Protocol Number:	SGNTUC-016
Version:	Amendment 4; 08-Nov-2023
Protocol Title:	Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer **(HER2CLIMB-02)**
Investigational Product:	Tucatinib
Brief Title:	A study of tucatinib vs. placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with advanced or metastatic HER2+ breast cancer
Indication:	Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer
Phase:	3
IND Number:	119421
EudraCT Number	2019-005017-39
EU CT Number	2023-506418-30
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	[redacted] Seagen Inc. Tel: [redacted] E-mail: [redacted]
SAE Email or Fax:	See email or fax number specified on the SAE report form.

PROTOCOL SYNOPSIS

Protocol Number	**Product Name**
SGNTUC-016	Tucatinib
Version	**Sponsor**
Amendment 4; 08-Nov-2023	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Phase	
3	

Protocol Title

Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer **(HER2CLIMB-02)**

Study Objectives

Primary

- Compare progression-free survival (PFS) by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between treatment arms

Key Secondary

- Compare overall survival (OS) between treatment arms
- Compare PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline (PFS.BM per investigator) between treatment arms
- Compare the objective response rate (ORR) by investigator assessment per RECIST v1.1 between treatment arms
- Compare overall survival in subjects with brain metastases at baseline (OS.BM) between treatment arms

Other Secondary

- Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1 between treatment arms
- Evaluate PFS by BICR per RECIST v1.1 in subjects with brain metastases at baseline (PFS.BM per BICR) between treatment arms
- Evaluate the ORR by BICR per RECIST v1.1 between treatment arms
- Evaluate the duration of response (DOR) by investigator assessment per RECIST v1.1 between treatment arms
- Evaluate the DOR by BICR per RECIST v1.1 between treatment arms
- Evaluate the clinical benefit rate (CBR; stable disease [SD] or non-complete response [CR]/non-progressive disease [PD] for ≥6 months or best response of CR or partial response [PR]) by investigator assessment per RECIST v1.1 between treatment arms
- Evaluate the CBR by BICR per RECIST v1.1 between treatment arms
- Evaluate the safety of tucatinib in combination with T-DM1

Exploratory

- Evaluate the pharmacokinetics of tucatinib and DM1 following administration of tucatinib and T-DM1 in combination
- Evaluate on-trial healthcare resource utilization (HCRU) between treatment arms
- Evaluate patient-reported outcomes (PROs) and health-related quality of life (QoL) between treatment arms

Study Population

Eligible subjects are at least 18 years of age or at least the age of majority in the geographic location and have unresectable locally-advanced or metastatic (LA/M) human epidermal growth factor receptor 2 positive (HER2+) breast cancer with a life expectancy of at least 6 months. Subjects must have histologically confirmed HER2+ breast carcinoma and had prior treatment with a taxane and trastuzumab in any setting (separately or in combination), and must have progressed or have been intolerant of the last systemic therapy (see Appendix L for France-specific requirements).

Hormone receptor status must also be known prior to randomization. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, adequate cardiac function, and adequate renal, hepatic, and hematologic function at baseline. Prior treatment with tucatinib, T-DM1, afatinib, trastuzumab deruxtecan (T-Dxd; DS-8201a), or any other investigational anti-HER2 or anti-epidermal growth factor receptor agent or HER2 tyrosine kinase inhibitor agent is not permitted. Lapatinib or neratinib are prohibited if received within 12 months of starting study treatment (except in cases where they were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity). Prior treatment with pyrotinib for recurrent or metastatic breast cancer (mBC) is not permitted (except in cases where pyrotinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity). Prior pertuzumab therapy is allowed, but not required. Subjects must be >3 weeks post-treatment from any prior systemic anticancer therapy (including hormonal therapy), noncentral nervous system radiotherapy (palliative or therapeutic), or participation in another interventional clinical trial.

Subjects with untreated brain metastases on screening brain magnetic resonance imaging (MRI) are eligible if immediate local therapy is not required. Subjects with brain metastases previously treated with local therapy are eligible if the brain metastases are stable since treatment; or, if there has been progression since the prior local central nervous system (CNS) therapy, immediate retreatment with local therapy is not required. If treatment for newly identified lesions or previously treated and progressing lesions is initiated, subjects may still be eligible if other sites of evaluable disease are present and treatment is completed prior to the first dose of study treatment as follows: stereotactic radiosurgery is completed ≥7 days prior, whole brain radiation therapy is completed ≥14 days prior, or time since surgical resection is ≥28 days. Ongoing use of systemic corticosteroids at a total daily dose of >2 mg of dexamethasone (or equivalent) for symptomatic control is not permitted. Subjects with poorly controlled generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy are not permitted.

Number of Planned Subjects

Approximately 460 subjects (approximately 230 subjects per treatment arm) will be randomized in the global portion of this study. After enrollment of the global portion of the study is completed, the study may remain open to enrollment in China alone until approximately 105 (up to 110) subjects in China (including those randomized in the global portion and China portion) have been randomized.

Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. Baseline disease assessments include measurement of all known sites of unresectable locally-advanced/metastatic disease through radiographic imaging. Assessment for brain metastases is performed with contrast MRI of the brain for all subjects, regardless of prior history of brain metastases. Subjects will be randomized in a 1:1 manner to receive 21-day cycles of either tucatinib or placebo in combination with T-DM1. Randomization will be stratified by line of treatment for metastatic disease, hormone receptor status, presence or history of brain metastases, and ECOG performance status.

While on study treatment, subjects will be assessed for progression every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. After completion of study treatment and after occurrence of disease progression, subjects in both arms of the study will continue to be followed for survival until study closure or withdrawal of consent.

An independent data monitoring committee will periodically review relevant aggregate safety data (blinded and unblinded) and will make recommendations to the sponsor. Safety will also be monitored in an ongoing, blinded basis by the sponsor throughout the study.

Investigational Product, Dose, and Mode of Administration

Subjects will be randomized in a 1:1 manner to receive study treatment on a 21-day cycle, either:

- Control arm: Placebo given orally twice a day (PO BID); T-DM1 3.6 mg/kg given intravenously (IV) every 21 days
- Experimental arm: Tucatinib 300 mg PO BID; T-DM1 3.6 mg/kg IV every 21 days

Duration of Treatment

Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. In the absence of clear evidence of radiographic progression, development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs. No crossover from placebo to tucatinib will be allowed. Subjects assessed as having isolated progression in the brain per RECIST v1.1 may be eligible to continue on study treatment for clinical benefit after undergoing local therapy to CNS disease, with approval from the medical monitor.

Efficacy Assessments

Disease response per RECIST v1.1 (Eisenhauer 2009) will be assessed by both investigator assessment and BICR. Response assessments will include measurement of all known sites of unresectable LA/M disease (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast computed tomography (CT), at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose interruptions. Positron emission tomography/CT (if high quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other known sites of disease (eg, skin lesion photography for skin lesions, nuclear bone scan imaging for bone lesions).

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

Treatment decisions will be made based upon local assessment of radiologic scans. Response assessments for each subject will continue until a PFS event per RECIST v1.1 by investigator assessment has been documented. Follow-up for survival will continue until study closure or withdrawal of consent.

Pharmacokinetic Assessments

Pharmacokinetic (PK) assessments will be performed from Cycle 3 to Cycle 6 in all subjects to assess the steady state pharmacokinetics of tucatinib and DM1. In the US only, approximately 50 subjects (25 from each treatment arm) will participate in a PK substudy with additional PK sampling on Days 1, 2, 3, and 5 in Cycle 2 to assess any effects of tucatinib on the pharmacokinetics of DM1.

Other Assessments – PROs and Health Care Resource Utilization

PROs will be assessed at protocol-specified time points using standardized assessment tools. These PRO instruments include the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L) instrument, 2 questions to capture global health status/quality of life from the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ IL6), the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE) questionnaire customized to focus on adverse events (AEs) or symptoms of interest, and 1 question from the Functional Assessment of Cancer Therapy – Breast (FACT-B GP5) questionnaire to capture the patients' perceptions of side effects. In addition, a summary of health care resource utilization (HCRU) will be presented.

Safety Assessments

Safety assessments will include surveillance and recording of AEs, physical examination findings, and laboratory tests. Assessment of cardiac ejection fraction will be performed by multigated acquisition scan or echocardiogram.

Statistical Methods

Stratification

Stratification factors will include line of treatment for metastatic disease (1st line metastatic versus other), hormone receptor status (positive/negative), presence or history of treated or untreated brain metastases (yes/no), and ECOG performance status (0 versus 1). Stratification for presence of brain metastases will be based upon medical history and investigator assessment of screening contrast brain MRI. Only subjects with parenchymal lesions are considered as having brain metastases at baseline for purposes of stratification.

Sample Size Considerations

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of PFS events (hazard ratio [HR] of 0.70; median PFS from 6 months in the control arm to 8.57 months in the experimental arm).

A total of 331 PFS events will provide 90% power to detect a HR of 0.70 at a 2-sided significance level of 0.05 using a log-rank test. Approximately 460 subjects will be randomized in a 1:1 ratio to either the experimental arm or the control arm to observe 331 PFS events in approximately 30 months after the first subject is randomized, assuming 24 months of subject accrual, and a 5% annual dropout rate.

It is planned that follow-up for OS will continue after the primary analysis of PFS. The final OS analysis will be performed when approximately 253 OS events have occurred. With 253 events, it will provide 80% power to detect a HR of 0.70 in OS at a 2-sided significance level of 0.05 using a log-rank test. The final analysis of OS is estimated to take place approximately 30 months after the primary analysis of PFS per investigator assuming that OS for the control arm follows an exponential distribution with a median of 29 months.

Follow-up of PFS.BM per investigator will continue after the primary analysis of PFS until the second interim analysis of OS. It is anticipated that approximately 175 PFS.BM events would have occurred, which will provide 65% power to detect a HR of 0.7 in PFS.BM at a 2-sided significance level of 0.05 using a log-rank test.

To evaluate the consistency of efficacy and safety in a China subpopulation compared with the global population, after completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 105 (up to 110) subjects in China including those randomized in the global portion and China portion is reached. Subjects in China randomized after completion of enrollment in the global portion will not be included in the analysis of the global portion. After the completion of the global portion, the study may remain open to complete the China portion as an extension of the study.

Analysis Methods

For the primary endpoint of PFS per investigator assessment, the 2 treatment groups will be compared using a 2-sided stratified log-rank test. Estimation of the HR will be based upon the stratified Cox regression model. PFS will also be summarized using the Kaplan-Meier method. All randomized subjects will be included in the primary analysis of PFS. Kaplan-Meier methodology will be used to estimate the PFS time curves, including the median. Similar methods will be used for the key and other secondary time-to-event endpoints and other exploratory time-to-event endpoints. No interim analyses will be performed for the primary endpoint.

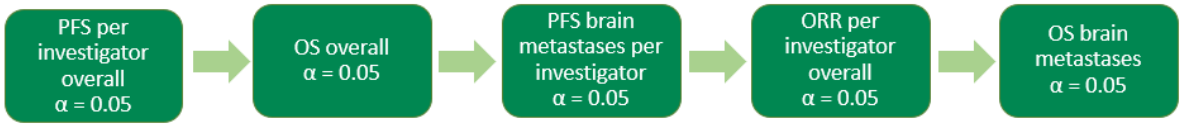
If PFS per investigator is statistically significant, then there will be 3 analyses of the key secondary endpoint of OS. The first OS interim analysis (OS IA1) will be conducted at the time of analysis of the primary endpoint when approximately 331 PFS events per investigator assessment have occurred. The second OS interim analysis (OS IA2) will be conducted when approximately 202 (80%) OS events have occurred. The final OS analysis (OS FA) is planned when approximately 253 OS events have occurred.

If both PFS and OS (OS IA1, OS IA2, or OS FA) results are statistically significant, then there will be 2 analyses of the key secondary endpoint of PFS.BM by investigator assessment per RECIST v1.1. The first PFS.BM analysis

will use the PFS.BM data at the time of analysis of the primary endpoint when approximately 331 PFS events per investigator assessment have occurred. The final PFS.BM analysis will use the PFS.BM data at the time of OS IA2.

If the results of PFS, OS, and PFS.BM are all statistically significant, a formal statistical test of ORR will be performed.

If the results of PFS per investigator, OS, PFS.BM per investigator and ORR per investigator are all statistically significant, then OS in subjects with brain metastases at baseline (OS.BM) will be formally tested. Hierarchical Testing Strategy



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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BICR	blinded independent central review
BID	twice per day
CBC	complete blood count
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DFS	disease-free survival
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire
EOT	end of treatment
EQ-5D-3L	European Quality of Life 5-Dimension 3-Level
EQ-VAS	European Qualify of Life Visual Analogue Scales
EuroQoL	European Quality of Life

FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-B GP5	Functional Assessment of Cancer Therapy – Breast, Item GP5
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FOCBP	females of childbearing potential
GFR	glomerular filtration rate
HCRU	healthcare resource utilization
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
LA/M	locally-advanced or metastatic
LFT	liver function test
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NCI PRO-CTCAE	National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
OS FA	final analysis of overall survival
OS IA1	overall survival interim analysis 1
OS IA2	overall survival interim analysis 2
PCR	polymerase chain reaction

PD	progressive disease
PDX	patient-derived
PET	positron emission tomography
PFS	progression-free survival
PFS.BM	progression-free survival in subjects with brain metastasis at baseline
P-gp	P-glycoprotein
PH	proportional-hazards
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic
PO BID	orally twice per day
PR	partial response
PRO	patient-reported outcome
PTT	partial thromboplastin time
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
Scr	serum creatine
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
WBRT	whole-brain radiation therapy

1. INTRODUCTION

1.1. HER2+ Breast Cancer

Breast cancer is the most common form of cancer in women worldwide, and the second leading cause of cancer-related death in the United States (Ferlay 2013; Siegel 2018). In 2018, the estimated number of men and women who were newly diagnosed with breast cancer in the United States was 268,670 and there were 40,920 deaths overall due to the disease (Siegel 2018). Approximately 15%–20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) (Owens 2004; Giordano 2014; Howlader 2014; American Cancer Society (ACS) 2018). HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Tumors that overexpress HER2 are more aggressive and historically have been associated with poorer overall survival (OS) compared to HER2 negative cancers (Slamon 1987).

The introduction of HER2-targeted therapy using either antibody-based therapies or small molecule tyrosine kinase inhibitors (TKI) has led to significant and ongoing improvements in disease-free survival (DFS), progression-free survival (PFS), and OS in both the neoadjuvant/adjuvant and metastatic settings (Slamon 2001; Geyer 2006; Baselga 2012b; Verma 2012). Trastuzumab, a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, was the first anti-HER2 agent approved by the Food and Drug Administration (FDA) for use in the treatment of HER2-positive (HER2+) breast cancer, and remains the backbone of treatment in the neoadjuvant, adjuvant, and metastatic settings, usually in combination with a taxane (Slamon 2001; Vogel 2002).

The development of trastuzumab has been followed by the approval of multiple anti-HER2 agents for the management of HER2+ breast cancer including:

- Pertuzumab, a monoclonal antibody that binds to the HER2 receptor at a site different from trastuzumab, was approved in combination with trastuzumab and docetaxel as first-line therapy for patients with metastatic disease (Swain 2015), and for the neoadjuvant treatment of patients with early-stage breast cancer (either greater than 2 cm in diameter or node positive) (Gianni 2016) (PERJETA® Prescribing Information, Genentech, Inc., December 2018). More recently, it was approved for the adjuvant treatment of patients with HER2+ early breast cancer at high risk of recurrence (von Minckwitz 2017).
- Ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate composed of trastuzumab, a thioether linker, and a derivative of the antimitotic agent maytansine, was approved for the treatment of patients with HER2+ metastatic breast cancer (mBC) who previously received trastuzumab and a taxane (prior therapy for metastatic disease, or development of recurrence during or within 6 months of completing adjuvant therapy) (Verma 2012) (KADCYLA® Prescribing Information, Genentech, Inc., December 2018). More recently, T-DM1 showed superior efficacy relative to trastuzumab in the adjuvant therapy management of subjects who had less than a pathological complete remission to neoadjuvant trastuzumab-based therapy in the KATHERINE trial (von Minckwitz 2019).

- Two TKIs, lapatinib and neratinib, have been approved. Lapatinib targets both the HER2 receptor and the epidermal growth factor receptor (EGFR) and was approved in combination with capecitabine in patients with metastatic disease who have progressed following prior trastuzumab, anthracycline, and taxane therapy (Geyer 2006) (TYKERB® Prescribing Information, Novartis Pharmaceuticals Corp., December 2018). Lapatinib has also been approved in combination with letrozole in postmenopausal patients with hormone receptor positive metastatic disease (Schwartzberg 2010). Neratinib, a pan-Erb inhibitor, was approved for the extended adjuvant treatment of patients with high-risk early-stage HER2+ breast cancer, to follow adjuvant trastuzumab-based therapy (Chan 2016). Lapatinib and neratinib have been associated with toxicities including diarrhea and rash that are likely associated with EGFR inhibition. For example, over 40% of subjects in the neratinib adjuvant ExteNET study experienced Grade ≥3 diarrhea, and antidiarrheal prophylaxis is now recommended with neratinib use (NERLYNX® Prescribing Information, Puma Biotechnology, Inc., June 2018). Therefore, more selective small molecule inhibitors of HER2 that could be combined with other anti-HER2 therapies to improve clinical outcomes are needed.

HER2-targeted therapies for the management of metastatic HER2+ breast cancer have led to meaningful prolongation in the median survival of these subjects; however, essentially all subjects in the metastatic setting ultimately progress (Verma 2012; Swain 2015). There have also been significant improvements in the outcomes for early-stage HER2+ breast cancer, but despite these improvements, up to a quarter of all subjects treated with anti-HER2 therapy in the adjuvant setting relapse (Gianni 2012; Chan 2016; von Minckwitz 2017). In addition, treatment and prevention of brain metastases continue to be a significant unmet need for subjects with HER2+ breast cancer, with up to 50% of subjects with metastatic disease eventually developing brain metastases (Clayton 2004; Goldhirsch 2013; Pestalozzi 2013).

1.2. Use and Sequencing of T-DM1 in the Metastatic Setting

As noted above, T-DM1 is approved for the treatment of HER2+ mBC. The sequencing of therapy may differ, however, depending on whether a subject has de novo versus relapsed HER2+ mBC.

The current preferred standard of care for patients with de novo HER2+ metastatic disease consists of treatment with pertuzumab plus trastuzumab and a taxane as first-line treatment based on results of the CLEOPATRA trial, followed by T-DXd (Enhertu®) in second-line based on results from the randomized, open-label DESTINY-Breast03 trial. T-DM1 remains a treatment option in this setting and in later treatment lines for patients who did not receive T-DM1 in the second-line setting (Giordano 2014). In 2013, T-DM1 was approved by the FDA as a second-line therapy based upon prolongation of PFS and OS in metastatic subjects previously treated with trastuzumab and taxane in the metastatic setting, or who relapsed within 6 months of completion of adjuvant therapy, based on the results of the EMILIA trial. Among 991 randomly assigned subjects, median PFS was 9.6 months with T-DM1 versus 6.4 months with lapatinib + capecitabine (HR=0.65; 95% CI: 0.55, 0.77; P<0.001), and median OS of 30.9 months versus 25.1 months (HR=0.68), respectively (Verma 2012).

The sequencing of therapies may differ for patients who relapse after treatment for early-stage disease with the approval of pertuzumab in both the neoadjuvant and adjuvant settings. Patients diagnosed with metastatic disease after relapsing from early-stage disease often have already been treated with pertuzumab, a clinical scenario which did not exist at the time of the EMILIA trial. The best treatment approach for these patients is not clear, as there are not sufficient data to support re-treatment with pertuzumab in this setting.

Another uncertainty, introduced by contemporaneous development of pertuzumab and T-DM1, is that efficacy of T-DM1 in the metastatic setting after treatment with pertuzumab-based regimens is not well known. Because pertuzumab was not yet available, the EMILIA pivotal trial did not include subjects previously treated with pertuzumab, so it may not reflect the current patient population in this setting. The TH3RESA trial of T-DM1 in the third-line or later setting demonstrated a median PFS of 6.2 months (95% CI: 5.59, 6.87) with T-DM1 treatment (Krop 2014), while the earlier line EMILIA trial had demonstrated PFS of 9.6 months (HR=0.65; 95% CI: 0.55, 0.77; P<0.001) (Verma 2012). However, more recent data from the post-pertuzumab era in subjects treated with T-DM1 after pertuzumab have reported time on treatment and PFS in the range of 4–5.3 months (Dzimitrowicz 2016; Fabi 2017; Tiwari 2018), suggesting that T-DM1 efficacy after pertuzumab may be less than the original efficacy reported in the EMILIA trial. Notwithstanding some of the above uncertainties regarding current T-DM1 efficacy, it is a standard of care therapy and can be further improved upon.

