A Phase II Non-randomized Study to Assess the Safety and Efficacy of the Combination of Tucatinib and Trastuzumab and Capecitabine for Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer

NCT#: 03501979

Date: 7/28/2022

A Phase II Non-randomized Study to Assess the Safety and Efficacy of the Combination of Tucatinib and Trastuzumab and Capecitabine for Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer

Protocol Number	TBCRC049/MDACC 2017-0615
Protocol Chairs	Rashmi K. Murthy, MD, MBE Assistant Professor, Department of Breast Medical Oncology University of Texas MD Anderson Cancer Center 1155 Pressler Street, CPB 5.3450, Unit 1354 Houston, TX 77030 Email: rmurthy1@mdanderson.org Barbara J. O'Brien, MD Assistant Professor, Department of Neuro-oncology University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd, Unit 431 Houston, TX 77030 Email: bjobrien@mdanderson.org Erica Stringer-Reasor, MD The University of Alabama at Birmingham Assistant Professor, Department of Medicine Section Hematology/Oncology Email: esreasor@uabmc.edu
Collaborators	Maria Gule-Monroe, MD Jason Johnson, MD Nicholas Navin, PHD John DeGroot, MD, PHD Ben Park, MD, PHD
Statistician	Donald A. Berry, PHD University of Texas MD Anderson Cancer Center
Supporters	Seattle Genetics, Inc.
Lead Site	University of Texas MD Anderson Cancer Center
Coordinating/IND Site	University of Alabama at Birmingham
Protocol Version:	October 10, 2018 (Version 1); April 25, 2019 (Version 2); November 19, 2019 (Version 3); February 28, 2020 (Version 4) March 18, 2020 (Version 5); April 07, 2020 (Version 6), November 20,2020 (Version 7)

Table of Contents

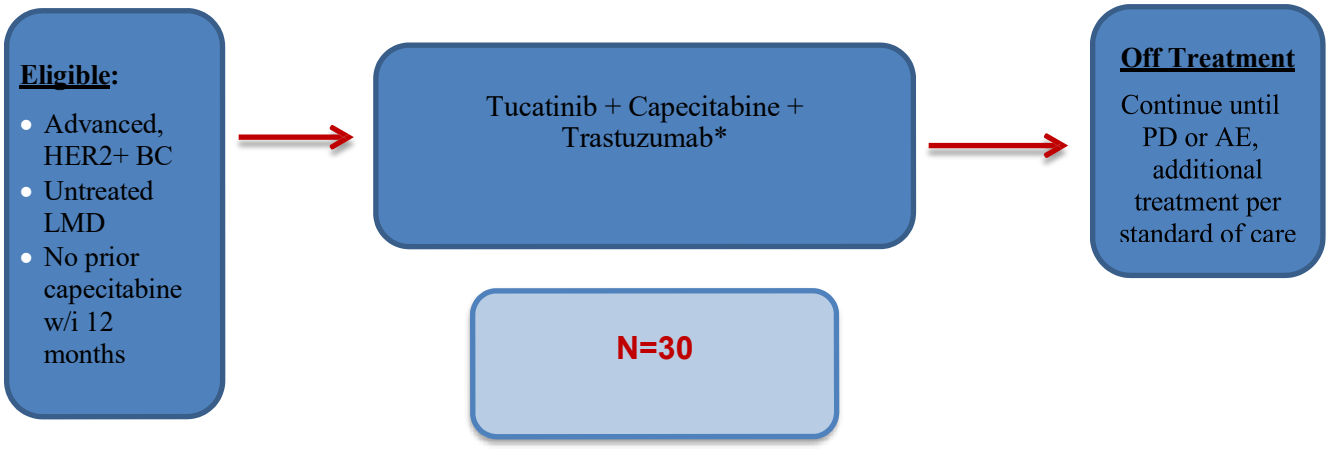
.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Activated partial thromboplastin time (aPTT)
Ado-Trastuzumab Emtansine (Kadcyla) (TDM-1)
Adverse Event (AE)
American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP)
Breast Cancer (BC)
Capecitabine (C)
Comprehensive Cancer Center (CCC)
Congestive Heart Failure (CHF)
Central Nervous System (CNS)
Case Report Form (CRF)
Cerebrospinal fluid (CSF)
Circulating tumor DNA (ctDNA)
Clinical Trials Network Monitoring Office (CTNMO)
Clinical Benefit Rate (CBR)
Computed Tomography (CT)
Creatnine (Cr)
Creatinine Clearance (CrCL)
Digital imaging and communications in medicine (DICOM)
Disease-free survival (DFS)
Electrocardiogram (ECG)
Epidermal Growth Factor Receptor (EGFR)
Extra – central nervous system (Extra – CNS)
Fluorescence in situ hybridization (FISH)
Food and Drug Administration (FDA)
Gastrointestinal (GI)
Hand foot syndrome (PPE)
Human Epidermal Growth Factor Receptor 2 (HER2)
Herceptin (Trastuzumab) (T)
Her2-neu positive breast cancer (HER2+ BC)
Hormone receptor positive (HR+)
Immunohistochemistry (IHC)
Infusion associated reaction (IAR)
Institutional Review Board (IRB)
International normalized ratio (INR)
Intrathecal (IT)
Intravenous (IV)
Karnofsky performance status (KPS)
Linear Analog Symptom Assessment – Quality of Life (LASA-QOL)
Leptomeningeal Disease (LMD)
Left Ventricular Ejection Fraction (LVEF)

Lumbar puncture (LP) Maximum concentration observed (Cmax)
Maximum tolerated dose (MTD)
Magnetic Resonance Imaging (MRI)
Metastatic Breast Cancer (MBC)
MD Anderson Cancer Center (MDACC)
MD Anderson Assessment Symptom Inventory – Brain Tumor (MDASI- BT)
Multigated acquisition scan (MUGA)
NCI Common Terminology Criteria for Adverse Event (CTCAE)
Neurologic Assessment in Neuro-oncology (NANO)
Objective Response Rate (ORR)
Ommaya Reservoir (OR)
Oral route (PO)
Overall survival (OS)
Perjeta (Pertuzumab)
Pharmacokinetic (PK)
Positron emission tomography-computed tomography (PET/CT)
Progression-free survival (PFS)
Progressive Disease (PD)
Quality of Life (QOL)
Response assessment for neuro-oncology – leptomeningeal disease (RANO-LMD)
Response evaluation criteria in solid tumors (RECIST)
Response Rate (RR)
Recommended phase 2 dose (RP2D)
Serious Adverse Event (SAE)
Stable Disease (SD)
Stereotactic radiosurgery (SRS)
Transaminases (AST/ALT)
Translational breast cancer research consortium (TBCRC)
Tucatinib (ONT-380)
Twice daily (BID)
Tykerb (Lapatinib)
Tyrosine Kinase Inhibitor (TKI)
University of Alabama at Birmingham (UAB)
Upper limit of normal (ULN)
Vascular Endothelial Growth Factor Receptor (VEGF)
Ventricular Access Device (VAD)
Whole Brain Radiation (WBRT)

1. SCHEMA



Biospecimen (blood and CSF): Please see study calendar for details

Imaging and Questionnaires: Neuroaxis imaging every 2 cycles and extra-CNS imaging every 4 cycles (or sooner if clinically indicated); MDASI-BT will be performed Day 1 of each cycle (within 72 hours prior) and LASA QOL will be performed at every 2 cycles CNS restaging visit (within 72 hours prior)

*Drug Dosing:

Tucatinib: 300 mg PO BID, Days 1-21

Capecitabine: 1000 mg/m^2 PO BID, Days 1-14

Trastuzumab: 6mg/kg IV, every 3 weeks (NOTE:If maintenance Trustuzumab not received within the prior 30days, a loading dose of 8 mg/kg should be given on C1D1

2. STUDY DESIGN/SUMMARY

Treatment strategies for patients with leptomeningeal disease (LMD) are an area of unmet clinical need in advanced HER2- positive breast cancer (HER2+ BC). The incidence of LMD is increasing, current treatments are not adequate, and prognosis is very poor. Further study is warranted and thus we propose a phase II trial to determine the efficacy of combining tucatinib (ONT-380) plus trastuzumab (T) plus capecitabine (C) in patients with metastatic HER2+ BC and LMD. The results would contribute to the field in an area of unmet clinical need. The ease of use and tolerability of tucatinib will be unparalleled and this HER2 specific inhibitor has the potential to become the first oral drug to be studied in a prospective fashion in patients with HER2+ BC and LMD. We hypothesize that combination therapy with tucatinib + T + C will improve OS in patients with metastatic HER2+ BC and LMD, for which no effective systemic therapy exists. Further, we hypothesize that this therapy will be safe and well-tolerated, will control extra-central nervous system (extra-CNS) disease, and will improve quality of life (QOL). Importantly, we will also collect and bank blood and CSF samples to assess drug bioavailability and identify candidate biomarkers which may predict response to therapy and provide better understanding of underlying mechanisms of metastasis to the leptomeninges.

3. OBJECTIVES

3.1 Primary Objective

To determine the efficacy in terms of overall survival (OS) for the combination of tucatinib plus T plus C in HER2+ BC with LMD

3.2 Secondary Objectives

3.2.1 To assess safety of the combination of tucatinib plus T plus C in HER2+ BC with LMD

3.2.2 To assess CNS progression free survival at 12 weeks.

3.2.3 To assess response rate (RR) and clinical benefit rate (CBR) (response or stable disease) in the CNS.

3.2.4 To evaluate RR and CBR of extra-CNS disease

3.2.5 To assess the impact on symptom burden and quality of life

3.3 Exploratory Objectives

3.3.1 To obtain and bank samples of blood and CSF from patients with HER2+ LMD

3.3.2 To determine bioavailability of tucatinib in the cerebrospinal fluid (CSF)

3.3.3 To assess levels of circulating tumor DNA (ctDNA) in the CSF and blood; and to correlate with response

3.3.4 To characterize the genomic profile from CSF ctDNA and to correlate with blood

ctDNA

Note: In cases where genomic information from primary and/or metastatic tissue is available, further correlations may be considered.

4. BACKGROUND AND RATIONALE

4.1 Study Disease

4.1.1 HER2-positive Breast Cancer (HER2+)

Approximately 20% of breast cancer (BC) overexpresses the human epidermal growth factor receptor 2 (HER2) indicating a more aggressive subtype. [1] HER2 is a trans-membrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Prior to the development of HER2-targeted therapies, the prognosis of HER2-positive patients was among the worse for all breast cancer patients. This has changed with the approval of trastuzumab(Herceptin®) in 1998 and more recently with lapatinib, pertuzumab, and ado-trastuzumab emtansine (T-DM1).

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.[2-6] Trastuzumab (T), a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, was the first anti-HER2 agent approved by the United States Food and Drug Administration (FDA) for use in the treatment of HER2+ breast cancer, and remains the backbone of treatment in the adjuvant and first-line metastatic settings, usually in combination with a taxane.

The approval of trastuzumab was followed by the approval of lapatinib (TYKERB®), a small molecule tyrosine kinase inhibitor (TKI) that targets both HER2 and epidermal growth factor receptor (EGFR).[7-9] In addition, pertuzumab (PERJETA®), another antibody-based therapy which binds to HER2 at a site different than trastuzumab and inhibits HER2 dimerization, has also been approved for use in combination with trastuzumab and docetaxel as first-line therapy for patients with HER2+ metastatic disease.[10,11] Finally, ado-trastuzumab emtansine (T-DM1; Kadcyla®), an antibody-drug conjugate, was approved by the FDA in February 2013, for patients who progress following prior therapy with trastuzumab and a taxane.[12]

Current standard of care for metastatic HER2+ BC is evolving, and depends in part upon which treatment patients received previously. The current standard of care for patients with HER2+ metastatic breast cancer (MBC) consists of treatment with pertuzumab plus trastuzumab and a taxane as first-line treatment, followed by T-DM1 in the secondline.[13,14] Treatment options for patients who progress after treatment with both pertuzumab and T-DM1 remain relatively limited. There is no standard sequencing in later lines, with better treatment options needed and clinical trials often being preferred.

4.1.2 Ongoing Medical Need in HER2+ Breast Cancer

Despite the improvements in outcomes for HER2+ BC, 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 pertuzumab and T-DM1.Treatment failures may result from primary or acquired resistance to HER2 blockade.[15-18] 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 in metastatic disease.[7,19] In particular, the combination of a small molecule TKI with an antibody-based therapy may help overcome resistance to antibody-mediated inhibition. Lapatinib, a dual epidermal growth factor receptor (EGFR)/HER2 oral TKI, is approved for use in combination with capecitabine in patients with metastatic disease who have progressed following prior trastuzumab and taxane therapy, or in combination with letrozole in patients with hormone receptor positive (HR+), HER2+ metastatic disease.[9,20,21] Lapatinib is also approved in combination with trastuzumab alone with efficacy noted in heavily pretreated patients.[7,22] Use of lapatinib, however, has been limited by the anti-EGFR/human epidermal growth factor receptor 1 (HER1) activity of the drug, which results in toxicities such as rash, diarrhea, and fatigue. Therefore, there is a need and enthusiasm for a more selective molecule inhibitor of HER2, such as tucatinib that could be combined with other anti-HER2 therapies to improve clinical outcomes and limit toxicities.

Recent data suggest that the incidence of first relapse occurring in the central nervous system (CNS) is increasing in patients who have received trastuzumab-based adjuvant therapy. [23] Approximately 30% of HER2+ patients with metastatic disease will develop CNS metastases.[23-27] The increasing prevalence of CNS metastases in HER2+ BC patients may be due to several factors. First, HER2+ BC appears to display tropism for the CNS. Second, with better control of non-CNS disease, patients may be living longer; subsequently CNS metastases 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.

Treatment options for CNS metastases are limited. Treatment of parenchymal CNS metastases currently consists of use of whole brain or stereotactic radiation, or surgical resection. Patients may also receive chemotherapy alone, or capecitabine and lapatinib, although response rates are generally modest.[28] The development of HER2 targeted therapies with clinical benefits in both CNS and extra-CNS sites could lead to improved clinical outcomes as well as quality of life by avoiding or delaying the use of local therapies, such as surgery or radiation that may cause neurocognitive impairment.

