored for the occurrence of liver toxicity, changes in cardiac function, and pulmonary toxicity, as well as nausea and any other expected and/or unexpected toxicities. Patients will be allowed to use concomitant medication to manage gastrointestinal symptoms. Due to the potential effect on T-DM1, concomitant use of a strong CYP3A4 inhibitor will be prohibited. Because metabolism studies have indicated that tucatinib is metabolized in human liver by CYP2C8, strong inducers or inhibitors of CYP2C8 will also be prohibited. Due to the potential effect on embryo-fetal development, all sexually active males and sexually active females of child-bearing potential will be required to use dual (two concurrent) forms of contraception from the time of signing consent until either 6 months after the last dose of tucatinib or T-DM1, whichever is longer. Dose modifications and treatment interruptions of both drugs will be allowed as described in section 5.3.

4 STUDY POPULATION

4.1 Inclusion Criteria

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

1) HER2+ metastatic breast cancer, documented as HER2+ by FISH and/or 3+ staining by IHC.

2) History of prior therapy with trastuzumab and a taxane, separately or in combination. For patients in dose escalation and MTD expansion cohorts, prior therapy with trastuzumab and a taxane must have been for metastatic disease. For patients in CNS disease expansion cohorts, trastuzumab and taxane (together or separately) may have been given at any time prior to study enrollment as part of neoadjuvant therapy, adjuvant therapy, or therapy for metastatic disease.

3) ≥ 18 years at time of consent.

4) If female and of child-bearing potential, has negative pregnancy test within 14 days prior to treatment.

5) If a sexually active male or a sexually active female of child-bearing potential, agrees to use dual (two concurrent) forms of medically accepted contraception from the time of consent until 6 months after the last dose of either tucatinib or T-DM1, whichever is longer.

6) Signed an informed consent document that has been approved by an IRB/IEC.

7) Must have target or non-target lesions as per RECIST 1.1.

8) All toxicity related to prior cancer therapies must have resolved to ≤ Grade 1, with the following exceptions: alopecia; neuropathy, which must have to resolved to ≤ Grade 2; and congestive heart failure (CHF), which must have been ≤ Grade 1 in severity and must have resolved completely.

9) ECOG performance status of 0 or 1 at screening.

10) In the opinion of the Investigator, life expectancy > 6 months.

11) Adequate hematologic function is defined by:

    a) Hemoglobin ≥ 9 g/dL

    b) ANC ≥ 1000 cells/µL

    c) Platelets ≥ 100,000/µL

12) Adequate hepatic function as defined by the following:

    a) Total bilirubin ≤ 1.5 x upper limit of normal (ULN)

    b) Transaminases (AST/SGOT and ALT/SGPT) ≤ 1.5 X ULN (< 2.5 X ULN if liver metastases are present)

13) INR and aPTT ≤ 1.5 X ULN unless on medication known to alter INR and aPTT.

14) Calculated creatinine clearance ≥ 60 mL/min.

15) Left ventricular ejection fraction (LVEF) must be within institutional limits of normal as assessed by ECHO or MUGA documented within four weeks prior to first dose of study drug.

4.2 Exclusion Criteria

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

1) Medical, social, or psychosocial factors that, in the opinion of the Investigator, could impact safety or compliance with study procedures.

2) Patient is breastfeeding.

3) Patient was treated with any experimental agent within 14 days or five half-lives of study treatment, whichever is greater.

4) Patient was treated with trastuzumab or other antibody-based therapy within three weeks of starting study treatment or with chemotherapy or hormonal cancer therapy within two weeks of starting study treatment.

5) Patient had prior exposure to a cumulative dose of doxorubicin that exceeded 360 mg/m^2 or its equivalent.

6) Previous treatment with T-DM1 at any time; or previous treatment with any small molecule HER2 inhibitors including (but not limited to) lapatinib, neratinib, or afatinib within the last 4 weeks prior to initiation of study therapy.

7) CNS disease:

    a) Patients with leptomeningeal disease are excluded.

    b) Dose escalation and MTD/RP2D expansion cohort: Patients with symptomatic CNS metastases are excluded. Patients with treated CNS metastases or untreated asymptomatic CNS metastases not requiring immediate local therapy may be

eligible. Enrollment of patients with metastases must be approved by the study medical monitor.

c) Optional CNS disease expansion cohort: Patients with asymptomatic untreated CNS metastases not needing immediate local therapy or patients with progressive CNS disease following local therapy may be eligible with medical monitor approval.

8) History of allergic reactions to compounds of similar chemical or biological composition to T-DM1 or tucatinib, except for a history of Grade 1 or Grade 2 Infusion Related Reaction to trastuzumab, which has been successfully managed.

9) Patients with uncorrectable electrolyte abnormalities.

10) Known to be HIV positive. HIV testing is not required for those patients who are not known to be positive.

11) Known carrier of Hepatitis B and / or Hepatitis C (whether active disease or not).

12) Known history of liver disease, autoimmune hepatitis, or sclerosing cholangitis.

13) Inability to swallow pills or any significant gastrointestinal diseases, which would preclude adequate absorption of oral medications.

14) Use of a strong CYP3A4 inhibitor within three elimination half-lives of the inhibitor prior to the start of study treatment. (See Appendix E).

15) Use of a strong CYP2C8 inducer or inhibitor within three elimination half-lives of the inducer or inhibitor prior to the start of study treatment. (See Appendix F).

16) Radiotherapy within 14 days of tucatinib; patient must have recovered from acute effects of radiotherapy to baseline.

17) Known impaired cardiac function or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, congestive heart failure, and uncontrolled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).

18) Myocardial infarction or unstable angina within 6 months prior to the first dose of study drug.

4.3 Criteria for Patient Withdrawal and Replacement

Reasons for patient discontinuation following receipt of study drug may be due to any of the following:

- Adverse event
- Progressive disease
- Death
- Withdrawal of consent
- Lost to follow-up
- Physician decision
- Patient decision
- Protocol violation
- Study termination by Sponsor
- Pregnancy or begins breast-feeding while on the trial
- Other

The reason for withdrawal must be recorded in the patient's electronic case report form (eCRF). The patient should complete the evaluations scheduled for the end of study visit (EOS), provided written consent to do so has not been withdrawn. Patients who withdraw from the study who are not evaluable for DLT may be replaced as needed to provide for an adequate number of DLT evaluable patients per the SMC. If an AE is the cause for withdrawal, then "Adverse Event" should be recorded as the reason for withdrawal rather than physician decision or patient decision. Patients who received both T-DM1 and tucatinib and discontinued T-DM1 due to a T-DM1-related toxicity or other reason, may continue receiving tucatinib alone following discussion with the study medical monitor. Patients who discontinue tucatinib and are receiving T-DM1 alone will be withdrawn from the study.

5 TREATMENTS

5.1 Treatments Administered

Patients in the study will receive treatment with T-DM1 and tucatinib. All treatments will be given on 21-day cycle. T-DM1 will be given at a dose of 3.6 mg/kg IV once every 21 days. Tucatinib will be given orally twice daily at a dose dependent upon the dosing cohorts to which the patient is enrolled.

5.1.1 Dose Modifications and Discontinuations

Table 7 through Table 12 provide dose modification guidance for both T-DM1 and tucatinib.

All AEs and clinically significant laboratory abnormalities should be assessed by the Investigator for relationship to T-DM1 and tucatinib. In the event that the relationship is unclear, discussion should be held with the study medical monitor, to discuss which study drug(s) should be held and/or modified. An AE may be considered related to T-DM1 alone, tucatinib alone, to both drugs, or to neither. Dosing should be modified (including holding the dose, dose reduction, or discontinuation of drug) as described below.

Dose reductions or treatment interruption for reasons other than those described below may be made by the Investigator if it is deemed in the best interest of patient safety. Whenever possible, these decisions should first be discussed with the study medical monitor.

Doses held for toxicity will not be replaced.

Tucatinib Dose Reductions

Tucatinib should be discontinued if a delay greater than two weeks is required due to treatment-related toxicity, unless a longer delay is approved by the study medical monitor.

Tucatinib should be held and/or doses modified according to Table 7 and Table 9 through Table 12. Up to three dose reductions in tucatinib are allowed (Table 7).

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

Table 7 Recommended Tucatinib Dose Reduction Schedule for Adverse Events*

Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
300 mg PO BID	250 mg PO BID	200 mg PO BID	150 mg PO BID
350 mg PO BID	300 mg PO BID	250 mg PO BID	200 mg BID
400 mg PO BID	350 mg PO BID	300 mg PO BID	250 mg PO BID

Abbreviations: oral (PO); twice daily (BID)

*Dose reductions greater than those listed in this table of recommendations may be made if considered clinically appropriate by the investigator and approved by the medical monitor

T-DM1 Dose Reductions

If the event is considered unrelated to T-DM1 no dose reduction is required. Dosing may be held based upon the judgment of the Investigator but is not required.