1.3. Brain Metastases

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

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

2009; Brown 2016; Kaidar-Person 2016). Subjects with brain metastases have historically been excluded from clinical trials.

Breast cancer subjects with HER2+ brain metastases have a worse prognosis relative to those without CNS disease. In population-based registries of HER2+ mBC subjects enrolled at diagnosis, evidence of brain metastases led to a shortened survival relative to subjects without brain metastases (Brufsky 2011). Among the 377 subjects with brain metastases, median OS from the date of initial mBC diagnosis was 26.3 months (range: 1.0 to 60.9 months) compared to 44.6 months (range: 0.5 to 59.7 months) in the 635 subjects who did not have CNS metastases (Brufsky 2011).

As with many systemic therapies, T-DM1 may also be less efficacious in patients with brain metastases. While subjects with active brain metastases were excluded from the EMILIA and TH3RESA T-DM1 trials, subjects with stable treated brain metastases were included. In the EMILIA trial, subjects with brain metastases treated with T-DM1 had no significant improvement in PFS compared to the control arm (5.9 months versus 5.7 months; HR=1.00; 95% CI: 0.54, 1.84; P=1.000) and the PFS.BM of 5.9 months compared unfavorably to the median PFS of 9.6 months in the trial overall, although there was an improvement in OS (Krop 2015). In the third-line+ TH3RESA trial, subjects with stable treated brain metastases had similar median PFS but shorter median OS compared to subjects without [PFS: 5.8 months versus 6.2 months (Krop 2015); OS: 17.3 months versus 23.7 months (Krop 2017)]. Most recently, data from the KATHERINE trial demonstrated that adjuvant treatment with T-DM1 for high-risk subjects yielded a significant improvement in DFS, but failed to have any significant impact on the development of brain metastases (von Minckwitz 2019). Therefore, development of treatments for this patient population remains an important unmet medical need, and addressing this need will require including these subjects in clinical trials.

1.4. Tucatinib

Tucatinib (ONT-380) is an orally-available, reversible HER2 small molecule TKI. Two key features of tucatinib are its potency and selectivity for HER2 compared to the closely-related kinase EGFR. Tucatinib is approximately 6-fold more potent in its inhibition of HER2 compared to lapatinib, the only currently approved HER2 TKI for patients with metastatic disease. In addition, tucatinib is highly selective for HER2 compared to EGFR. With a 500-fold increase in potency for HER2 inhibition compared to EGFR, it has the potential to inhibit HER2 signaling while avoiding known EGFR-related side effects (eg, severe skin rash and gastrointestinal toxicity). This unique feature also differentiates tucatinib from other HER2 inhibitors, including both neratinib and lapatinib, which inhibit HER2 and EGFR with similar potency and are associated with side effects related to EGFR inhibition.

Tucatinib is being developed as a novel treatment for patients with HER2+ mBC, including patients with brain metastases. The pivotal trial HER2CLIMB demonstrated that in subjects with HER2+ locally advanced or metastatic breast cancer who had previously received trastuzumab, pertuzumab, and T-DM1, the addition of tucatinib to trastuzumab and capecitabine significantly improved PFS and OS, in the overall study population and in subjects with brain metastases at baseline (Lin 2020; Murthy 2020). Tucatinib is currently approved in combination with trastuzumab and capecitabine to treat patients with HER2+ breast cancer in over 45 countries.

A complete summary of the nonclinical and clinical data for tucatinib is provided in the investigator's brochure.

1.4.1. Rationale for Tucatinib in Combination with T-DM1

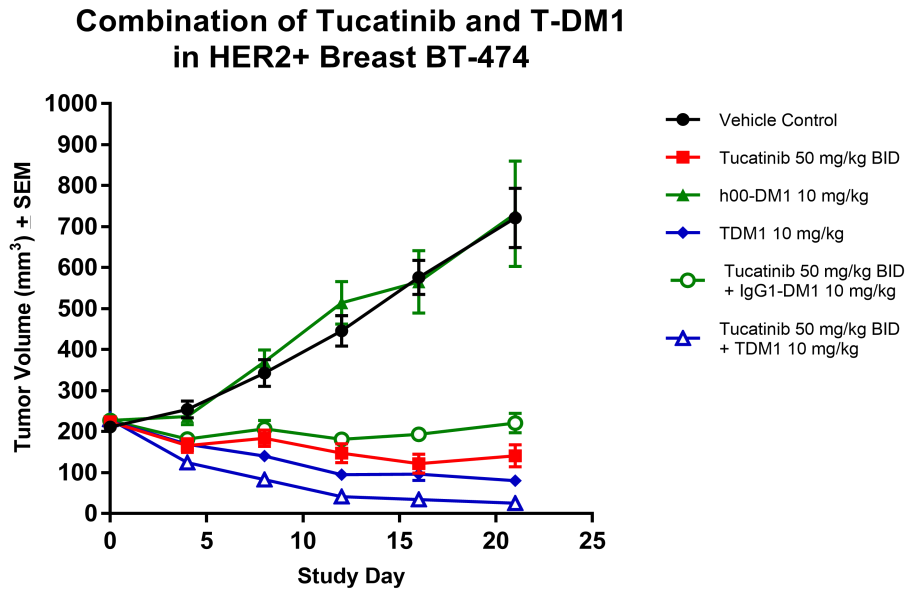
Treatment failures in HER2+ breast cancer may result from primary or acquired resistance to HER2 blockade (Lu 2001; Nahta 2006; Scaltriti 2007; Pohlmann 2009). There is evidence that dual targeting of HER2, either through combination of 2 different HER2-targeted antibodies or through use of an antibody-based therapy and a TKI, can lead to further improvements in efficacy in metastatic disease (Baselga 2012a; Baselga 2012b). In particular, combination of a small molecule TKI with an antibody-based therapy may be effective, as it may help overcome resistance to antibody-mediated inhibition through an alternative mechanism of receptor inhibition. For example, lapatinib has been shown to have increased activity in combination with trastuzumab compared to lapatinib alone, even when given to subjects who have previously progressed on prior trastuzumab-based therapy (Blackwell 2010; Blackwell 2012).

T-DM1 treatment results in the targeted delivery of the potent antimitotic DM1 to HER2+ tumor cells, which binds to tubulin and causes mitotic arrest and cell death (Lewis Phillips 2008). Combining tucatinib with T-DM1 may potentially improve upon the efficacy of T-DM1 through increased inhibition of HER2 signal transduction, including blockade of both the -Erk-/MEK and phosphatidylinositol 3-kinase (PI3K)/AKT pathways. Inhibition of pro-survival signaling mediated by the PI3K/AKT pathway, together with DM1 toxin delivery, may result in increased cell death, potentially overcoming or delaying the development of resistance.

1.4.2. Tucatinib + T-DM1 Nonclinical Experience

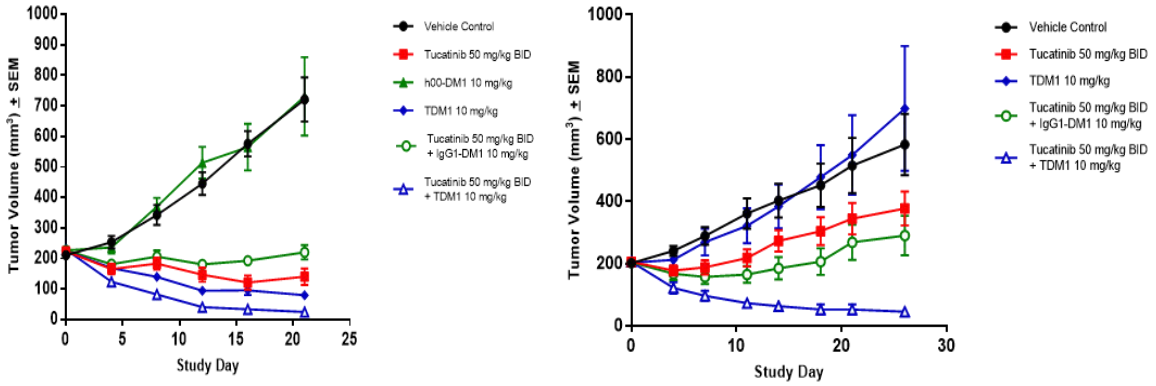
Nonclinical data show the combination of tucatinib with T-DM1 results in improved antitumor activity in HER2+ breast cancer models. In HER2+ tumor-derived cell lines, tucatinib in combination with T-DM1 can result in additive or synergistic activity (data not shown). In addition, the combination of tucatinib and T-DM1 was more effective than either drug individually in the BT-474 cell line-derived xenograft model (Figure 1) and in 2 HER2+ patient-derived (PDX) breast cancer models (Figure 2). Each of the HER2+ PDX models are estrogen receptor/progesterone receptor negative, immunohistochemistry 3+ for HER2, and contain genomic amplification of the HER2 gene.

Figure 1: Combination of tucatinib and T-DM1 in HER2+ breast cell line-derived xenograft model



Mice bearing BT-474 subcutaneous xenografts were treated by oral gavage with tucatinib, intravenous (IV) T-DM1 or control IgG1-DM1, or a combination of tucatinib with both drugs, at the dose levels and schedules as indicated.

Figure 2: Combination of tucatinib and T-DM1 in HER2+ patient-derived breast cancer model



Mice bearing HER2+ subcutaneous xenografts were treated by oral gavage with tucatinib, IV T-DM1 or control IgG1-DM1, or a combination of tucatinib with both drugs, at the dose levels and schedules as indicated.

In the T-DM1 resistant PDX models, tucatinib inhibited tumor growth and the combination of tucatinib with T-DM1 produced increased tumor control when compared with either drug alone in the cell line derived BT-474 model, and in both PDX models.

1.4.3. Tucatinib + T-DM1 Clinical Experience

One clinical trial has been conducted to evaluate the safety, tolerability, and preliminary clinical activity of tucatinib in combination with T-DM1. Study ONT-380-004 is a phase 1b, open-label, multicenter, 3+3 dose-escalation study in subjects with HER2+ mBC, designed to identify the maximum-tolerated dose (MTD) or recommended phase 2 dose of tucatinib in combination with

T-DM1. Subjects had a history of prior therapy with trastuzumab and a taxane, separately or in combination; for subjects in the dose-escalation and MTD-expansion cohorts, prior therapy with trastuzumab and a taxane must have been for metastatic disease. For subjects in the CNS disease-expansion cohorts, trastuzumab and taxane (together or separately) might have been given at any time prior to study enrollment as part of neoadjuvant therapy, adjuvant therapy, or therapy for metastatic disease.

Fifty-seven T-DM1-naive subjects were treated (Borges 2018). The tucatinib MTD was determined to be 300 mg administered orally twice per day (PO BID) in combination with the approved dose of T-DM1 (3.6 mg/kg every 21 days). Among the 50 subjects treated at the MTD, the most common adverse events (AEs) occurring in ≥40% of subjects were nausea, diarrhea, fatigue, epistaxis, headache, vomiting, constipation, and decreased appetite; the majority of AEs were Grade 1 or 2. In these 50 subjects, the median PFS was 8.2 months (95% CI: 4.8, 10.3); the clinical benefit rate (CBR; subjects with best response of complete response [CR] or partial response [PR], or stable disease [SD] for >6 months) among 48 evaluable subjects was 58% (28 subjects). Thirty-four of 50 subjects (68%) treated with the MTD had measurable disease and were evaluable for response with an objective response rate (ORR) of 47% (1 subject with CR, 15 subjects with PR, 14 subjects with SD, and 4 subjects with progressive disease [PD]). Among the subjects whose disease responded to treatment, the median duration of response (DOR) was 6.9 months (95% CI: 2.8, 19.8). Thirty of 50 subjects (60%) treated at the MTD had brain metastases at study entry. Of these, 21 of 30 subjects (70%) had either untreated or previously treated and progressive brain metastases. Median PFS among subjects with brain metastases was 6.7 months (95% CI: 4.1, 10.2). [redacted] (Seagen internal data). The combination of tucatinib with T-DM1 was found to have a tolerable safety profile, with evidence of clinical activity, including in subjects with brain metastases.

1.4.4. Rationale for Study

The development and approval of multiple targeted agents for HER2+ breast cancer over the last 20 years has led to improvements in response rates, PFS, and OS. However, in most cases, subjects with mBC progress on currently available therapy and cannot be cured. The intent of this phase 3, randomized trial is to assess whether the addition of tucatinib to T-DM1 can not only improve the efficacy observed with T-DM1 as second-line therapy in subjects with HER2+ mBC that failed trastuzumab and taxane, but also whether the combination can be effective against CNS metastases in HER2+ breast cancer (an area of continued medical need).

Given tucatinib's selectivity for HER2 over EGFR, it has the potential to provide dual HER2 inhibition by combining with other oral anti-HER2 agents with fewer significant EGFR-related toxicities such as severe diarrhea. The combination of tucatinib and T-DM1 was found to be well tolerated and showed clinical activity in the ONT-380-004 study. ONT-380-004 included a meaningful number of subjects with brain metastases, and preliminary data suggests activity, including intracranial responses and a similar median PFS in subjects with brain metastases compared to those without (Borges 2018; Murthy 2018). A systemic therapy such as tucatinib that effectively treats existing brain metastases could control neurologic symptoms of brain

metastases and potentially delay the need for radiotherapy or surgical resection, thus avoiding the sequelae associated with progressive brain metastases and their local treatment. Furthermore, a systemic treatment effective against micrometastases could potentially prevent or delay the eventual development of clinically evident brain metastases. Based on nonclinical data demonstrating improved antitumor activity of tucatinib in combination with T-DM1, as well as the experience on the phase 1b ONT-380-004 trial, the addition of tucatinib to T-DM1 could potentially further improve the efficacy of T-DM1 and the standard-of-care management, including in subjects with brain metastases.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of tucatinib versus placebo in combination with T-DM1 in subjects with unresectable locally-advanced or metastatic (LA/M) HER2+ breast cancer. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and corresponding endpoints

Objective	Corresponding Endpoint
Primary	
• Compare PFS by investigator assessment per RECIST v1.1 between treatment arms	• PFS per RECIST v1.1, as determined by investigator assessment
Key Secondary	
• Compare OS between treatment arms	• OS
• Compare PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline (PFS.BM per investigator) between treatment arms	• PFS.BM per RECIST v1.1, as determined by investigator assessment
• Compare the ORR by investigator assessment per RECIST v1.1 between treatment arms	• ORR per RECIST v1.1, by investigator assessment
• Compare overall survival in subjects with brain metastases at baseline (OS.BM) between treatment arms	• OS.BM
Other Secondary	
• Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1 between treatment arms	• PFS per RECIST v1.1, as determined by BICR
• Evaluate PFS by BICR per RECIST v1.1 in subjects with brain metastases at baseline (PFS.BM by BICR) between treatment arms	• PFS.BM per RECIST v1.1, by BICR
• Evaluate the ORR by BICR per RECIST v1.1 between treatment arms	• ORR per RECIST v1.1, by BICR
• Evaluate the DOR by investigator assessment per RECIST v1.1 between treatment arms	• DOR per RECIST v1.1, by investigator assessment
• Evaluate the DOR by BICR per RECIST v1.1 between treatment arms	• DOR per RECIST v1.1, by BICR
• Evaluate the CBR (SD or non-CR or non-progressive disease [PD] for ≥6 months or best response of CR or PR) by investigator assessment per RECIST v1.1 between treatment arms	• CBR per RECIST v1.1, by investigator assessment
• Evaluate the CBR by BICR per RECIST v1.1 between treatment arms	• CBR per RECIST v1.1, by BICR
• Evaluate the safety of tucatinib in combination with T-DM1	• Incidence of AEs
Exploratory	

Objective	Corresponding Endpoint
• Evaluate the pharmacokinetics of tucatinib and DM1 following administration of tucatinib and T-DM1 in combination	• Pharmacokinetic (PK) parameters for tucatinib and DM1
• Evaluate on-trial healthcare resource utilization (HCRU) between treatment arms	• HCRU based on the number of medical care encounters and other procedures of interest
• Evaluate patient-reported outcomes (PROs) and health-related QoL between treatment arms	• QoL measured by the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L), European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ IL6), National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE), and Functional Assessment of Cancer Therapy – Breast (FACT-B GP5)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. Subjects will be randomized in a 1:1 manner to receive 21-day cycles of treatment in 1 of the following 2 treatment groups:

- Control arm: Placebo given PO BID; T-DM1 3.6 mg/kg given intravenously (IV) every 21 days
- Experimental arm: Tucatinib 300 mg PO BID; T-DM1 3.6 mg/kg IV every 21 days

Tucatinib or placebo will be dispensed to subjects in a double-blinded manner. Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing date, allowing for dose holds or delays with T-DM1. Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.

Disease response and progression will be assessed using RECIST v1.1. While on study treatment, radiographic disease evaluations will be performed every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. In the absence of clear evidence of radiographic progression, development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs. Subjects assessed as having isolated progression in the brain per RECIST v1.1 may be eligible to continue on study treatment for clinical benefit after undergoing local therapy for CNS disease, with approval from the medical monitor (see Section 4.4.1.1).

After completion of study treatment and after occurrence of disease progression, subjects in both arms of the study will continue to be followed for survival until study closure or withdrawal of consent.

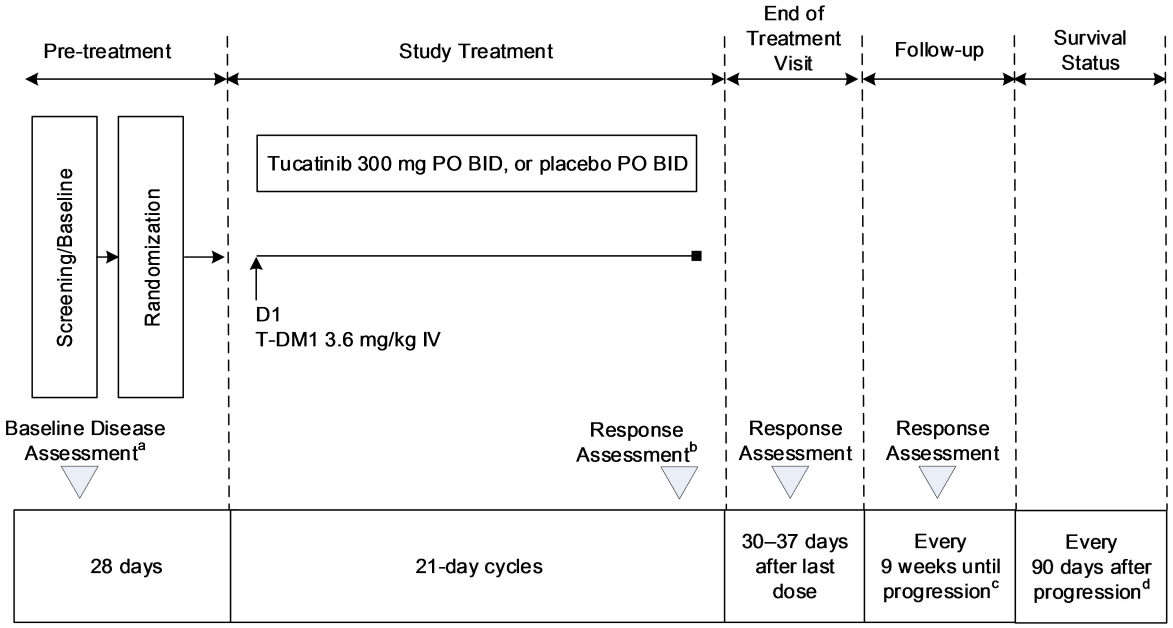
Safety will be monitored on a blinded basis by the sponsor throughout the study. An independent data monitoring committee (IDMC) will regularly review all relevant aggregate safety data (blinded and unblinded).

Approximately 460 subjects (approximately 230 subjects per treatment arm) will be randomized in this study. A study schema is provided in Figure 3. See Appendix A for a schedule of evaluations.