4.1.3 Leptomeningeal Disease

Leptomeningeal disease (LMD) refers to the seeding of tumor cells to the leptomeninges and dissemination in the cerebrospinal fluid (CSF), which is located

between the pia and arachnoid and within the ventricular system, by metastatic tumor cells.[29] The mechanism of this seeding is not well understood. Synchronous or pre- existing parenchymal CNS metastases are common in patients with LMD. Classically, LMD presents with multifocal neurological deficits and progressive neurologic decline. LMD is diagnosed based on clinical findings, brain and spine imaging findings, and/or CSF cytology. As newer therapies increase the life span of cancer patients, and as the sensitivity of imaging studies improves, more patients with solid tumors are being diagnosed with this generally late complication of cancer. As more targeted therapies are developed for metastatic HER2+ breast cancer, the incidence of LMD may increase with better treatments and overall longer survival of these patients. In patients with a diagnosis of LMD and HER2+ BC, the median OS from time of LMD diagnosis to death is 4.4 months.[30,31] Recent data from a retrospective study from a second large institution showed a survival time of

5.2 months from the time of LMD diagnosis.[32] Despite the poor prognosis, there is no standard of care treatment for LMD. The current management of LMD utilizes a multidisciplinary approach to try to penetrate the blood brain barrier and in an attempt to thoroughly treat the entire neuroaxis. Treatments may include external beam radiotherapy, and systemic and/or intrathecal (IT) chemotherapy. There have been few clinical trials directly addressing LMD and data with regard to PFS and RR is limited, as there are no standardized parameters for determining response to treatment in LMD.[33-38] There is an ongoing clinical trial that is evaluating IT trastuzumab for LMD in HER2+ Breast Cancer (NCT01325207) and has recently completed accrual (results are pending). Continued investigations are required to improve the long-term outcome of patients with LMD and to minimize the potential toxicities of treatment. Future advances in the development of systemic therapies that penetrate the CNS and recognition of molecular changes that allow or cause CNS seeding may result in improvement in outcomes. Additionally, the identification of subgroups of patients who may be predicted to develop LMD will be useful for the implementation of potential preventative measures

4.2 Study Drugs

4.2.1 Tucatinib (formerly Array-380, ONT-380)

4.2.1.1 Overview : Product Description and Mechanism of Action

Tucatinib is an oral, potent, HER2-specific TKI that is being developed by Seattle Genetics, as a novel treatment for HER2+ BC. Unlike other small molecule inhibitors of HER2 that are currently either approved or in development for treatment of HER2+ BC, 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 minimizing many of the side effects associated with dual inhibitors, including skin and gastrointestinal (GI) toxicity.

4.2.1.2 Tucatinib: Preclinical

Tucatinib has nanomolar activity against purified HER2 enzyme and was approximately 500-fold selective for HER2 versus EGFR in cell-based assays,[39] properties that could potentially translate clinically into a favorable toxicity profile in comparison to less specific HER2 TKIs that also inhibit EGFR.[40-42] tucatinib also significantly inhibited phosphorylation of truncated HER2 (p110/p95), which is thought to be associated with trastuzumab resistance in HER2+ breast cancer. Nonclinical in vivo pharmacology studies of tucatinib as a single agent, as well as in combination with standard-of-care therapies, demonstrated significant tumor growth inhibition in HER2-dependent tumor xenograft models, including models of breast cancer.[39,43] tucatinib treatment also significantly enhanced survival in HER2-driven intracranial tumor xenograft models.[44] Combined, these preclinical data supported the rationale for the first- in-human Phase 1 study of tucatinib.

4.2.1.3 Tucatinib Clinical Trial Summary

The first in human phase I trial of tucatinib demonstrated an acceptable safety profile and established the maximum tolerated dose.[45] As of June 14 2016, tucatinib has been investigated in six clinical studies. Three studies have been completed, including two completed Phase 1 formulation studies in healthy subjects (Appendix A). The initial phase I single-agent study showed objective responses with no treatment-related grade 3 diarrhea (Appendix A). Three other clinical trials are active to examine the safety and efficacy of tucatinib when combined with other anti-

HER2 therapies (Appendix B). Currently, an international Phase 2 randomized, double-blinded, placebo-controlled study of tucatinib in combination with trastuzumab and capecitabine in patients with pretreated, unresectable locally advanced or metastatic HER2+ MBC (NCT02614794), recently named HER2CLIMB is actively recruiting patients.[46] Patients with or without brain metastases are eligible and the primary endpoint is bi-compartmental progression free survival (PFS) based on assessment of both CNS and extra-CNS disease.[47]

4.2.1.4 Phase I Single-Agent Tucatinib Study (ARRAY-380-101)

In a phase I, open-label study, tucatinib was studied to determine the maximum tolerated dose (MTD) and to assess safety, pharmacokinetics, and preliminary antitumor activity with HER2- positive advanced solid tumors, and with an expansion cohort of patients with HER2+ MBC. Fifty patients received tucatinib, 33 in the dose-escalation and 17 in the expansion; 43 patients had HER2+MBC. 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.

Dose-limiting toxicities of increased transaminases occurred at 800 mg BID, thus 600 mg oral route(PO), twice daily(BID) was established as the MTD. Thirty- one patients received doses at or above the MTD of 600 mg BID. Common adverse events (AEs) were usually Grade 1/2 in severity and included nausea (56%), diarrhea (52%), fatigue (50%), vomiting (40%) and constipation, pain in extremity and cough (20% each). The half-life of tucatinib was 5.38 hours and increases in exposure were approximately dose proportional. 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 was partial response (PR) in 5 patients (14%), stable disease (SD) in 18 patients (51%), and progressive disease (PD) in 12 patients (34%). Tumor shrinkage was seen in both skin and visceral lesions, including liver metastases. The manuscript has been accepted and is pending publication.[48]

4.2.1.5 Phase IB, Combination Tucatinib with and without capecitabine and trastuzumab (ONT380-005)

In a phase IB study, with 3+3 dose escalation study design, tucatinib combined with 1) C alone, 2) T alone, 3) C and T was evaluated to assess safety, tolerability and maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D). The study was initiated in December 2013 and enrollment completed (n=60) in December 2015, with patients (n=15) still active on study. As of June 14, 2016, the combination of tucatinib with C + T shows anti-tumor activity in patients treated with a median of three prior HER2 agents including pertuzumab with an objective response rate (ORR) of 58% (14/24) with responses seen in patients with and without brain metastases. Also, an encouraging duration of treatment was noted in the high risk population with a median of 6.3 months.

Additionally, the combination was well tolerated with majority of AEs being grade 1 without need for dose reductions of the study drug. There was also encouraging data in the tucatinib doublet arms with an ORR of 40% in the tucatinib + Trastuzumab arm. Updated efficacy results from the phase IB trial were recently published and further study of the triplet combination is ongoing in the randomized phase 2 study (HER2CLIMB; NCT02614794). [46,49]

4.3 Standard of Care Agents

4.3.1 Trastuzumab (T)

4.3.1.1 Summary

T or its biosimilar: Ogivri, Herzuma ,Ontruzant ,Trazimera Kanjinti)is a humanized anti-HER2 antibody that binds to subdomain IV of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2 cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand- independent, HER2-mediated mitogenic signaling. [50]

4.3.1.2 Efficacy

The clinical benefit of T in women with MBC has been demonstrated in multiple clinical studies. One large open label randomized Phase 3 study showed that, compared to chemotherapy alone, the addition of T significantly increased PFS, ORR, median duration of response, and OS.[2] Based on these data, trastuzumab was approved by the FDA for use in HER2+ metastatic BC in combination with paclitaxel for first-line treatment and as a single agent for patients whose cancers progressed after prior chemotherapy for metastatic disease. Since this initial pivotal clinical trial, data have emerged demonstrating efficacy of trastuzumab in the metastatic setting combined with a variety of chemotherapeutic agents, as well as other HER2 targeted agents, including capecitabine.[13] Data support the use of trastuzumab in multiple lines of treatment in the setting of metastatic disease, even after failure of first line regimens that included trastuzumab and a taxane.[51]

4.3.1.3 Safety

The most common adverse reactions in patients receiving trastuzumab in the adjuvant and metastatic BC setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of trastuzumab treatment include congestive heart failure (CHF), significant decline in left ventricular ejection fraction (LVEF), severe infusion reactions, and pulmonary toxicity. Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. T can also cause asymptomatic decline in LVEF. There is a 4- to 6-fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving T as a single agent or in combination therapy compared with those not receiving T. The highest absolute incidence occurs when T is administered with an anthracycline.

4.3.2 Capecitabine (C)

4.3.2.1 Summary

C is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis.

4.3.2.2 Efficacy

The clinical benefit of C in women with MBC has been demonstrated in multiple clinical studies.

Use of capecitabine as monotherapy was evaluated in patients with metastatic breast cancer at a dose of 1000mg/m2 PO BID with demonstrated efficacy and safety.[52] C has also been approved to be used in combination with the oral HER2/EGFR inhibitor lapatinib at a dose of 1000 mg/m2 PO BID based on the results of studies showing an increase in PFS by adding lapatinib to capecitabine when compared to C alone.[21] Also, the addition of capecitabine to trastuzumab in patients who had previously progressed on trastuzumab showed an improvement in efficacy when compared to capecitabine alone.[7] C has also been used in combination with the oral HER2/EGFR inhibitor lapatinib in the treatment of brain metastasis, with response rates noted in small single-arm studies.[53]

4.3.2.3 Safety

The most common adverse reactions in patients receiving capecitabine in the MBC setting include palmar-plantar erythrodysesthesia, diarrhea, nausea, stomatitis, vomiting, fatigue, abdominal pain, and constipation. Diarrhea with C may sometimes be severe, and patients with diarrhea must be closely monitored, and given fluid and electrolyte replacement if they become dehydrated. In addition, less commonly, cardiotoxicity may occur with capecitabine, including myocardial infarction/ischemia, angina, dysrhythmia, cardiac failure, sudden death, electrocardiogram(ECG) changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

4.4 Rationale for the Combination

4.4.1.1 Tucatinib and CNS Activity

As previously discussed, one of the key challenges in HER2 MBC is development of effective tolerable therapies that treat CNS disease. In support of this concept, data was presented from patients in the two ongoing phase Ib combination studies (+TDM1 and +/- C +/-T) (NCT02025192; NCT01983501) with response-evaluable CNS metastases treated with tucatinib 300mg PO BID demonstrating good overall tolerability and evidence of CNS activity. [54,55]

This early clinical activity of tucatinib against HER2 positive disease with brain metastases will be further studied and confirmed in the ongoing randomized phase 2 study ((HER2CLIMB; NCT02614794).[46] In addition, there is an ongoing clinical trial evaluating different doses of tucatinib in combination with trastuzumab (NCT01921335); results were recently reported showing early signs of clinical benefit in the CNS.[56]

4.5 Symptom Burden and Quality of Life Assessment

Symptom burden and quality of life (QOL) assessments will be conducted throughout the study. Symptom burden will be assessed using the MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT), a validated patient questionnaire at study initiation and at each cycle visit (Q21 days) (Appendix E). The 22 item MDASI-BT demonstrated validity and reliability in patients with primary brain tumors and has also be utilized in the LMD patient population.[57] The questions address the severity of symptoms caused by disease or by treatment and how they affect normal function and interfere with a patient's life. This is a self-reporting instrument that can be used to identify symptom occurrence throughout the disease trajectory and to evaluate interventions designed for symptom management; the questionnaire takes approximately 10-15 minutes to complete. Quality of life will be assessed using the Linear Analog Scale Assessment Quality of Life

(LASA QOL) (Appendix F) and will be completed at study initiation and at each restaging visit (Q42 days).

4.6 Correlative Science Background

Integration of CSF and blood sample collection into this phase II clinical trial will help us to potentially achieve multiple translational advances. Almost no information exists about the underlying biology and molecular characteristics of tumor cells in CSF in patients with LMD.[58] The gold standard test for diagnosis and response assessment in LMD, the identification of malignant cells on CSF cytology, is less than ideal with several key limitations, including poor sensitivity, which makes diagnosis and response assessment difficult.[29] A more uniform and precise method for assessment of disease status, and response to therapy in LMD is needed. New technology and techniques allow for isolating and characterizing blood circulating tumor DNA (ctDNA) and early studies indicate the potential for identifying ctDNA in the CSF.[59-61] This has potential for characterizing LMD and providing insights into molecular features that promote CSF metastasis and survival in the leptomeninges.

We will obtain and bank samples from the blood and CSF from each patient enrolled on the study.

To determine the CSF bioavailability of tucatinib in patients with LMD, we will conduct pharmacokinetic (PK) studies in the CSF, with parallel assessments in the blood, on day 1 & 2 of cycles 1 and 2. These collections will occur in the first 15 patients enrolled. We intend to collect parallel samples at time 0 (baseline), 2-3h(T-max), and 5-7h (T ½) following administration of tucatinib on Day 1. In addition, collection is recommended on Day 2, 24h (trough)(day 2) following administration of the dose of tucatinib.

We will attempt to identify and evaluate ctDNA levels in the banked CSF and correlate to ctDNA levels in the blood. This would explore whether we can use CSF and/or blood monitoring to follow tumor burden and identify response to treatment. Of note, a pilot study is currently underway at the University of Texas MD Anderson Cancer Center to attempt to assess levels of ctDNA in CSF and blood samples of patients with metastatic breast cancer and LMD.

Additionally, we aim to collect genomic information from the primary and/or metastatic disease sites as available. Correlation of these genomic profiles with the genomic profile obtained from the CSF and blood ctDNA may enable better understanding of the molecular mechanisms behind LMD metastasis.
In subsequent studies, we will propose to evaluate potential biomarkers for response: HER2 mutation, vascular endothelial growth factor (VEGF) levels, cytokines, chemokines, IL-6, IL-8, IMP-9, and other proteins.

4.7 Summary

Treatment strategies for patients with LMD are an area of unmet clinical need in advanced HER2+ BC. As more targeted therapies are developed for metastatic HER2+ BC, the incidence of LMD may continue to increase as a late complication. Prognosis is poor and there are no standard therapeutic options. Future advances in the development of systemic targeted therapies that are well- tolerated and penetrate the CNS may result in improvement in outcomes.

Tucatinib has been well-tolerated and has demonstrated single-agent and combinatory anti-tumor activity, including partial responses in heavily treated patients and those with CNS metastases. Notably, toxicities associated with dual EGFR/HER2 inhibitors have been uncommon. Based upon the preclinical and clinical profile observed to date, tucatinib may address unmet needs in the treatment of patients with HER2+ BC and LMD, and can be combined with other HER2-directed therapies and cytotoxic chemotherapies.