Up to two dose reductions of T-DM1 will be allowed (Table 8). In the case of recurrent toxicity after two dose reductions, treatment with T-DM1 should be discontinued.

T-DM1 dose should not be re-escalated after a dose reduction is made.

Table 8 Recommended T-DM1 Dose Reduction Schedule for Adverse Events

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 9 Clinical Adverse Events Other Than Liver Function Abnormalities, Left Ventricular Dysfunction, or Thrombocytopenia Related to Either Tucatinib or T-DM1

	Tucatinib	T-DM1
Clinical Adverse Event	Related to tucatinib	Related to T-DM1
≥ Grade 3 AEs with the exception of: Grade 3 fatigue lasting ≤ 3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to ≤ Grade 1 within 7 days; or cerebral edema which occurs in patients with CNS metastases who are treated with corticosteroids and who have resolution of all neurologic symptoms to baseline or ≤ Grade 1 within 5 days	Hold until severity ≤ Grade 1 or pre-treatment level Restart at next lowest dose level	Do not administer until severity ≤ Grade 1 or pre-treatment level Reduce to next lowest dose level
Grade 3 nausea, vomiting or diarrhea WITHOUT maximal use of anti-emetics or anti-diarrheals	Hold until severity ≤ Grade 1 or pre-treatment level. Initiate appropriate therapy. Restart without dose reduction	Do not administer until severity ≤ Grade 1 or pre-treatment level. Initiate appropriate therapy. Optional dose reduction to next lowest dose level
Grade 3 nausea, vomiting or diarrhea WITH maximal use of anti-emetics or anti-diarrheals	Hold until severity ≤ Grade 1 or pre-treatment level Restart at next lowest dose level	Do not administer until severity ≤ Grade 1 or pre-treatment level Optional dose reduction to next lowest dose level.
Grade 4 nausea, vomiting or diarrhea regardless of use of anti-emetics or anti-diarrheals	Do not administer until severity ≤ Grade 1 Reduce to next lowest dose level	Do not administer until severity ≤ Grade 1 Reduce to next lowest dose level
Grade 1 or 2 diarrhea with complicating features[b]	Hold until severity ≤ Grade 1 or pre-treatment level Restart at next lowest dose level	Do not administer until severity ≤ Grade 1 or pre-treatment level Optional dose reduction to next lowest dose level.
Grade 3 rash WITHOUT maximal use of corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pre-treatment level. Initiate appropriate therapy. Restart without dose reduction	Do not administer until severity ≤ Grade 1 or pre-treatment level. Initiate appropriate therapy. Optional dose reduction to next lowest dose level
Grade 3 rash WITH maximal use of corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pre-treatment level Restart at next lowest dose level	Do not administer until severity ≤ Grade 1 or pre-treatment level Optional dose reduction to next lowest dose level.

Grade 4 rash regardless of use of corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pre-treatment level Restart at next lowest dose level	Do not administer until severity ≤ Grade 1 or pre-treatment level Restart at next lowest dose level

a. No dose modifications are required for alopecia
b. Moderate to severe abdominal cramping, nausea or vomiting ≥ NCI CTCAE Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration.

Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities, regardless of relationship to study drug (Table 10).

Table 10 Liver Function Abnormalities (Regardless of Relationship to Study Drug)

	Tucatinib	T-DM1
Elevation of ALT and/or AST of > 2.5 - ≤ 5 X ULN	Dose modification not required	Dose modification not required
Grade 3 elevation of ALT and/or AST (> 5–20 X ULN)	Hold until severity ≤ Grade 1 Restart at next lowest dose level	Hold until severity ≤ Grade 1 Restart at next lowest dose level
Grade 4 elevation of ALT and/or AST (> 20X ULN)	Discontinue drug	Discontinue drug
Elevation of ALT and/or AST > 3X ULN AND Bilirubin > 2X ULN	Discontinue drug	Discontinue drug
Grade 2 elevation of bilirubin (>1.5–3 X ULN)	Hold until severity ≤ Grade 1 Restart at same dose level	Hold until severity ≤ Grade 1 Restart at same dose level
Grade 3 elevation of bilirubin (>3 - ≤ 10 X ULN)	Hold until severity ≤ Grade 1 Restart at next lowest dose level	Hold until severity ≤ Grade 1 Restart at next lowest dose level
Grade 4 elevation of bilirubin (>10 X ULN)	Discontinue drug	Discontinue drug
Abbreviations: alanine aminotransferase (ALT); aspartate aminotransferase (AST); upper limit of normal (ULN).		

Nodular regenerative hyperplasia

Tucatinib and T-DM1 should be discontinued permanently in patients diagnosed with nodular regenerative hyperplasia.

Thrombocytopenia

T-DM1 dose modification guidelines for thrombocytopenia are provided in Table 11. Dose modifications of tucatinib are not required for thrombocytopenia.

Table 11 Dose Modification Guidelines for Thrombocytopenia

	Tucatinib	T-DM1
Grade 3 thrombocytopenia Platelet count 25,000/mm^3 to < 50,000/mm^3	Dose modification not required	Hold until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then restart at same dose level
Grade 4 thrombocytopenia Platelet count < 25,000/mm^3	Dose modification not required	Hold until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level

Left Ventricular Dysfunction

T-DM1 and tucatinib dose modification guidelines for left ventricular dysfunction are provided in Table 12.

Table 12 Dose Modifications for Left Ventricular Dysfunction

Symptomatic CHF	LVEF < 40%	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	LVEF > 45%
Discontinue T-DM1 and tucatinib	Do not administer T-DM1 or tucatinib. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue T-DM1 and tucatinib.	Do not administer T-DM1 or tucatinib. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue T-DM1 and tucatinib.	Continue treatment with T-DM1 and tucatinib. Repeat LVEF assessment within 3 weeks.	Continue treatment with T-DM1 and tucatinib.

Abbreviations: Congestive Heart Failure (CHF); Left Ventricular Ejection Fraction (LVEF).

Pulmonary Toxicity

T-DM1 should be permanently discontinued in patients diagnosed with interstitial lung disease (ILD) or pneumonitis.

5.2 Identity of Investigational Products

5.2.1 Tucatinib

Tucatinib drug product is supplied as yellow capsule-shaped tablets in a 50 or 150 mg dosage strength for PO administration.

5.2.2 T-DM1

T-DM1 is commercially available as KADCYLA®. KADCYLA® is an FDA approved HER2-targeted antibody and microtubule inhibitor conjugate, which is indicated as a single agent for the treatment of patients with HER2+ metastatic breast cancer who have previously received trastuzumab and a taxane, either separately or in combination.

5.3 Study Drug Supplies

5.3.1 Packaging and Labeling

Tucatinib

Refer to the tucatinib pharmacy manual for information regarding tucatinib packaging and labeling.

T-DM1

T-DM1 is available via a commercial source. Refer to the package insert.

5.3.2 Preparation and Administration

Tucatinib

Each tablet contains either 50 mg or 150 mg of active ingredient. Patients will be instructed by the pharmacist or Investigator as to the specific number of tablets required for each dose in accordance with the level of the dose cohort to which the patient is assigned. Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will be provided to study patients, and will include the minimum times between doses, dosing relation to meals, and instructions for missed doses.

T-DM1

T-DM1 should be prepared and administered per instructions in the KADCYLA® package insert. T-DM1 will be administered intravenously under the direction of the Investigator.

5.3.3 Storage and Handling

Tucatinib

Bottles of tucatinib drug product (tablets) are to be stored under refrigeration (2 to 8°C). Refer to the study pharmacy manual for more information regarding tucatinib.

T-DM1

T-DM1 should be stored according to the package insert.

5.4 Study Drug Accountability

An initial drug supply of tucatinib will be shipped to the study site following receipt by Cascadian Therapeutics, Inc. (or designee) of written IRB/IEC approval and other appropriate study documentation as detailed in Cascadian Therapeutics, Inc. standard operating procedures.

Tucatinib should be handled according to the Sponsor's instructions in the study pharmacy manual. Tucatinib is to be tracked and documented from the time of receipt at the site, through patient dosing, and until return to the Sponsor or designee or destruction. All supplies, including partially used or empty bottles, should be tracked. Accountability logs will be provided by the Sponsor and should contain the identification of the patient to whom the drug was dispensed and the date and quantity of the drug dispensed to the patient.

All unused bottles of tucatinib are to be retained at the site until inventoried or approved for destruction by the Sponsor or designee The Sponsor or designee will conduct drug accountability during the course of the study. Tucatinib used during the course of the study should be handled according to the Sponsor's instructions and either disposed of or destroyed at the site or returned to the Sponsor or designee. Appropriate site procedures must be in place prior to destruction of used tucatinib at the study site.