China Portion of the Study

After completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 105 (up to 110) subjects in China is reached. After the completion of the global portion, the study may remain open to complete the China portion as an extension of the study.

Figure 3: Study schema



a Includes measurement of all known sites of unresectable LA/M disease through radiographic imaging. Assessment for brain metastases is performed with contrast magnetic resonance imaging (MRI) of the brain for all subjects, regardless of prior history of brain metastases.

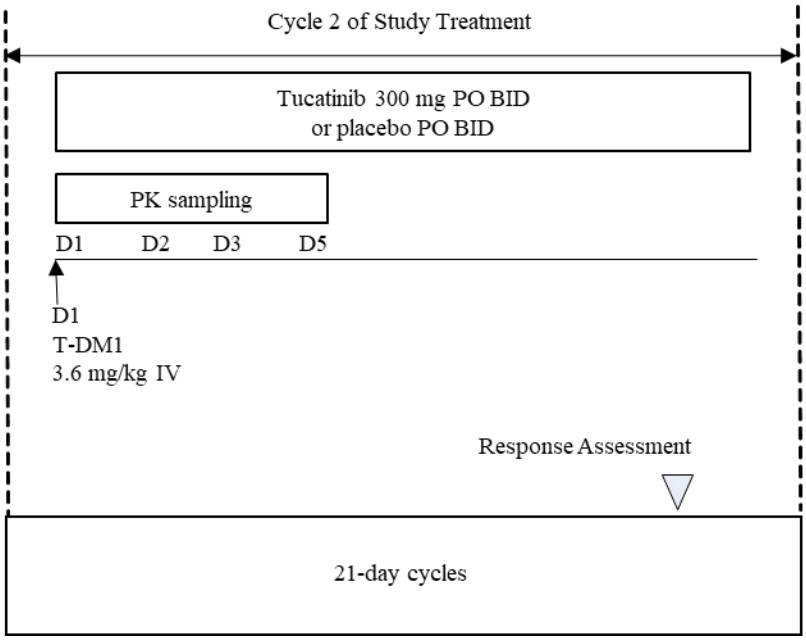
b Response assessments are performed every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter, irrespective of dose holds or interruptions. Contrast brain MRI is required on this same schedule only in those subjects with known brain metastases.

c For subjects who discontinue study treatment for any reason prior to documented disease progression by investigator assessment (per RECIST v1.1), response assessments are performed every 9 weeks until disease progression, death, withdrawal of consent, or study closure. Contrast brain MRI is required on this same schedule only in those subjects with known brain metastases.

d After documented progression (per RECIST v1.1) or clinical progression by investigator assessment, continued follow-up for survival is performed every 90 days until death, withdrawal of consent, lost to follow up, or study closure, whichever comes first (Refer to Section 6.6 for more details).

In the US only, a pharmacokinetics substudy will assess the effects of tucatinib on the pharmacokinetics of DM1. With additional consent, approximately 50 subjects (enrollment will continue until at least 25 subjects from each treatment arm have completed the substudy) will participate in a pharmacokinetics substudy in which additional PK assessments on Days 1, 2, 3, and 5 in Cycle 2 are performed (Figure 4; Table 9; Section 7.3).

Figure 4: Pharmacokinetics substudy (US only), Cycle 2 only



3.1.1. Independent Data Monitoring Committee

The IDMC will be responsible for monitoring the safety of subjects in the study at regular intervals. The IDMC will look at blinded and unblinded data including deaths, discontinuations, dose reductions, AEs, and serious adverse events (SAEs) on a regular basis. The IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study for excessive toxicity. A separate IDMC Charter will outline the committee's composition, members' roles and responsibilities, and describe IDMC procedures. The sponsor will provide a copy of each IDMC recommendation to the investigators.

3.1.2. Stopping Criteria

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

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects, either through a safety review by the sponsor or an independent safety assessment by the IDMC.
- Subject enrollment is unsatisfactory.

3.1.3. End of Study

The study ends once the number of events required for analysis of endpoints (see Section 9.2) has been reached (estimated 5 years after first subject enrolled) or when the last subject completes the last visit, or last contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.3.2).

3.2. Discussion and Rationale for Study Design

Despite advances in treatment, unresectable LA/M HER2+ breast cancer is incurable. The primary goals of treatment remain to extend life and palliate symptoms while preserving QoL. As demonstrated by the phase 1 clinical experience, tucatinib has shown activity and a manageable safety profile in heavily pretreated subjects with unresectable LA/M HER2+ breast cancer, including those with brain metastases (Moulder 2017; Borges 2018; Hamilton 2018; Murthy 2018). All subjects enrolled in this study will receive either tucatinib or placebo in combination with T-DM1, a recommended standard of care regimen for treatment of patients with HER2+ mBC who have progressed after prior treatment with trastuzumab and a taxane. Treatment with T-DM1 has been shown to prolong both PFS and OS in this population when compared to capecitabine and lapatinib (Verma 2012).

Patients with brain metastases from HER2+ breast cancer represent an important unmet medical need, and these patients are frequently excluded from clinical trials. This trial screens all subjects at baseline to determine if occult brain metastases are present, and subjects with brain metastases are included in the trial provided they do not require immediate local therapy and with medical monitor approval. The inclusion of this subject population is supported by data from ONT-380-004, the phase 1b study of tucatinib + T-DM1, in which a majority of subjects had brain metastases (Murthy 2018). Subjects with brain metastases in this trial had similar safety and efficacy outcomes compared to subjects without, and the activity of this combination will be further evaluated in this trial. Subjects randomized to placebo will be treated with T-DM1, which has been described in multiple smaller series to also show early evidence of activity in subjects with brain metastases (Krop 2015; Jacot 2016; Krop 2017).

The randomized, blinded trial design and the selection of PFS as the primary endpoint are based on the considerations outlined in the FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and the European Medicines Agency (EMA; "Guideline on the Evaluation of Anticancer Medicinal Products in Man", EMA/CPMP/ 205/95 Rev.5) for approval of anticancer drugs. Defined as the time from randomization until objective tumor progression or death, PFS is a direct reflection of tumor growth and can be assessed before determination of a survival benefit. Furthermore, because PFS includes death from any cause, it may be a correlate to OS, a secondary endpoint of this study. An additional advantage of PFS is that its determination is not confounded by subsequent therapy. Standardized criteria (RECIST v1.1) will be employed to evaluate progression. To ensure consistent unbiased application of these criteria, all imaging studies performed to confirm disease status and to assess progression during the study will be submitted to an independent third-party imaging core laboratory for blinded review, and all subjects will have evaluations for progression performed on the same schedule.

3.2.1. Method of Assigning Subjects to Treatment Groups

Following informed consent and screening assessments, subjects will be randomly assigned to study treatment in a 1:1 ratio. Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the study manual.

Randomization will be stratified by:

- Line of treatment for metastatic disease: 1st line metastatic versus other
- Hormone receptor status: negative versus positive
- Presence or history of treated or untreated brain metastases: yes versus no
- Eastern Cooperative Oncology Group (ECOG) performance status: 0 versus 1

3.2.2. Rationale for Selection of Doses

In Study ONT-380-004, the phase 1b study of tucatinib administered in combination with T-DM1, the recommended phase 2 dose was defined as 300 mg PO BID. T-DM1 will be given at the full dose of 3.6 mg/kg IV every 21 days as approved for single-agent use.

3.2.3. Blinding and Unblinding

Maintaining the blind of the study is crucial for achieving the study objectives. Unblinding an individual subject treatment assignment may only occur when one of the following circumstances is applicable:

1. At the time of study closure, the study treatment assignment will be provided to the investigator.
2. Unblinding a subject's treatment assignment prior to study closure must be limited to safety emergency circumstances only where knowledge of the treatment assignment would affect decisions regarding the immediate clinical management of the subject. In the event of such an emergency circumstance, the investigator will assume full responsibility for unblinding the study treatment and a formal unblinding procedure, carried out by a third-party organization, will be followed to allow the investigator to immediately access a subject's treatment assignment (see study manual). Information on study treatment assignment must not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, the sponsor is to be notified within 24 hours of the occurrence.

Details regarding unblinding procedures are described in the study manual.

3.2.3.1. Unblinding for Safety Monitoring

Safety data is monitored by an IDMC. Unblinding of aggregate safety data for ongoing safety monitoring and risk/benefit assessment by the IDMC will be performed through an independent data coordinating center to ensure the integrity of the study.

Suspected unexpected serious adverse reactions (SUSARs) will be unblinded in accordance with local regulatory reporting requirements. Prespecified personnel from the sponsor's Global Safety and Risk Management will unblind the identity of study medication for any unexpected (as per the investigator's brochure) SAEs that are considered to be related to the blinded study drug (tucatinib or placebo).

4. STUDY POPULATION

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

4.1. Inclusion Criteria

1. Histologically confirmed HER2+ breast carcinoma, as determined by sponsor-designated central laboratory testing on tumor tissue submitted prior to randomization (see Section 7.1.1) from either:
   a. Archival tissue (most recent tumor tissue sample preferred)
   b. If archival tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion that has not been previously irradiated is required
2. History of prior treatment with a taxane and trastuzumab in any setting, separately or in combination. Prior pertuzumab therapy is allowed, but not required (see Appendix L for France-specific requirements)
3. Have progression of unresectable LA/M breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy.
4. Measurable or nonmeasurable disease assessable by RECIST v1.1 (Appendix F)
5. Hormone receptor (estrogen receptor/progesterone receptor) status must be known prior to randomization
6. Age ≥18 years at time of consent or ≥ the age of majority in the geographic location
7. ECOG performance status score of 0 or 1 (see Appendix B) for conversion of performance status using Karnofsky scale, if applicable)
8. Life expectancy ≥6 months, in the opinion of the investigator
9. Adequate hepatic function as defined by the following:
   a. Total bilirubin ≤1.5 × upper limit of normal (ULN), except for subjects with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 × ULN
   b. Transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT] and alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT]) ≤2.5 × ULN (≤5 × ULN if liver metastases are present)
10. Adequate baseline hematologic parameters as defined by:
    a Absolute neutrophil count ≥1.0 × 10^3/μL
    b Platelet count ≥100 × 10^3/μL
    c Hemoglobin ≥9 g/dL
    d In subjects transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support

11. Estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation (see Section 7.7.4)
12. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5 × ULN, unless on medication known to alter INR and PTT/aPTT
13. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan documented within 4 weeks prior to first dose of study treatment (see Section 6.2.2 for exceptions)
14. For subjects of childbearing potential, as defined in Section 4.3, the following stipulations apply:
    a Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of study treatment. A subject with a false positive result and documented verification that the subject is not pregnant is eligible for participation.
    b Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study drug administration
    c Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study drug administration
    d If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix K) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration
15. For subjects who can father children, the following stipulations apply:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final study drug administration
    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix K) starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration
    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use 1 of 2 highly effective methods of birth control (as defined in Appendix K) starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration
16. The subject must provide written informed consent
17. Subject must be willing and able to comply with study procedures
18. ***CNS Inclusion*** – Based on screening contrast brain magnetic resonance imaging (MRI), subjects must have at least **one** of the following:

a. No evidence of brain metastases

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

c. Previously treated brain metastases

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

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

      - Time since SRS is ≥7 days prior to first dose of study treatment, time since whole-brain radiation therapy (WBRT) is ≥14 days prior to first dose of study treatment, or time since surgical resection is ≥28 days
      - Other sites of evaluable disease are present

   iii. Relevant records of any CNS treatment must be available to allow for classification of target and nontarget lesions

4.2. Exclusion Criteria

1. Prior treatment with tucatinib, afatinib, trastuzumab deruxtecan (DS-8201a), or any other investigational anti-HER2, anti-EGFR, or HER2 TKI agent. Prior treatment with lapatinib or neratinib within 12 months of starting study treatment (except in cases where they were given for ≤21 days and discontinued for reasons other than disease progression or severe toxicity). Prior treatment with pyrotinib for recurrent or mBC (except in cases where pyrotinib was given for ≤21 days and discontinued for reasons other than disease progression or severe toxicity)
2. Prior treatment with T-DM1 in any treatment setting
3. History of allergic reactions to trastuzumab or compounds chemically or biologically similar to tucatinib, except for Grade 1 or 2 infusion-related reactions to trastuzumab that were successfully managed, or known allergy to any of the excipients in the study drugs
4. Treatment with any systemic anticancer therapy (including hormonal therapy), non-CNS radiation (palliative or therapeutic), experimental agent or participation in another interventional clinical trial ≤3 weeks prior to first dose of study treatment. An exception for the washout of hormonal therapies is gonadotropin releasing hormone agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
5. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:

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

6. Clinically significant cardiopulmonary disease such as:
   - Ventricular arrhythmia requiring therapy
   - Symptomatic hypertension or uncontrolled asymptomatic hypertension as determined by the investigator
   - Any history of symptomatic CHF, symptomatic left ventricular systolic dysfunction, or symptomatic decrease in ejection fraction
   - For France and Italy only: Any history of interstitial lung disease or pneumonitis
   - Severe dyspnea at rest (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy
   - ≥ Grade 2 QTc prolongation on screening electrocardiogram (ECG)
7. Known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
8. Known carrier of Hepatitis B or Hepatitis C or has other known chronic liver disease
   - For Italy: Positive for Hepatitis B by surface antigen expression, positive for Hepatitis C infection, or the presence of known chronic liver disease. Subjects who have been treated for Hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks. The latest local guidelines should be followed regarding the testing of Hepatitis B DNA levels by polymerase chain reaction (PCR). Subjects with Hepatitis B DNA levels by PCR that require nucleoside analogue therapy are not eligible for the trial.
9. Subjects known to be positive for human immunodeficiency virus (HIV) if they meet any of the following criteria:
   - CD4+ T-cell count of <350 cells/μL
   - Detectable HIV viral load
   - History of an opportunistic infection within the past 12 months
   - On stable antiretroviral therapy for <4 weeks
10. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months following the last dose of study drug
11. Unable to swallow pills or has significant gastrointestinal disease which would preclude the adequate oral absorption of medications
12. Use of a strong cytochrome P450 (CYP) 3A4 or CYP2C8 inhibitor within 1 week, or use of a strong CYP3A4 or CYP2C8 inducer within 5 days prior to the first dose of study

treatment (see Appendix C and Appendix D). CYP3A4 or CYP2C8 inducers and inhibitors are also prohibited as concomitant medications within 1 week of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates (Appendix E) should be avoided 1 week before enrollment and during study treatment.

13. Unable to undergo contrast MRI of the brain
14. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
15. Systemic therapy for another malignancy within 2 years of the start of study treatment
16. ***CNS Exclusion*** – Based on screening brain MRI, subjects must not have any of the following:
    a. Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor
    b. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or equivalent). However, subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible with approval of the medical monitor.
    c. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to the subject (eg, brain stem lesions). Subjects who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS Inclusion 18c (ii).
    d. Known or concurrent leptomeningeal disease as documented by the investigator
    e. Poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

4.3. Childbearing Potential

A person of childbearing potential is anyone born female, who has experienced menarche, and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes.

A person who can father children is anyone born male, who has testes, and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

4.4. Removal of Subjects From Therapy or Assessment

Seagen or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and case report form (CRF).

4.4.1. Discontinuation of Study Treatment

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

- AE
- PD (per RECIST v1.1), as assessed by the investigator
- Second disease progression after isolated progression in brain (see Section 4.4.1.1 regarding initial CNS-only progression)
- Investigator decision due to clinical progression
- Pregnancy or begins breastfeeding while on trial
- Investigator decision (other)
- Subject decision, non-AE
- Study termination by sponsor
- Other, non-AE

In the absence of clear evidence of disease progression (per RECIST v1.1), or development of CNS symptoms or radiographic changes thought to pose potential immediate risk to subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs (Section 7.2), as defined in RECIST v1.1. If study treatment is discontinued for reasons other than unequivocal disease progression (per RECIST v1.1) or death, subjects will continue in long-term follow-up until criteria for subject withdrawal from the study are met (Section 4.4.2). Every effort should be made to collect scans and clinical data until disease progression, in order to document a PFS event date. Following disease progression, subjects will continue in long-term follow-up for survival.

Subjects who withdraw consent from the interventional portion of the study should specify whether to allow continued follow-up and further data collection subsequent to their withdrawal of consent, including (but not limited to) follow-up through medical records, public records, or other public platform. Every attempt should be made to follow the subject until progression, death, or administrative study closure.

In the absence of progression, subjects who discontinue T-DM1 due to a T-DM1-related toxicity may continue receiving tucatinib/placebo alone. Subjects who discontinue tucatinib/placebo may continue to receive T-DM1 alone, provided progression has not occurred.

4.4.1.1. Continuation on Study Treatment After CNS-Only Progression

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

treatment arm assigned initially, and may continue on study provided the following criteria are met and the subject continues to receive clinical benefit:

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

Study treatment may be held up to 6 weeks to allow local CNS therapy. Longer holds must be discussed and approved by the medical monitor. Interruption and re-initiation of study treatment is described in Section 5.2.

4.4.2. Subject Withdrawal From Study

Any subject may be discontinued from the study for any of the following reasons:

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

5. TREATMENTS

5.1. Treatments Administered

Subjects will be randomized in a 1:1 manner to receive 1 of the following study treatments, either:

- Control arm: Placebo tablets PO BID, and T-DM1 3.6 mg/kg IV every 21 days, or
- Experimental arm: Tucatinib 300 mg PO BID, and T-DM1 3.6 mg/kg IV every 21 days

5.1.1. Investigational Study Drug (Tucatinib or Placebo)

Tucatinib, the investigational agent under study in this protocol, is a kinase inhibitor that selectively inhibits HER2, and displays limited activity against the related kinase EGFR.

Tucatinib and placebo are supplied as yellow oval (150 mg) or round (50 mg) capsule-shaped tablets for oral administration. Investigational study drug (tucatinib or placebo) will be supplied in a blinded manner. No treatment crossover from placebo to tucatinib will be allowed.

Detailed information describing the preparation, administration, and storage of the investigational study drug (tucatinib or placebo) is located in the pharmacy instructions.

5.1.1.1. Description

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

Tucatinib matching placebo tablets are formulated with common pharmaceutical excipients, but they do not contain the active ingredient. They are coated to be identical in appearance to active tablets and are supplied in the same format to maintain blinding.

5.1.1.2. Method of Procurement

The investigational study drug (tucatinib or placebo) will be provided by the sponsor.

5.1.1.3. Dose and Administration

The investigational study drug (tucatinib or placebo) will be administered PO BID and may be taken with or without food. Dose modifications of tucatinib or placebo are described in Section 5.2. Subjects will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, subjects will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

Subjects will be instructed to take tucatinib/placebo tablets twice each day (once in the morning, and once in the evening) approximately 8-12 hours between doses in the same calendar day. It is recommended that if a subject misses a scheduled dose of tucatinib and less than 6 hours have

passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait and take the next regularly scheduled dose. Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed, or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose.

Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will also be provided to study subjects and will include the minimum times between doses, dosing in relation to meals, and instructions for missed doses. Subject compliance with investigational study drug dosing instructions will be assessed with the use of subject diaries and study drug accountability.

5.1.1.4. Overdose

In the event of an overdose of investigational study drug (tucatinib or placebo), defined as any dose greater than the prescribed dose, study personnel should:

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

5.1.1.5. Storage and Handling

Tablets of tucatinib and placebo are packaged in round, high-density polyethylene bottles containing a desiccant, with an induction sealed liner and child-resistant plastic closure cap. For storage information, refer to the tucatinib Pharmacy Instructions.

The tablets are coated with a nonhazardous film to prevent any exposure to the active pharmaceutical ingredient during routine handling. Avoid breaking or crushing tablets. In the event the tablets are broken or crushed, wash hands and exposed skin thoroughly with soap and water.

Refer to the pharmacy instructions for more information.

5.1.1.6. Packaging and Labeling

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

5.1.1.7. Study Drug Accountability

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

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

5.1.2. T-DM1

5.1.2.1. Description

T-DM1 (KADCYLA®) is a HER2-targeted antibody and microtubule inhibitor conjugate, which is indicated, as a single agent, for the treatment of patients with HER2+ mBC who have previously received trastuzumab and a taxane, either separately or in combination.

5.1.2.2. Method of Procurement

T-DM1 is commercially available and details regarding sourcing of T-DM1 may vary by site and/or region as outlined in other documents such as clinical trial agreements.