We propose a phase II trial to determine the safety, tolerability, and efficacy of combining tucatinib plus T plus C in patients with metastatic HER2+ BC and LMD.

The results would contribute to the field in an area of unmet clinical need. The ease of use and tolerability of tucatinib will be unparalleled and this HER2 specific inhibitor has the potential to become the first oral drug to be effective and studied in a prospective fashion in patients with metastatic HER2+ BC and LMD. The frequent collection of CSF samples (as part of typical clinical practice) in a study such as this provides translational scope to characterize potential biomarkers for diagnosis and response assessment and for recognition of molecular changes that cause CNS seeding.

5. PARTICIPANT SELECTION

5.1 Inclusion Criteria

5.1.1 Men and women, age ≥ 18 years at time of consent

5.1.2 Histologically proven metastatic infiltrating carcinoma of the breast that is HER2 positive – Immunohistochemistry (IHC) 3+ and/or Fluorescence in situ hybridization (FISH) ratio > 2.0, or average HER2 copy number > 6.0 signals per cell or per current ASCO-CAP (American Society of Clinical Oncology – College of American Pathologists) or NCCN (National Comprehensive Cancer Network) guidelines. (NOTE: HER2 testing may be performed on primary and/or metastatic site; Any estrogen and progesterone [ER/PR] status is allowed.)

5.1.3 Evidence of leptomeningeal disease (LMD) as diagnosed by a) presence of malignant cells in CSF (+CSF cytology) and/or b) Magnetic Resonance Imaging (MRI) evidence of LMD, plus clinical signs and/or symptoms. NOTE: Measurable extra- CNS disease is not required (Appendix K). Note: Patients who have MRI evidence of focal LMD with negative cytology and no symptoms are not eligible for enrollment.

5.1.4 Performance status: Karnofsky Performance Status ≥50 or Eastern Cooperative Oncology Group (ECOG) ≤ 3 (see Appendix C)

5.1.5 Patient is able and willing to undergo study-required testing, including:

- Contrast-enhanced MRI (See *MRI brain and spine acquisition manual*). Note: If patient's have implants in place that are MRI incompatible, these must be removed prior to enrollment.
- Placement of an Ommaya reservoir (or other ventricular access device (VAD)). Note: This is mandatory for the first 15 patients enrolled onto the protocol.In the second stage, this is strongly recommended per protocol. If a patient cannot or

chooses not to undergo Ommaya placement or other VAD in the second stage, the patient will be allowed to enroll.

- Evaluation by medical oncologist at baseline and at every cycle (required)
- Evaluation by neurologist/neuro-oncologist at baseline and at every cycle (strongly recommended); if this is not possible at a site, a medical oncologist may per perform the protocol specified evaluations at each visit.

5.1.6 Patients who are on steroids due to CNS disease or LMD diagnosis, should be on a stable dose for at least 5 days prior to registration.

5.1.7 Prior treatment allowances are as follows:

- >14 days since last dose of any previous endocrine therapy, chemotherapy, trastuzumab or other antibody-based therapy.

NOTE: If patients have been previously receiving trastuzumab on a weekly basis (at a dose of 2mg/kg), only a 7 day washout will be required.

- > 14 days or five half-lives since previous treatment with any experimental agent, whichever is greater
- Cumulative dose of doxorubicin > 360 mg/m2 or previous treatment with another anthracycline with cumulative dose equivalent to > 360 mg/m2 doxorubicin is not allowed.
- Patients must not have received any therapy specifically directed at LMD, including prior radiation for bulky/diffuse LMD or intrathecal therapy for LMD.
- Patients with hx of treated parenchymal brain metastasis or new/active concurrent parenchymal brain metastasis are allowed on trial.
    - Previously treated or progressive parenchymal brain metastases allowed
        - Washout from WBRT = 14 days
        - Washout from focal radiotherapy (SRS/GK) = 7 days
    - Concurrent new parenchymal brain metastasis
        - Untreated new brain metastasis not needing urgent local therapy may proceed on study treatment
            - *It is strongly encouraged to defer WBRT where possible*
        - If lesions are large and require urgent local therapy
            - Washout from WBRT = 14 days
            - Washout from focal radiotherapy (SRS/GK) = 7 days
                - *It is strongly encouraged to defer WBRT where possible*
- Radiotherapy:
    - Patients may not receive radiotherapy concurrently with the study drug.
    - Patients must not have received whole brain radiotherapy (WBRT) for parenchymal metastases within the last 2 weeks (14 days) or focal CNS radiotherapy/stereotactic radiosurgery (SRS) within 1 week (7 days) prior to

- first dose of study drug. (See 5.1.7 regarding patients with parenchymal brain metastasis)
- Radiation for the purpose of palliation in the setting of a painful bone or dural metastasis while on study treatment can be allowed with hold of treatment at the discretion of the treating physicians.

5.1.8 All toxicity related to prior cancer therapies must have resolved to ≤ Grade 1, with the following exceptions: alopecia; neuropathy, which must have resolved to ≤ Grade 2; and CHF, which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely. Must be without significant systemic illness (e.g. infection unresponsive to treatment after 7 days)

5.1.9 Adequate hematologic, liver, and renal function, as follows:

- Hemoglobin ≥ 9 g/dL
- ANC ≥ 1000 cells/µL
- Platelets ≥ 100,000/µ
- Total bilirubin ≤ 1.5 X ULN, unless a known history of Gilbert's disease (≤3 X ULN)
- Transaminases (AST/SGOT and ALT/SGPT) ≤ 2.5X ULN (< 5 X ULN if liver metastases are present)
- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 X ULN
- Creatinine clearance (CrCL) ≥ 50 mL/min

5.1.10 Left ventricular ejection fraction (LVEF) must be within institutional limits of normal as assessed by ECHO or MUGA documented within 4 weeks prior to enrollment on the study.

5.1.11 Able to understand the study requirements and document informed consent indicating his/her awareness of the investigational nature and the risks of this study.

5.2 Exclusion Criteria

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

5.2.2 Patient is pregnant or is breastfeeding. Note: If female and of child-bearing potential (females who are not surgically sterile or who have had a period in the last 12 months), has negative pregnancy test within 7 days prior to treatment. 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.

5.2.3 History of allergic reactions to compounds of similar chemical or biological composition to capecitabine (Group A only), trastuzumab or tucatinib, except for a history of Grade 1 or Grade 2 infusion related reaction to trastuzumab, that has been

successfully managed.

5.2.4 Known to be HIV positive, or a carrier for Hepatitis B and/or Hepatitis C (whether active disease or not)

5.2.5 Known liver disease, autoimmune hepatitis, or sclerosing cholangitis

5.2.6 Inability to swallow pills or any significant gastrointestinal diseases, which would preclude adequate absorption of oral medications
Use of a strong CYP2C8/CYP3A4 inducer or inhibitor within three elimination half-lives of the inducer or inhibitor prior to the start of study treatment (Appendix D).
Note: Concomitant use of tucatinib and sensitive CYP3A substrates should be avoided (see Appendix D Table 1).

5.2.7 Known impaired cardiac function or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy or congestive heart failure. Note: Patients with hypertension must have controlled disease defined as systolic blood pressure < 150 mmHg and/or diastolic blood pressure < 100 mmHg on antihypertensive medications.

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

5.2.9 Patient with known dihydropyrimidine dehydrogenase deficiency

5.2.10 Previous treatment with tucatinib.

5.2.11 Previous treatment with capecitabine within 12 months prior to study registration

5.2.12 Prior history of other cancer (except non melanoma skin, cervical intraepithelial neoplasia) with evidence of disease within the last 5 years.

5.3 Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined. This trial is open to the accrual of men and women.

6. REGISTRATION PROCEDURES

6.1 Oversight

The University of Alabama at Birmingham (UAB) in Birmingham, AL will be the overall study sponsor, primary IRB of record, and coordinating center for this study. Dr. Erica Reasor at UAB will hold the IND for this study. Dr. Erica Reasor will serve as TBCRC Co-Chair for this study along with Dr. Rashmi Murthy and Dr. Barbara O'Brien from MD Anderson who have scientifically developed this study. All three protocol chairs will have key input on the medical decisions (i.e. eligibility questions, toxicity management, and response assessments) for the duration of the trial though may share and/or designate these responsibilities based upon type of questions (e.g., medical oncology vs. neurologic nature) or availability during the course of the study.

6.2 Guidelines for Coordinating Institution

The Clinical Trials Network Monitoring Office (CTNMO) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under good clinical practice conditions at participating sites to achieve timely study subject enrollment.
Once a study subject has been screened and deemed eligible for study entry by the participating site, a study-specific study subject eligibility checklist, a copy of the dated and signed consent form, and corresponding source documentation are faxed to the participating site study coordinator for eligibility verification. Subsequently, a study- specific number is assigned to the study subject and sent to the participating site. Finally, a patient registration form is completed and faxed by the CTNMO site to the participating site coordinator for clarification or correction. Once the participating site addresses queries, any corrected data forms or copies of corrected source documentation are faxed to the CTNMO.

Prior to accepting the registration, the registration office will verify the following:

- Institutional review board (IRB) approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- Pre-treatment tests and procedures must be completed within the guidelines specified in the protocol including assessment of baseline symptoms
- Study drugs availability on site

6.3 Guidelines for Other TBCRC Institutions

Eligible participants will be entered on study centrally at UAB by the StudyCoordinator or designee. Once a patient is identified as a candidate for the trial the investigator or his/her designee will contact UAB CTNMO registration office (Tel: 205- 975-5387, Fax: 205-975-9875) prior to obtaining informed consent to verify treatment availability.

Registration will be completed upon submission of documentation of eligibility to the registration office.

The registration procedures are as follows:

1) Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2) Complete the protocol specific UAB eligibility checklist using the eligibility assessment documented in the participant's medical/research record. To be eligible for registration to the study, the participant must meet all inclusion and exclusion criteria as described in the protocol and reflected on the eligibility checklist.
3) Fax the eligibility checklist(s) and all pages of the consent form(s) to UAB CTNMO (Attn: Pam Dixon) at 205-975-9875.
4) The registrar will validate eligibility and register the participant on the study.
5) An email confirmation of the registration will be sent to the protocol chairs, site PI, site study coordinator(s), treating investigator(s) and registering person

6) Immediately following the registration.
7) Patient can proceed with treatment.

Please contact the lead study coordinator and/or registrar at 205-975-5387 with any questions regarding this process.

Note: All registration materials will be provided to each site by the UAB CTNMO at the site initiation visit. Turnaround time on registration will be same day.

Participants MUST be registered with the Coordinating Institution prior to the start of protocol treatment.

Following registration, participants should begin protocol treatment within 10 days. Issues that would cause treatment delays should be discussed with the protocol chairs and site principal investigator. If a participant does not receive protocol therapy following registration within allowed time period, the participant may be determined by the protocol chairs or site PI to become ineligible and cancelled from the study. Any requests for eligibility exceptions and/or deviations must be approved by the protocol chairs prior to execution. All enrolled patients will need evaluation at study start and with each cycle by a medical oncologist and a neuro-oncologist/neurologist. If there is a barrier or lack of access to a neuro-oncologist/neurologist at any given site, a medical oncologist may perform all protocol specified evaluations.

Note: The decision to enroll a patient in this study will be made following a discussion by members of the local multidisciplinary team and this should be documented in the medical record.

7. AGENT ADMINISTRATION AND EXPECTED TOXICITY

7.1 Overview

Subjects in the study will receive combination treatment with tucatinib + capecitabine + trastuzumab on an every 21 day cycle.

Tucatinib will be taken at 300 mg PO BID, starting with cycle 1, Day 1. Capecitabine will be taken at 1000 mg/m2 PO BID on days 1-14 of a 21-day cycle, starting on Cycle 1, Day 1. Trastuzumab will be given as a loading dose of 8 mg/kg IV on Cycle 1, Day 1, and then at 6 mg/kg IV once every 21 days, starting with Cycle 2 Day 1.

For patients who are continuing trastuzumab treatment from the prior regimen, the loading dose will be deferred and they will receive the standard 6mg/kg dose with cycle 1 of study treatment. These patients will receive trastuzumab at 6 mg/kg each cycle, starting at Cycle 1 Day 1. Trastuzumab may alternately be given on a weekly basis at 2 mg/kg IV q 7 days. Trastuzumab infusion rates will be per institutional guidelines.

7.2 Sequence of Administration

Sequence of treatment for cycles 1-2 is recommended as follows to coordinate with PK assessments for the first 15 patients enrolled with OR or VAD in place:

1) CSF and blood collections for PK analysis at time 0.
2) 1st dose of tucatinib (Recommend in the AM to allow time for subsequent PK collections throughout the day).
3) CSF and blood PK collections at 2-3h and 5-7h, after the dose of tucatinib. If trastuzumab infusion is not possible to be organized on the same day after PK collection, then it may be deferred to Day 2 of the cycle at the discretion of the treating physician. Additionally, capecitabine may be administered in conjunction with tucatinib on day 1 or its initiation may be deferred to Day 2 at the discretion of the treating physician. Note: Regardless of start date of capecitabine, patients should intend to complete the 14 day course per cycle.
4) 2nd dose of tucatinib (can be taken by the patient at home).
5) On Day 2, it is strongly encouraged to obtain trough PK CSF and blood collections at 24H (prior to 3rd dose of tucatinib)

Sequence of treatment for cycles 3 and beyond in patients with OR will be per the treating physician's guidance.

Sequence of treatment will be per the treating physician's guidance for patients without an OR in place or those who will not have PK assessments.

7.3 Handling of Missed Doses

If doses of the oral medications (capecitabine, tucatinib) are missed or vomited, they should not be retaken. Patients should continue with the next scheduled dose.

7.4 Study Drug Accountability

Tucatinib used during the course of the study should be handled according to the provided instructions. Tucatinib is to be tracked and documented from the time of receipt at the site, through patient dosing, and until returned to the sponsor or designee for destruction. All supplies, including partially used or empty bottles, should betracked.

Each site designee will conduct drug accountability monitoring during the course of the study and will conduct final drug accountability monitoring at site closure. All used and unused tucatinib bottles should be handled according to the provided instructions. In addition, drug compliance will be documented in the form a drug diary by each subject (Appendix J).

7.5 Study Agents

7.5.1 Capecitabine

Capecitabine is approved by the FDA and is an oral drug available via a commercial source. Capecitabine should be prepared and administered per instructions in the package insert. Capecitabine will be administered orally under the direction of the treating physician. Per package insert, it is recommended that capecitabine be administered with food. Capecitabine should be stored according to the package insert.