The Sponsor or designee will conduct final drug accountability at site closure. All used and unused tucatinib bottles should be handled according to the Sponsor's instructions and either returned to the Sponsor or designee, or destroyed at the site.

5.5 Method of Assigning Patients to Treatment Groups

Patients will be assigned to the open dose cohort sequentially.

5.6 Blinding

This study is open label. No blinding will be done.

5.7 Concomitant Therapy

5.7.1 Required Concomitant Therapy

There are no required concomitant therapies. For patients with CNS metastases, prophylactic pre-treatment systemic corticosteroids may be administered at the discretion of the investigator.

5.7.2 Permitted and Prohibited Concomitant Therapy

Supportive treatments will be given according to label instructions as medically indicated for patients in each cohort. All concomitant medications will be recorded in the case report form. Concomitant medications can be administered at the Investigator's discretion to conform to standard practice during the treatment period.

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

- Investigational drugs and devices.
- Chemotherapy or hormonal therapy.
- Radiation therapy, except for palliative radiotherapy at focal sites, which may be given after consultation with the medical monitor, provided that there remain other sites of measurable disease accessible by RECIST 1.1.
- Strong inhibitors of CYP3A4. Known strong inhibitors of CYP3A4 include, but are not limited to, ketoconazole, itraconazole, clarithromycin, atazanivir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole. Known inducers of CYP3A4 should be used with caution. Inducers of CYP3A4 include, but are not limited to, rifampicin, phenytoin, carbamazepine, barbiturates, St. John's Wort. These lists are only partial. For additional information including drug elimination half-lives of strong inhibitors, please see Appendix E.
- Strong inhibitors or inducers of CYP2C8. Known strong inhibitors of CYP2C8 include, but are not limited to gemfibrozil, trimethoprim, montelukast, quercetin, and rosiglitazone. Known strong inducers of CYP2C8 include, but are not limited to rifampin. These are only partial lists. For additional information including drug elimination half-lives of strong inhibitors and inducer, please see Appendix F.

5.8 Treatment Compliance

Compliance will be assessed on a patient-by-patient basis. The pharmacist or designee will record the number of tucatinib tables dispensed to each individual patient, and the number of tablets returned to the clinic at the end of each cycle. Dose modifications and interruptions will be documented in the clinical database.

6 SCHEDULE OF EVENTS

The schedule of events is summarized in Appendices A through D. Study activities are listed by visit in this section and descriptions of all study assessments are presented in section 7.

Patients still in the study as of Amendment 8 will be allowed to continue receiving study drug in the Long-Term Extension phase. During this phase of the study, safety and efficacy assessments that include determination of disease progression will be performed as per institutional guidelines and investigator-determined usual and customary clinical care. Only SAEs and AOIs will be collected by the Sponsor.

6.1 Screening/Baseline (Days -28 to 1)

The following will be obtained or confirmed:

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Document HER2+ status, with biopsy showing HER2+ by FISH and/or 3+ staining by IHC
- Document concomitant medications
- Document baseline medical conditions
- Physical examination including breast exam
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- 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.
- ECOG performance status
- Blood samples for hematology, clinical chemistry (including calcium, magnesium, and phosphorus), and liver function tests
- Blood samples for coagulation panel
- 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 confirmatory testing may be required after discussion with medical monitor.)

- Urine sample for urinalysis
- Computed tomography (CT) or magnetic resonance imaging (MRI) scan of all known sites of disease or as symptoms direct to document sites of extracranial disease and assessment of tumor burden based upon RECIST 1.1
- MRI of the brain; CT of the brain may be allowed in patients with known contraindications to undergoing MRI imaging
- Electrocardiogram (ECG)
- Pregnancy test within 14 days prior to treatment (not required for males or females of non-child-bearing potential)
- Collect archived tissue sample for biomarker assessment, if available
- Enrollment into dose cohort MUST occur on or before Cycle 1 Day 1

6.2 Cycle 1 Day 1 (24 hours prior to Cycle 1, Day 2)

- Document AEs
- Document concomitant medications
- Physical examination*
- Vital signs
- ECG*
- ECOG performance status*
- Blood samples for hematology and clinical chemistry (Results must be reviewed and confirmed that patient is still eligible prior to first dose)*
- Blood samples for liver function tests (regardless of when liver function tests were taken for screening labs; Results must be reviewed and confirmed that patient is still eligible prior to first dose)
- Blood sample for PK analysis (pre-dose)**
- Administer the morning dose of tucatinib (Patient will self-administer the evening dose)
- Blood sample for PK analysis at 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, and 6 hours following dose of tucatinib **

- Remind patient NOT to take their morning dose of tucatinib before coming to the clinic the next day

* These evaluations do not need to be repeated if a patient is screened within 96 hours of scheduled first dose of tucatinib.

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.3 Cycle 1 Day 2

- Document AEs
- Document concomitant medications
- Vital signs
- Blood samples for PK analysis (pre-dose)**
- Administer the morning dose of tucatinib (Patient will self-administer the evening dose)
- Administer T-DM1 at 3.6 mg/kg given intravenously
- Blood sample for PK analysis 1 hour following completion of T-DM1 infusion**

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.4 Cycle 1 Day 8 (± 48 hours)

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Blood samples for PK analysis anytime during the visit**

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.5 Cycle 1 Day 15 (± 48 hours)

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Blood samples for PK analysis anytime during the visit**
- Remind patient NOT to take their morning dose of tucatinib before coming to the clinic for the next visit (Cycle 2 Day 1)

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.6 Cycle 2 Day 1 (± 24 hours)

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECG
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Urine sample for urinalysis
- Blood samples for PK analysis prior to dosing tucatinib and T-DM1**
- Administer the morning dose of tucatinib (Patient will self-administer the evening dose)
- Administer T-DM1 at 3.6 mg/kg given intravenously
- Blood sample for PK analysis at 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, and 6 hours following dose of tucatinib **

- Blood sample for PK analysis at 1 hour following completion of T-DM1 infusion**

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.7 Cycle 2 Day 8 (± 48 hours)

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Blood samples for PK analysis anytime during the visit**

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.8 Cycle 2 Day 15 (± 48 hours)

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Blood samples for PK analysis anytime during visit**
- Remind the patient NOT to take their morning dose of tucatinib before coming to the clinic for their next visit (Cycles 2–5 only)

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.9 Cycle 2 Day 21 (± 7 days)

- CT/MRI scan of all known sites of disease and assessment of tumor burden as per RECIST 1.1

6.10 Cycle 3 Day 1 (± 24 hours), and all Day 1 of all Subsequent Cycles

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECG
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Urine sample for urinalysis
- Blood samples for PK analysis prior to dosing with tucatinib (through Cycle 6 only)**
- Administer the morning dose of tucatinib (Patient will self-administer the evening dose) (Cycles 3-6 only; **after Cycle 6, patient may self-administer both morning and evening dose of tucatinib at home**)
- Administer T-DM1 at 3.6 mg/kg given intravenously

**No samples will be collected from patients enrolled under Protocol Amendment 6.

6.11 Cycle 3 Day 10 and Cycle 4 Day 10 (± 72 hours)

- Blood samples for clinical chemistry and liver function tests

6.12 Cycle 4 Day 21 (± 7 days)

- CT/MRI scan of all known sites of disease and assessment of tumor burden as per RECIST 1.1
- ECHO or MUGA, using the same cardiac testing modality performed in screening/baseline*

*If cycles are delayed for any reason or there is an interim assessment, then perform 90 days (±) 7 days from first ECHO or MUGA.

6.13 Cycle 6 Day 21 (and thereafter at the end of every third cycle; ± 7 days)

- CT/MRI scan of all known sites of disease and assessment of tumor burden as per RECIST 1.1

6.14 Cycle 8 Day 21 (and thereafter at the end of every fourth cycle; ± 7 days)

- ECHO or MUGA, using the same cardiac testing modality performed in screening/baseline*

*If cycles are delayed for any reason or there is an interim assessment, then perform 90 days (±) 7 days from the last ECHO or MUGA.

6.15 End of Study (30 days, ± 7, after last dose of T-DM1 or Tucatinib, whichever is later) During Dose Escalation and Expansion Phases

- Document AEs
- Document concomitant medications
- Physical examination
- Vital signs
- ECG
- ECOG performance status
- Blood samples for hematology, clinical chemistry, and liver function tests
- Blood sample for coagulation panel
- Urine sample for urinalysis
- CT/MRI scan and assessment of tumor burden based upon RECIST 1.1 if needed (discuss with medical monitor)
- ECHO or MUGA, as appropriate, if not done within previous 90 days

6.16 Long-Term Extension Phase – Beginning of each Cycle and End of Treatment

Patients still in the study as of Amendment 8 will be allowed to continue receiving study drug.