5.1.2.3. Dose, Preparation, and Administration

T-DM1 3.6 mg/kg IV will be administered on Day 1 of each 21-day cycle. T-DM1 should be prepared and administered per instructions in the KADCYLA package insert. T-DM1 will be administered intravenously per institutional guidelines, under the direction of the investigator.

Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing date, allowing for dose holds or delays with T-DM1. Dose modifications of T-DM1 are described in Section 5.2.

5.1.2.4. Overdose

For this trial, an overdose will be defined as any dose greater than the prescribed dose of T-DM1. In the event of an overdose, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of T-DM1.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of T-DM1 administered, subject weight) and AEs, if any.

5.1.2.5. Storage and Handling

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

5.2. Dose Modifications

Investigational study drug (tucatinib or placebo) and T-DM1 dose-reduction recommendations are described in Table 2 and Table 3, respectively. Guidelines for dose modification recommendations (including dose holds, dose reduction, or discontinuation of drug) in response to potential AEs are described in the tables in Section 5.2.3. Dose reductions or treatment interruption/discontinuation for reasons other than those described in Section 5.2.3 may be made

by the investigator if it is deemed in the best interest of subject safety. Whenever possible, these decisions should first be discussed with the study medical monitor.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to tucatinib/placebo and T-DM1. An AE may be considered related to tucatinib/placebo alone, T-DM1 alone, to both drugs, or to neither. In the event that the relationship is unclear, discussion should be held with the study medical monitor, to discuss which study drug(s) should be held and/or modified.

Doses held for toxicity will not be replaced. Investigational study drug (tucatinib or placebo) or T-DM1 should be discontinued if a delay greater than 6 weeks is required due to treatment-related toxicity, unless a longer delay is approved by the study medical monitor.

In the event of isolated progression in the CNS, study treatment may be held up to 6 weeks to allow local CNS therapy. Tucatinib/placebo and T-DM1 are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib and T-DM1 is unknown. Study treatment may be reinitiated ≥7 days after completion of SRS, ≥14 days after WBRT, and ≥28 days after surgical resection. Plans for holding and reinitiating study drugs before and after local therapy will require discussion with, and documented approval from, the medical monitor.

Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing, allowing for dose holds or delays with T-DM1. In the event T-DM1 is discontinued but study treatment with tucatinib/placebo continues, protocol-defined visits and cycle numbering will proceed using a 21-day cycle regardless of dose holds or delays for tucatinib/placebo.

5.2.1. Tucatinib or Placebo Dose Reductions

Up to 3 dose reductions of tucatinib/placebo are allowed. In the case of recurrent toxicity after 3 dose reductions, treatment with tucatinib/placebo should be discontinued. Dose reductions of larger intervals than those described in Table 2 may be made at the discretion of the investigator, but dose reductions to below 150 mg BID are not allowed. Subjects who would require a dose reduction to below 150 mg BID should discontinue treatment with tucatinib/placebo.

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

Table 2: Tucatinib/placebo: Recommended dose reduction schedule for adverse events*

Dose Reduction Schedule	Tucatinib/Placebo Dose Level
Starting dose	300 mg PO BID
1st dose reduction	250 mg PO BID
2nd dose reduction	200 mg PO BID
3rd dose reduction	150 mg PO BID
Requirement for further dose reduction	Discontinue treatment

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

5.2.2. T-DM1 Dose Reductions

Up to 2 dose reductions of T-DM1 will be allowed (Table 3). In the case of recurrent toxicity after 2 dose reductions, treatment with T-DM1 should be discontinued.

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

Table 3: T-DM1: Recommended dose reduction schedule for adverse events

Dose Reduction Schedule	T-DM1 Dose Level
Starting dose	3.6 mg/kg
1st dose reduction	3 mg/kg
2nd dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

5.2.3. Dose Modifications for Adverse Events

5.2.3.1. General Guidelines

General dose modification guidelines for investigational study drug (tucatinib or placebo) and T-DM1 are provided in Table 4 for clinical AEs.

Separate dose modification guidelines are provided for AEs of hepatotoxicity (Table 5), nodular regenerative hyperplasia (Section 5.2.3.3), thrombocytopenia (Table 6), left ventricular dysfunction (Table 7), and pulmonary toxicity (Section 5.2.3.6).

Table 4: Dose modifications for clinical adverse events related to either tucatinib/placebo or T-DM1

	Tucatinib/Placebo	T-DM1
Clinical Adverse Event	Related to tucatinib/placebo	Related to T-DM1
All ≥ Grade 3 AEs except the following: Grade 3 fatigue lasting ≤3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Reduce to next lowest dose level. Note: Dose reduction is not required for hematologic abnormalities (other than thrombocytopenia[b]) that recover to ≤ Grade 1 prior to dosing.
Grade 3 nausea, vomiting, or diarrhea WITHOUT maximal use of antiemetics or antidiarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Optional dose reduction to next lowest dose level.
Grade 3 nausea, vomiting, or diarrhea WITH maximal use of antiemetics or antidiarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Optional dose reduction to next lowest dose level.
Grade 4 nausea, vomiting, or diarrhea regardless of use of anti-emetics or antidiarrheals	Do not administer until severity ≤ Grade 1. Reduce to next lowest dose level.	Do not administer until severity ≤ Grade 1. Reduce to next lowest dose level.
Grade 1 or 2 diarrhea with complicating features[c]	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Optional dose reduction to next lowest dose level.
Grade 3 rash WITHOUT maximal use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Optional dose reduction to next lowest dose level.
Grade 3 rash WITH maximal use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Optional dose reduction to next lowest dose level.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.

a No dose modifications are required for alopecia
b Refer to Table 6 for thrombocytopenia dose reduction requirements
c Moderate to severe abdominal cramping, nausea, or vomiting ≥ National Cancer Institute's (NCI) CTCAE Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration

5.2.3.2. Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities, regardless of relationship to study drug (Table 5).

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

Table 5: Dose modification guidelines for liver function abnormalities (regardless of relationship to tucatinib/placebo or T-DM1)

	Tucatinib/Placebo	T-DM1
Grade 2 elevation of ALT and/or AST of >3.0 to ≤5 × ULN	Dose modification not required	Dose modification not required
Grade 3 elevation of ALT and/or AST (>5–20 × ULN)	Hold until severity ≤ Grade 1. Restart at next lowest dose level.	Hold until severity ≤ Grade 1. Restart at next lowest dose level.
Grade 4 elevation of ALT and/or AST (>20 × ULN)	Discontinue drug	Discontinue drug
Elevation of ALT and/or AST >3 × ULN AND Bilirubin >2 × ULN	Discontinue drug	Discontinue drug
Grade 2 elevation of bilirubin (>1.5–3 × ULN)	Hold until severity ≤ Grade 1. Restart at same dose level.	Hold until severity ≤ Grade 1. Restart at same dose level.
Grade 3 elevation of bilirubin (>3 to ≤10 × ULN)	Hold until severity ≤ Grade 1. Restart at next lowest dose level.	Hold until severity ≤ Grade 1. Restart at next lowest dose level.
Grade 4 elevation of bilirubin (>10 × ULN)	Discontinue drug	Discontinue drug

5.2.3.3. Nodular Regenerative Hyperplasia

Investigational study drug (tucatinib or placebo) and T-DM1 should be discontinued permanently in subjects diagnosed with nodular regenerative hyperplasia, regardless of relationship to study drug.

5.2.3.4. Thrombocytopenia

T-DM1 dose modification are required for thrombocytopenia, regardless of relationship to T-DM1 (Table 6). Dose modification of investigational study drug (tucatinib or placebo) is not required for thrombocytopenia.

Table 6: Dose modification guidelines for thrombocytopenia

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

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

5.2.3.5. Left Ventricular Dysfunction

Investigational study drug (tucatinib or placebo) and T-DM1 dose modification guidelines for left ventricular dysfunction, regardless of relationship to study drug, are provided in Table 7.

Table 7: Dose modification guidelines for left ventricular dysfunction

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

5.2.3.6. Pulmonary Toxicity

T-DM1 should be permanently discontinued in subjects diagnosed with interstitial lung disease or pneumonitis, regardless of relationship to T-DM1.

5.3. Concomitant Therapy

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

Any planned non-CNS surgery (major or minor) not directly related to cancer that occurs on study requires prior consultation with the sponsor medical monitor. In France and Italy, subjects are required to suspend study treatment 3 to 7 days prior to surgery and, depending on the nature of the surgery, resume study treatment 3 to 21 days postoperatively. The medical monitor must be contacted prior to subjects resuming treatment. It is not necessary for both study treatments to resume simultaneously post procedure. Refer to Section 4.4.1 for additional guidance regarding dose modifications when resuming treatment and for CNS surgery. For emergency surgeries, contact the medical monitor as soon as feasible to discuss resumption of study treatment postoperatively.

5.3.1. Required Concomitant Therapy

There are no required concomitant therapies. For subjects with CNS metastases, prophylactic pretreatment systemic corticosteroids may be administered at the discretion of the investigator.

5.3.2. Permitted Concomitant Therapy

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

Supportive treatments will be given according to label instructions as medically indicated. Concomitant medications can be administered at the investigator's discretion to conform to standard practice during the treatment period.

- Routine prophylaxis with vaccines (without live virus) are permitted during the study
- If surgery or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor), these concomitant procedures are permitted for nontarget, non-CNS lesions only in situations where other disease remains assessable by RECIST v1.1 (Appendix F). These interventions should be avoided if clinically feasible until after the second response assessment. The medical monitor must be consulted prior to the intervention occurring.
- Corticosteroids
    - Subjects requiring systemic corticosteroids for control of brain metastases at a dose of >2 mg of dexamethasone (or equivalent) on the first day of study treatment are not eligible to begin study treatment, and should not be randomized until doses ≤2 mg can be achieved
    - After initiation of study treatment, corticosteroids may be initiated for control of CNS symptoms only after consultation and approval of the medical monitor
    - For subjects with CNS metastases, prophylactic pretreatment systemic corticosteroids may be administered at the discretion of the investigator
    - Premedication with corticosteroids solely for contrast used in scans or MRI can be used without prior medical approval
    - Subjects requiring systemic steroids for control of other comorbidities (eg, asthma or auto-immune diseases) may be eligible after consultation and approval of the medical monitor
- Transfusion support with blood products is permitted. (However, note that no transfusions are permitted from <14 days prior to starting study treatment until the initiation of study treatment in order to establish adequate hematologic parameters for study eligibility independent of transfusion support)

5.3.3. Prohibited Concomitant Therapy

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

- Investigational drugs and devices

- Anticancer therapy, including but not limited to chemotherapy or hormonal therapy
- Radiation therapy, except for palliative radiotherapy at focal sites, which may be given after consultation with the medical monitor, provided that there remain other sites of measurable disease accessible by RECIST v1.1 (see Section 5.3.2)
- Strong inhibitors or inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of study treatment (see Appendix C)
- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib/placebo treatment (see Appendix D)

The following therapies should be used with caution during the study

- Subjects on anticoagulant treatment should be closely monitored during study treatment
- Sensitive substrates of CYP3A (Appendix E); tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided. Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information
- Concomitant use of tucatinib with digoxin, a P-gp substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

5.4. Treatment Compliance

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

Study-drug compliance will be assessed on a subject-by-subject basis using subject diaries. The pharmacist or designee will record the number of investigational study drug (tucatinib or placebo) tablets dispensed to each individual subject, and the number of tablets returned to the clinic.

Data regarding the administration and dose of T-DM1 will also be collected by the site after each cycle. Dose modifications and interruptions of any study drug will be documented in the source documents and the CRF.

6. STUDY ACTIVITIES

6.1. Schedule of Events

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

Study assessments will continue regardless of any dose holds or delays.

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

6.2. Screening Period

6.2.1. HER2 Testing (Up to 1 Year Before the Screening Visit)

Subjects may consent to submit an archival tumor specimen for central assessment to complete HER2 expression testing up to one year before the screening visit. Subjects must be informed that HER2 testing consent is not informed consent for the study and participation in HER2 testing does not guarantee study eligibility.

- HER2 expression testing consent
- Submission of archival tumor specimen for central assessment to confirm HER2 expression meets eligibility requirements (see Section 7.1.1)
- Confirmatory central HER2 testing, with archival tissue showing HER2-positivity by in situ hybridization (ISH). In China, refer to the laboratory manual for details regarding HER2 testing.

6.2.2. Screening Visit (Day −28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- For Italy only: Hepatitis B and C testing (See Section 7.7.4)
- Collection of concomitant medication information
- Confirm HER2+ status
    - Confirmation from an archival tumor specimen for central assessment to confirm HER2 expression (see Section 7.1.1 for eligibility requirements).
    - If archival tissue that meets requirements is not available, a fresh tumor biopsy must be obtained and submitted for central assessment for HER2 testing
- Hormone receptor status must be known prior to randomization (hormone receptor positive: estrogen receptor positive and/or progesterone receptor positive; hormone

receptor negative: both estrogen receptor negative and progesterone receptor negative)

- ECG (see Section 7.7.6.2, must be collected prior to first dose of any study treatment)
- ECHO, or MUGA scan to include at a minimum LVEF (see Section 7.7.6.1); the testing modality chosen in screening should be used for subsequent cardiac assessments to allow comparison
- High-quality spiral contrast computed tomography (CT; preferred); positron emission tomography (PET)/CT (if high quality CT scan is included), and/or nonbrain MRI scan may be done as appropriate (see Section 7.2). At a minimum, scans must include chest, abdomen, and pelvis. Additional appropriate imaging of any other known sites of disease (eg, skin lesion photography for skin lesions, bone imaging for bone lesions) should also be performed at the investigator's discretion.
- Contrast MRI scan of the brain for all subjects for assessment of brain tumor burden (see Section 7.2.1)
    - For subjects with brain metastases discovered during screening or a history of brain metastases, confirm that relevant MRI brain reports and CNS treatment records can be obtained

* For subjects with unsuspected brain metastases discovered at screening and who go on to receive immediate local therapy to the CNS or who require a fresh tumor biopsy for HER2 confirmation, the screening process may be delayed beyond the 28-day screening window. Certain screening evaluations may not need to be repeated outside the 28-day screening window with medical monitor approval. This includes the following: informed consent and ECHO/MUGA. All other safety laboratories and assessments will need to be repeated per the schedule of events for these subjects. If local CNS therapy involves radiation treatment, do not repeat the contrast MRI of the brain prior to starting study treatment. If local CNS therapy involves surgical resection, a postoperative contrast MRI of the brain is required prior to starting study treatment.

6.2.3. Baseline Visit (Day −7 to Day 1)

- Physical examination (see Section 7.7.2), including height and weight
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECOG performance status (Appendix B)
- Blood samples for laboratory testing (as listed in Section 7.7.4)
    - Chemistry
    - Liver function tests (LFTs)
    - Complete blood count (CBC) with differential
    - Coagulation panel
- For persons of childbearing potential, serum or urine pregnancy test (see Section 7.7.5) within 7 days of first study treatment

- Review HER2+ status and laboratory results, and confirm eligibility prior to randomization

6.3. Randomization (Day −5 to Day 1)

- Occurs after eligibility per inclusion/exclusion criteria is confirmed. Randomization MUST occur on or before Cycle 1 Day 1, such that dosing commences within 5 days after randomization.

6.4. Treatment Period (21-day cycles)

6.4.1. Cycle 1 Day 1

- Physical examination, including weight*
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECOG performance status*
- Predose blood samples for laboratory testing. Review results to confirm eligibility prior to first dose of study treatment:
    - Chemistry *
    - LFTs*
    - CBC with differential*
- QoL questionnaires* (Section 7.6; to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment):
    - EQ-5D-3L
    - EORTC QLQ IL6
    - FACT-B GP5
    - NCI PRO-CTCAE
- Dispense tucatinib or placebo and administer the first dose of tucatinib/placebo and provide dosing diary to subject. (Subject will self-administer the remainder of doses during the treatment cycle and document in the diary) ‡
- Administer T-DM1 at 3.6 mg/kg IV ‡

* Predose assessments do not need to be repeated if performed within 1 day prior to Cycle 1, Day 1.

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

6.4.2. Cycle 1 Day 12 (±3 days)

- Physical examination, including weight
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)

- ECOG performance status
- EORTC QLQ IL6
- NCI PRO-CTCAE
- FACT-B GP5
- Review subject diary for tucatinib/placebo drug compliance
- Blood samples for laboratory testing
    - Chemistry
    - LFTs
    - CBC with differential
- Provide tucatinib/placebo day-of dosing instructions for the Cycle 2 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (ie, 2 hours prior to tucatinib/placebo)

6.4.3. Cycle 2 Day 1, and Day 1 of All Subsequent Cycles (−1 to +3 days)

- QoL questionnaires (to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment)*:
    - EQ-5D-3L
    - EORTC QLQ IL6
    - FACT-B GP5
    - NCI PRO-CTCAE
- Review HCRU during the previous treatment cycle (see Section 7.5)*
- Physical examination, including weight*
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECOG performance status*

* Predose assessments do not need to be repeated if performed within 1 day prior to Day 1.

Blood sample collections:

- All cycles: Predose blood samples for laboratory testing. Must be performed within 1 day prior to Day 1 of the treatment cycle. Review results prior to the administration of study treatment to confirm continued study treatment and allow for potential dose adjustments:
    - Chemistry
    - LFTs
    - CBC with differential
    - For persons of child-bearing potential only: predose serum or urine pregnancy test (see Section 7.7.5) within 7 days prior to Day 1 of the treatment cycle.

- Cycles 3–6 only: Predose blood sample (up to 2 hours prior to dosing with tucatinib/placebo) and end of infusion (up to 15 minutes after end of T-DM1 infusion) for PK analysis
- Cycle 3 only:
    - Postdose blood sample (1–4 hours postdose) for PK analysis following administration of tucatinib/placebo

Study treatment administration:

- Review subject diary for tucatinib/placebo drug compliance from previous cycle and dispense tucatinib/placebo for next cycle
- Administer the first dose of tucatinib/placebo for the current cycle. (Subject will self-administer the evening dose, unless the cycle began in the afternoon.) ‡
- Administer T-DM1 given intravenously ‡
- Cycles 3–5 only: Provide tucatinib/placebo day-of dosing instructions for the next cycle's Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (ie, 2 hours prior to tucatinib/placebo) and ensure subject withholds AM tucatinib dose on Day 1 of next cycle

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

6.4.4. Cycle 2 Day 1, 2, 3, and 5 (PK Substudy Subjects Only)

- Blood samples for PK analysis of tucatinib and DM1 on Cycle 2 Day 1 predose (up to 2 hours predose), after end of T-DM1 infusion (up to 15 minutes after end of infusion) on Cycle 2 Day 1, and 24 (± 4 hours), 48 (±4 hours) and 96 (±6 hours) hours after end of infusion on Cycle 2 Day 2, Cycle 2 Day 3, and Cycle 2 Day 5, respectively

6.4.5. Cycle 2 Day 12 (±3 days)

- Blood sample for LFTs (total bilirubin, AST, ALT, and alkaline phosphatase [ALP])
- Review subject diary for tucatinib/placebo drug compliance
- Provide tucatinib/placebo day-of dosing instructions for the Cycle 3 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (ie, 2 hours prior to tucatinib/placebo)
- EORTC QLQ IL6
- FACT-B GP5
- NCI PRO-CTCAE

6.4.6. Every 6 Weeks (−7 days) as Determined by Cycle 1 Day 1, through Week 24, then Every 9 Weeks (−7 days) Through End of Treatment

- High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or nonbrain MRI scan may be done as appropriate (see Section 7.2).

The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.

- Contrast MRI of the brain (only in subjects with brain metastases at baseline, as defined in Section 7.2.1) and assessment of CNS lesions (brain and/or dura)
- If cycles are delayed for any reason, continue with initial scan schedule as determined by the date of Cycle 1 Day 1 visit.
- If an interim unscheduled assessment is performed, scans should continue to be done on schedule, with scheduling determined by the date of Cycle 1 Day 1. In cases of medical contraindication for repeat scans, contact the medical monitor to discuss as, in some instances, assessments done at an unscheduled timepoint may not need to be repeated if medically contraindicated as approved by the medical monitor.

6.4.7. Every 12 Weeks as Determined by Screening Exam (−7 days)

- ECHO or MUGA, using the same cardiac testing modality performed in Screening/Baseline
- If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment

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

The time of End of Treatment (EOT) visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy. If EOT visit evaluations are completed before 30 days after the last dose of study treatment, the subject will be contacted 30 to 37 days following the last dose of study treatment to assess for AEs.