Risks Associated with Capecitabine:
Risks associated with Capecitabine include but are not limited to diarrhea,

coagulopathy, cardiotoxicity, hand-and-foot syndrome (PPE), and hyperbilirubinemia. Please see package Insert/national prescribing information for more details.

Management of capecitabine toxicities may require temporary interruption, dose reduction, or treatment discontinuation with capecitabine as per guidelines in Section 8.

7.5.2 **Trastuzumab**

Trastuzumab is approved by the FDA and is available via a commercial source.

Trastuzumab should be prepared and administered per instructions in the package insert. Trastuzumab will be administered IV under the direction of the Investigator.

Trastuzumab should be stored according to the package insert.

Risks Associated with Trastuzumab:

Risks associated with trastuzumab include but are not limited to fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, myalgia, and CHF. Please see the Trastuzumab® SmPC or Package Insert/national prescribing information for more details. Management of increased left ventricular dysfunction, pulmonary toxicity, or infusion reactions may require temporary interruption or treatment discontinuation of trastuzumab as per guidelines provided in the package insert as well as in Section 8.

7.5.3 **Tucatinib** (ONT-380)

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

Chemical Name: (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6- (4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength for PO. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidine-vinyl acetate copolymer (PVP-VA), which is then combined with standard pharmaceutical excipients and compressed into tablets.

Tucatinib tablets in a 50mg dosage strength will also be provided for any dose reductions needed.

Each tucatinib tablet contains either 150mg or 50 mg of active ingredient. Complete dosing instructions will be provided to study patients by the pharmacist or treating physician at each study site.

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

Bottles of tucatinib drug product (tablets) are to be stored under refrigeration (2 to 8°C). Drug is required to be maintained in cold packs (e.g., coolers) after being dispensed to the subject; the cold packs will be provided by each site. The subject will be instructed to place drug in the

refrigerator as soon as possible. Refer to the investigator's brochure for additional details.

Risks Associated with the tucatinib in combination with trastuzumab alone and with trastuzumab and capecitabine:

Overall, tucatinib has been well tolerated in clinical trials to date. The most frequent AEs seen with tucatinib have been mild to moderate in severity, and toxicities associated with dual EGFR/HER2 inhibitors such as Grade 3 diarrhea and rash have been uncommon.

The most likely potential overlapping toxicities seen for the combination of tucatinib plus capecitabine and trastuzumab in this study include GI toxicity, such as nausea, constipation, and diarrhea, as well as elevation of liver function tests and fatigue. In 13 patients treated in study ONT-380-005 using this three-drug combination (at a dose of tucatinib dose of 300 mg BID), the most common AEs (occurring in >15% patients) were diarrhea, nausea, fatigue, PPE, vomiting, constipation, dizziness, and headache. The majority of these AEs have been Grade 1 or Grade 2. Grade ≥3 events seen with the three-drug combination and considered related to tucatinib included reversible Grade 3, AST/ALT elevation (n=1) and Grade 4 cerebral edema with related events of Grade 3 dysarthria and Grade 3 visual field deficit (n=1). Similar AE profiles have also been seen in patients treated with tucatinib 300 mg PO BID plus capecitabine alone (n=7) and tucatinib 300 mg PO BID plus trastuzumab alone (n=13), although the combination of tucatinib plus trastuzumab was not associated with PPE.

While decreased left ventricular function and interstitial lung disease (ILD) have not been reported with tucatinib, these events have been seen with other HER2-inhibitors, and therefore represent a potential risk. Other theoretical risks exist which have not yet been seen in patients treated with tucatinib.

Patients will be closely monitored for occurrence of GI and liver toxicity, and cardiac function will also be monitored closely. The specific safety plans for monitoring for cardiac toxicity and hepatotoxicity are outlined in Section 8.

In addition, patients will be closely monitored throughout the study for the occurrence of any other expected and/or unexpected toxicities. Patients will be allowed to use concomitant medication to manage GI and other symptoms, per treating physician discretion. Because metabolism studies have indicated that tucatinib is metabolized in human liver by CYP2C8, strong inducers or inhibitors of CYP2C8 will be prohibited. In addition, because tucatinib is also metabolized by CYP3A4 to a lesser extent, strong inhibitors and inducers of CYP3A4 will also be prohibited. Dose modifications and treatment interruptions of any of the study drugs will be allowed as described in Section 8. See Appendix D for list of CYP2C8 and CYP3A4 inducers and inhibitors of particular interest in this trial.

Preliminary data from an ongoing drug-drug interaction (DDI) study (ONT-380-012 indicate that co-administration of multiple doses of tucatinib (300 mg BID) with midazolam (a sensitive CYP3A substrate) increased the geometric mean midazolam exposure (AUC) approximately 5.85-fold (90%CI 5.14 to 6.66) in healthy subjects, compared with administration of midazolam alone. The findings indicate a potential safety risk to humans exposed to tucatinib who are taking concomitant medications that are sensitive CYP3A substrates, as administration of tucatinib may potentially increase exposure to the concomitant medication. Therefore, concomitant use of tucatinib with

sensitive CYP3A substrates should be avoided (see Appendix D Table 1).

8. DOSE MODIFICATIONS

All AEs and clinically significant laboratory abnormalities should be assessed by the Investigator for relationship to tucatinib, capecitabine, and trastuzumab, as applicable. In the event that the relationship is unclear, discussion should be held with the study PI and/or protocol chairs to discuss which study drug(s) should be held and/or modified. An AE may be considered related to tucatinib alone, capecitabine alone, trastuzumab alone, both of the drugs, or to none. 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. Doses held for toxicity will not be replaced.

8.1 Tucatinib

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 PI or protocol chairs. Tucatinib should be held for any patients who experiences a Grade 3 or greater AE considered related to tucatinib or to the combination of tucatinib and capecitabine or trastuzumab; except for nausea, vomiting, or diarrhea in the absence of use of optimal anti-emetic or anti-diarrheal medications. Up to 3 dose reductions of tucatinib are allowed as shown below.

8.1.1 Recommended Tucatinib Dose Reduction Schedule

Starting Dose[a]	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
a. Dose reductions of greater increments than those listed in this table (i.e. more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator. However, tucatinib may not be dose reduced below 150 mg BID.			

8.1.2 Dose Modifications of Tucatinib and Trastuzumab for Clinical Adverse Events Other Than Left Ventricular Dysfunction Related to Either Tucatinib and/or Trastuzumab, or Hepatocellular Toxicity *

Clinical Adverse Event	Related to Tucatinib	Related to Trastuzumab
≥ Grade 3 AEs other than Grade 3 fatigue lasting ≤ 3 days; alopecia; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to ≤Grade 1 within 7 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. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITHOUT optimal 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. Restart without dose reduction.

anti-emetics or anti-diarrheals.	next lowest dose level.	level. Restart without dose reduction.
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. Restart without dose reduction.
Grade 3 rash WITHOUT optimal use of topical 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. Restart without dose reduction.
Grade 3 rash WITH optimal use of topical 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 without dose reduction.
Grade 4 rash regardless of use of topical 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 without dose reductions.
a. No dose modifications are required for alopecia *Note that if the AE in question does not recover to the Grade required for restarting study medication as outlined in the table, the patient may need to discontinue the drug completely. Patients requiring a hold of tucatinib for > 6 weeks must discontinue study treatment, unless a longer delay is approved by the investigator.		

8.2 Trastuzumab

There are no dose reductions for trastuzumab. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV q 7 days, but only in the circumstance that trastuzumab infusion has been delayed, and weekly infusions are required to resynchronize the cycle length to 21 days. If trastuzumab cannot be restarted at the same dose after being held for an AE, it must be discontinued. As trastuzumab is given as an IV infusion, infusion- associated reactions (IARs) may occur.

If a significant IAR occurs, the infusion should be interrupted and appropriate medical therapies should be administered (per the package insert). Permanent discontinuation should be considered in patients with severe IAR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

No standard premedication is required for future treatments if patients have developed an infusion syndrome. Patients may be given acetaminophen prior to treatments. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of study agent as indicated.

8.3 Capecitabine

Capecitabine doses should be modified as described below. Capecitabine should be held for any patient who experiences a Grade 2 or greater AE considered related to capecitabine. Capecitabine dose should not be re-escalated after a dose reduction is made.

NOTE: Patients who discontinue capecitabine for any reason except disease progression, may continue receiving tucatinib and trastuzumab alone.

8.3.1 Dose Modification of Capecitabine for Clinical Adverse Events Considered Related to Capecitabine

8.3.2

CTCAE Grades	During a Course of Therapy	Dose Adjustment for Next Treatment (% of Starting Dose)[a]
Grade 1	Maintain dose level.	Maintain dose level.
Grade 2		
1st appearance	Interrupt until resolved to Grade ≤ 1.	100%
2nd appearance	Interrupt until resolved to Grade ≤ 1.	75%
3rd appearance	Interrupt until resolved to Grade ≤ 1.	50%
4th appearance	Discontinue permanently.	NA
Grade 3		
1st appearance	Interrupt until resolved to Grade ≤ 1.	75%
2nd appearance	Interrupt until resolved to Grade ≤ 1.	50%
3rd appearance	Discontinue permanently.	NA
Grade 4		
1st appearance	Discontinue permanently.	
Abbreviations: Common Terminology Criteria for Adverse Events (CTCAE); not applicable (NA). a. Dose modification table is based upon XELODA® package insert; dose rounding should be performed per institutional guidelines		

8.4 Combination Therapy – Specific Adverse Events

8.4.1 Dose Modification for Liver Dysfunction

Dose modification may be required in the case of liver function abnormalities.
For dose modifications of tucatinib and capecitabine, see Table 10.4 below. Dose modification of trastuzumab is not required but dosing should be held at investigator discretion.

8.4.2 Dose Modifications of Tucatinib and Capecitabine for Liver Function Abnormalities

Liver Function Abnormalities	Action for Tucatinib Regardless of Relationship to Drug	Capecitabine
Grade 2 elevation of ALT and/or AST (>3 - ≤5 x ULN)	Dose modification not required	If abnormalities are considered related to capecitabine, please follow guidelines as per Table in section 8.3.1. If abnormalities are not considered related to capecitabine, modifications are not mandated but may be made at the discretion of the investigator.
Grade 3 elevation of ALT and/or AST (>5–20 x ULN)	Hold until severity ≤ Grade 1 Restart at next lowest dose level	
Grade 4 elevation of ALT and/or AST (>20 x ULN)	Discontinue drug	
Elevation of ALT and/or AST (>3 x ULN) AND Bilirubin (>2 x ULN)	Discontinue drug	
Grade 2 elevation of bilirubin (>1.5–3 x ULN) AND both ALT and AST (<3 x ULN)	Hold until severity ≤ Grade 1 Restart at same dose level	
Grade 3 elevation of bilirubin (>3 – ≤10 x ULN) AND both ALT and AST (<3 x ULN)	Hold until severity ≤ Grade 1 Restart at next lowest dose	
Grade 4 elevation of bilirubin (>10 x ULN)	Discontinue drug	
Abbreviations: alanine aminotransferase (ALT); aspartate aminotransferase (AST); upper limit of normal (ULN).		

Dose Modifications for left ventricular dysfunction

Tucatinib and trastuzumab dose modification guidelines for left ventricular dysfunction are provided below:

Symptomatic CHF	**LVEF < 40%**	**LVEF below institutional limits of normal and ≥ 10% points below pretreatment baseline, or ≥16% absolute decrease from pretreatment baseline**	**LVEF 40% to ≤ 45% and decrease is < 10% points from baseline**	**LVEF > 45%**
Discontinue tucatinib and trastuzumab.	Do not administer tucatinib or trastuzumab. Repeat LVEF assessment within 4 weeks. If LVEF < 40% is confirmed, discontinue tucatinib and trastuzumab.	Do not administer tucatinib, or trastuzumab. Repeat LVEF assessment within 4 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue tucatinib and trastuzumab, as applicable.	Continue treatment with tucatinib and trastuzumab. Repeat LVEF assessment within 4 weeks.	Continue treatment with tucatinib and trastuzumab.
Abbreviations: Congestive Heart Failure (CHF); Left Ventricular Ejection Fraction (LVEF).				

If tucatinib and trastuzumab is held for decreased LVEF, hold for at least 4 weeks. If LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%, trastuzumab and tucatinib may be restarted. Permanently discontinue tucatinib and trastuzumab for persistent (i.e., > 4 weeks) LVEF decline or for suspension of dosing on > 3 occasions for cardiomyopathy.

8.5 Special considerations

For toxicities which are considered by the treating investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption.

The treating investigator may reduce a subject's dose for a toxicity of any grade/duration where s/he believes it to be in the best interests of the subject.

9. CONCOMITANT THERAPY AND SUPPORTIVE CARE GUIDELINES

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use and rationale for use is documented in the medical records. The administration of any other therapies intended to treat the primary condition including chemotherapy and biologic agents is NOT permitted. Similarly, the use of other concurrent investigational drugs is not allowed.

No other targeted therapy, chemotherapy, anti-estrogen therapy, radiation therapy, or investigational systemic therapy is allowed concomitant with study treatment. Continuation of bisphosophonate therapy for the treatment of bone metastases is allowed. Use of growth factor support neutropenia in accordance with the NCCN guidelines is allowed to address

neutropenia.

9.1 Allowed Therapy

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

- During study treatment, patients may receive supportive care to include bisphosphonates, hematologic and anti-infectious support and pain management
- Supportive care medications such as anti-diarrheals, anti-emetics, antacids, and laxatives are permitted. Prophylactic use of anti-diarrheals are permitted at the discretion of the investigator
- Use of topical 10% urea cream or other topical emollients are permitted for prophylaxis and treatment of PPE related to capecitabine use
- Prophylactic and symptomatic treatment of nausea and vomiting may be used per standard of care
- Thoracentesis or paracentesis may be performed, if needed for comfort
- Acetaminophen may be used to manage drug-related AEs such as fever, myalgias or arthralgias and anti-histamines may be used to manage drug-related AEs such pruritus
- Systemic corticosteroids such as dexamethasone and prednisone may be used in certain circumstances.
    - Patients requiring systemic corticosteroids for control of LMD symptoms are eligible for enrollment as long as they are on a stable dose for at least 5 days prior to initiation of treatment.
    - Patients on a stable dose of systemic corticosteroids for indications other than control of LMD will be allowed to continue on corticosteroids and to undergo enrollment and initiation of study treatment.