- Only SAEs and AOIs (AST or ALT elevations that are > 3 X ULN with concurrent elevation [within 21 days of AST and/or ALT elevations] of total bilirubin > 2 X the ULN, except in patients with documented Gilbert's syndrome, asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment, any event of cerebral edema not clearly attributable to progression of disease, CTCAE ≥ Grade 3 diarrhea) will be collected.
- All other assessments per usual and customary practice
- Pregnancy testing as per institutional guidelines in women of child-bearing potential

7 STUDY ASSESSMENTS

7.1 Efficacy Measures

Following initiation of study treatment, CT/MRI scans of all areas of known disease will be obtained at the end of every two treatment cycles through Cycle 6, and then at the end of every three treatment cycles, until PD, initiation of a new therapy, or withdrawal of consent. Additional imaging, such as nuclear bone scans, may also be done as appropriate at the discretion of the Investigator. These scans will be assessed per RECIST 1.1 for the purpose of determining the ORR, defined as a best response of CR or PR. For patients with CNS metastases, exploratory assessments utilizing modified RECIST 1.1 criteria and/or volumetric response may be performed. (See Appendix G for Modified RECIST 1.1 and Volumetric Response Criteria). Efficacy measures will also include disease control rate (DCR), defined as the proportion of patients with best response of CR, PR, or SD, and clinical benefit rate (CBR), defined as the proportion of patients with best response of CR, PR, or SD for ≥ 6 months. Brain MRI images for patients with CNS metastases may be collected for an additional independent review. However, all treatment decisions will be made on the basis of local review of radiologic imaging.

Duration of response will be measured in patients with complete or partial response from the date that the patient first meets the criteria of CR or PR to the date that the patient progresses (radiologically or symptomatically), or until death from any cause. For each patient who is not known to have progressed or died, duration of response will be censored at the date that the patient was last known to be alive and progression-free.

7.2 Biomarker Assessments

Biomarker assessments will be performed using paraffin-embedded tissue blocks obtained at the time of diagnosis or tumor staging to identify molecular signatures that may be associated with response or resistance to treatment. Tissue samples may be used to assess HER2 or other relevant protein levels or genetic changes to tumor DNA that may confer resistance or sensitivity to tucatinib therapy.

7.3 Pharmacokinetic Measures

Plasma and serum samples to assess the effect of combination treatment on the PK of both tucatinib and T-DM1 will be collected. Plasma samples will be collected to measure levels of tucatinib and its metabolite as well as serum samples to measure levels of T-DM1 and its metabolites. Tucatinib PK will be assessed at the start of treatment (Cycle 1 Day 1), and again at the beginning of Cycle 2 (Cycle 2 Day 1) to evaluate whether tucatinib and related metabolite levels may be altered following prolonged exposure to T-DM1. Samples will also be collected prior to administration of tucatinib on the first day of Cycles 3–6 to assess trough levels. Samples to evaluate T-DM1 levels will be collected

pre- and post-T-DM1 administration for the first two cycles, starting on Cycle 1 Day 2. In addition, samples will be collected to assess T-DM1 levels on a weekly basis for the first six weeks. No samples will be collected from patients enrolled under Protocol Amendment 6. Table 13 describes the tucatinib and T-DM1 PK blood sample schedule. Following approval of Amendment 8, no PK assessments will be performed in patients enrolled on the Long-Term Extension phase of the study.

Table 13 PK Blood Sample Schedule

Cycle	Day	Time point	PK Tucatinib (Plasma)	PK T-DM1 (Serum)
1	1	0 h (pre-dose)	1 x 5 mL	
		0.5 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		1 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		2 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		3 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		4 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		6 h (±30 minutes) following dosing of tucatinib	1 x 5 mL	
1	2	24 hours (±30 minutes) following dosing of tucatinib on Day 1 (and prior to Cycle 1 Day 2 morning dosing of tucatinib); and prior to dosing of T-DM1 on Cycle 1 Day 2	1 x 5 mL	1 x 5 mL
		1h (±30 minutes) following administration of T-DM1		1 x 5 mL
1	8	T-DM1 collection Cycle 1 Day 8 (±48 hours)		1 x 5 mL
1	15	T-DM1 collection Cycle 1 Day 15 (±48 hours)		1 x 5 mL
2	1	0 h (pre-dose) prior to dosing of tucatinib and administration of T-DM1	1 x 5 mL	1 x 5 mL
		0.5 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		1 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		1 h (± 30 minutes following administration of T-DM1)		1 x 5 mL
		2 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		3 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		4 h (±5 minutes) following dosing of tucatinib	1 x 5 mL	
		6 h (±30 minutes) following dosing of tucatinib	1 x 5 mL	
2	8	T-DM1 collection Cycle 2 Day 8 (±48 hours)		1 x 5 mL
2	15	T-DM1 collection Cycle 2 Day 15 (±48 hours)		1 x 5 mL
3	1	1 hour (±30 minutes) prior to dosing of tucatinib	1 x 5 mL	
4	1	1 hour (±30 minutes) prior to dosing of tucatinib	1 x 5 mL	
5	1	1 hour (±30 minutes) prior to dosing of tucatinib	1 x 5 mL	
6	1	1 hour (±30 minutes) prior to dosing of tucatinib	1 x 5 mL	

*PK samples are not collected for patients enrolled under Protocol Amendment 6

7.4 Safety Assessments

Safety will be assessed by physical examinations, measurement of vital signs, clinical laboratory evaluation, ECG, and either ECHOs or MUGA scans. Clinically significant changes in these parameters may be captured as AEs.

The Investigator is responsible for the appropriate medical care and the safety of patients who have entered this study. The Investigator must document all AEs and notify the Sponsor of any SAE experienced by patients who have entered this study. Contact information for the Sponsor's medical expert is provided on the protocol cover page.

Following approval of Amendment 8, only SAEs and AOIs (AST or ALT elevations that are > 3 X ULN with concurrent elevation [within 21 days of AST and/or ALT elevations] of total bilirubin > 2 X the ULN, except in patients with documented Gilbert's syndrome, asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment, any event of cerebral edema not clearly attributable to progression of disease, CTCAE ≥ Grade 3 diarrhea) will be collected in patients participating in the Long-Term Extension phase of the study.

7.4.1 Clinical Laboratory Evaluation

The chemistry panel is to include the following tests: calcium, magnesium, inorganic phosphorus, uric acid, total protein, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, bicarbonate, glucose, potassium, chloride, albumin, and sodium.

Liver function tests (LFT) are to include the following: AST/SGOT, ALT/SGPT, total bilirubin, and alkaline phosphatase.

The hematology panel is to include the following tests: complete blood count (CBC) with differential, hemoglobin, hematocrit, and platelets.

The coagulation panel is to include the following tests: INR, prothrombin time (PT), and activated partial thromboplastin time (aPTT).

The urinalysis to be performed by dipstick is to include the following tests: color, appearance, specific gravity, pH, leukocyte esterase, nitrites, protein, glucose, ketones, urobilinogen, bilirubin, and blood.

Following approval of Amendment 8, clinical laboratory evaluation is to be determined by the investigator or institutional practice guidelines.

7.4.2 Adverse Events

7.4.2.1 Definitions of Adverse Events

According to the International Conference on Harmonisation (ICH) guidelines (Federal Register/Vol. 75, No. 188/September 29, 2010), 21 CFR Parts 312, and 320 (Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans), and ICH E2A (Clinical Safety and Data Management: Definitions and Standards for Expedited Reporting),

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

The following information should be considered when determining whether or not to classify a test result, medical condition or other incident as an adverse event:

- Adverse events will be recorded from the time of informed consent.
- Abnormal laboratory values should not generally be recorded as an adverse event unless an intervention is required, the laboratory abnormality results in a serious adverse event, the lab abnormality results in study termination or interruption/discontinuation of study treatment or the lab abnormality is associated with clinical signs or symptoms. When recording an adverse event resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin."
- Medical conditions present at screening should be identifiable as pre-existing conditions on the electronic case report form (eCRF) so that worsening or improvement of the conditions during the study may be tracked.
- Pre-existing medical conditions that have worsened in either severity or frequency or changed in character during the protocol-defined reporting period should be recorded as AEs.
- Complications that occur in association with a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be recorded as AEs.

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis under a single event term. For example, cough, rhinitis and sneezing might be grouped together as "upper respiratory tract infection". If possible, abnormal laboratory results that meet the definition of an adverse event (see above) should be reported as a clinical diagnosis rather than the abnormal value itself (e.g., "anemia" rather than "decreased blood count").