- QoL questionnaires (to be completed prior to evaluation by study personnel [physical examination, review of AEs]):
  - EQ-5D-3L
  - EORTC QLQ IL6
  - FACT-B GP5
  - NCI PRO-CTCAE
- Review HCRU since the last study visit
- Physical examination, including weight
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECG
- ECOG performance status
- Blood samples for laboratory testing
  - Chemistry

- LFTs
- CBC with differential
- Coagulation panel
- For females of childbearing potential (FOCBP) only (if not done within the last 30 days): serum or urine pregnancy test (see Section 7.7.5)

- Only in subjects who discontinue study treatment for reasons other than radiographic disease progression: high-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan included), and/or nonbrain MRI scan may be done as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated. Not required if imaging was performed within 30 days of discontinuing study treatment.
- Contrast MRI of the brain for all subjects and assessment of CNS lesions. Not required if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study.
- ECHO or MUGA, using the same cardiac testing modality performed in Screening/Baseline. Not required if ECHO/MUGA was done within the previous 12 weeks (excluding the Screening/Baseline assessment).
- Review subject diary for tucatinib/placebo drug compliance from last cycle of study treatment.
- For persons of childbearing potential: Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment. Testing may be performed at home. If performed at home, site staff will contact the subject monthly to confirm testing was performed and obtain pregnancy test results.

6.6. Long-Term Follow-up

Subjects who discontinue study treatment will remain on study for follow-up until withdrawal from the study. A subject may discontinue study treatment without withdrawing from the study (Section 4.4.1). If a subject discontinues study treatment, every attempt should be made to follow the subject until progression, death, or administrative study closure.

For subjects who discontinue study treatment for any reason prior to documented disease progression per RECIST v1.1, the following assessments must be obtained every 9 weeks (±1 week) starting from the date of the last imaging scan, until investigator-assessed disease progression (per RECIST v1.1), death, withdrawal of consent, or study closure, in order to document a PFS event date:

- High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or nonbrain MRI scan as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.
- Contrast MRI of the brain (only in subjects with brain metastases at baseline, as defined in Section 7.2.1) and assessment of CNS lesions (brain and/or dura)

- QoL questionnaires (to be completed prior to any study assessments or evaluation by study personnel):
    - EQ-5D-3L
    - EORTC QLQ IL6
- For persons of childbearing potential (for 7 months after the last dose of study treatment; see Section 7.7.5):
    - Confirm with the subject that monthly pregnancy tests have been performed and review results
    - Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment

Subsequent long-term follow-up scan windows are based on the most recent scan completed.

Once a subject experiences PD (per RECIST v1.1) or clinical progression as assessed by the investigator, subjects will continue in long-term survival follow-up. The following information must be collected starting 90 days (±7 days) from the date of the last imaging scan or 90 days from the last study visit, whichever is later, and continuing every 90 days (±7 days) until death, withdrawal of consent, lost to follow up, or study closure.

- Subject contact or in-person assessment of OS and/or disease recurrence, as well as collection of information regarding any additional anticancer therapies administered after completion of study treatment. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to contact the subject are unsuccessful. For subjects who are lost to follow up or withdraw consent from study participation, data for OS will be collected from public records if allowed per local regulations.
- Administer QoL questionnaires (can be administered by phone once the patient has experienced a progression event as determined by RECIST v1.1)
    - EQ-5D-3L
    - EORTC QLQ IL6
- For persons of childbearing potential (for 7 months after the last dose of study treatment; see Section 7.7.5):
    - Confirm with the subject that monthly pregnancy tests have been performed and have been negative
    - Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment
- More frequent long-term follow-up may be conducted as needed for OS event tracking (eg, for subjects with clinical progression, OS event tracking may be conducted at the same time radiographic scans and PFS event tracking will be performed every 9 weeks, until PD per RECIST v1.1 is confirmed, at which time PFS tracking ends and OS event tracking may be performed starting 90 days [±7 days] from the date of the last imaging scan)

6.7. Subject End of Study/End of Follow-up

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

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only subjects who meet all inclusion and exclusion criteria specified in Sections 4.1 and 4.2 will be enrolled in this study.

Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing to determine subject eligibility; confirmatory HER2 testing may be performed on archival tissue or a newly-obtained baseline biopsy of an accessible tumor lesion that has not been previously irradiated (see Section 7.1.1).

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

All measurable and evaluable lesions will be assessed and documented at Screening/Baseline (see Section 7.2). A contrast MRI of the brain is performed to evaluate for the presence of brain metastases (see Section 7.2.1). Subjects with brain metastases at study entry may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 7.1.2.

A physical examination including height and weight (Section 7.7.2), vital signs (Section 7.7.3), ECOG performance status (Appendix B), clinical laboratory testing (Section 7.7.4), and pregnancy testing (Section 7.7.5) will be done at Screening/Baseline.

7.1.1. Confirmation of HER2 Expression for Study Eligibility

Archival or freshly-obtained tumor tissue (most recent tumor tissue sample requested) must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing prior to randomization. The central laboratory will require sufficient tumor tissue to generate unstained, positively-charged slides for HER2 expression testing. Archived tumor samples must be formalin-fixed and paraffin-embedded. If archival tissue that meets sample requirements is not available, fresh tissue from a tumor site (metastatic site preferred as applicable) suitable for biopsy must be obtained and submitted for confirmatory HER2 testing.

HER2 expression will be analyzed using ISH (DAKO IQFISH pharmDx), and positivity will be assessed according to the package insert for HER2 interpretation. In China, refer to the laboratory manual for details regarding HER2 testing.

A tumor suitable for biopsy should be accessible, not previously irradiated, and without contraindication to biopsy, in the opinion of the investigator. Tissue samples obtained through resection, excision, punch (skin lesions only), or core needle from a tumor site are suitable for testing. Fine needle aspiration, brushing, cell pellets from pleural effusion, forceps, and lavage samples are not acceptable. Tumor tissue should be of good quality based on total and viable tumor content; eg, samples should contain tumor cells that preserve cellular context and tissue architecture, regardless of the needle gauge used to collect the sample or the retrieval method.

See the central laboratory manual for more details.

7.1.2. Treatment for Brain Metastases Prior to Study Entry

Subjects with brain metastases at study entry may be eligible for study participation if they meet the eligibility criteria described in Sections 4.1 and 4.2. In order to minimize the risk of symptomatic cerebral edema in subjects with brain metastases in this study, subjects with high-risk metastases, including those requiring immediate local therapy, those with rapidly progressing lesions, those requiring corticosteroids at the start of the study (>2 mg of dexamethasone or equivalent per day) for control of CNS symptoms, and those with larger untreated lesions are excluded from the trial. However, if these subjects are amenable to immediate CNS-directed therapy with either surgery or radiation, they may undergo local therapy and then be eligible for the trial. Under select circumstances subjects may receive corticosteroid therapy for acute management of symptomatic local edema, as long as contrast brain MRI does not show clear evidence of CNS progression and requires approval from the study medical monitor.

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

- For subjects who receive brain radiotherapy during the screening period, the original baseline contrast brain MRI will serve as the baseline for comparison for further response assessments.
- For subjects who undergo surgical resection of brain metastases during the screening period, a postoperative contrast brain MRI will be performed and will serve as the baseline for comparison for further response assessments.

For subjects with brain metastases discovered during screening or a history of brain metastases, relevant MRI brain reports and CNS treatment records should be obtained and available for CRF source verification.

7.2. Response/Efficacy Assessments

Radiographic scans and additional imaging assessments (if applicable) will be performed at protocol-specified time points outlined in Section 6 and Appendix A, or if disease progression is suspected. Clinical response of PD, SD, PR, or CR will be determined at each assessment according to RECIST v1.1 (Eisenhauer 2009), by the investigator and by BICR. Clinical management decisions will be based on local investigator assessment to ensure that treatment decisions are made in a timely manner; results of centralized review will not be available to investigators for clinical decision making.

All known sites of LA/M unresectable disease should be assessed by radiographic imaging at Screening/Baseline to document sites of extracranial disease and tumor burden and chosen as either target or nontarget lesions. Imaging, preferably by high quality spiral contrast CT scan (with oral and/or IV contrast), should include the chest, abdomen, and pelvis, at a minimum; PET/CT (if high quality CT scan is included) and/or MRI scan may also be done as appropriate. If a CT scan with contrast is contraindicated (ie, in subjects with contrast allergy or impaired renal clearance), a noncontrast CT scan of the chest may be performed instead, with MRI scans of the abdomen and pelvis. At the investigator's discretion, other appropriate imaging (eg, skin lesion photography for skin lesions, nuclear bone scan imaging for bone lesions) should be used

to assess additional known sites of disease. The same imaging modalities employed in Screening/Baseline should be used for all subsequent response assessments during study treatment and in the follow-up period, unless otherwise clinically indicated. If any other radiographic or assessment exam, including pathology from any on-study biopsies or procedures, is conducted per standard of care, the assessment information will be collected in the CRF. All imaging will be collected for retrospective BICR.

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

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee) upon request. All imaging will be submitted or uploaded for retrospective BICR as soon as reasonably possible (eg, within approximately 2 weeks) following the date of assessment. Refer to the study manual for instructions on collecting and submitting tumor imaging studies to the third-party imaging core laboratory for BICR.

7.2.1. Evaluation of Brain Metastases

Brain MRI imaging will be performed locally and collected prospectively for centralized independent review. However, treatment decisions will be made on the basis of local review of radiologic imaging.

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

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

Only subjects with documented brain metastases at baseline, as defined above, will continue to have follow-up contrast MRIs of the brain on the same schedule as non-CNS response assessments (Section 6.4.6 and Appendix A). Contrast MRIs of the brain may also be performed in subjects without known brain metastases if there is clinical suspicion of new brain lesions. All subjects will have an additional contrast MRI of the brain at the EOT visit, unless one has been performed within 30 days of discontinuing study treatment or the reason for going off treatment was progression in the brain.

In subjects with baseline brain lesions, all brain lesions should be included in the baseline RECIST lesion selection as either a target or nontarget lesion. When unsuspected brain metastases are discovered at screening and immediate CNS-directed therapy is administered, treated lesions should not be selected as target lesions but as nontarget lesions for the purpose of disease assessment by RECIST v1.1.

Copies of brain imaging must be made available for review by the sponsor (or its designee) upon request. Copies of all brain imaging will be submitted or uploaded for retrospective BICR as soon as reasonably possible (eg, within approximately 2 weeks) following the date of assessment. Refer to the study manual for instructions on collecting and submitting brain imaging studies to the third-party imaging core laboratory for BICR.

7.2.2. Isolated Progression in the Brain

In subjects with isolated progression in the brain per RECIST v1.1 (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and do not have progression of disease outside the CNS, subjects may be eligible to continue on study treatment after completion of local treatment (radiotherapy or surgery) to the brain/dural metastases to allow for clinical benefit with medical monitor approval. This approach approximates standard clinical practice in this clinical scenario.

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

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

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

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

7.3. Pharmacokinetic Assessments

In all subjects, measurements from Cycle 3 to Cycle 6 will be obtained to assess the steady-state pharmacokinetics of tucatinib and DM1 (Table 8). Additional blood samples will be collected and processed for exploratory PK assessment.

Additionally, approximately 50 subjects (US only; enrollment will continue until at least 25 subjects from each treatment arm have completed the substudy) will participate in a PK substudy with additional PK sampling on Days 1, 2, 3, and 5 in Cycle 2 to assess tucatinib and DM1 plasma concentrations (Table 9). Additional blood samples will be collected and processed for exploratory PK assessment.

A liquid chromatography/tandem mass spectrometry assay will be used to assess plasma concentrations of tucatinib and DM1. Other assays may be performed if further characterization is required on the exploratory PK sample. Additional PK data analyses, including population pharmacokinetics and exploratory exposure-response analyses may be conducted; such analyses will be described in a separate analysis plan.

Trough (predose) PK samples should continue to be collected on schedule regardless of dose holds or interruptions of tucatinib/placebo on Day 1 of Cycles 3–6. The Cycle 3 Day 1 postdose sample should not be collected during dose hold or interruptions of tucatinib/placebo.

Table 8: Pharmacokinetic sampling – all subjects

Cycle	Day	Timepoint	Tucatinib/Placebo	Exploratory PK	DM1
3	1	0 hour (−2 hours) prior to administration of tucatinib/placebo	X	X	X
		End of T-DM1 infusion (+15 minutes)		X	X
		1–4 hours following administration of tucatinib/placebo	X		
4–6	1	0 hour (−2 hours) prior to administration of tucatinib/placebo	X	X	X
		End of T-DM1 infusion (+15 minutes)		X	X

Table 9: Pharmacokinetic sampling – Pharmacokinetics substudy (US only) subjects

Cycle	Day	Timepoint	Tucatinib/ Placebo	Exploratory PK	DM1
2	1	0 hour (−2 hour) prior to T-DM1 administration	X	X	X
		End of T-DM1 infusion (+15 minutes)	X	X	X
2	2	24 hours post-end of T-DM1 infusion (±4 hours)	X	X	X
2	3	48 hours post-end of T-DM1 infusion (±4 hours)	X	X	X
2	5	96 hours post-end of T-DM1 infusion (±6 hours)	X	X	X

7.4. Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seagen and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of sensitivity and resistance mechanisms to targeted therapeutics, and the identification of pharmacodynamic

biomarkers of potential targeted therapeutics. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.5. Healthcare Resource Utilization Data Collection

All healthcare encounters related to the subject's breast cancer, cancer treatment, or cancer-related assessments will be collected for all subjects until the EOT visit. HCRU data include, but are not limited to, procedures that occur on study, such as length of stay, hospitalizations, emergency department visits, planned/unplanned provider visits, medication use, radiology, and other treatments and procedures. See Appendix A and Section 6 for timing of HCRU data collection, and see the study manual for detailed guidance.

7.6. Patient-Reported Outcomes

QoL questionnaires will be administered as specified in Appendix A and Section 6. The objective is to compare improvements, deteriorations, and stabilization in health-related QoL between treatment arms. During study treatment, these questionnaires must be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days. Questionnaires may be collected by phone once a subject experiences disease progression (per RECIST v.1.1) by investigator assessment and is in long-term survival follow-up.

7.6.1. EQ-5D-3L – Utility Measurement

The EQ-5D-3L is a standardized instrument developed by the European Quality of Life (EuroQol) Group for use as a generic, preference-based measure of health-related QoL outcomes that can be used in a wide range of health conditions and treatments (van Agt 1994). The EQ-5D-3L consists of a descriptive system questionnaire and the EuroQoL visual analog scale (EQ-VAS; Appendix G).

The descriptive system questionnaire assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 3 levels: no problems, some problems, and extreme problems. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preference compared to other health profiles. The recall time frame for the descriptive system is the day in which the questionnaire is administered. The EQ-VAS records the subject's self-rated health status on a vertical visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) and can be used as a quantitative measure of health outcome that reflects the subject's own judgment.

7.6.2. EORTC QLQ IL6

The EORTC QLQ was developed to measure aspects of health-related QoL pertinent to subjects with a broad range of cancers who are participating in international clinical trials (Aaronson 1993; Bjordal 1994; Sneeuw 1998). The core instrument, the QLQ-C30 (Version 3.0), is a 30-item questionnaire consisting of the following:

- 5 functional domains (physical, role, cognitive, emotional, social)

- 3 symptom scales (fatigue, pain, nausea and vomiting)
- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease
- 2 global items (health, overall QoL)

The questionnaire has been streamlined based on a patient-centric approach to minimize the number of questions being asked as part of the patient-reported outcome (PRO) data collection, therefore only Questions 29 and 30 of the questionnaire, which make up the 'global health status/QoL' scale of the QLQ-C30, will be used for this study (Appendix H). The EORTC refers to this set of questions as the EORTC QLQ IL6.

7.6.3. FACT-B

The FACT-B is a self-report instrument designed to measure multidimensional QoL in patients with breast cancer (Brady 1997). It is reliable, relates to similar measures in an expected pattern, and performs as predicted in relation to change in clinical status over time. To minimize the number of questions to reduce patient burden, only Question 5 (ie, GP5) regarding patient's perception of bother due to treatment side effects will be used (Appendix I). Responses to this question will be collected while subjects are receiving study treatment and until the EOT visit.

7.6.4. NCI PRO-CTCAE

The NCI PRO-CTCAE is a validated PRO measurement system developed to characterize the frequency, severity, and interference of 78 symptomatic treatment toxicities (Smith 2016). These include symptomatic toxicities such as pain, fatigue, nausea, and cutaneous side effects such as rash and hand-foot syndrome, all toxicities that can be meaningfully reported from the patient perspective. The NCI PRO-CTCAE allows for customization; thus, symptomatic toxicities of interest (17 items) in both the control and experimental arms will be collected as part of the PRO data collection (Appendix J).

7.7. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored over the course of the study by an IDMC as described in Section 3.1.1.

7.7.1. Adverse Events

7.7.1.1. Definitions

Adverse Event

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

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

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 that increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study treatment) should be recorded from study Day 1 (predose) through the end of the safety reporting period (see Section 7.7.1.3). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in an SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

Serious Adverse Events

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

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission through a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.1.6 for the definition of potential DILI)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, Version 4.03. These criteria are provided in the study manual.

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

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (tucatinib or placebo, T-DM1) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.7.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

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

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

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

Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or

symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

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

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and the SAE form.

The following should be considered when recording SAEs:

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

Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms “Disease Progression”, “Progression of Disease”, or “Malignant disease progression” and other similar terms should not be used to describe an AE or SAE. Symptomatic clinical deterioration due to disease progression as determined by the investigator will not be reported as an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs. The events described above are the only protocol-defined events which do not need immediate reporting from the investigator to the sponsor for this study.

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 7 months after the last dose of study drug(s), including any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male subject’s partner if the estimated date of conception is after the male subject’s first study drug dose. Email or fax to the sponsor’s Drug Safety Department within 24 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF

All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s), will also be recorded on the Adverse Events and Pre-existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

7.7.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT Visit or 30 days after the last study treatment (tucatinib or placebo, T-DM1), whichever is later. However, all study protocol-related AEs are to be recorded from the time of study informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

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

7.7.1.4. Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email address or fax number specified on the SAE report form).

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

7.7.1.5. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.7.1.4).

The sponsor will report all SAEs, including SUSARs, to regulatory authorities as required per local legislation or regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity, as well as other SAEs that are not study endpoints but are known consequences of the underlying disease or condition that are anticipated to occur

in the study population, should not be reported to the FDA as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Assessment for IND Safety Reporting Guidance for Industry (draft guidance December 2015).

In this study, the SAEs that do not require individual IND safety reports to the FDA are progression of the underlying cancer. These anticipated SAEs will be reviewed periodically by an IDMC and the Seagen Drug Safety Department. If upon review, an SAE is occurring at a higher rate than that which would be expected for the study drug treatment arm, then an IND safety report for the SAE will be submitted to the FDA.

7.7.1.6. Adverse Events of Special Interest

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

The AESIs will need to be reported to the sponsor irrespective of regulatory seriousness criteria or causality within 24 hours (Section 7.7.1.4).

Potential drug-induced liver injury

The following 2 types of LFT elevations are considered AESIs:

- AST or ALT elevations that are >3 × ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2 × ULN, except in subjects with documented Gilbert's syndrome
- Grade 4 AST, ALT, or bilirubin elevations

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

Asymptomatic left ventricular systolic dysfunction

In general, asymptomatic declines in LVEF should not be reported as AEs since LVEF data are collected separately in the electronic CRF (eCRF). However, an asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment is considered an event of special interest and an SAE, and must be reported to the sponsor.

Cerebral Edema

Any event of cerebral edema not clearly attributable to progression of disease should be reported as an AESI.

7.7.2. Physical Examination

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

7.7.3. Vital Signs

Vital sign measurements are to include heart rate, systolic and diastolic blood pressure, temperature, and respiration rate. Vital signs should be measured after the subject has been sitting/resting.