9.2 Prohibited therapy

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

- Investigational drugs and devices
- Anti-cancer therapy, including but not limited to chemotherapy and hormonal therapy
- Radiation therapy, except for palliative radiotherapy at to non-CNS sites which may be given upon consultation with protocol chairs.
- Warfarin
- Strong inhibitors or inducers of CYP2C8 – Selected listing of strong inhibitors and inducers may be found in Appendix D.
- Strong inhibitors or inducers of CYP3A4 – Selected listing of strong inhibitors and inducers may be found in Appendix D.

Note: Preliminary data from an ongoing drug-drug interaction (DDI) study (ONT-380-012 indicate that co-administration of multiple doses of tucatinib (300 mg BID) with midazolam (a sensitive CYP3A substrate) increased the geometric mean midazolam exposure (AUC) approximately 5.85-fold (90%CI 5.14 to 6.66) in healthy subjects, compared with administration of midazolam alone. The findings indicate a potential safety risk to humans exposed to tucatinib who are taking concomitant medications that are sensitive CYP3A substrates, as administration of tucatinib may potentially increase exposure to the concomitant medication. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided (see Appendix D Table 1). Consider using an alternate medication which is not a sensitive CYP3A substrate. If the use of sensitive CYP3A substrates is unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Table 1: Examples of clinical substrates for CYP3A-mediated metabolism

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

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.
Abbreviations: AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; OATP1B1: organic anion transporting polypeptide 1B1.
a Listed based on pharmacogenetic studies.
b Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.
c Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
d Acid form is an OATP1B1 substrate
This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].
Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

10. DURATION OF PARTICIPATION

Patients may continue participation in the study until any of the criteria below are met. Long- term follow-up will continue every three months following the last study treatment, until loss to follow-up, death, withdrawal of consent, or study closure. Patients will be contacted by telephone or have an in-person assessment of OS and/or disease recurrence, as well as information regarding any additional anticancer therapies administered after completion of study treatment.

Review of medical records may be used to obtain this information if reasonable efforts to make phone or personal contact are unsuccessful.

All reasons for discontinuation of treatment and withdrawal must be clearly recorded in the patient's medical record and case report form.

10.1 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment may continue for an unspecified time period until one of criteria in Section 10.4 applies. The patient should complete the evaluationsscheduled for the end of study visit, provided written consent has not been withdrawn.

Upon treatment discontinuation, further management will be determined by the patient's treating physicians as clinically indicated.

10.2 Duration of Follow-Up

Participants will be followed every 6 weeks via telephone call and/or chart review for 6 months after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable AEs will be followed in the same method. Note: Only subjects who initiate protocol treatment will be followed.

In the event that a subject does not continue her post-study care at the institution, every attempt will be made to collect this information either by direct contact or through communication with her outside physician(s).

10.3 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 10.5 applies. All patients who initiate protocol treatment will be included in the overall evaluation of survival (intent-to-treat analysis). Patients who sign consent but then do not initiate study treatment for any reason will not be included in the analysis. All reasons for discontinuation of therapy should be documented clearly in the medical record.

If a subject discontinues or withdraws from the study, but has provided research blood and/or CSF samples, these may be used for planned or future correlative studies. Every attempt will be made to get a research blood and CSF samples if the subject is able and willing to do so.

10.4 Discontinuation of Treatment

The reasons for discontinuation of protocol treatment include:

- Evidence of disease progression in the CNS and/or extra-CNS.
- Non-compliance with the study protocol; including, but not limited to not attending the majority of scheduled visits. The Protocol Chair will determine when non-compliance should lead to removal from study. Note: The patients will still be included in the overall evaluation of survival (intent-to-treat analysis).
- Unacceptable major toxicity (i.e., adverse event). Note: The patients will still be

- Included in the overall evaluation of survival (intent-to-treat analysis).
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment.
- At subject's own request. Note: The reason for discontinuation from the study must be documented. The patients will be included in the overall evaluation of survival (intent-to-treat analysis) if any protocol therapy was administered prior to withdrawal.
- Study is closed for any reason (e.g. new information shows that the patient's welfare would be at risk if she continued study treatment).
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

10.5 Withdrawal from Study

The reasons for withdrawal of a subject from the study include:

- Withdrawal consent
- Loss to follow-up
- Death
- Study is terminated for any reason

10.6 Additional Information

Any remuneration for participants in appreciation of their taking part in this study may be determined by the individual institution per their specific institutional and IRB standards. There is no subject remuneration planned.

11. CORRELATIVE/SPECIAL STUDIES

11.1 Blood Samples

Pharmacokinetic(PK) studies: Peripheral blood samples will be obtained per the Study Calendar. Blood Samples will be collected at each time point in designated tubes in a PK kit provided by the Seattle Genetics.

Non-Pharmacokinetic (PK) studies: Approximately 30 ml total of peripheral blood will be obtained for research purposes from each participant per the Study Calendar:

- Up to 20 ml will be collected for ctDNA analysis
- Up to 10ml will be collected for banking (optional).

11.2 CSF Samples

PK studies: CSF samples will be obtained per the Study Calendar. CSF Samples will be

collected at each time point in a designated tubes in a PK kit provided by Seattle Genetics.

Non-PK studies: Up to 20 ml total of CSF will be obtained for research purposes from each participant per the Study Calendar.

- Up to 10 ml will be collected for ctDNA analysis
- Up to 10 ml will be collected for banking (optional).

11.3 Specimen collection

Specimen collection will be standardized across all sites, as will cytopreservation and packaging. Samples will be collected in designated tubes and all tubes will be labeled with HIPPA compliant participant identifier, and sealed in plastic bags labeled as biohazard. Processing, storage, and shipment information will be provided in laboratory manuals.

PK samples will be processed and shipped to the sponsor according to the Laboratory Manual. PK analyses will be conducted by Seattle Genetics and sample kits including tubes/packing materials will be provided to each site. All blood and CSF samples for PK studies will be stored at the site and shipped directly to the sponsor. Non- PK blood and CSF research specimens will be banked and analyzed at MD Anderson.

Note: Please see supplemental lab manuals for details regarding supplies, collection, processing, and shipments.

11.4 Genetic Testing

Participants will be given information as part of the informed consent process that samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing

done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the Protocol Chair of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a
CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the coordinating center and local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

12. SPECIMEN BANKING

The study PI and collaborators have approval by the TBCRC to use all research bio-specimens

collected during the conduct of this trial to address the research questions described in the protocol document. All future use of residual or repository specimens collected in this trial for

purposes not prospectively defined will require review and approval by the TBCRC according to its established policies.

Secondary use of bio-specimens for new endpoints must be submitted to the TBCRC Central Office for possible review by the TBCRC Correlative Science Review Committee.

13. STUDY CALENDAR

Parameter	Baseline[1]	Treatment Cycles 1	2	3	4	5	6	7	8**	End of Study[13]
Demographics	X									
CLINICAL EVALUATIONS:										
History and Physical	X	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X	X
Height	X									
Vital signs and Weight	X	X	X	X	X	X	X	X	X	X
Neurologic Exam[2]	X	X	X	X	X	X	X	X	X	X
LABORATORY/OTHER EVALUATIONS:										
Hematology (CBC/diff, plt)[3]	X	X	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel[3]	X	X	X	X	X	X	X	X	X	
Pregnancy Test (serum or urine)[4]	X									
CSF Evaluation[5]	X	X	X	X	X	X	X	X	X	X
LVEF (Echocardiogram or MUGA)	X									
RADIOLOGIC EVALUATIONS:										
Extra-CNS/Systemic Staging[6]	X					X				X
CNS/Neuroaxis Imaging[7]	X			X		X		X		X
TREATMENT ADMINISTRATION: [8]										
Tucatinib + Capecitabine + Trastuzumab		X	X	X	X	X	X	X	X	
CORRELATIVE STUDIES:										
PK Samples: Blood and CSF[9]		X	X							
Non-PK Samples: CSF[10]		X	X	X	X	X	X	X	X	X
Non-PK Samples: Blood[11]		X	X	X	X	X	X	X	X	X
Symptom/QOL Questionnaires[12]		X	X	X	X	X	X	X	X	X

NOTE: Additional tests may be performed at the discretion of the treating investigator as clinically indicated. The sample collection schedules outlined above are based on an ideal subject. The sample schedule should be followed as closely as is realistically possible;

however,the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinicclosure, poor weather conditions, vacations, etc.).

**The above study calendar reflects 8 cycles of treatment. However, responding patients may continue on for additional cycles and would undergo the same study assessments as noted aboveat every other cycle.

1. Within 28 days prior to starting treatment, unless otherwise noted.
2. Neurologic exam performed by neurologist or neuro-oncologist at each site. NANO Scoring performed at Day 1 of each cycle or within 72 hours prior. (Appendix G).
3. Hematology and serum chemistry within 72 hours prior to Day 1 of each cycle. Serum chemistry includes measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase.
4. For women of childbearing potential only, within 7 days of initiating treatment.
5. CSF evaluation: Obtain sample to assess standard parameters (i.e., cell count, differential, glucose, protein, cytolopathology) via OR or VAD (OR or VAD placement is mandatory for the first 15 patients) and/or LP (lumbar puncture). These studies will be performed at each study site on Day 1 of each cycle (within 72 hours prior).
6. Systemic/Extra-CNS Staging: CT (or MRI) of the chest, abdomen, and pelvis, and bone scan or PET/CT. For subjects with extra-CNS disease: Repeat assessments to include only the imaging required to monitor for sites of disease and are required at least every 4 cycles. For subjects without extra-CNS disease: imaging may be repeated at physician discretion. In all subjects, systemic imaging is required at End of Study (or within the 6 weeks prior) and imaging may be performed at closer intervals per treating physician's discretion.
7. Neuro-axis Imaging: Contrast-enhanced MRI of the brain and spine with specific recommended neuroaxis imaging sequences (See *MRI brain and spine acquisition manual*). Repeat scans at least every 2 cycles or per treating physician discretion (e.g., suspicion or evidence of progression clinically).
8. All patients will receive trastuzumab, capecitabine and tucatinib. NOTE: If capecitabine is discontinued by treating physician due to toxicity (not progression), then patients may continue treatment/assessments with tucatinib and trastuzumab alone.
9. PK Studies: Cycles 1 and 2 Day 1 at time 0 (pre-treatment), and at 2-3h and 5-7h following administration of dose of tucatinib (within 1 hour of the parallel blood sample). An additional sample will be obtained 24 hs (+/- 1 hr) following administration of dose of tucatinib on Day 1 and before administration of dose of tucatinib on Day 2 of Cycles 1 and 2. (Note: PK studies will be performed in patients with OR or VAD (n=15).
10. Non- PK CSF samples: Day 1 of each cycle (within 72 hours prior)
11. Non-PK Blood Samples: Day 1 of each cycle (within 72 hours prior)
12. MDASI-BT will be performed Day 1 of each cycle (within 72 hours prior) and LASA QOL will be performed at every 2 cycles CNS restaging visit (within 72 hours prior) (Appendices C & D, respectively).
13. End of study (i.e., end of study drug treatment) procedures will be requested of all patients, as feasible. End of study is when patients are taken off protocol due to disease

progression or adverse event.

14. MEASUREMENT OF EFFECT

CNS response will be assessed by clinical, cytological, and radiographic means as a composite. Systemic response will be assessed by standard clinical and radiographic parameters. Measurable disease is not required.

Participants should be re-evaluated every cycle with neurologic exam and CSF analysis. Every 2 cycles (every 6 weeks), patients will undergo radiographic evaluation with neuroaxis imaging, in addition to neurologic exam and CSF analysis, for CNS restaging purposes. Extra-CNS restaging will be performed every 4 cycles (every 12 weeks). More frequent CNS and extra-CNS restaging can be performed at the discretion of the treating physician.

Response in the CNS and in extra-CNS sites will be evaluated and recorded separately in this trial. Extra-CNS response will be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST V 1.1) Committee. Response of parenchymal brain metastases will be evaluated with Response Assessment in Neuro-oncology Brain Metastases (RANO-BM) criteria.[47] Response of LMD will be evaluated in this study using a composite criteria further defined below.

14.1 Definitions

Evaluable for Overall Survival. All patients who initiate protocol treatment will be considered evaluable for the primary endpoint, which is overall survival.

Evaluable for Toxicity. All patients who receive at least one dose of tucatinib + capecitabine + trastuzumab will be evaluable for toxicity from the time of their first dose. Those patients who enroll on study but never receive study treatment will not be evaluable for toxicity analysis.

Evaluable for Objective Response. Only those patients who have received at least one cycle of therapy, and have had their disease re-evaluated by established CNS response assessment parameters (CSF cytopathology, neuroaxis imaging, clinical evaluation) will be considered evaluable for objective response in the CNS.

14.2 Response Categories

See below for LMD response categories: Response, progressive or refractory disease, stable disease. Extra-CNS response will be classified per RECIST V 1.1 (Appendix K).

14.2.1 Systemic Disease Parameters

The status of extra-CNS disease will be monitored using standard staging studies. Per treating physician discretion, CT chest, abdomen, and pelvis plus/minus bone scan or PET/CT will be performed at baseline (within 28 days of enrollment) and reassessed every 4 cycles (12 weeks), per protocol.

Response in extra-CNS sites will be evaluated in this study using RECIST v 1.1.
Measurable disease by RECIST V 1.1 is not required (Appendix K).

Note: In cases of LMD response/stable disease, but disease progression in extra-CNS sites, patients may be continued or taken off protocol at the treating physician's discretion.

14.2.2 LMD Disease Parameters

The LMD response evaluation used in this trial comprises a composite assessment derived from the RANO-LMD working group (per publication and direct communication).[62] The composite assessment includes CSF cytopathology, neuroaxis imaging, and a neurologic clinical evaluation which includes 1) a neurologic examination utilizing the Neurological Assessment in Neuro-Oncology Group (NANO) scoring instrument and 2) an evaluation of symptoms (MDASI-BT).

Note: In patients with concurrent active parenchymal brain metastases, response will be evaluated using the RANO-BM Criteria.

14.2.3 CSF Cytopathology Assessment

CSF cytology slides will be interpreted by an experienced pathologist at each study site for the presence of malignant cells to evaluate cytologic response. CSF cytology will be assessed on day 1 cycle 1 and CSF cytologic response will be assessed on day 1 of each subsequent cycle (every 3 weeks +/- 3 days) while patient remains on treatment. "Positive" CSF cytology is defined as malignant cells identified in the CSF. Cytologic failure (indicating progressive or refractory disease) will be defined as persistent positive cytology (if initially positive) at 6 weeks or the development of positive cytology after two serial negative cytologies. Cytologic response will be defined as initially positive cytology that is negative on subsequent CSF evaluation, and confirmed negative on followup CSF evaluation 3 weeks later.