7.4.2.2 Documenting and Monitoring Adverse Events

All baseline conditions and adverse events encountered during the clinical trial following patient consent through 30 days after the last dose of study drug will be recorded on the eCRF (Dose Escalation and Expansion phases) or in the source records (Long-Term Extension phase).

Special considerations:

- Elective procedures or routinely scheduled treatments are not considered adverse events. However, an untoward medical event occurring during a prescheduled elective procedure should be recorded as an adverse event.
- A baseline condition is not considered an adverse event unless the condition worsens following study drug administration.
- Death itself is not considered an adverse event; it is, instead, the outcome of an adverse event.
- Disease progression itself is not considered an adverse event. However, signs and symptoms resulting from disease progression should be recorded as adverse events.

Serious adverse events (SAEs) that are considered related (i.e., determined to be possibly, probably, or definitely related) to tucatinib or T-DM1, by the Investigator or Sponsor should be followed until the event resolves or stabilizes (section 7.4.3 [Serious Adverse Events]).

7.4.2.3 Assessment of Adverse Events

For each AE, the start and resolution dates, severity, seriousness (i.e., whether the event meets the definition of an SAE [section 7.4.3Serious Adverse Events]), relationship of the event to the study drug, action taken regarding study drug, and outcome of the event will be documented on the eCRF (Dose Escalation and Expansion phases) or in the source records (Long-Term Extension phase).

Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 should be used to assess and grade severity of each AE, including laboratory abnormalities judged to be clinically significant. If the event is not covered in the CTCAE, the guidelines shown in the following table should be used to grade severity.

Table 14 Adverse Events Severity Grading Scale (CTCAE Version 4.03)

Severity	Grade	Description
Mild	**1**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	**2**	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Severe	**3**	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Life-threatening	**4**	Life-threatening consequences; urgent intervention indicated.
Death	**5**	Death related to adverse event.

The term "severe" is a measure of intensity; a severe AE is not necessarily serious.

Relationship

The relationship of an AE to study drug should be assessed using the guidelines presented in the table below. An AE for which there has been no causal relationship reported will require follow-up to determine causality.

Table 15 Adverse Event Relationship to Study Drug

Relationship to Drug	Description
Definitely Related	The adverse event:
	Exhibits previously known toxicity of agent; or
	Follows a reasonable temporal sequence from administration of the drug;
	Follows a known or expected response pattern to the suspected drug;
	Is confirmed by stopping or reducing the dosage of the drug; and
	Is not explained by any other reasonable hypothesis.
Probably Related	The adverse event:
	Follows a reasonable temporal sequence from the time of study drug administration; and/or
	Follows a known response pattern to the study drug;
Possibly Related	The adverse event:
	Follows a reasonable temporal sequence from the time of study drug administration; and/or
	Follows a known response pattern to the study drug; but could have been produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy.
Unlikely Related	The adverse event:
	Does not follow a reasonable temporal sequence from the time of study drug administration; and
	Was likely produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy, but for which relationship cannot be definitely ruled out.
Not Related	The adverse event can be determined with certainty to have no relationship to the study drug.

Outcome

Each AE will be characterized according to the outcomes described in the following table:

Table 16 Adverse Event Outcomes

Outcome	Description
Recovered/Resolved	The patient has fully recovered from the event with no observable residual effects.
Recovering/Resolving	The effects of the event are improving, or events have stabilized (are constant and not expected to improve or worsen) but have not returned to baseline.
Not recovered/Not Resolved	The effects of the event are still present and changing. The event is not considered stabilized or resolved.
Recovered/Resolved with Sequelae	The patient has fully recovered from the event with some observable residual effects.
Fatal	The event was the primary cause of death (may or may not be the immediate cause of death).
Unknown	The event outcome is unknown.

Death is an outcome of an event and not an event per se. Sudden death or death due to unexplainable cause(s) is to be reported, but follow-up will be pursued whenever possible until cause of death is determined.

Action Taken with Study Drug

Action taken with study drug in relation to each AE will be characterized as follows:

- None
- Drug withdrawn
- Drug interrupted
- Dose reduced
- Unknown
- Not applicable
- Other (specify on eCRF)

7.4.3 Serious Adverse Events

Any AE or abnormal laboratory test value that is serious (see definition below) and occurs after administration of study drug must be reported to the Sponsor within 24 hours of discovery of the event. An event occurring after informed consent but before administration of study drug that is considered serious and possibly related to a protocol procedure must also be reported to the Sponsor within 24 hours of discovery of the event.

7.4.3.1 Definition and Reporting Procedures

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

Table 17 Definition of Serious Adverse Events

Fatal:	The adverse event resulted in death. Note that death due to disease progression will not be considered a Serious Adverse Event.
Life Threatening:	The adverse events placed the patient at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. 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 serious adverse events 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. If disease progression leads to a serious adverse event such as hospitalization, then the primary sign or symptom leading to the hospitalization should be listed as adverse event, and not disease progression itself.
Disabling/Incapacitating:	Resulted in a substantial and permanent disruption of the patient's ability to carry out activities of daily living.
Congenital Anomaly or Birth Defect:	An adverse outcome in a child or fetus of a patient exposed to the study drug or study treatment regimen before conception or during pregnancy.
Medically Significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.

Every SAE (regardless of suspected causality) should be reported to the Sponsor within 24 hours of discovery of the event. The processes for reporting and documenting SAEs are provided in the study manual. Investigators are responsible for reporting these events to their IRB/IEC in accordance with federal and institutional laws and regulations.

Additional updates from the Investigator may be necessary as more information becomes available on the SAE, and all treatment-related SAEs will be followed until the acute event has resolved or stabilized, even if the patient discontinues study participation prior to SAE resolution. Any new information or follow-up information pertaining to previously reported SAEs will be reported to the Sponsor within 24 hours of becoming aware of the new or follow-up information.

New or follow-up information should be sent to the Sponsor's drug safety department at: Fax: 1-206-801-2127 or Email: safetydesk@cascadianrx.com.

Any SAE that occurs after study completion and is considered by the Investigator to be related to either study drug, should be reported to the Sponsor.

Reporting Serious Adverse Events to Regulatory Agencies

The Sponsor will determine which SAEs qualify for expedited reporting to regulatory agencies. SAEs that qualify for expedited reporting will be submitted to regulatory agencies in accordance with federal regulations (CFR 312.32, 312.320, and 600.80).

7.4.3.2 Follow-up of Adverse Events and Laboratory Test Abnormalities

Adverse event information will be collected during the clinical trial from the time the patient signs informed consent through 30 days after the last dose of study drug. Serious adverse events that are considered related to study drug by the Investigator or Sponsor should be followed until the events resolve or stabilize.

7.4.3.3 Pregnancy Reporting

Cases of pregnancy must be reported through 6 months after the last dose of study drug (tucatinib or T-DM1, whichever is later). If a patient or the female partner of a male patient becomes pregnant during participation in the study, the Sponsor must be notified. If a study participant becomes pregnant during administration of the drug, treatment should be discontinued. The Sponsor will ask for follow up evaluation of the pregnancy, fetus, and child. Additional instructions for reporting the pregnancy and outcome will be provided by the Sponsor at the time of notification.

7.4.3.4 Overdose

Occurrences of study drug overdose should be reported to the Sponsor for tracking purposes.

Additional instructions for reporting overdose information will be provided by the Sponsor at the time of notification.

7.5 Appropriateness of Measurements

The safety measures that will be used in this study are considered standard procedures for evaluating the potential adverse effects of study drugs. Adverse events and, when applicable, clinical laboratory data will be graded using NCI CTCAE Version 4.03.

Standardized criteria (RECIST 1.1) will be employed by the Investigator to evaluate tumor lesions in the determination of ORR, disease progression, disease control, PFS, and duration of response in this study.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Study Monitoring

The following are required of the Sponsor or its representatives to ensure accurate, complete and reliable data:

- Provide instructional material to the study sites, as appropriate
- Conduct an initiation/start-up training session to instruct the Investigators and study personnel on the protocol, completion of the eCRFs, study procedures, and good clinical practices
- Make periodic monitoring visits to the study site
- Be available for consultation and stay in contact with the study-site personnel by mail, telephone, and/or fax
- Monitor the patient data recorded in the eCRF against source documents at the study site
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection

8.2 Data Management

Web-based eCRFs will be used to collect patient data in this study. This system, provided by a contract research organization, also includes electronic queries to resolve any questions or data discrepancies. All eCRFs and resulting data will be developed and maintained in a manner consistent with currently available regulations and guidances pertinent to the use of computerized systems in clinical trials. All Sponsor, Sponsor designees, and study-site users of the eCRF system will be trained prior to the use of the system.