7.7.4. Clinical Laboratory Tests

The following laboratory assessments will be performed by the local laboratory to evaluate safety at scheduled timepoints (see Appendix A) and make clinical decisions during the course of the study:

- The chemistry panel is to include the following tests: blood urea nitrogen or urea, creatinine, glucose, lactate dehydrogenase, potassium, and sodium.
- LFTs include ALT/SGPT, AST/SGOT, ALP, and total bilirubin (and direct bilirubin when total bilirubin is >ULN)
- The CBC with differential is to include the following tests: CBC with differential that includes hemoglobin, hematocrit, platelet count, and white blood cell count with 5-part differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- The coagulation panel is to include the following tests: INR, prothrombin time, and PTT/aPTT
- The estimated GFR should be calculated using the MDRD equation, with serum creatinine (Scr) reported in mg/dL

GFR (mL/min/1.73 m^2) = $175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.212$ if African American)

- A serum or urine β-hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) for subjects of childbearing potential (see Section 7.7.5)
- For Italy only: Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B surface antigen (anti-HBs), antibodies to Hepatitis B core antigen (anti-HBc), Hepatitis B DNA levels by PCR (as applicable; refer to latest local guidelines for the management of Hepatitis B virus infection), and antibodies to Hepatitis C (anti-HCV). If positive, contact medical monitor.

7.7.5. Pregnancy Testing

For subjects of childbearing potential, a serum or urine β-hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) will be performed at baseline, within 7 days prior to Day 1 of each treatment cycle, and at the EOT Visit. A negative pregnancy result is required before the subject may receive study treatment.

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

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

7.7.6. Cardiac Function

7.7.6.1. MUGA or ECHO

Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

7.7.6.2. Electrocardiogram

An ECG will be performed during screening (must be collected prior to first dose of any study treatment). To correct for heart rate, QT intervals should be calculated using the Fridericia formula (QTcF).

7.8. Appropriateness of Measurements

Response will be assessed according to RECIST v1.1 (Eisenhauer 2009), which are standardized criteria for evaluating response in solid tumors. The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and subject inconvenience associated with CT and PET scanning.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and clinical laboratory data will be graded using standardized criteria for oncology (NCI CTCAE v4.03).

The PRO instruments included in this study (EORTC QLQ IL6, EQ-5D-3L, and FACT-B GP5) are validated questionnaires that have been incorporated into previous clinical trials to assess global health status and quality of life as well as perception of side effects, respectively.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

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

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current investigator's brochure/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Subject coding and randomization
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

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

8.2. Data Management Procedures

Seagen will provide CRF completion guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3. Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4. Accuracy and Reliability of Data

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

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5. Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seagen as part of the written record.

8.6. Data Handling and Record Keeping

8.6.1. Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2. Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum

period required by the country and institution in which the study will be conducted, or for the period specified by Seagen, whichever is longer. The investigator must contact Seagen prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed-upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seagen.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of PFS events (HR 0.70; median PFS from 6 months in the control arm to 8.57 months in the experimental arm).

A total of 331 PFS events will provide 90% power to detect a HR of 0.70 at a 2-sided significance level of 0.05 using a log-rank test. Approximately 460 subjects will be randomized in a 1:1 ratio to either the experimental arm or the control arm to observe 331 PFS events in approximately 30 months after the first subject is randomized, assuming 24 months of subject accrual, and a 5% annual dropout rate.

If the final analysis of the primary endpoint is statistically significant, a formal statistical test of OS is planned at the same time. It is also planned that follow-up for OS will continue after the primary analysis of PFS. The final OS analysis will be performed when approximately 253 OS events have occurred. With 253 events, it will provide 80% power to detect a HR of 0.70 in OS at a 2-sided significance level of 0.05 using a log-rank test. The final analysis of OS is estimated to take place approximately 30 months after the primary analysis of PFS, assuming that the OS for the control follows an exponential distribution with a median of 29 months.

If both PFS and OS results are statistically significant, a formal statistical test of PFS.BM is planned. Follow-up of PFS.BM will continue after the primary analysis of PFS. It is anticipated that approximately 175 PFS.BM events would have occurred, which will provide 65% power to detect a HR of 0.7 in PFS.BM at a 2-sided significance level of 0.05 using a log-rank test, assuming that PFS.BM for the control arm follows an exponential distribution with a median of 5.7 months.

China Portion of the Study

To evaluate the consistency of efficacy and safety in a China subpopulation compared with the global population, after completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 105 (up to 110) subjects in China is reached. Subjects in China randomized after completion of enrollment in the global portion will not be included in the analysis of the global portion. After the completion of the global portion, the study may remain open to complete the China portion as an extension of the study. The details will be provided in the statistical analysis plan (SAP).

9.2. Study Endpoint Definitions

9.2.1. Primary Endpoint: PFS per Investigator Assessment

PFS per investigator is defined as the time from the date of randomization to the investigator assessment of disease progression according to RECIST v1.1 or death from any cause, whichever occurs first. For subjects who continue on study treatment after isolated CNS progression per RECIST v1.1, PFS per investigator will be calculated from the date of randomization to the first (or earliest) investigator assessment of disease progression. Subjects

without documentation of PD, or death at the time of analysis, will be censored at the date of the last tumor assessment with an overall response of CR, PR, SD or non-CR/non-PD.

If there is no radiographic postbaseline tumor assessment, PFS will be censored at the date of randomization.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, is provided in the SAP.

9.2.2. Key Secondary Endpoints

9.2.2.1. Overall Survival

OS is defined as the time from randomization to death due to any cause.

For a subject who is not known to have died by the end of study follow-up, observation of OS is censored on the date the subject was last known to be alive (ie, the date of last contact). Subjects lacking data beyond the day of randomization will have their survival time censored on the date of randomization (ie, OS duration of 1 day).

9.2.2.2. PFS per Investigator Assessment in Subjects With Brain Metastases at Baseline (PFS.BM per Investigator)

PFS.BM is defined in the same manner as the primary endpoint of PFS per investigator assessment. For this endpoint, PFS per investigator assessment will be analyzed in subjects with brain metastases at baseline.

9.2.2.3. Objective Response Rate by Investigator Assessment

ORR is defined as the proportion of subjects with confirmed CR or PR according to RECIST v1.1. Subjects whose disease response cannot be assessed will be considered as nonresponders for calculating the ORR. ORR by investigator assessment is based on investigator response assessments.

9.2.2.4. OS in Subjects with Brain Metastases at Baseline (OS.BM)

OS.BM is defined in the same manner as the key secondary endpoint of OS. For this endpoint, OS will be analyzed in subjects with brain metastases at baseline.

9.2.3. Other Secondary Endpoints

9.2.3.1. PFS per BICR

PFS per BICR is defined as the time from the date of randomization to the centrally-reviewed documented disease progression according to RECIST v1.1 or death from any cause, whichever occurs first. Subjects without documentation of PD or death at the time of analysis, will be censored at the date of last radiographic disease assessment with an overall response of CR, PR, SD or non-CR/non-PD.

9.2.3.2. PFS per BICR in Subjects With Brain Metastases at Baseline (PFS.BM per BICR)

PFS.BM per BICR is defined in the same manner as the primary endpoint of PFS per investigator assessment. For this endpoint, PFS per BICR will be analyzed in the subset of subjects with brain metastases at baseline per the CRF.

9.2.3.3. Objective Response Rate by BICR

ORR is defined as the proportion of subjects with CR or PR according to RECIST v1.1. Subjects whose disease response cannot be assessed will be considered as nonresponders for calculating the ORR. ORR per BICR is based on BICR response assessments.

9.2.3.4. Duration of Response

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

9.2.3.5. Clinical Benefit Rate

CBR is defined as the proportion of subjects with SD or non-CR or non-PD for ≥6 months or best response of CR or PR according to RECIST v1.1. CBR per investigator is based on investigator response assessments and CBR per BICR is based on BICR response assessments.

9.2.4. Exploratory Endpoints

9.2.4.1. PK Analysis

The pharmacokinetics of tucatinib and DM1 will be evaluated.

9.2.4.2. Healthcare Resource Utilization

HCRU data include healthcare encounters related to the subject's breast cancer, cancer treatment, or cancer-related assessments.

9.2.4.3. Patient-Reported Outcomes

Changes in PROs will be assessed using the EQ-5D-3L, EORTC QLQ IL6, NCI PRO-CTCAE, and FACT-B GP5.

9.3. Statistical and Analytical Plans

The statistical methods are outlined below; additional analysis details of the global portion and China population will be provided in the SAP. The SAP will be finalized prior to study unblinding. Exploratory analyses of the data not described in the following subsections may be conducted as deemed appropriate. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

9.3.1. General Considerations

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

9.3.1.1. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study. Subjects will be randomized in a 1:1 manner to receive either tucatinib or placebo in combination with T-DM1. Randomization will be stratified by line of treatment for metastatic disease, hormone receptor status, presence or history of brain metastases, and ECOG performance status.

Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the study manual.

The blinding plan for the safety and efficacy data will be specified in the SAP.

9.3.1.2. Adjustments for Covariates

Stratified analyses will include adjustment for the stratification factors as recorded at randomization (described in Section 9.3.1.1). Please note, if the sample size of one strata by a stratification factor is too small, the statistical analysis will not include this randomization stratification factor in the statistical analysis, such as stratified log-rank test and stratified Cox regression model. This minimum sample size requirement will be specified in the SAP. Covariates may be considered for adjustment in exploratory analyses. Only subjects with parenchymal lesions are considered as having brain metastases at baseline for purposes of stratification.

9.3.1.3. Handling of Dropouts and Missing Data

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

9.3.1.4. Multicenter Studies

This study will be conducted at multiple study centers, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

9.3.1.5. Multiple Comparisons and Multiplicity

To maintain strong control of the family-wise type I error rate at 0.05, a fixed sequential testing procedure will be used to test the primary endpoint of PFS per investigator assessment and the key secondary endpoints of OS, PFS.BM per investigator assessment, and ORR per investigator.

If the PFS per investigator assessment is positive at the 2-sided 0.05 level, OS will be tested 3 times with an overall 2-sided alpha of 0.05. The first analysis of OS (OS interim analysis 1 [OS IA1]) will be performed at the same time as the primary PFS analysis when approximately

331 PFS events per investigator assessment are observed. The second OS interim analysis (OS IA2) is planned when approximately 202 (80% information fraction) OS events have been observed. The final analysis of OS (OS FA) will occur when approximately 253 OS events are observed from the study. The Lan-DeMets O'Brien-Fleming approximation spending function (Chen 2014) will be used for the calculation of the alpha level at each test of OS based on the actual number of OS events observed at the time of each analysis.

If both PFS and OS (OS IA1, OS IA2, or OS FA) results are statistically significant, then PFS.BM by investigator assessment per RECIST v1.1 will be tested twice with an overall 2-sided alpha of 0.05. The first PFS.BM analysis will use the PFS.BM data at the time of the primary endpoint analysis when approximately 331 PFS events per investigator assessment have occurred and the p-value will be compared with a nominal 2-sided alpha of 0.0001 (Haybittle-Peto approach). The final PFS.BM analysis will use the PFS.BM data at the time of OS IA2, and the p-value will be compared with a 2-sided alpha of 0.05.

If the results of PFS, OS, and PFS.BM are all statistically significant, the ORR per investigator assessment will be formally tested between 2 arms at the 2-sided significance level of 0.05. Specifically, ORR will be tested once with the same data as used at the PFS analysis.

If the results of PFS per investigator, OS, PFS.BM per investigator, and ORR per investigator are all statistically significant, then OS in subjects with brain metastases at baseline (OS.BM) will be formally tested between treatment arms at the 2-sided significance level of 0.05 (Figure 5). It is anticipated that approximately 134 OS.BM events would have occurred at the time of final OS analysis, which will provide 83% power to detect a HR of 0.6 in OS.BM at a 2-sided significance level of 0.05 using a log-rank test assuming OS.BM for the control arm follows an exponential distribution with a median of 26 months.

Detailed rejection boundaries of P-values will be specified in the SAP.

Baseline values used in all statistical analyses will be the most recent nonmissing measurement prior to the first dose of study treatment unless otherwise specified in the analysis plan.

9.3.1.6. Analysis Sets

The intent-to-treat (ITT) analysis set will include all randomized subjects. Subjects will be included in the treatment group assigned at randomization regardless of the actual treatment received. The primary analysis of the efficacy endpoints will be based on the ITT analysis set.

The safety analysis set will include all randomized subjects who receive at least one dose of tucatinib or placebo, or T-DM1. Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment.

China Portion of the Study

Subjects in China who are randomized in the China portion will not be included in the analysis population for the global portion. The China ITT population, including all subjects in China randomized in both the global portion and the China portion will be analyzed in the China-specific efficacy analyses. The China safety analysis set, including all randomized subjects in China (both the global portion and the China portion) who receive at least one dose of tucatinib or placebo, or T-DM1 will be analyzed in the China-specific safety analyses.

Any additional analysis sets will be included in the SAP.

9.3.1.7. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.8. Timing of Analyses

There is only one formal analysis of the primary endpoint, PFS per investigator assessment, which will occur after approximately 331 PFS events in the ITT analysis set have occurred. The analysis cutoff date for this analysis will be determined once approximately 331 PFS events per investigator assessment have been observed. This is estimated to be approximately 30 months after randomization of the first subject.

The key secondary endpoint of OS will be analyzed 3 times. OS IA1 will be performed at the same time as the primary analysis of PFS per investigator assessment. OS IA2 is planned when approximately 202 (80%) OS events have occurred, which is estimated to be approximately 46 months after randomization of the first subject. The final analysis of OS will occur when approximately 253 OS events have occurred. The final OS analysis is estimated to occur 60 months after randomization of the first subject.

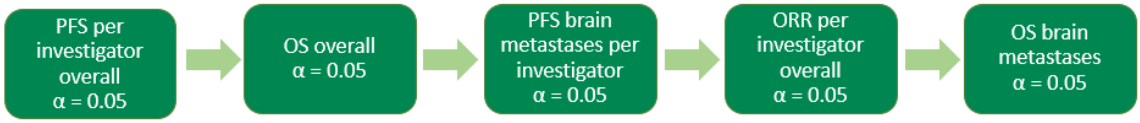
PFS.BM will be analyzed twice. The first analysis will be performed using the PFS.BM data at the same time as the primary analysis of PFS per investigator assessment. The final PFS.BM analysis will be conducted using the PFS.BM data at the time of OS IA2. If the OS result is not statistically significant at the second analysis but statistically significant at the final OS analysis, then PFS.BM will be formally tested again along with the OS final analysis.

ORR by investigator assessment will be formally tested if the results of the PFS, OS, and PFS.BM analyses are all statistically significant, using the data at time of the primary analysis of PFS.

If the results of PFS per investigator, OS, PFS.BM per investigator and ORR per investigator are all statistically significant, then OS in subjects with brain metastases at baseline (OS.BM) will be formally tested.

The hierarchical testing strategy is represented in Figure 5.

Figure 5: Hierarchical Testing Strategy



9.3.2. Subject Disposition

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

9.3.3. Subject Characteristics

The following baseline characteristics will be summarized by treatment group

- Subject demographics
- Disease history
- Prior disease-related therapies; and
- Baseline disease characteristics

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

Details will be provided in the SAP.

9.3.4. Treatment Compliance

Treatment compliance (percent of actual to planned dosing) for tucatinib/placebo will be summarized by treatment group.

9.3.5. Efficacy Analyses

9.3.5.1. Primary Efficacy Analyses

The stratified log-rank test will be used in the primary evaluation of PFS differences between the treatment arms in the ITT analysis set using a 2-sided significance level of 0.05. A stratified Cox proportional-hazards (PH) model will be used to estimate the HR and its 95% CI. Both stratified log-rank and Cox PH models will take into account the stratification factors for randomization. Please note, if the sample size of one stratum from a stratification factor is too small, statistical analysis may not include this stratification factor. The minimum sample size for a stratum to be included in the statistical model will be specified in the SAP.

All events entered in the database at the time of analysis will be included in the analysis of PFS per investigator, even if there are more than the prespecified number of events.

Kaplan-Meier curves depicting PFS in the 2 treatment arms will be generated. Additionally, median PFS and the 2-sided 95% CIs for the median will be reported using the complementary log-log transformation method (Collett 1994). Detailed methodology is provided in the SAP.

9.3.5.2. Secondary Efficacy Analyses

OS will be analyzed using similar methods used for the primary endpoint. The stratified log-rank test will be used to evaluate the OS differences between the treatment arms. A stratified Cox PH model will be used to estimate the HR and its 95% CI. Both stratified log-rank and Cox PH models will take into account the stratification factors for randomization. Please note, if the sample size of one strata by a stratification factor is too small, statistical analysis may not include this stratification factor. The minimum sample size for a strata to be included in the statistical model will be specified in the SAP.

Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment group using the ITT analysis set. The median OS and its 2-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment group.

Secondary endpoints of PFS.BM and PFS by BICR will be analyzed using same method used for the primary endpoint.

Response Rates – Objective Response Rate and Clinical Benefit Rate

Data summaries for ORR will be provided for the response evaluable set (subjects in ITT with measurable disease at baseline). The 95% CI of ORR will be estimated for each treatment group. Additionally, comparison of ORR between treatment groups will be conducted using 2-sided Cochran-Mantel-Haenszel test controlling for the study stratification factors.

A similar approach will be used for the CBR analysis, but the analysis for CBR will be applied to the ITT analysis set.

Duration of Response

Only subjects with a confirmed response will be included in the analysis of DOR. DOR is defined as the time from first documented objective response (CR or PR that is subsequently confirmed) to documented disease progression per RECIST v1.1 or death from any cause, whichever occurs first. DOR will be graphically described using Kaplan-Meier methodology. The median DOR and its 95% CI will be provided for the 2 treatment arms.

9.3.6. Pharmacokinetic Analyses

Individual (subject) plasma tucatinib and DM1 concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will also be calculated.

For subjects in the PK substudy (US only), summary statistics comparing the concentration time profiles of DM1 will be calculated.

Additional exploratory PK analyses may be conducted.

Exploratory analyses investigating the relationship between tucatinib and/or DM1 exposure and efficacy and safety endpoints may be conducted.

9.3.7. Health Outcomes Analyses

PRO assessments based on the EQ-5D-3L, EORTC QLQ IL6, NCI PRO-CTCAE, FACT-B GP5, and HCRU data will be summarized using descriptive statistics by treatment group.

PRO assessments will be analyzed to determine if treatment affects PRO scores. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment timepoint may be presented. Additional statistical modeling for PRO and HCRU measures may be performed separately in post hoc analyses.

9.3.8. Safety Analyses

Safety is assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in ECOG performance status, and changes in cardiac ejection fraction results. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE criteria.

9.3.8.1. Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by treatment arm using the safety analysis set. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.8.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all treatment-emergent AEs (TEAEs), treatment-related TEAEs, Grade 3 and higher TEAEs, treatment-emergent SAEs, treatment-related treatment-emergent SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

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

All collected AE data will be listed by treatment group, study site, subject number, and cycle. Separately, all SAEs and AESIs (eg, any DILI, asymptomatic left ventricular systolic dysfunction, and/or cerebral edema) will be analogously listed.

A separate listing of all on-study deaths will be presented.

9.3.8.3. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.8.4. Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range.

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

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

9.3.8.5. Vital Signs, Physical Examination Findings, and ECOG Performance Status

The frequency and percentage of subjects with postbaseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs. ECOG performance status shift tables will likewise be provided by treatment group and scheduled visit.

9.3.8.6. Cardiac Ejection Fraction

Cardiac ejection fraction data will be summarized by treatment group by baseline and postbaseline assessment. Corresponding shift tables will also be provided by treatment group and baseline and postbaseline assessment.

9.3.9. Interim Analyses

No formal interim analyses are planned for the primary endpoint.

The key secondary endpoint of OS will be analyzed 3 times. OS IA1 is at the time of analysis of primary endpoint when approximately 331 PFS events per investigator assessment have occurred. OS IA2 is planned when approximately 202 (80%) OS events have occurred. OS FA will be performed when approximately 253 OS events have occurred. The Lan-DeMets O'Brien-Fleming approximation spending function (Chen 2014) will be used for calculation of the alpha level at each test of OS based on the actual number of OS events observed at the interim.

If the PFS and OS (OS IA1, OS IA2 or OS FA) results are statistically significant, a formal statistical test of the PFS.BM analysis will be performed twice. The first PFS.BM analysis will use the PFS.BM data at the time of analysis of the primary endpoint when approximately 331 PFS events per investigator assessment have occurred, and the p-value will be compared with a nominal 2-sided alpha of 0.0001. The final PFS.BM analysis will use the PFS.BM data at the time of OS IA2, and the p-value will be compared with a 2-sided alpha of 0.05.