Note: Standard CSF evaluation including cytology, cell count, glucose, and protein will be performed and processed/interpreted at each study site.

14.2.4 Neuroaxis Radiographic Assessment

Neuroaxis imaging (MRI brain and spine with and without contrast) will be performed at baseline (within 28 days of enrollment) and reassessed every 2 cycles (6 weeks +/- 3 days) after the first dose of study drug. Recommended MRI prerequisites and sequences are detailed in the *MRI Brain and Spine Image Acquisition Manual.*

Radiographic findings may be interpreted by the treating physician(s) in collaboration with an experienced radiologist at each site to determine treatment response at each staging visit. In addition, the findings will be recorded on the supplemental *CNS response assessment scorecard* form by the radiologist at each site. Patients will be given an overall radiographic response assessment for LM as follows: complete response (CR), partial response(PR), stable disease (SD), or progressive disease (PD).

For the composite LMD response assessment, radiographic CR or PR will be considered *definitive improvement*. In cases of definite radiographic worsening, patients will be considered to have disease progression based upon LMD response

criteria, and discontinued from the protocol (however, in cases of clinical benefit, patients may be continued on the study drug, at the treating physician's discretion).

For patients with parenchymal brain metastases, CNS objective response will be classified as CR,

PR, SD, or PD based on the RANO-BM Criteria. If a patient is found to have isolated progression in the CNS (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and does not have progression of disease outside the CNS, the patient may be eligible to continue on study drugs after completion of focal local treatment (SRS) of the brain/dural metastases to allow for clinical benefit. Continuation of study treatment requires discussion with and documented approval from the overall study PIs and may continue until either systemic progression, LMD progression, or a second isolated CNS progression. The patient may continue on study provided the following criteria are met and the patient continues to receive clinical benefit:

- The patient is not experiencing any worsening of cancer-related symptoms. Patients who are clinically deteriorating and unlikely to receive further benefit from continued treatment should discontinue study treatment.
- The patient is tolerating study drug
- Review and concurrence by the overall Study PIs
- Patient has no evidence of unequivocal systemic progression
- Patient has not had a previous isolated CNS progression while on study
- Patient does not require treatment with whole brain radiation or neuro-surgery

Study treatment may be held up to 3 weeks to allow local CNS therapy with SRS. Longer holds must be discussed and approved by the Study PIs. Oral study drugs (tucatinib/placebo and capecitabine) are to be held 1 week prior to planned CNS- directed therapy. The potential for radiosensitization with tucatinib is unknown.
Capecitabine is a known radiation sensitizer and therefore needs to be held prior to CNS-directed radiotherapy. Trastuzumab has been shown not to potentiate radiation and therefore may continue as per protocol schedule during radiotherapy. Oral study drugs may be re-initiated 7 days or more after completion of SRS. Plans for holding and re-initiating study drugs before and after local therapy will require discussion with, and documented approval from, the Study PIs. Because the primary goal of the study is to assess response in LMD, every effort should be made to avoid radiation to LMD target lesions.

Note: Neuro-axis imaging (MRI brain and spine) will be uploaded onto a DICOM formatted disc and sent to MD Anderson within 5 business days for central review by the collaborating neuro-radiologist, who will evaluate the results and complete an independent CNS radiographic response scorecard (Appendix I) for cenral review.

14.2.5 Neurologic Clinical Evaluation

A neurologic clinical evaluation will be performed at day 1 (every 3 weeks, +/- 3 days) of every cycle. The neurologic clinical evaluation will be comprised of 2 parts: 1) neurologic examination utilizing an adaptation of the standardized NANO instrument (Appendix G), and 2) clinical assessment of neurologic symptoms (i.e., seizures, headaches). Note: The treating physicians *may* utilize the MDASI-BT questionnaire (Appendix E) for the clinical assessment.

Selection of Target Deficits: (Up to 4 may be selected at baseline)
Among the neurologic deficits (neurologic sign or symptom) noted at baseline by neurologic exam

and/or clinical symptom assessment, up to 4 will be selected as target deficits; if there are fewer than 4 deficits noted, then all will be included as target deficits. These target deficits may be a combination of neurologic signs identified on neurologic exam and/or symptoms reported by the patient. Note:

The term "deficit" is used to encompass both the terms "symptom," which is subjective and typically reported by the patient (for example, headache) and "sign," which is an objective exam finding (for example, facial droop). A meaningful neurologic clinical evaluation takes into account both symptoms and signs and this is why it is recommended to choose up to 4 target "deficits" to monitor.

Neurologic clinical response will be determined as follows: In regards to target deficits identified in the neurologic examination (as measured using the adapted NANO instrument (Appendix G)), progression of disease is defined by a change of 2 or more levels in a given domain (eg, gait) or alternatively by a change to level 3 (or level 2 in domains defined by only 3 levels) in any one domain. In regards to target deficits identified in the clinical symptom assessment, progression of disease will be determined at the discretion of the treating physician, based upon evaluation of deficits, as per standard clinical practice. It is expected that best response to treatment usually will be stabilization of neurological function (as assessed by neurological examination and symptom assessment). It is acknowledged that attribution of disease progression can be challenging, as change in neurological function may occur due to concurrent brain metastases, extra-CNS disease progression, concurrent medications, or treatment-related toxicity (Chamberlain, Neuro Oncol 2017).

Note: It is strongly recommended that a neurologist or neuro-oncologist perform the neurologic assessments at each visit.

14.3 LMD Response Criteria

Response assessment of LMD to treatment will be determined by using an adaptation of the RANO-LMD criteria (Response, Progressive or refractory disease, stable disease).[62]

The table below provides the overview for the composite response criteria based on cytology, neurological exam as well as imaging data.

Assessment	**Response[A]**	**Progressive or refractory disease[B]**		**Stable disease[C]**
		Neurological/clinical defined progression[#]	Radiologic defined progression[&]	
Neurological clinical evaluation[1]	Improved or stable[4]	Worse	Stable[&] or Worse	Stable
CSF cytology[2]	Negative^	Negative or Positive^^		
CNS Imaging[3]	Definite improvement [5]	Stable	Progressive disease (PD)[x]	Stable[y]

Legend:
[1] Based on neurologic exam and symptom assessment. Target deficits will be identified and followed by the treating neurologist/neuro-oncologist
[2]CSF cytology: Negative = true negative or atypical; Positive = true positive or suspicious
[3]CNS imaging: Hydrocephalus, LM linear enhancement, and parenchymal metastases, either brain or spine, are noted as present or absent but not used for LM response determination.
[4] Stable neurologic clinical evaluation in the setting of definitive improvement in CNS imaging will be classified as response
[5]Definitive improvement on CNS imaging is defined as CR (complete response) or PR (partial response)
^ Initially positive cytology that is negative on subsequent CSF evaluation, and confirmed negative on followup CSF evaluation 3 weeks later
^^Cytologic failure (indicating progressive or refractory disease) will be defined as persistent positive cytology (if initially positive) at 6 weeks or the development of positive cytology after two serial negative cytologies, spaced 3 weeks apart. In cases of clinical benefit, patients may be continued on study drug despite cytologic progression, at treating physician's discretion.
[#]As determined by the treating investigator in consultation with the neurologist/neuro-oncologist, neurologic exam (neurologic signs) and/or symptoms must be worse
[&]In cases of clinical benefit, patients may be continued on study drug despite radiologic progression, at treating physician's discretion
[x] Unequivocal progression
[y] Any indeterminate or equivocal progression will be considered as stable disease
Note: Any patient with neurologic clinical progression (as determined by the treating physician) may be removed from the study, regardless of the status of the other measures (CSF cytology and/or neuroaxis imaging).

14.4 Response Review

Response evaluations will be completed by the treating physician(s) at each study site based on the parameters noted above. Treating physician(s) will determine an overall assessment: Stable disease, continue on protocol; response, continue on protocol; progression, discontinue protocol; or, discontinue protocol for any other reason

The LMD Composite response criteria - (1) Response, 2) Progression or refractory disease, 3) Stable disease – will be assigned by the study team based on review and discussion with treating physicians, site PI and overall study PIs.

Note: Treating physicians and study teams may reference *Composite CNS Response Assessment Manual*

15. ADVERSE EVENT REPORTING REQUIREMENTS

15.1 General

AE collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

AEs experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

15.2 Definitions

15.2.1 Adverse Event (AE)

An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

15.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;

- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above;
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Events **not** considered to be SAEs are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

15.2.3 Expectedness

- Expected: Expected AEs are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- Unexpected: An AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

15.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

15.3 Reporting Procedures

15.3.1 General

All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

15.3.2 Serious Adverse Events

All SAEs, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the

Coordinating Center and pharmaceutical supporter, Seattle Genetics at drug.safety@seattlegenetics.com.

All SAEs must be reported to the Coordinating Center within 1 business day after the investigator becomes aware of the event. Events should be reported using a MedWatch form (3500A) as available on the FDA website (see link below).

Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Protocol Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study medication. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

15.3.3 Institutional Review Board

All AEs and SAEs will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

15.3.4 Food and Drug Administration (FDA)

In this trial, unexpected adverse events believed to be definitely, probably, or possibly related to the medications will be reported to the Food and Drug Administration via MedWatch (using the online form available at https://www.accessdata.fda.gov/scripts/medwatch/. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

15.3.5 Other

The coordinating center will be required to report any SAEs to the pharmaceutical supporter – Seattle Genetics at drug.safety@seattlegenetics.com.

16. DATA AND SAFETY MONITORING

16.1 Data Management and Reporting

All information will be collected on study-specific electronic case report forms utilizing the web based REDCap database system by the study staff at each institution. Site access will be granted to sites specific on their study role.

The data submission schedule is as follows:

At the time of enrollment:

- Registration Form
- Informed Consent Form (signed by the subject)
- Eligibility Checklist
- Source documents related to eligibility

Within 2 weeks after treatment initiation:

- Baseline study case report forms
- Pertinent source documents

Within 2 weeks after each cycle is completed:

- Per-cycle case report forms
- Pertinent source documents

Every 2 months during follow-up:

- Follow-up case report forms
- Pertinent source documents (if necessary)

16.2 Meetings/Teleconferences

All study data will be reviewed for completeness and accuracy by the protocol chairs and/or their designees. The principal investigator (or his/her designee) at each respective institution is responsible for review, and ensuring the completeness and accuracy, of the data generated by his or her institution.

The protocol chairs or his/her designated representative will schedule teleconferences to take place as needed depending on the rate of accrual and will include the principal investigators from each site. The following study team members involved with the conduct of the trial will be included as appropriate: study coordinators, data managers, research nurses, sub investigators, collaborators (if applicable), and statistician.

During these meetings, matters related to the following will be discussed: subjects with progressive disease in the CNS and/or systemically, enrollment rate relative to

expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), validity and integrity of the data, safety data, analysis of biospecimen samples, and plans for further analyses.

At these meetings, the data pertaining to overall survival, toxicity, and response will also be reviewed, dependent upon rate of accrual as outlined in Section 19.

A summary of the items discussed at each teleconference will be prepared by the protocol chair or his/her representative and forwarded to each participating site. In addition, study investigators meet 2-3 times each year in regularly scheduled TBCRC meetings.

16.3 Data and Safety Monitoring

As an IND is required for this study, it will be conducted in accordance with the data and safety monitoring program established by the Clinical Research Office of the University of Alabama at Birmingham (UAB).

The UAB Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP) instituted by the CTNMO will monitor subjects treated at UAB and the other TBCRC institutions participating in the trial. The Clinical Trials Monitoring Committee (CTMC) will closely (on a weekly basis) monitor adverse reactions observed during treatment.
The CTMC is responsible for data and safety monitoring of the trial and adherence to DSMP. The office of CTNMO will also report any SAE at participating sites outside UAB to the CTMC. The independent Quality Assurance Committee (QAC) is responsible for oversight of the operation of CTMC, including adherence to DSMP. Reports from the CTMC are reviewed monthly by the QAC.

All data will be sent to the Coordinating Center for central collation and review. Subject cases from sites will undergo a thorough review; it is unclear how often this may occur; however, each site will be asked to provide copies of all source documents and to ensure that all data is current. There are no formal on-site evaluations planned by the Coordinating Center; however, these may occur depending on site accrual rate, identified problems or concerns, or other reasons, as appropriate.

A medical expert committee or formal data safety monitoring board are not planned or required at this time. However, there will be an internal data monitoring committee comprising of the protocol chairs, in addition to a neuro-radiologist, and the study statistician will be constituted to review all enrolled patients on active treatment. In addition, a biospecimen committee will be named to review and advise on proper collection and handling of biospecimens for the duration of the study.

17. REGULATORY CONSIDERATIONS

17.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study and any other necessary documents must be submitted, reviewed, and approved by a properly constituted IRB governing each study location.

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chairs (or his/her designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

17.2 Informed Consent

All participants must be provided a consent form describing this study and the investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

17.3 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

18. MULTI-CENTER GUIDELINES

18.1 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The investigator or his/her designee must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study of each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, and imaging media.

18.2 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies. Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

18.3 Publication

Upon completion of protocol accrual, the results of the primary and secondary endpoints will be submitted for possible presentation at the American Society of Clinical Oncology annual meeting or the San Antonio Breast Cancer Symposium, or other relevant meetings depending on the timing of result availability. Final results will be submitted for publication in a peer reviewed scientific journal within 2 years of the date of completion and will be available to the public at that time. There may be multiple publications to cover both study endpoints and exploratory endpoints. The protocol chairs will have access to all study data, will lead the data analysis, and will hold

primary responsibility for publication and poster presentation of all study results. Seattle Genetics, collaborators and the TBCRC investigators will be provided all manuscripts and abstracts prior to submission to review data and provide comments. Final approval of all submitted work will be made by the protocol chairs. It is understood that any manuscript or releases resulting from the collaborative research must be approved by the Protocol Chairs and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation. Additionally, any publication of study data and results must conform to the publications policy as stated the Translational Breast Cancer Research Consortium's (TBCRC) "Policies and Procedures".