Following approval of Amendment 8, data will no longer be collected in eCRFs. Sites will be required to provide periodic patient updates (by periodic monitoring visits) to the Sponsor and continue to submit SAEs and AOIs (AST or ALT elevations that are > 3 X ULN with concurrent elevation [within 21 days of AST and/or ALT elevations] of total bilirubin > 2 X the ULN, except in patients with documented Gilbert's syndrome, asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment, any event of cerebral edema not clearly attributable to progression of disease, CTCAE ≥ Grade 3 diarrhea).

8.3 Quality Assurance Audits

The study site may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. The Sponsor must be notified immediately if an Investigator is contacted by a regulatory agency to schedule an audit in relation to this study.

Sponsor audits may be conducted to verify data, protocol compliance and overall adherence to good clinical practices (GCP). The Investigator and/or clinical staff must agree to allow the auditor direct access to all trial-related documents (i.e., source medical records), and must allocate time to meet with the auditor when applicable. Contact information for the Sponsor is provided in the study manual.

9 STATISTICAL METHODS

9.1 Determination of Sample Size

This study is designed as a traditional 3+3 dose escalation trial. It will enroll up to 63 evaluable patients including up to 30 evaluable patients at the MTD/RP2D and up to 15 evaluable patients with untreated asymptomatic CNS disease. The escalation and stopping rules imply the by-patient incidence rate for DLT is less than 33% at the MTD. The theoretical minimum sample size is two DLT evaluable patients. With four dose levels and two expansion cohorts, the theoretical maximum sample size is 63 DLT evaluable patients.

With a sample size of 30 evaluable subjects for the MTD/RP2D cohort, a DLT with a true patient incidence rate of 10% will almost surely (95.8%) be seen in at least one patient in the study. Based on an expected combined DLT rate of approximately 20%, the 1-sided Wilson score 95% confidence upper limit for 6 DLTs in 30 subjects would be 34.3%.

Due to a smaller potential patient population, the planned sample size for the CNS cohort is 15 evaluable patients. A DLT with a true 10% patient incidence rate has a 79.4% chance of being seen in at least once in the study. The 1-sided 95% confidence upper limit is 40.9% for an observed 20% DLT rate. In addition to evaluating safety in the CNS cohort, an exploratory objective for this cohort is evaluate the effect of tucatinib in combination with T-DM1 on CNS metastases. Should the true response rate be 20% in this cohort, the chance of observing at least one responder in 15 patients is 95.8%.

9.2 Statistical Analysis

9.2.1 Patient Analysis Sets

Safety Analysis Patient Set:

All patients who receive at least one dose of either T-DM1 or tucatinib will be included in the Safety Analysis Patient Set. This set of patients will be used for primary safety analysis.

DLT Evaluable Patient Set:

All DLT evaluable patients as defined in section 3.2 (Dose Escalation/Cohort Administration Guidelines) will be included in the DLT Evaluable Patient Set.

Efficacy Evaluable Patient Set:

All patients in the Safety Analysis Patient Set who had at least one measurable lesion at Baseline and at least one disease assessment after Baseline will be included in the

Efficacy Evaluable Patient Set. In addition, patients who discontinued the study prior to their first post-Baseline disease assessment due to death, clinical or radiologic progressive disease, or an AE will also be included in the Efficacy Evaluable Patient Set.

9.3 Statistical and Analytical Plans

This section outlines the statistical methods to be used in the study, which will be described in detail in the Statistical Analysis Plan (SAP) which will be finalized prior to database lock. Any change to the data analysis methods described in this protocol requires a protocol amendment only if a principal feature of the protocol will be altered. Any changes to the methods described in the final SAP will also be described and justified in the clinical study report.

Unless otherwise specified, all summaries will be presented both by cohort and across all cohorts.

All statistical analyses will be performed using SAS Version 9.1 or above, or other commercially available validated software.

9.3.1 General Considerations

9.3.1.1 Adjustments for Covariates

There will be no adjustments for covariates in any analyses.

9.3.1.2 Handling of Missing Data

Missing data will not be imputed. For the analysis of ORR, DCR, and CBR, patients in the Efficacy Evaluable Patient Set who are not evaluable due to missing disease assessments will be analyzed as non-responders.

Incomplete data resulting from patients who terminate the study for reasons other than disease progression or death will be censored for calculation of duration of response and PFS as described in Section 9.3.4.2.

9.3.2 Patient Characteristics

Demographics, disease characteristics, and other baseline patient characteristics will be summarized by descriptive statistics. Categorical variables will be summarized as frequencies and proportions for each category; continuous measures will be summarized by mean, standard deviation, median, minimum, and maximum.

9.3.3 Safety Analyses

Safety results will be summarized by cohort and treatment cycle.

9.3.3.1 Adverse Events

For the primary safety endpoint of patient incidence and severity of AEs throughout the study period, each AE will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. The number and proportion of patients in the Safety Evaluable Patient Set reporting a given SOC/PT will be tabulated according to the worst severity reported. Severity will be graded according to CTCAE Version 4.03. Separate tables will be presented for (a) all reported AEs, (b) AEs judged to be related (possibly, probably, or definitely related to tucatinib, (c) AEs judged to be related (possibly related, probably related, or definitely related) to T-DM1, (d) DLTs (for patients in the DLT Evaluable Patient Set only), (e) SAEs, (f) AEs leading to premature discontinuation of tucatinib, (g) AEs leading to premature discontinuation of T-DM1, (h) AEs leading to premature withdrawal from the study, and (i) fatal AEs.

9.3.3.2 Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as AEs. Events with a fatal outcome will be listed.

9.3.3.3 Clinical Laboratory Results

Summary statistics for actual value, change from baseline, and proportion of patients with abnormal values will be tabulated as appropriate for laboratory results.

Summaries of NCI CTCAE Version 4.03 grading and shifts from baseline will be tabulated as appropriate.

9.3.3.4 Other Safety Analyses

Summary statistics for observed values and change from baseline will be tabulated for vital signs.

9.3.4 Efficacy Analyses

9.3.4.1 Primary Efficacy Endpoint

This Phase 1b study does not have a primary efficacy endpoint.

9.3.4.2 Secondary Efficacy Endpoints

Objective response will be defined as a best response of CR or PR. Duration of tumor response will be calculated for all patients who achieve an objective response and will be defined as the time from first objective status assessment of CR or PR to death or documented disease progression. Patients who stop study treatment and receive subsequent anticancer therapy prior to documentation of disease progression will be

censored at the last adequate tumor assessment prior to the start of the subsequent therapy. Patients who do not progress, do not die, and do not receive subsequent anticancer therapy will be censored on the date of last tumor assessment. The ORR will be calculated as the proportion of patients in the Efficacy Evaluable Patient Set who achieve an objective response. Any objective responses observed will be individually described.

Disease control will be defined as a best response of CR, PR, or SD. The DCR will be calculated as the proportion of patients in the Efficacy Evaluable Patient Set who achieve disease control.

Clinical benefit will be defined as a best response of CR, PR, or SD for ≥ 6 months. The CBR will be calculated as the proportion of patients in the Efficacy Evaluable Patient Set who achieve clinical benefit.

PFS will be defined as the time from first dose of study drug until documentation of disease progression or death from any cause. Patients who stop study treatment and receive subsequent anticancer therapy prior to documentation of disease progression will be censored at the last adequate tumor assessment prior to the start of the subsequent therapy. Patients who do not progress, do not die, and do not receive subsequent anticancer therapy will be censored on the date of last tumor assessment. If no adequate post-treatment tumor assessments were obtained for a patient, PFS will censored at Day 1. PFS curves will be estimated using the Kaplan-Meier method based on patients in the Safety Analysis Patient Set.

Additional efficacy analyses may be conducted as deemed appropriate. Further details of the efficacy analyses will be provided in the SAP.

9.3.4.3 Exploratory Efficacy Endpoints

Exploratory biomarker results will be summarized using descriptive statistics and correlated with efficacy endpoints, as appropriate. Exploratory CNS response rates will be defined by using modified RECIST 1.1 and/or Volumetric Response criteria as outlined in Appendix G.

9.3.4.4 Concomitant Medications

Concomitant medication use will be summarized for patients in the Safety Evaluable Population by cohort within phase. This summary will include all medications taken after the first dose of study drug (T-DM1 or tucatinib). The WHODRUG medication dictionary will be used for coding medications.

9.3.5 Patient Disposition

An accounting of study patients by disposition will be tabulated by treatment group. The number of patients in each analysis population will be summarized by treatment group. Patients who discontinue study drug prematurely or withdraw from the study will be summarized and listed, with the reason for early termination and/or withdrawal.

9.3.6 Patient Characteristics

Demographic and other baseline characteristics and concomitant medications will be listed and summarized by treatment group.

9.3.7 Treatment Compliance

9.3.8 Protocol Deviations

Eligibility criteria that were not met will be listed along with whether or not an exception was granted. All protocol deviations will be listed. A separate listing of important protocol deviations will be provided.