If the results of the PFS, OS, and PFS.BM analyses are all statistically significant, a formal test of ORR per investigator assessment will be performed.

If the results of PFS per investigator, OS, PFS.BM per investigator, and ORR per investigator are all statistically significant, then OS in subjects with brain metastases at baseline (OS.BM) will be formally tested between treatment arms at the 2-sided significance level of 0.05 (Figure 5). It is anticipated that approximately 134 OS.BM events would have occurred at the time of final OS analysis.

Detailed rejection boundaries of P-values will be specified in the SAP.

10. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1. Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects are reconsented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

10.2. Ethical Review

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

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

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

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

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

10.3. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1. Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2. Protocol Amendments and Study Termination

Protocol amendments will be submitted to the IRB/IEC prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

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

10.4. Study Documentation, Privacy, and Records Retention

To protect the safety of subjects in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5. Clinical Trial Agreement

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

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

American Cancer Society. Breast cancer facts & figures (2017-2018). 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf. Accessed: Dec 12, 2019.

Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol. 1998;46(2):101-10.

Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012a;379(9816):633-40.

Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012b;366(2):109-19.

Bjordal K, Ahlner-Elmqvist M, Tollesson E, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncol. 1994;33(8):879-85.

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. 2010;28(7):1124-30.

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. 2012;30(21):2585-92.

Borges VF, Ferrario C, Aucoin N, et al. Tucatinib combined with ado-trastuzumab emtansine in advanced ERBB2/HER2-positive metastatic breast cancer: a phase 1b clinical trial. JAMA Oncol. 2018;4(9):1214-20.

Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol. 1997;15(3):974-86.

Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA. 2016;316(4):401-9.

Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res. 2011;17(14):4834-43.

Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016;17(3):367-77.

Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037-44.

Chen LM, Ibrahim JG, Chu H. Flexible stopping boundaries when changing primary endpoints after unblinded interim analyses. J Biopharm Stat. 2014;24(4):817-33.

Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer. 2004;91(4):639-43.

Collett D. Interval-censored survival data. Modelling survival data in medical research. London, Chapman & Hall. 1994:237-51.

Dzimitrowicz H, Berger M, Vargo C, et al. T-DM1 activity in metastatic human epidermal growth factor receptor 2-positive breast cancers that received prior therapy with trastuzumab and pertuzumab. J Clin Oncol. 2016;34(29):3511-7.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Fabi A, Giannarelli D, Moscetti L, et al. Ado-trastuzumab emtansine (T-DM1) in HER2+ advanced breast cancer patients: does pretreatment with pertuzumab matter? Future Oncol. 2017;13(30):2791-7.

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Accessed Sep 09, 2018. http://globocan.iarc.fr. 2013.

Gerstner ER, Fine RL. Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. J Clin Oncol. 2007;25(16):2306-12.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355(26):2733-43.

Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32.

Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-

positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791-800.

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. J Clin Oncol. 2014;32(19):2078-99.

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. 2013;382(9897):1021-8.

Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010;5(1):61-72.

Hamilton E, Murthy R, Ferrario C, et al. Prolonged progression-free survival (PFS) in advanced HER2+ metastatic breast cancer with or without brain metastases: a pooled analysis of tucatinib phase 1b studies. Cancer Res. 2018;78(Suppl 4):Abstract P5-20-01.

Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5):dju055.

Jacot W, Pons E, Frenel JS, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. Breast Cancer Res Treat. 2016;157(2):307-18.

Kaidar-Person O, Anders CK, Zagar TM. Whole brain radiotherapy for brain metastases: is the debate over? JAMA. 2016;316(4):393-5.

Kerb R, Brockmoller J, Staffeldt B, Ploch M, Roots I. Single-dose and steady-state pharmacokinetics of hypericin and pseudohypericin. Antimicrob Agents Chemother. 1996;40(9):2087-93.

Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(7):689-99.

Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017;18(6):743-54.

Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol. 2015;26(1):113-9.

Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res. 2008;68(22):9280-90.

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

Lin NU, Murthy RK, Anders CK, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB). J Clin Oncol. 2020;38(15 Suppl):Abstract 1005.

Lu Y, Zi X, Zhao Y, Mascarenhas D, Pollak M. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). J Natl Cancer Inst. 2001;93(24):1852-7.

Moulder S, Hamilton E, Ferrario C, et al. Progression-free survival (PFS) and site of first progression in HER2+ metastatic breast cancer (MBC) patients (pts) with (w) or without (w/o) brain metastases: a pooled analysis of tucatinib phase I studies. Ann Oncol. 2017;28(Suppl 5):85.

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. 2018;19(7):880-8.

Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597-609.

Nahta R, Esteva FJ. HER2 therapy: molecular mechanisms of trastuzumab resistance. Breast Cancer Res. 2006;8(6):215.

Olson EM, Abdel-Rasoul M, Maly J, et al. Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab. Ann Oncol. 2013a;24(6):1526-33.

Olson EM, Najita JS, Sohl J, et al. Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the post-trastuzumab era. Breast. 2013b;22(4):525-31.

Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer. 2004;5(1):63-9.

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. 2013;14(3):244-8.

Pohlmann PR, Mayer IA, Mernaugh R. Resistance to trastuzumab in breast cancer. Clin Cancer Res. 2009;15(24):7479-91.

Scaltriti M, Rojo F, Ocana A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. J Natl Cancer Inst. 2007;99(8):628-38.

Schwartzberg LS, Franco SX, Florance A, et al. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. Oncologist. 2010;15(2):122-9.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.

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. 1987;235(4785):177-82.

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. 2001;344(11):783-92.

Smith AW, Mitchell SA, De Aguiar CK, et al. News from the NIH: person-centered outcomes measurement: NIH-supported measurement systems to evaluate self-assessed health, functional performance, and symptomatic toxicity. Transl Behav Med. 2016;6(3):470-4.

Sneeuw KC, Aaronson NK, Sprangers MA, et al. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. J Clin Epidemiol. 1998;51(7):617-31.

Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.

Tiwari SR, Sussman T, Kota K, et al. T-DM1 activity in metastatic HER2-positive breast cancer patients who have received prior trastuzumab and pertuzumab: NSABP B-005. Cancer Res. 2018;78(Suppl 4):Abstract P5-21-26.

van Agt HME, Essink-Bot ML, Krabbe PFM, Bonsel GJ. Test-retest reliability of health state valuations collected with the EuroQol questionnaire. Soc Sci Med. 1994;39(11):1537-44.

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20(3):719-26.

von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380(7):617-28.

von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377(2):122-31.

APPENDIX A. SCHEDULE OF EVENTS

		Prescreening[H]	Screening/ Baseline		Randomization	Cycle 1		Subsequent 21-Day Cycles		Response Assessments		ECHO/ MUGA	EOT	Follow-up	Survival Status
	Day	Up to 1 year before Screening Visit	D −28 to 1	D −7 to 1	Within 5D of 1st dose	D1	D12	D1	D12[A]	Every 6 weeks, through Week 24[B]	Every 9 weeks, beginning Week 24[B]	Every 12 weeks[C]	Within 30–37D after last dose[D]	Every 9 weeks until progression[E]	After progression, every 90 days[F]
	Visit Window						±3d	−1 to +3d	±3d	−7d	−7d	−7d		±1 week	±7d
HER2 Expression Testing	HER2 testing consent	X			Eligibility documentation submitted to sponsor prior to randomization										
	Submit tumor sample for HER2 testing (Section 7.1.1)	X[G]	X[G, H]												
Screening/ Baseline Assessments	Study informed consent		X[H]												
	Inclusion/exclusion		X												
	Medical history		X												
	Physical examination			X		X[I]	X	X[I]					X		
	Height			X											
	Weight			X		X[I]	X	X[I]					X		
	Vital signs[L]			X		X	X	X					X		
Safety Assessments	ECOG performance status			X		X[I]	X	X[I]					X		
	ECHO or MUGA[J]		X									X	X[K]		
	ECG		X										X		
	CBC with differential			X		X[I]	X	X[M]					X		
	Chemistry			X		X[I]	X	X[M]					X		
	Liver function tests			X		X[I]	X	X[M]	X				X		
	Coagulation panel			X									X		
	Pregnancy test (FOCBP)[N]			X				X					X[O]	X[O]	X[O]
	Italy only: Hepatitis B and C screening[X]		X[x]												
	Concomitant medications and AEs		Collect any related to study protocol procedures[P]			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later									

		Prescreening[H]	Screening/ Baseline		Randomization	Cycle 1		Subsequent 21-Day Cycles		Response Assessments		ECHO/ MUGA	EOT	Follow-up	Survival Status
	Day	Up to 1 year before Screening Visit	D −28 to 1	D −7 to 1	Within 5D of 1st dose	D1	D12	D1	D12[A]	Every 6 weeks, through Week 24[B]	Every 9 weeks, beginning Week 24[B]	Every 12 weeks[C]	Within 30–37D after last dose[D]	Every 9 weeks until progression[E]	After progression, every 90 days[F]
	Visit Window						±3d	−1 to +3d	±3d	−7d	−7d	−7d		±1 week	±7d
Treatment	Dispense tucatinib/placebo					X		X							
	Administer T-DM1					X		X							
	Review subject diary						X	X	X				X		
	Provide dosing instructions for next visit's day-of dose						X	X[Q]	X						
PRO/QoL	EQ-5D-3L[R]					X		X					X	X	X
	EORTC QLQ IL6[R]					X	X	X	X				X	X	X
	NCI PRO-CTCAE[R]					X	X	X	X				X		
	FACT-B GP5[R]					X	X	X	X				X		
HCRU	Healthcare resource utilization							X					X		
PK	Blood samples for PK[S]					See Section 7.3									
Response Assessments	CT (chest, abdomen, pelvis)[J]		X							X	X		X[T]	X[T]	
	Additional imaging of other known sites of disease, as appropriate[J]		X							X	X		X[T]	X[T]	
	Brain MRI		X[U]							X[V]	X[V]		X[W]	X[T, V]	

A Cycle 2 only.
B Scheduling determined by date of Cycle 1 Day 1 visit.
C Scheduling determined by date of Screening ECHO/MUGA. However, if there is an interim assessment, subsequent ECHO/MUGAs should be performed every 12 weeks as determined by the date of the most recent interim assessment. See Section 7.7.6.1.
D If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.
E Scheduling determined by date of the last imaging scan. See Section 6.6.
M Predose laboratory testing must be done within 1 day prior to study visit. Confirm laboratory results prior to continuing study treatment dosing.
N FOCBP only: can be performed within 7 days prior to study treatment dosing on Day 1 of cycle. Confirm negative pregnancy test prior to continuing study treatment dosing.
O FOCBP only: monthly pregnancy tests should be performed for 7 months after the last dose of study treatment. Subject will be asked to confirm that monthly pregnancy tests have been performed and have been negative.
P From time of study informed consent.
Q Cycles 3–5 only.

F Scheduled 90 days (±7 days) from the date of the last imaging scan or 90 days from the last study visit, whichever is later and continuing every 90 days (±7 days) until death, withdrawal of consent, lost to follow up, or study closure. May be an in-person assessment, contact by telephone, review of medical records, or review of publicly available information if allowed per local regulations (if reasonable efforts to contact the subject are unsuccessful). See Section 6.6

G Archival tissue specimen may be submitted up to 1 year prior to Screening visit. If archival tissue is unavailable, a fresh tumor biopsy must be obtained (Section 6.2.2).

H All subjects must sign informed consent for the study before Screening/Baseline procedures are conducted, including obtaining a fresh tumor biopsy for those subjects who require one to be performed for HER2 confirmation. The HER2 testing prescreening consent is not informed consent for the study. Subjects who remain in prescreening for >1 year must resign the prescreening consent.

I Assessment does not need to be repeated, if already done within 1 day of study visit (eg, as part of Screening/Baseline visit). Confirm laboratory results prior to initiating study treatment dosing.

J Use the same assessment modality throughout the study.

K Perform ECHO/MUGA if not done within the previous 12 weeks (excluding the Screening/Baseline assessment).

L Assessment to be done predose on days when study drug(s) are administered.

R Subject should complete questionnaires prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days (ie, within 1 day prior to study treatment). Questionnaires may be completed by phone after a subject experiences disease progression (per RECIST v1.1) and is in long-term survival follow-up. See Section 7.6.

S See Table 8 and Table 9 for predose and postdose PK sample collection details.

T Only in subjects who discontinue study treatment for reasons other than radiographic disease progression. Response assessments at the EOT visit are not required if performed within 30 days of discontinuing study treatment.

U For subjects with brain metastases discovered during screening or a history of brain metastases, confirm that relevant MRI brain reports and CNS treatment records can be obtained.

V Required only for subjects with brain metastases at baseline, as defined in Section 7.2.1.

W Contrast MRI of the brain required for all subjects. Not required if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study.

X For sites in Italy only: Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B surface antigen (anti-HBs), antibodies to Hepatitis B core antigen (anti-HBc), Hepatitis B DNA levels by PCR (as applicable; refer to latest local guidelines for the management of Hepatitis B virus infection), and antibodies to Hepatitis C (anti-HCV). If positive, contact medical monitor.

APPENDIX B. PERFORMANCE STATUS SCALES CONVERSION

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

APPENDIX C. CYP3A4 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES

CYP3A4 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a, b, c]	Elimination Half-life[d] (hours)
Strong Inhibitors	
Macrolide Antibiotics	
Clarithromycin	3–7 hours
Troleandomycin	2 hours
Azole Antifungals	
Itraconazole	16-28 hours (single dose), 34–42 hours (repeat dose)
Ketoconazole (systemic)	2–8 hours
Voriconazole	Dose dependent
Posaconazole	27–35 hours
Antivirals	
Boceprevir	3–4 hours
Indinavir	1–2 hours
Nelfinavir	3–5 hours
Ritonavir	3–5 hours
Telaprevir	9–11 hours
Other	
Nefazodone	2–4 hours
Diltiazem	3–4 hours
White grapefruit juice	~ 4–5 hours[e]
Strong Inducers	
Barbiturates	Variable
Carbamazepine	25–65 hours (single dose), 12–17 hours (repeat dose)
Phenytoin	7–42 hours
Rifampin	3–4 hours (single dose), 2–3 hours (repeat dose)
St. John's Wort	9–43 hours[f]

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

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

b EMA. “Guideline on the investigation of drug interactions” (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)
c Strong CYP3A inhibitors are defined as those drugs that increase the area under the concentration-time curve (AUC) of oral midazolam or other CYP3A substrates ≥5-fold.
d Drug package insert
e (Bailey 1998)
f (Kerb 1996)

APPENDIX D. CYP2C8 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES

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

Drug[a, b]	Elimination Half-life[c] (hours)
Strong Inhibitors	
Gemfibrozil	1–2 hours
Moderate Inhibitors	
Clopidogrel	6 hours
Strong Inducer	
Rifampin	3–5 hours

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

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

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

c Drug package insert

APPENDIX E. CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

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

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

Note: Sensitive substrates are drugs that demonstrate an increase in area under the concentration-time curve (AUC) of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2- to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

a Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
b Acid form is an organic anion transporting polypeptide 1B1 (OATP1B1) substrate.
c Listed based on pharmacogenetic studies.
d Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad 2010).

Source:
(https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1)

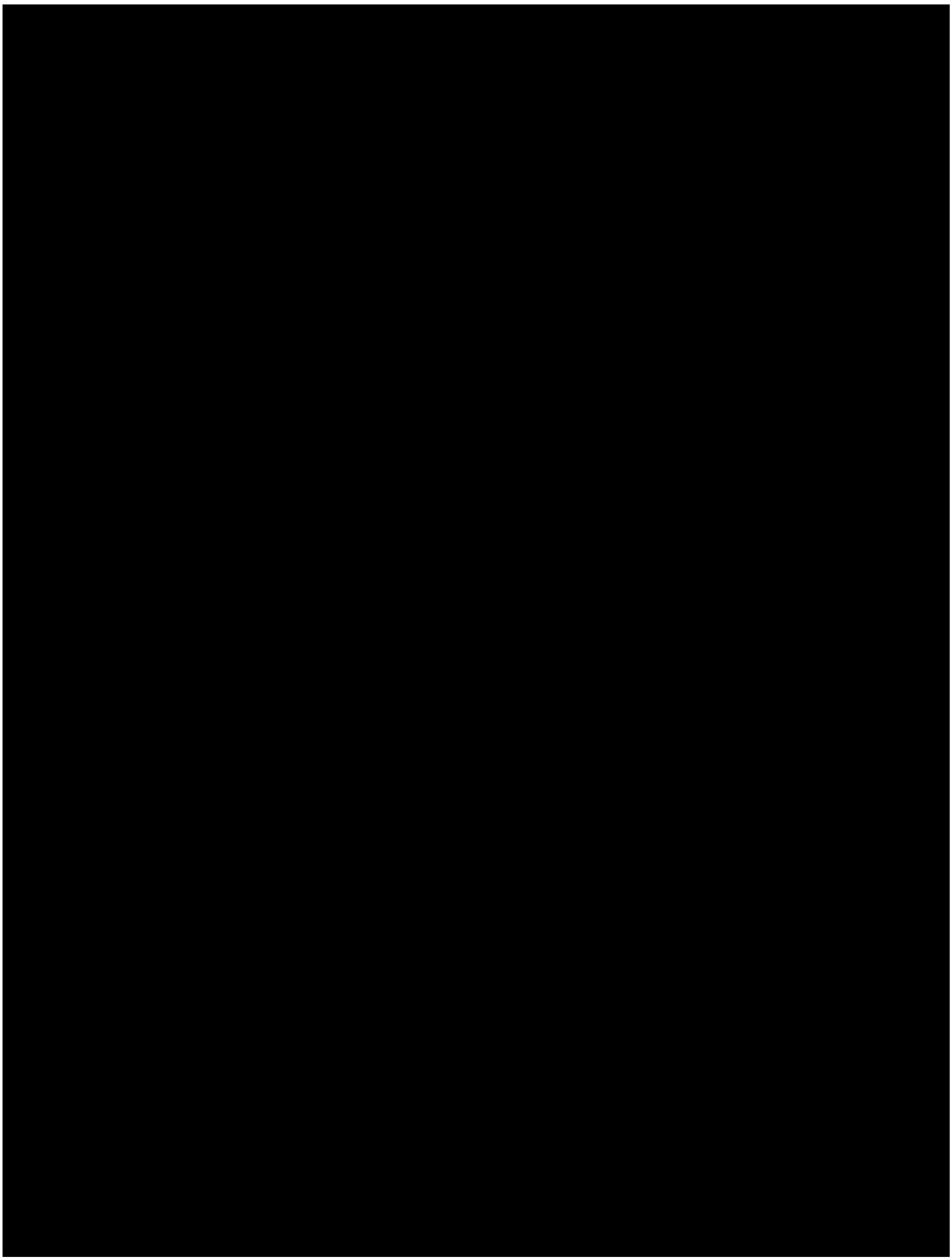
APPENDIX F. RECIST VERSION 1.1

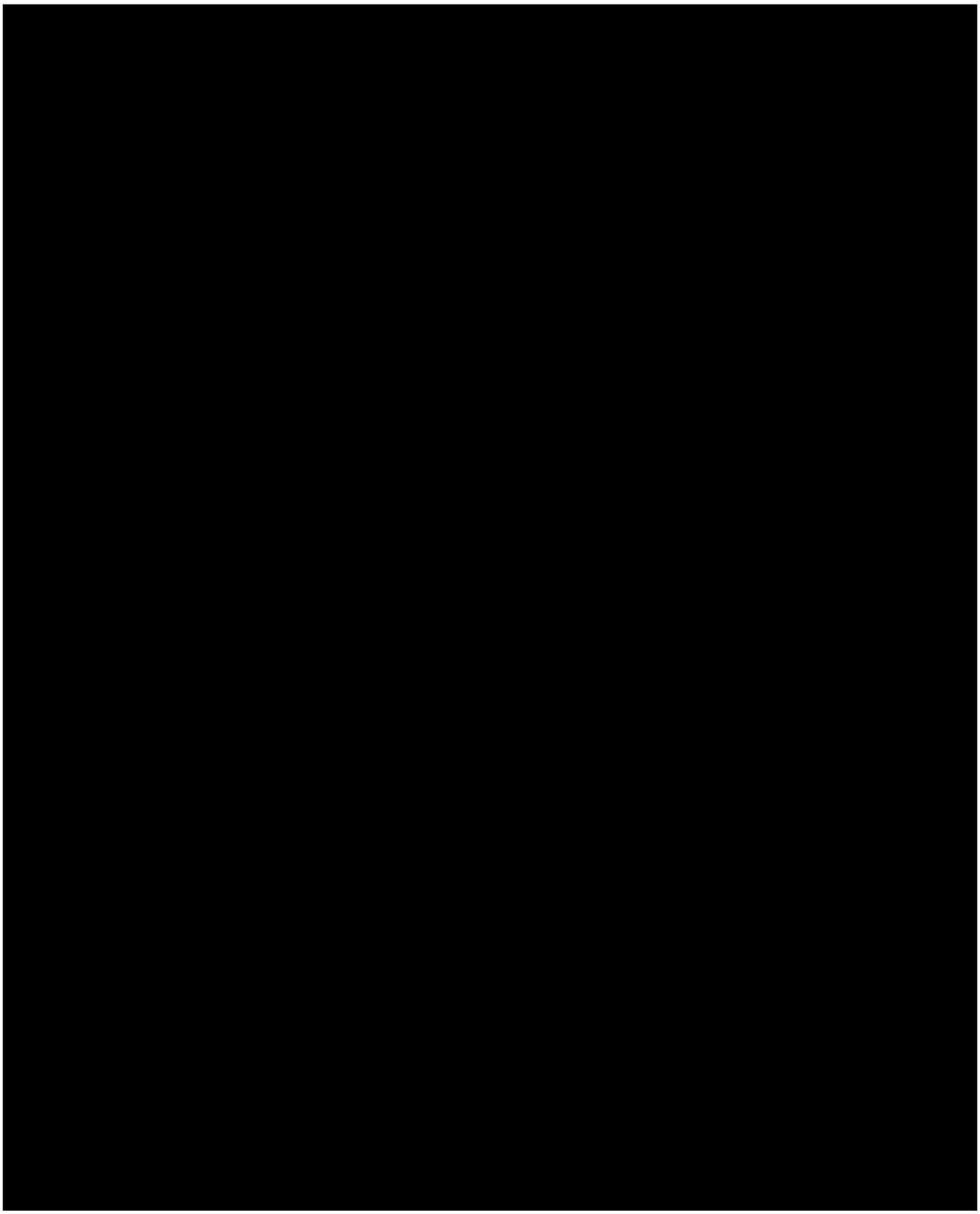
Response Evaluation Criteria in Solid Tumors