19. STATISTICAL CONSIDERATIONS

19.1 Study Design/ Endpoints

This phase II study will aim to estimate the efficacy of the combination and verify safety. Based on retrospective data from a single tertiary care institution, the median overall survival from the time of LMD diagnosis to death in 56 patients with HER2+ BC is estimated to be 4.4 months.[30] This information was used for the development of the statistical plan after acknowledging the limitations and biases inherent to retrospective data as there is no prospective data in this rare patient population.

Primary Endpoint: Overall Survival (OS)

We propose a Gehan-like trial design with an interim futility analysis and overall intent to estimate OS.[63] Enrollment is planned for 30 patients total. This design uses an early clinical benefit endpoint for interim analysis after the first 15 patients enrolled with the ultimate goal of estimating the overall survival curve if the trial goes to completion.

For the interim analysis, we define *success* to be CNS progression-free survival for 12 weeks. An event will be considered to be either CNS progression before 12 weeks or death from any cause. We would stop enrollment with fewer than 2 successes in the first 15 patients. The probability of stopping after the first 15 patients enrolled is 95% if the true success rate is 2.5%, 83% for a true rate of 5%, 55% for a true rate of 10%, 17% for a true rate of 20%, 4% for a true rate of 30%, and 1% for a true rate of 40%.

If the trial continues to completion, we aim to estimate median overall survival and would consider the trial successful if the median overall survival is $\geq$ 4.4 months (historical control). Computer simulations indicate that if the true median OS is 6.0 months, the 95% confidence interval for the Kaplan-Meier median OS will have width of about 6.9 months (assuming uniform accrual and exponential survival). The combination treatment will be declared to be worthy of further study if we see a median OS that matches or is higher than the historical control. Simulations indicate that if the true median OS is 6.0 months, we will observe a median > 4.4 with a probability of 88%. With regard to clinical benefit, if we see 6/30 successes (20%), the corresponding exact 95% confidence interval = (8%, 39%), while if we see 12/30 successes (40%), the corresponding interval = (23%, 59%).

19.2 Sample Size, Study Duration, and Evaluable Subjects

We plan to enroll a total of 30 patients with a 6-month post-accrual additional follow-up.

Study Duration: 3 years; Patients will receive treatment until disease progression or unacceptable toxicity or death.

All patients who initiated treatment on protocol will be considered evaluable in the intent to treat analysis for the primary endpoint (OS). Patients who withdraw from the study after enrollment/registration and prior to initiation of study treatment for any reason will be replaced, and will not be counted towards the accrual goal of evaluable subjects.

19.3 Analysis of Endpoints

- Safety
- Response in the CNS
- Response of extra-CNS disease
- Symptom Burden and QOL

QOL assessments will be analyzed descriptively with reporting of frequencies, means, and correlations. We will estimate OS curves using the Kaplan-Meier method. We will tabulate response data. We will estimate response rates along with exact binomial 95% confidence intervals. We will analyze the correlation between ctDNA and response using logistic regression analysis and graphical analysis.

MDASI-BT data will be collected on day 1 of each cycle and at end of study. We will summarize the MDASI-BT data at each time point using descriptive statistics and evaluate the change of MDASI-BT over time and its correlation with response and/or treatment tolerance using linear mixed models, where random effects will be used to account for within-subject correlations.

APPENDICES

(following pages)

APPENDIX A: Phase I formulation studies in healthy subjects

Study ID	Design	Treatment	Population	Results
ARRAY 380-102	Phase I, open- label, single-dose, fixed-sequence, 4- period cross over study to evaluate the PK, relative bioavailability, and safety of four ONT-380 formulations in healthy subjects	Single 300mg PO dose of ONT-380 in 4 treatment formulations: 1. Capsule (control) 2. Micronized 3. Aqueous suspension 4. Captisol/apple juice solution	14 healthy subjects	Bioavailability of ARRY-380 (AUC and Cmax) was > following the micronized and aqueous formulations and < following the captisol/apple juice solution compared to the control.
ARRAY-380-103	Phase I, 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 ONT-380 PO capsules and tablets in healthy subjects.	Single 300mg PO dose of ONT-380 in each of 4 treatment periods: 1. Capsules 2. Tablets (fasted) 3. Tablets (fed) 4. Tablets (fasted) following omeprazole 40mg x 5 days	12 healthy subjects	ONT-380 metabolism was not affected by formulation, food, or gastric pH. Tablet and capsule had similar bioavailability. Higher drug exposure was observed with tablet in fed state.

Abbreviations: intravenous (IV); twice daily (BID); maximum-tolerated dose (MTD); oral (PO); pharmacokinetics (PK); area under the curve (AUC); Cmax (maximum concentration observed); partial response (PR); recommended Phase 2 dose (RP2D); stable disease (SD).

APPENDIX B: Completed or ongoing clinical studies

Study ID	Design/Objective	Treatment	Status
ARRAY-380-101	Phase I, single-agent, open-label, dose-escalation study to identify the MTD/RP2D of ONT-380 capsules and to assess safety, PK, and preliminary efficacy	Dose escalation phase: 25-800mg PO BID in 28-day cycles Expansion phase: 600mg PO BID in 28 day cycles	Completed, N=50, including 31 at dose ≥ 600. MTD/RP2D 600mg PO BID. Among 35 evaluable patients for efficacy, 5 with PR (14%), 18 with SD (51%).
ONT-380-004 (Oncothyreon) (NCT02025192)	Phase Ib, open-label, dose-escalation trial to determine the MTD/RP2D of ONT-380 tablets given in combination with T-DM1 in patients with MBC previously treated with trastuzumab and taxane. Optional expansion cohort in patients with CNS metastasis at the MTD/RP2D.	ONT-380, in escalating doses, starting at 300mg PO BID. T-DM1 given at 3.6mg/kg IV q3weeks.	N=57 Last patient enrolled July 2015 MTD = 300mg PO BID
ONT-380-005 (Oncothyreon) (NCT1983501)	Phase Ib, open-label, dose-escalation trial to determine the MTD/RP2D of ONT-380 tablets given in combination with trastuzumab, capecitabine, and trastuzumab + capecitabine in patients with MBC previously treated with trastuzumab and T-DM1. Optional expansion cohort in patients with CNS metastasis at MTD/RP2D.	ONT-380, in escalating doses, starting at 300mg PO BID. C given at 1000mg/m2 PO BID on Days 1-14 of each 21-day cycle. H given as a loading dose of 8mg/kg followed by 6mg/kg once q21 days.	N=60 Last patient enrolled December 2015
DFCI-13-198 (NCT01921335)	Phase I, dose-escalation trial of ARRY-380 (ONT-380) tablets in combination with H in participants with brain metastases from HER2+ MBC to determine the MTD/RP2D of ONT-380 given in combination with trastuzumab.	Phase Ib, CNS only. ONT-380, in escalating doses, starting at 450mg PO BID. Additional arm with once daily dosing of ONT-380 starting at 750mg PO daily. Trastuzumab given at 6mg/kg IV q3 weeks.	N=40, enrollment complete
ONT-380-206 (HER2CLIMB) (NCT02614794	Phase 2, randomized, blinded study of ONT-380 vs. Placebo in combination with capecitabine and trastuzumab in patients with metastatic HER2+ breast cancer.	ONT 380 MTD/RP2D = 300mg PO BID, Allows CNS metastasis	Enrollment ongoing (n=180), first patient enrolled in Feb. 2016

Abbreviations: intravenous (IV); twice daily (BID); maximum-tolerated dose (MTD); oral (PO); recommended Phase 2 dose (RP2D); metastatic breast cancer (MBC)

APPENDIX C: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs of symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX D: CYP3A4, CYP2C8, and CYP3A4 inducers and inhibitors

NOTE: This is a selected listing of strong and moderate CYP3A4, CYP2C8, and CYP3A4 inducers and inhibitors for this trial.

CYP3A4 Strong Inhibitors (1/2 life): Chloramphenicol (4hrs), Clarithromycin(3-7hrs), Itraconazole (21 hrs single dose, 64 hrs steady state), Ketoconazole (systemic) (2-8hrs), Nefazodone(2-4hrs), Telithromycin(10hrs), Voriconazole (dose-dependent)

CYP3A4 Strong Inducers (1/2 life): Barbituates (variable), Carbamazepine (25-65 hrs), Phenytoin (7-42 hrs), Rifampin (3-4 hrs), St. John's Wort (9-43 hrs)

CYP2C8 Strong Inhibitors (1/2 life): Gemfibrozil (1-2 hrs), Montelukast (3-6 hrs), Quercetin (<2 hrs), Rosiglitazone (16-24 hrs)

CYP2C8 Strong Inducer: Rifampin (3-5 hrs)

- FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhbitors, and Inducers"(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInterac tionsLabeling/ucm093664.htm#potency).
- EMA. "Guideline on the investigation of drug interactions" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeli ng/ucm093664.htm#potency).
- Strong CYP3A inhibitors are defined as those drugs that increase the AUC of oral midazolam or other CYP3A substrates > 5 fold. Ritonavir, indinavir, nelfinavir, atazanivir, and saquinavir are also strong CYP3A3 inhibitors, but would not be used in this study as patients with known HIV are excluded.

Table 1: Examples of clinical substrates for CYP3A-mediated metabolism

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

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.
Abbreviations: AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; OATP1B1: organic anion transporting polypeptide 1B1.
a Listed based on pharmacogenetic studies.
b Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.
c Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
d Acid form is an OATP1B1 substrate
This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].
Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

APPENDIX E: MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)

Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: ☐☐☐

MD Anderson # : ☐☐☐☐☐☐☐ PDMS # : ☐☐☐☐

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

SAMPLE

Copyright 2000 The University of Texas M. D. Anderson Cancer Center
All rights reserved.

Date: ☐☐ / ☐☐ / ☐☐ (month / day / year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: _____

MD Anderson # : ☐☐☐☐☐☐ PDMS # : ☐☐☐☐

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

SAMPLE

Part II. How have your symptoms interfered with your li

Symptoms frequently interfere with h[illegible] we[illegible] function. How much have your symptoms interfered with the following items in the last 2[illegible]:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Copyright 2000 The University of Texas M. D. Anderson Cancer Center
All rights reserved.

APPENDIX F: Linear Analog Self Assessment (LASA)

Linear Analog Self Assessment (LASA): Quality of Life Assessment

Subject ID: _____ Date: _____

Directions: Please circle the number (0–10) best reflecting your response to the following that describes your feelings during the past week, including today.

1. How would you rate your physical well being over the past week?
   This question refers to such things as fatigue, activity, etc.

0 1 2 3 4 5 6 7 8 9 10

(0= As bad as it can be; 10 = As good as it can be)

2. How would you rate your emotional well being over the past week?
   This question refers to such things as depression, anxiety, stress, etc.

0 1 2 3 4 5 6 7 8 9 10

(0= As bad as it can be; 10 = As good as it can be)

3. How would you rate your spiritual well being over the past week?

This question refers to such things as a sense of meaning and purpose, relationship with God, etc.

0 1 2 3 4 5 6 7 8 9 10

(0= As bad as it can be; 10 = As good as it can be)

4. How would you rate your intellectual well being over the past week?

This question refers to such things as the ability to think clearly, to concentrate, to remember, etc.

0 1 2 3 4 5 6 7 8 9 10

(0= As bad as it can be; 10 = As good as it can be)

5. How would you rate your overall well being over the past week?

   0 1 2 3 4 5 6 7 8 9 10

(0= As bad as it can be; 10 = As good as it can be)

APPENDIX G: NANO (Neurologic Assessment in Neuro-Oncology)

Domain	Level of Function Score			
	0	1	2	3
Gait	Normal	Abnormal but walks without assistance	Abnormal and requires assistance (companion, cane, walker, etc.)	Unable to walk
	Key Considerations: 1. Walking is ideally assessed by at least 10 steps.			
Strength	Normal	Movement present but decreased against resistance	Movement present but none against resistance	No movement
	Key Considerations: 1. Each limb should be tested separately. 2. Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups. 3. Score should reflect worst performing area. 4. Patients with pre-existing level 3 function in one major muscle group/limb at baseline can be scored based on assessment of other major muscle groups/limb.			
Sensation	Normal	Decreased but aware of sensory modality	Unaware of sensory modality	---
	Key Considerations: 1. Recommend evaluating major body areas separately (face, limbs and trunk). 2. Score should reflect worst performing area. 3. Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception. 4. Patients with pre-existing level 2 function in one major body area at baseline can be scored based on assessment of other major body areas.			
Vision	Normal	Partial monocular visual loss	Complete monocular visual loss	Bilateral visual loss
	Key Considerations: 1. Patients who require corrective lenses should be evaluated while wearing corrective lenses. 2. Each eye should be evaluated and score should reflect worst performing eye.			
Eye movements	Normal	Abnormality noted in 1 direction of gaze	Abnormality noted in more than 1 gaze direction, but not all	Unable to move the eye in any gaze direction
	Key Considerations: 1. Test eye movements for each eye individually. 2. The score will reflect the worst performing eye (i.e. the highest score.			

Domain	Level of Function Score			
	0	1	2	3
Facial Strength	Normal	Mild facial weakness (nasolabial fold flattening, asymmetric smile, decreased forehead contraction or partial eye closure)	Severe facial weakness (severe NLF flattening, asymmetric smile with limited or no movement of face, incomplete eye closure, or labial incompetence	Bilateral facial weakness
	Key Considerations: 1. Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrow.			
Hearing	Normal	Impaired but residual serviceable hearing	Absent unilateral hearing	Bilateral hearing loss
	Key Considerations: 1. Each ear should be evaluated and score should reflect worst performing ear.			
Swallowing	Normal	Impaired but not requiring change in diet formulation, not aspirating by bedside testing	Unable to swallow without risk of aspiration by bedside testing	----------
	Key Considerations: 1. Bedside testing comprised of a swallow test with a small glass of water.			
Level of Consciousness	Normal	Drowsy (easily arousable & responsive)	Somnolent (difficult to arouse & poorly responsive)	Coma (unarousable & unresponsive)
	Key Considerations: N/A			
Behavior	Normal	Mild/moderate alteration	Severe alteration	---------
	Key Considerations: 1. Alteration includes but is not limited to apathy, disinhibition and confusion. 2. Consider subclinical seizures for significant alteration.			
Other*	Normal	Occasional or mild	Persistent, moderate to severe	----------

*Other neurological findings not otherwise defined in the current examination for example ataxia.

APPENDIX H: Study Drug Diary

Instructions:
You will use this diary to record each dose of tucatinib and capecitabine that you take. You should also use this diary to record any side effects that you experience and medications that you take other than the study drugs. Please be sure to bring this diary with you to your next clinic visit.