Important protocol deviations are defined as:

- Any unauthorized protocol deviations that result in a significant added risk to the study subject (e.g., wrong concentration is administered)
- Non-adherence to inclusion or exclusion criteria without prior Sponsor approval
- Non-adherence to GCP, FDA regulations, and/or ICH guidelines (e.g., failure to obtain proper informed consent or failure to report serious adverse events)
- Frequent unauthorized non-adherence to study procedures or schedules that do not involve eligibility (e.g., a lab testing timepoint that is missed)
- Development of withdrawal criteria during the study without corresponding patient withdrawal
- Receipt of a prohibited concomitant medication by a patient

9.3.8.1 Extent of Exposure

Duration of treatment will be summarized and listed.

9.3.8.2 Interim Analyses

During the dose escalation phase of the study, the SMC will meet to review AEs and laboratory toxicities for the current dose cohort to determine if escalation to the next

sequential dose cohort is warranted.The SMC will meet and review safety data after each cohort is enrolled and/or approximately once every 3 months unless otherwise agreed upon, and on an ad hoc basis as needed.

Following approval of Amendment 8 at all sites, and upon closure of the clinical database, an efficacy analysis will be performed and the Clinical Study Report will be written.

10 INFORMED CONSENT, ETHICAL REVIEW, AND ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the protocol and ethical principles stated in the 2008 version of the Declaration of Helsinki or the applicable good clinical practice guidelines and all applicable federal, state, and local laws, rules, and regulations.

10.1 Informed Consent

The Investigator is responsible for presenting the risks and benefits of study participation to the patient in clear and understandable terms according to the most current, IRB-approved informed consent document. The Investigator will ensure that the patient is provided ample time to make an informed decision and that the written informed consent is obtained from each patient or patient's legally authorized representative, including all appropriate signatures and dates required on the informed consent document, prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from the legally authorized representative of a patient who is unable to provide informed consent at study entry, and later the patient is able to provide informed consent, the Investigator must obtain written informed consent from the patient.

10.2 Ethical Review

The Investigator will provide the Sponsor or its designee with documentation of the IRB or IEC approval of the protocol and the informed consent document before the study begins at the investigative site(s). The name and address of the reviewing ethics committee are provided in the Investigator file.

The Investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The Investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol
- The IRB/IEC approvals of the protocol and informed consent document, and any amendments or revisions
- Submission to IRB/IEC of safety and SAE reports, as appropriate

10.3 Administrative and Regulatory Considerations

10.3.1 Investigator Information

The contact information and qualifications of the principal Investigator and subinvestigators and the name and address of the research facilities are included in the trial master files. After reading the protocol, each principal Investigator will sign the protocol's signature page (section Signatures) and return it to the Sponsor or the Sponsor's designee.

10.3.2 Protocol Amendments and Study Termination

The Sponsor may periodically and officially amend the protocol to address safety issues or other developing issues. Any Investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the Sponsor prior to seeking approval from the IRB/IEC, and prior to implementation.

The Sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy, and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary.

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies and applicable IRB/IEC with direct access to original source documents. The Investigator will also provide appropriate facilities for periodic monitoring by the Sponsor or designee.

Records containing patient medical information must be handled by the Investigator in accordance with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and consistent with the terms of the patient authorization contained in the informed consent document for the study. Care should be taken to ensure

that such records are not shared with any person or for any purpose not contemplated by the authorization. Furthermore, eCRFs and other documents to be transferred to the Sponsor or Sponsor designee should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of patient identities.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written approval must be obtained from the Sponsor.

10.5 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 described in the Clinical Trial Agreement.

11 ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	activities of daily living
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvate transaminase
anti-HBc	antibodies to Hepatitis B core
anti-HCV	antibodies to Hepatitis C
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CHF	congestive heart failure
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	disease control rate
DDI	drug-drug interaction
DFS	disease-free survival
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FISH	fluorescence *in situ* hybridization
GCP	good clinical practices
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act Privacy Rule
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
ILD	interstitial lung disease
IV	intravenous

IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mon	month
MRI	magnetic resonance imaging
mRNA	message ribonucleic acid
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PIC	powder in capsule
PK	pharmacokinetics
PO	oral
PR	partial response
PT	prothrombin time
PVP VA	polyvinylpyrrolidine-vinyl acetate copolymer
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
SOC	system organ class
SAP	statistical analysis plan
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

12 LITERATURE REFERENCES

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Appendix A: Schedule of Events for Cycle 1

		Cycle 1				
Study Procedure and Day		Day -28 to 1	Day 1 (24 hours prior to Cycle 1 Day 2)	Day 2	Day 8 (± 48 hours)	Day 15 (± 48 hours)
Screening and baseline assessments	Informed consent	X				
	Study eligibility	X				
	Document HER2+ status	X				
	Physical exam	X[a]	X[g]		X	X
	Vital signs	X	X	X	X	X
	ECHO/MUGA	X				
	ECOG PS	X	X[g]		X	X
	Labs[b]	X	X[g]		X	X
	Hepatitis B and C screening[h]	X				
	Coagulation	X				
	Urinalysis	X				
	CT/MRI[c]	X				
	Brain MRI	X				
	ECG	X	X[g]			
	Pregnancy test[d]	X				
	Document Con Meds	X	X	X	X	X
	Document Baseline medical conditions	X				
	Document AEs		X	X	X	X
Study Drug Treatment	Tucatinib[e]		X	X		
	T-DM1[f]			X		
PK/Pharmacodynamics	Archive tissue	X				
	Blood samples[i]		X	X	X	X

a Includes breast exam.
b Blood samples for hematology, clinical chemistry (including calcium, magnesium, and phosphorus), and liver functions tests.
c CT/MRI scan of all known sites of disease and assessment of tumor burden as per RECIST 1.1. Additional imaging, such as nuclear bone scans, may also be done as appropriate at the discretion of the Investigator.
d Pregnancy test within 14 days prior to treatment (not required for males or females of non-child-bearing potential).
e Tucatinib is administered PO BID, on a 21-day cycle. On Day 1 and Day 2 the morning dose is administered in the office.
f T-DM1 is administered IV, once every 21 days.
g These evaluations do not need to be repeated if a patient is screened within 96 hours of scheduled first dose of tucatinib, with the exception of liver function tests, which must be repeated on Cycle 1 Day 1 regardless of when taken for screening. Results must be reviewed and confirmed that patient is still eligible prior to first dose.
h Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to HgB core (anti-HBc), and antibodies to Hepatitis C (anti-HCV).
i Blood samples will not be collected to evaluate PK for patients enrolled under Protocol Amendment 6.
Abbreviations: echocardiogram (ECHO); electrocardiogram (ECG); multiple-gated acquisition scan (MUGA); computed tomography (CT); magnetic resonance imaging (MRI); Eastern Cooperative Oncology Group (ECOG); performance status (PS); adverse events (AE); pharmacokinetic (PK), concomitant medications (Con Meds); twice daily (BID); oral (PO); intravenous (IV).

Appendix B: Schedule of Events for Cycle 2

		Cycle 2			
Study Procedure and Day		Day 1 (± 24 hours)	Day 8 (± 48 hours)	Day 15 (± 48 hours)	Day 21 (± 7 days)
Assessments	Physical exam	X	X	X	
	Vital signs	X	X	X	
	ECOG PS	X	X	X	
	Labs[a]	X	X	X	
	Urinalysis	X			
	ECG	X			
	Document Con Meds	X	X	X	
	Document AEs	X	X	X	
	CT/MRI[e]				X[d]
Study Drug Treatment	Tucatinib[b]	X			
	T-DM1[c]	X			
PK/Pharmacodynamics	Blood samples[f]	X	X	X	

a Blood samples for hematology, clinical chemistry (including calcium, magnesium, and phosphorus), and liver functions tests.
b Tucatinib is administered PO BID, on a 21-day cycle. On Day 1 the morning dose is administered in the office.
c T-DM1 is administered IV, once every 21 days.
d Cycle 2 Day 21 and at the end of all even-numbered cycles (± 7days) through Cycle 6, and thereafter every third cycle.
e CT/MRI scan of all known sites of disease and assessment of tumor burden as per RECIST 1.1. Additional imaging, such as nuclear bone scans, may also be done as appropriate at the discretion of the Investigator.
f Blood samples will not be collected to evaluate PK for patients enrolled under Protocol Amendment 6.
Abbreviations: electrocardiogram (ECG); computed tomography (CT); magnetic resonance imaging (MRI); Eastern Cooperative Oncology Group (ECOG); performance status (PS); adverse event (AE); pharmacokinetic (PK), concomitant medications (Con Meds); twice daily (BID); oral (PO); intravenous (IV).