Tucatinib: Tucatinib is taken twice a day, every day.

Capecitabine: Capecitabine is taken twice a day for 14 days, followed by 7 days of no drug (or rest). The study team will tell you if you will also take capecitabine.

- Please take both tucatinib and capecitabine at about the same times twice each day (usually morning and evening).
- If you forget to take a dose of either study drug, you should skip that dose and take the next dose at the next regular time.
- If you vomit after taking a dose of study drug, you should not make up the dose or take additional pills, you should take the next dose at the next regular time. Please, do not retake the pills.
- Always bring your tucatinib pill bottles (including those that are empty) and your diary with you to each clinic visit.

If you have any questions, please ask a study team member or your doctor.

Subject Number:

Subject Initials: _____

Cycle Number: _____

Start Date: _____

STUDY STAFF USE ONLY

Staff member reviewing diary at end of study cycle:

_____ _____

Staff initials Date reviewed

Tucatinib dose/number of pills to take at each dose: _____

Capecitabine dose/number of pills to take at each dose: _____

Other information/Comments:

_____

_____

_____

_____

Subject Number/Initials: Cycle:

Cycle Day	Due Date	Date Taken	Time Taken	Tucatinib	Capecitabine	Comments (Side effects, complaints, medications)
				# of pills taken at each dose		
1			AM			
			PM			
2			AM			
			PM			
3			AM			
			PM			
4			AM			
			PM			
5			AM			
			PM			
6			AM			
			PM			
7			AM			
			PM			
8			AM			
			PM			
9			AM			
			PM			
10			AM			
			PM			
11			AM			
			PM			
12			AM			
			PM			
13			AM			
			PM			
14			AM			
			PM			

Continued on Next Page

Subject Number/Initials:_____ Cycle:_____

Cycle Day	Due Date	Date Taken	Time Taken	Tucatinib # of pills taken at each dose	Capecitabine # of pills taken at each dose	Comments (Side effects, complaints, medications)
15			AM		NO CAPECITABINE	
			PM			
16			AM		NO CAPECITABINE	
			PM			
17			AM		NO CAPECITABINE	
			PM			
18			AM		NO CAPECITABINE	
			PM			
19			AM		NO CAPECITABINE	
			PM			
20			AM		NO CAPECITABINE	
			PM			
21			AM		NO CAPECITABINE	
			PM			

Comments: _____

_____

_____

_____

_____

APPENDIX I: RECIST Criteria V 1.1

RECIST V1.1 is to be used to assess all extra-CNS sites of disease. Selected sections from RECIST V1.1 criteria are below; for detailed guidelines, see the published guideline. [64]

Measurability of Tumor Lesions at Baseline

Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] with a minimum size of 10 mm with spiral CT scan with slice thickness no greater than 5 mm or if CT scan with slice thickness > 5 mm, the minimum lesion size must have a longest diameter twice the actual slice thickness or nonmeasurable (all other lesions, including small lesions [longest diameter < 10 mm with spiral CT scan] and truly nonmeasurable lesions).

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks (approximately 30 days) before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques. Lytic bone lesions and cystic lesions must meet criteria detailed in RECIST 1.1.

Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Examination – Clinically detected lesions will be considered measurable only when they are superficial (e.g., skin nodules and palpable lymph nodes). For
the case of skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is required.

Chest X-ray – Lesions on chest X-rays may be considered measurable lesions when they are clearly defined and surrounded by aerated lung.

CT and MRI – CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm or less contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, whereas head and neck tumors and those of the extremities usually require specific protocols.

Ultrasound –It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor Response Evaluation

Baseline Evaluation

Assessment of Overall Tumor Burden and Measurable Disease – To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion, but measurable disease is not required for this protocol.

Baseline Documentation of "Target" and "Nontarget" Lesions – All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, may be identified as target lesions and recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference by which to characterize the objective tumor response. All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Equivocal New Lesions

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Pseudoprogression or Equivocal Progression

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Response Criteria

Evaluation of Target Lesions – This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: CR—the disappearance of all target lesions; PR—at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters; PD—at least a 20% increase in the sum of the of diameters of target lesions, taking as reference the smallest sum of diameter recorded since the treatment started or the appearance of one or more new lesions; SD—neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameter since the treatment started.

Evaluation of Non-target Lesions – This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: CR—the disappearance of all non- target lesions and normalization of tumor marker level; incomplete response/SD—the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits; and PD—the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

REFERENCES

1. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-82, 1987
2. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-92, 2001
3. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-84, 2005
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-72, 2005
5. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-83, 2011
6. Viani GA, Afonso SL, Stefano EJ, et al: Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer 7:153, 2007
7. Blackwell KL, Burstein HJ, Storniolo AM, et al: Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 28:1124-30, 2010
8. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-43, 2006
9. Johnston S, Pippen J, Jr., Pivot X, et al: Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 27:5538-46, 2009
10. Baselga J, Cortes J, Kim SB, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109-19, 2012
11. Swain SM, Kim SB, Cortes J, et al: Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 14:461-71, 2013
12. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783-91, 2012
13. Giordano SH, Temin S, Kirshner JJ, et al: Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 32:2078-99, 2014
14. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer. Version 1.2018.
15. Nahta R, Yu D, Hung MC, et al: Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. Nat Clin Pract Oncol 3:269-80, 2006
16. Lu Y, Zi X, Zhao Y, et al: Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). J Natl Cancer Inst 93:1852-7, 2001
17. Saez R, Molina MA, Ramsey EE, et al: p95HER-2 predicts worse outcome in patients with HER-2-positive breast cancer. Clin Cancer Res 12:424-31, 2006
18. Pohlmann PR, Mayer IA, Mernaugh R: Resistance to Trastuzumab in Breast Cancer. Clin Cancer Res 15:7479-7491, 2009

19. Baselga J, Cortes J, Kim SB, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109-19, 2012

20. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. The New England journal of medicine 355:2733-43, 2006

21. Pivot X, Manikhas A, Zurawski B, et al: CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol 33:1564-73, 2015

22. Blackwell KL, Burstein HJ, Storniolo AM, et al: Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol 30:2585-92, 2012

23. Clayton AJ, Danson S, Jolly S, et al: Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer 91:639-43, 2004

24. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al: 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet 382:1021-8, 2013

25. Pestalozzi BC, Holmes E, de Azambuja E, et al: CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol 14:244-8, 2013

26. Lin NU, Bellon JR, Winer EP: CNS metastases in breast cancer. J Clin Oncol 22:3608-17, 2004

27. Lin NU, Winer EP: Brain metastases: the HER2 paradigm. Clinical cancer research : an official journal of the American Association for Cancer Research 13:1648-55, 2007

28. Ekenel M, Hormigo AM, Peak S, et al: Capecitabine therapy of central nervous system metastases from breast cancer. J Neurooncol 85:223-7, 2007

29. Chamberlain MC: Leptomeningeal metastases: a review of evaluation and treatment. J Neurooncol 37:271-84, 1998

30. Abouharb S, Ensor J, Loghin ME, et al: Leptomeningeal disease and breast cancer: the importance of tumor subtype. Breast Cancer Res Treat 146:477-86, 2014

31. Yust-Katz S, Garciarena P, Liu D, et al: Breast cancer and leptomeningeal disease (LMD): hormone receptor status influences time to development of LMD and survival from LMD diagnosis. J Neurooncol 114:229-35, 2013

32. Morikawa A, Jordan L, Rozner R, et al: Characteristics and Outcomes of Patients With Breast Cancer With Leptomeningeal Metastasis. Clin Breast Cancer, 2016

33. Chamberlain M, Soffietti R, Raizer J, et al: Leptomeningeal metastasis: a Response Assessment in Neuro-Oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro Oncol 16:1176-85, 2014

34. Hitchins RN, Bell DR, Woods RL, et al: A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol 5:1655-62, 1987

35. Grossman SA, Finkelstein DM, Ruckdeschel JC, et al: Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. J Clin Oncol 11:561-9, 1993

36. Shapiro WC, Schmid, M., Glantz, M., Miller, J.J.: A randomized phase III/IV study to determine benefit and safety of cytarabine liposome injection for treatment of neoplastic meningitis., ASCO, 2006

37. Groves MD, Glantz MJ, Chamberlain MC, et al: A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies. Neuro Oncol 10:208-15, 2008

38. Glantz MJ, Jaeckle KA, Chamberlain MC, et al: A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 5:3394-402, 1999

39. Pheneger T, Bouhana K, Anderson D, et al: In vitro and in vivo activity of ARRY-380: A potent, small molecule inhibitor of ErbB2. Presented at the American Association of Cancer Research 100th Annual Meeting Apr 18-22, 2009; Cancer Res 69 (abstr 1795)

40. Frankel C, Palmieri FM: Lapatinib side-effect management. Clinical journal of oncology nursing 14:223-33, 2010

41. Lucchini E, Pilotto S, Spada E, et al: Targeting the epidermal growth factor receptor in solid tumors: focus on safety. Expert opinion on drug safety 13:535-49, 2014

42. Sandler AB: Nondermatologic adverse events associated with anti-EGFR therapy. Oncology (Williston Park, N.Y.) 20:35-40, 2006

43. Lee P, Napier C, Garrus J, et al: In vivo activity of ARRY-380: A potent, small molecule inhibitor of ErbB-2 in combination with trastuzumab or docetaxel in a BT-474 human breast carcinoma xenograft model. Presented at the American Association of Cancer Research 100th Annual Meeting, Denver CO, Apr 18-22 2009; Cancer Res 69 (abstr 5581)

44. Dinkel V, Anderson D, S. W, et al: ARRY-380, a potent, small-molecule inhibitor of ErbB2, increases survival in intracranial ErbB2+ xenograft models in mice. Presented at the American Association of Cancer Research 103rd Annual Meeting 2012, Chicago, IL, Mar 31-Apr 04, 2012; Cancer Res 72, (abstr 852)

45. Borges VF, Chia, S.K.L., D'Aloisio, S., Fernetich, G., Sajan, B., Mcspadden, T., Chavira, R., Barrett, E., Guthrie K., Garrus, J., Baetz, T., Moulder, S.L.: ONT-380 (ARRY-380) - an oral HER2 inhibitor - Final Phase I Results and Conclusions. Presented at the AACR, San Diego, 2013

46. Hamilton E, Borges, V., Murthy, R., Anders, C., Cameron, D., Carey, L., Müller, V., Curigliano, G., Gelmon, K., Hortobagyi G., Krop, I., Loibl, S., Pivort, X., Pegram, M., Slamon, D., Hurvitz, S., Tsai, M., Winer, E.: A phase 2 randomized, double-blinded, controlled study of ONT-380 vs. placebo in combination with capecitabine (C) and trastuzumab (T) in patients with pretreated HER2+ unresectable locally advanced or metastatic breast carcinoma (MBC) (HER2CLIMB) (OT1-02-09), San Antonio Breast Cancer Symposium (SABCS) Annual Meeting. San Antonio, TX, 2016

47. Lin NU, Lee EQ, Aoyama H, et al: Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 16:e270-8, 2015

48. Moulder SL, Borges, V.F., Baetz, T., Mcspadden, T., Fernetich, G., Murthy, R.K., Chavira, R., Guthrie, K., Barrett, E., Chia, S.K.: Phase I study of ONT-380, a HER2 inhibitor, in patients with HER2+ advanced solid tumors, with an expansion cohort in HER2+ metastatic breast cancer(MBC). Clinical Cancer Research (pending publication), 2017

49. Murthy R, Borges VF, Conlin A, et al: Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. Lancet Oncol 19:880-888, 201

50. Arteaga CL, Sliwkowski MX, Osborne CK, et al: Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol 9:16-32, 2012

51. von Minckwitz G, du Bois A, Schmidt M, et al: Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 27:1999-2006, 2009

52. Rossi D, Alessandroni P, Catalano V, et al: Safety profile and activity of lower capecitabine dose in patients with metastatic breast cancer. Clin Breast Cancer 7:857-60, 2007

53. Bachelot T, Romieu G, Campone M, et al: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 14:64-71, 2013

54. Ferrario C, Welch, S., Chaves, J., Walker, L., Krop I., Hamilton, E., Borges V., Moulder, S.: ONT-380 in the treatment of HER2+ breast cancer central nervous system metastases (#612), American Society of Clinical Oncology (ASCO) Annual Meeting. Chicago, IL, 2015

55. Murthy RK, Hamilton, E., Borges, V., Moulder, S., Aucoin, N., Welch, S., Chaves, J., Falkson, C.I., Walker, L., Ferrario, C.: ONT-380 in the treatment of HER2+ breast cancer central nervous system (CNS) metastases (P4-14-19), San Antonio Breast Cancer Symposium (SABCS) Annual Meeting San Antonio, TX, 2015

56. Metzger O, Barry, W., Guo, H., Younger, J., Lawler, E., Walker, L., Freedman, R., Tolaney, S., Krop, I., Winer, E.P., Lin, N.: Phase I dose escalation trial of ONT-380 in combination with trastuzumab in patients (pts) with HER2+ breast cancer brain metastases (P1-12-04), San Antonio Breast Cancer Symposium (SABCS) Annual Meeting. San Antonio, TX, 2016

57. Walker J, Tremont, I., O'Brien, B., Armstrong, T. : QOL-26 Describing Symptom Burden in patients with leptomeningeal metastases: Selecting an instrument. , 20th Annual Scientific Meeting of the Society for Neuro-Oncology. San Antonio, Oxford University Press, 2015, pp 193-194

58. Boogerd W, Hart AA, van der Sande JJ, et al: Meningeal carcinomatosis in breast cancer. Prognostic factors and influence of treatment. Cancer 67:1685-95, 1991

59. Wang Y, Springer S, Zhang M, et al: Detection of tumor-derived DNA in cerebrospinal fluid of patients with primary tumors of the brain and spinal cord. Proc Natl Acad Sci U S A 112:9704-9, 2015

60. Navin N, Kendall J, Troge J, et al: Tumour evolution inferred by single-cell sequencing. Nature 472:90-4, 2011

61. Pentsova EI, Shah RH, Tang J, et al: Evaluating Cancer of the Central Nervous System Through Next-Generation Sequencing of Cerebrospinal Fluid. J Clin Oncol 34:2404-15, 2016

62. Chamberlain M, Junck L, Brandsma D, et al: Leptomeningeal metastases: a RANO proposal for response criteria. Neuro Oncol, 2016

63. Gehan EA: The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. J Chron Dis:346-353, 1961

64. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009