Appendix C: Schedule of Events for Cycle 3 and All Subsequent Cycles

		Cycle 3 and all subsequent cycles	Cycle 3 and Cycle 4	Cycle 4 and subsequent cycles with Day 21 assessments	Cycle 4
Study Procedure and Day		Day 1 (± 24 hours)	Day 10 (± 72 hours)	Day 1 (± 24 hours)	Day 21 (± 7 days)
Assessments	Physical exam	X		X	
	Vital signs	X		X	
	ECOG PS	X		X	
	Labs[a]	X	X[h]	X	
	Urinalysis	X		X	
	ECG	X		X	
	Document Con Meds	X		X	
	Document AEs	X		X	
	CT/MRI[b]				X[f]
	ECHO/MUGA				X[g]
Study Drug Treatment	Tucatinib[c]	X		X	
	T-DM1[d]	X		X	
PK/Pharmacodynamics	Blood samples[i]	X[e]		X[e]	

a Blood samples for hematology, clinical chemistry (including calcium, magnesium, and phosphorus), and liver functions tests.
b CT/MRI scan of all known sites of disease and assessment of tumor burden as per RECIST 1.1. Additional imaging, such as nuclear bone scans, may also be done as appropriate at the discretion of the Investigator.
c Tucatinib is administered PO BID, on a 21-day cycle. Cycles 3–6, on Day 1 the morning dose is administered in the office.
d T-DM1 is administered IV, once every 21 days.
e Blood samples for PK analysis only through Cycle 6.
f CT/MRI performed on Day 21 of Cycle 4 and Cycle 6; thereafter every three cycles (e.g., Cycle 9, Cycle 12, Cycle 15, etc.).
g ECHO/MUGA performed every four cycles (or 90 days) only (e.g., Cycle 8, Cycle 12, etc.).
Abbreviations: echocardiogram (ECHO); electrocardiogram (ECG); multiple-gated acquisition scan (MUGA); computed tomography (CT); magnetic resonance imaging (MRI); Eastern Cooperative Oncology Group (ECOG); performance status (PS); adverse events (AE); pharmacokinetic (PK), concomitant medications (Con Meds); twice daily (BID); oral (PO); intravenous (IV).
h Blood samples for clinical chemistry and liver function tests only.
i Blood samples will not be collected to evaluate PK for patients enrolled under Protocol Amendment 6.

Appendix D: Schedule of Events for End of Study Visit and Long-Term Extension Phase

Study Procedure and Day		EOS Visit (30 days, ± 7 days after last dose of Tucatinib or T-DM1, whichever is later)	Long-Term Extension Phase (Continuation on treatment following approval of Amendment 8)
	Physical exam	X	
	Vital signs	X	
	ECOG PS	X	
	Labs[a]	X	
	Coagulation	X	
	Urinalysis	X	
	ECG	X	
	Document Con Meds	X	
	Document AEs	X	X[d]
	CT/MRI	X[b]	
	ECHO/MUGA	X[c]	

a Blood samples for hematology, clinical chemistry (including calcium, magnesium, and phosphorus), and liver functions tests.
b CT/MRI scan and assessment of tumor burden based upon RECIST 1.1 if needed (discuss with medical monitor). Additional imaging, such as nuclear bone scans, may also be done as appropriate at the discretion of the Investigator.
c ECHO/MUGA, as appropriate, if not done within previous 90 days.
d SAEs and AOIs (AST or ALT elevations that are > 3 X ULN with concurrent elevation [within 21 days of AST and/or ALT elevations] of total bilirubin > 2 X the ULN, except in patients with documented Gilbert's syndrome, asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment, any event of cerebral edema not clearly attributable to progression of disease, CTCAE ≥ Grade 3 diarrhea).
Abbreviations: echocardiogram (ECHO); End of Study (EOS); electrocardiogram (ECG); multiple-gated acquisition scan (MUGA); computed tomography (CT); magnetic resonance imaging (MRI); Eastern Cooperative Oncology Group (ECOG); performance status (PS); adverse events (AE); concomitant medications (Con Meds).

Appendix E: List of Selected Strong Inhibitors or Inducers of CYP3A4 and Their Elimination Half Lives[a, b]

Drug[c]	Half Life
clarithromycin	3–7 hours
telithromycin	10 hours
chloramphenicol	4 hours
itraconazole	21 hours single dose, 64 hours steady state
ketoconazole (systemic)	2–8 hours
nefazodone	2–4 hours
voriconazole	Dose-dependent
rifampicin (inducer)	3–4 hours
phenytoin	7–42 hours
carbamazepine	25–65 hours
barbiturates	Variable
St. John's Wort	9–43 hours

a. From FDA Website "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency).
b. Strong CYP3A inhibitors are defined as those drugs that increase the AUC of oral midazolam or other CYP3A substrates ≥ 5-fold.
c. Ritonavir, indinavir, nelfinavir, and saquinavir are also strong CYP3A3 inhibitors, but would not be used in this study as patients with known HIV are excluded.

Appendix F: List of Selected Strong Inhibitors and Inducers of CYP2C8 and Their Elimination Half Lives[a]

Drug	Half Life
Gemfibrozil	1-2 hours
Trimethoprim	8-10 hours
Montelukast	3-6 hours (drug insert)
Quercetin	< 2 hours
Rosiglitazone	16-24 hours
Lapatinib	24 hours
Rifampin (inducer)	3-5 hours

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

Appendix G: Modified RECIST 1.1 and Volumetric Response Criteria for CNS Disease

Modified RECIST 1.1 Criteria

Confirmatory scans are not required.

CNS Complete Response (CR): All of the following must be satisfied:
- Complete resolution of all CNS target and non-target lesions
- No new CNS lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST 1.1

CNS Partial Response (PR): All of the following must be satisfied:
- At least 30% decrease in the sum of diameters of CNS target lesions, taking as reference the baseline sum diameters. No progression of non-target and/or non-measurable lesions*
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST 1.1

CNS Stable Disease (SD): All of the following must be satisfied:
- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD in target lesions, taking as reference the smallest sum diameters while on study. No progression of non-target and/or non-measurable lesions*
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST

CNS Progression (PD): Patients will be considered to have PD if ANY of the following are satisfied:
- At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study, with at least a 5 mm absolute increase in the sum of all target lesions, OR
- Progression of non-target and/or non-measurable lesions*, OR

- New lesions (new lesion defined as ≥ 6 mm), OR
- New/progression tumor-related neurologic signs and symptoms (NSS) except for transient worsening lasting ≤ 14 days, OR
- Progression of systemic (non-CNS) disease as assessed by RECIST 1.1

Note: An isolated increase in steroid dose will not constitute disease progression. In this case, patients may continue on protocol therapy.

- *Note: Progression of non-measurable CNS lesions is defined as follows:
- A lesion initially at baseline ≤ 5 mm in diameter that increases to ≥ 10 mm in diameter, OR
- A lesion initially at baseline 6–9 mm in diameter that increases by at least 5 mm in diameter.

These criteria were chosen to minimize classifying subjects as having progressive disease due to MRI sampling error, given an MRI slice thickness of 5 mm.

Volumetric Response Parameters for CNS disease

CNS Complete Response (CR): All of the following must be satisfied:
- Complete resolution of all measurable (≥ 1cm diameter) and non-measurable brain metastases
- No new CNS lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST 1.1

CNS Partial Response (PR): All of the following must be satisfied:
- ≥ 50% reduction in the volumetric sum of all measurable (≥ 1 cm diameter) brain metastases compared to baseline
- No progression of non-measurable lesions
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST 1.1

CNS Stable Disease (SD): All of the following must be satisfied:
- < 50% reduction in the volumetric sum of all measurable (≥ 1 cm diameter) brain metastases compared to baseline, and not fulfilling the criteria for progressive disease

- No progression of non-measurable lesions
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST 1.1

Note: CNS lesions which were initially evaluable (≥ 1 cm diameter) at baseline and have decreased in size on trial therapy to < 1 cm diameter will continue to be assessed volumetrically for response.

CNS Progression (PD): Patients will be considered to have PD if ANY of the following are satisfied:

- ≥ 40% increase in the volumetric sum of all measurable lesions as compared to the smallest volume since protocol-based therapy was initiated, OR
- Progression of non-measurable lesions*, OR
- New lesions (new lesion defined as ≥ 6 mm), OR
- Increasing steroid requirement, OR
- New/progression tumor-related neurologic signs and symptoms (NSS) except for transient worsening lasting ≤ 14 days. OR
- Progression of systemic (non-CNS) disease as assessed by RECIST

*Note: Progression of non-measurable CNS lesions is defined as follows:

- A lesion initially at baseline ≤ 5 mm in diameter that increases to ≥ 10 mm in diameter, OR
- A lesion initially at baseline 6–9 mm in diameter that increases by at least 5 mm in diameter.