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

From RECIST v1.1 (Eisenhauer 2009)

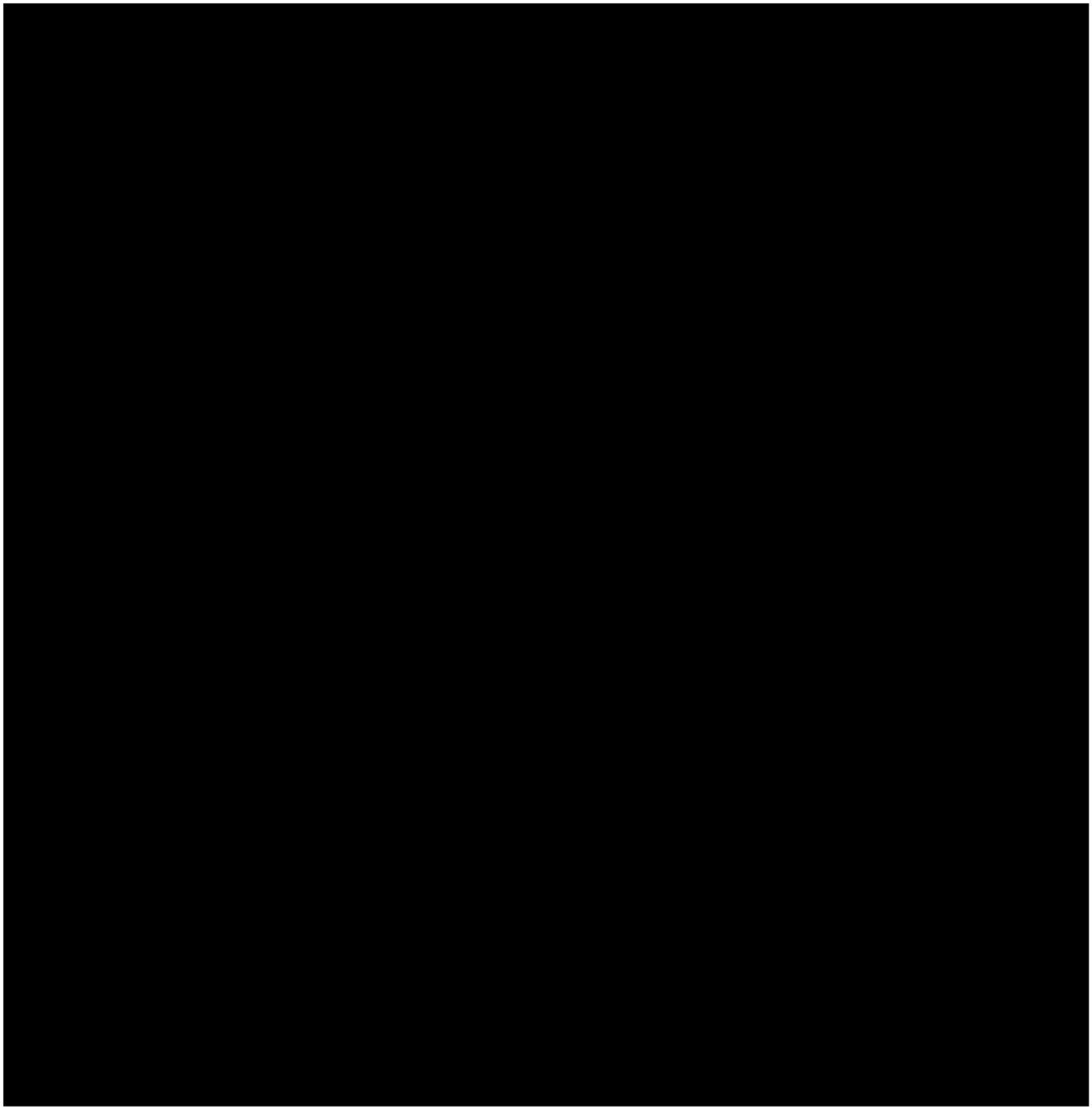
APPENDIX G. EQ-5D-3L



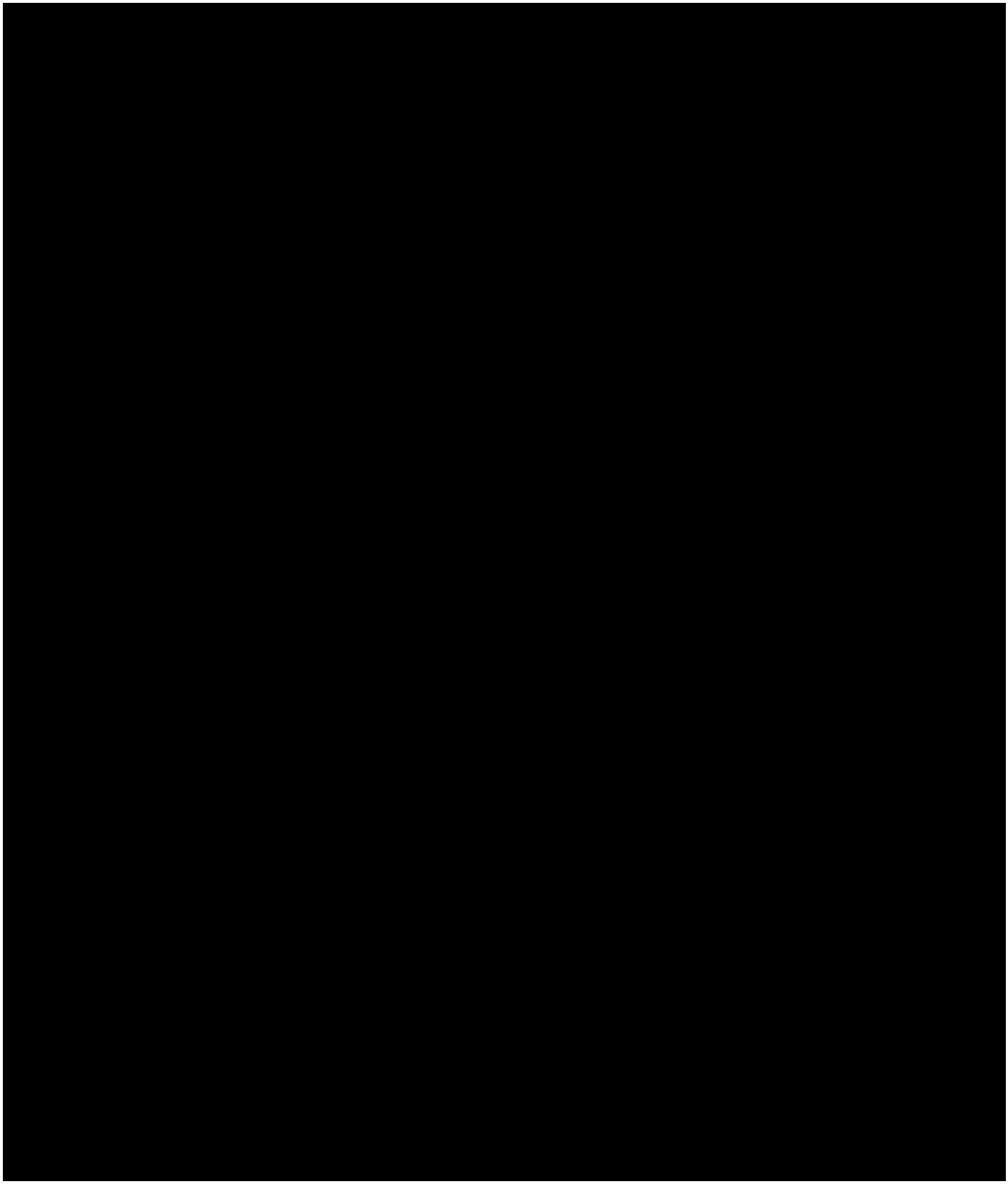


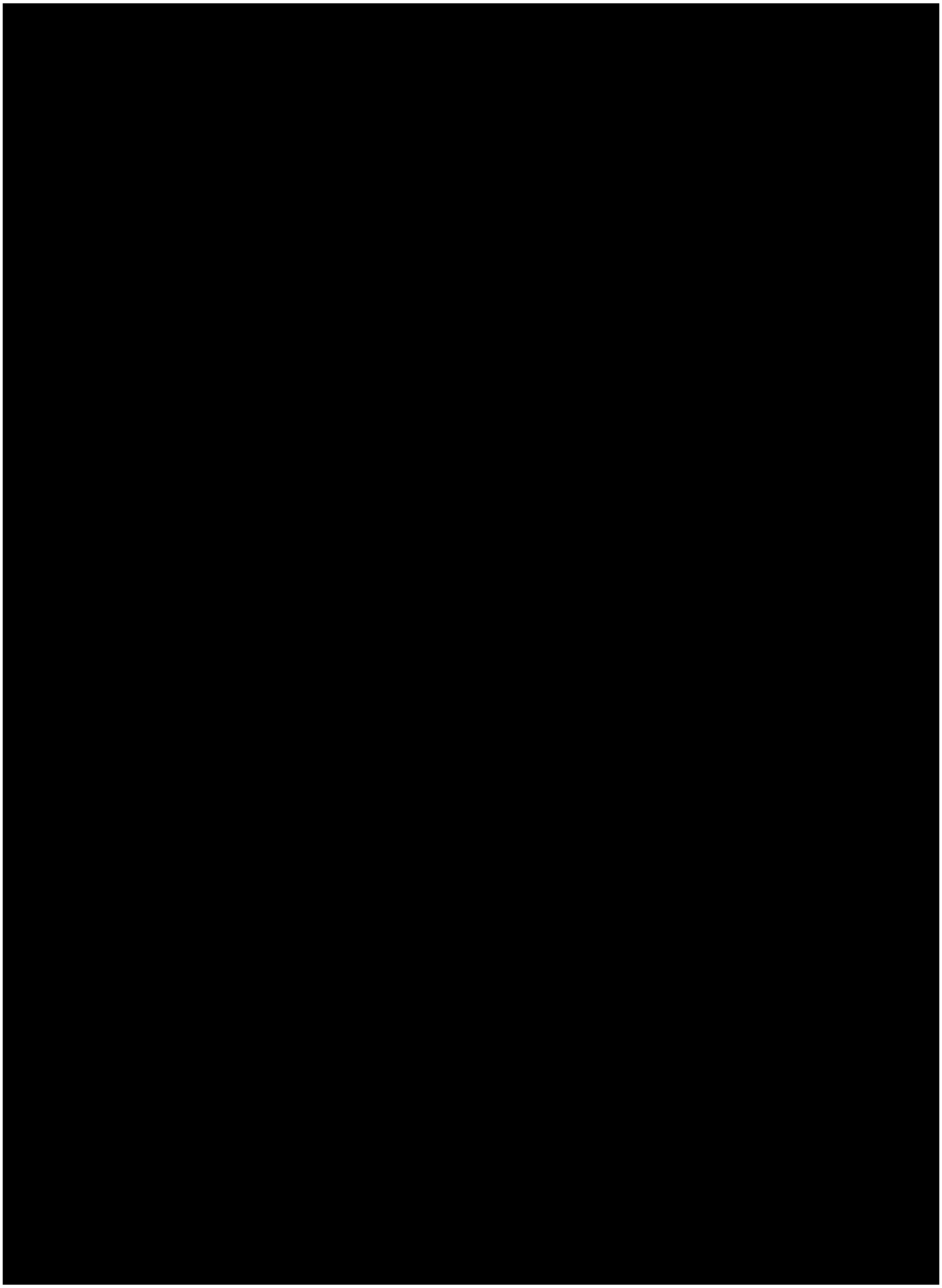
APPENDIX H. EORTC QLQ IL6

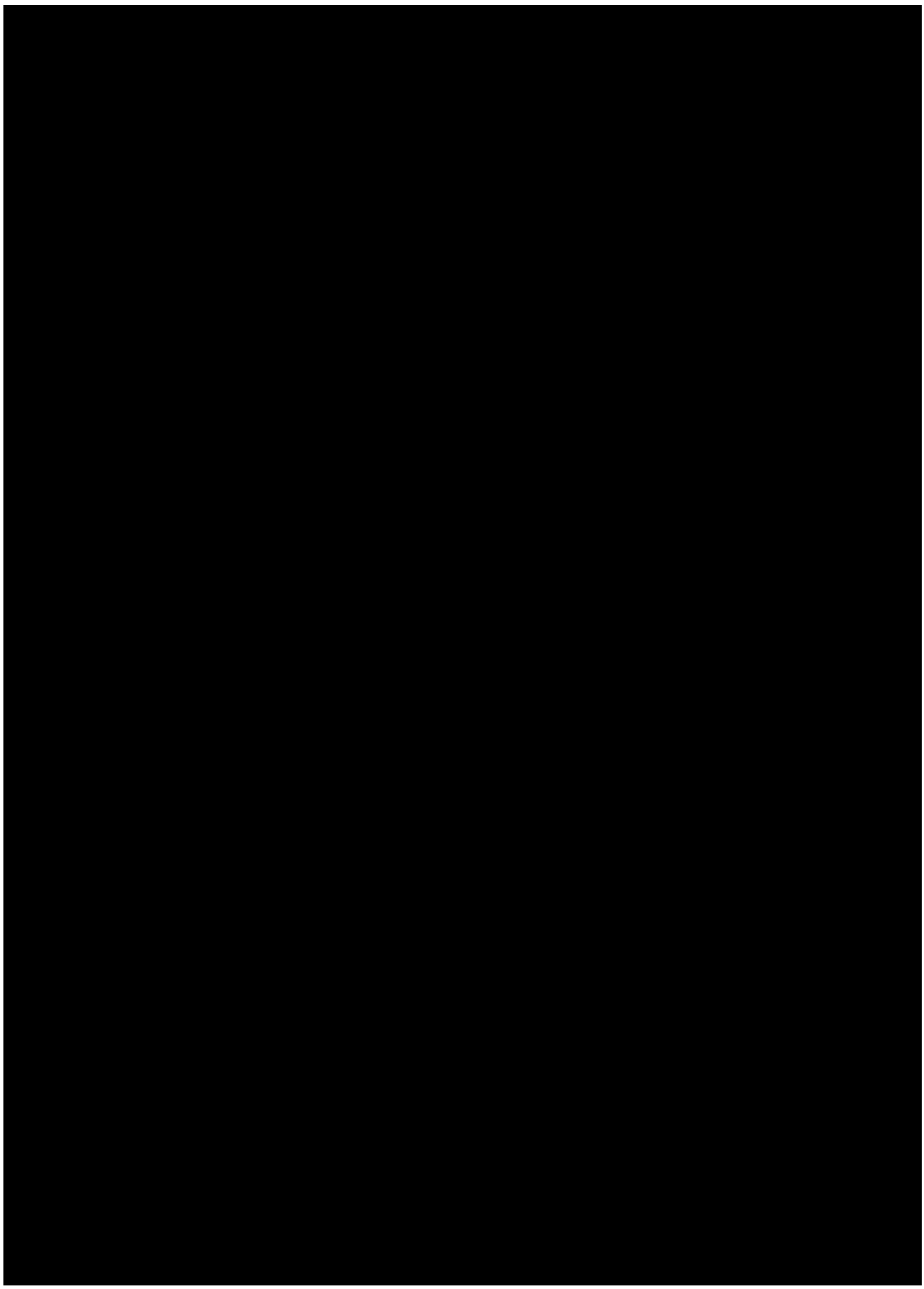
APPENDIX I. FACT-B GP5



APPENDIX J. NCI PRO-CTCAE







APPENDIX K. GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 7 months after the final dose of study drug; see Section 4.3).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]

[a] A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.
[b] A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:

- Hormonal method and vasectomy
- Hormonal method and barrier method
- Intrauterine device and vasectomy
- Intrauterine device and barrier method
- Tubal ligation and vasectomy
- Tubal ligation and barrier method

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant person must use a male condom (even if the subject has had a vasectomy).

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

Unacceptable methods of contraception

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

APPENDIX L. FRANCE SPECIFIC REQUIREMENTS

In France, the Study Population section of the synopsis should include:

> Subjects must have histologically confirmed HER2+ breast carcinoma and had progression after prior treatment with a taxane, trastuzumab, and pertuzumab for advanced/metastatic HER2+ breast cancer. Subjects with recurrence during or within 6 months of completing adjuvant treatment are also eligible with a history of prior treatment with a taxane or trastuzumab. Subjects who received T-DM1 in the adjuvant setting and relapsed during or within 6 months of completing adjuvant treatment are not allowed.

In France, inclusion criterion #2 should read as follows:

> Subjects must have documented disease progression after prior treatment with a taxane, trastuzumab, and pertuzumab for advanced/metastatic HER2+ breast cancer. Subjects with recurrence during or within 6 months of completing adjuvant treatment are also eligible with a history of prior treatment with a taxane and trastuzumab. Note: Subjects who received T-DM1 in the adjuvant setting and relapsed during or within 6 months of completing adjuvant treatment are not allowed.

In France, an additional section is included as follows:

> **Section 4.4.3 Commitment to Continue Providing Tucatinib**
>
> The Sponsor commits to continue providing tucatinib in accordance with local regulations to subjects who are continuing to demonstrate clinical benefit while receiving tucatinib upon study closure.

APPENDIX M. INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer." **(HER2CLIMB-02)**

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX N. DOCUMENT HISTORY

Version	Date
Original	24-Apr-2019
Amendment 1	13-Aug-2019
Amendment 1.1	20-Dec-2019
Amendment 2	07-Apr-2021
Amendment 3	01-Mar-2022
Amendment 4	08-Nov-2023

SUMMARY OF CHANGES IN AMENDMENT 1.1

Section(s)	Change	Rationale
Cover page	EudraCT number was added.	Documents the assigned study identifier in the European Union. Update was made to enable clinical trial applications in Europe.
Synopsis	Included the Secondary Endpoint - Evaluate the duration of response (DOR) by BICR per RECIST v1.1 between treatment arms	To be consistent with the body of the protocol.
Section 5.2	The minimum time allowed between whole-brain radiotherapy and the initiation of study treatment was changed from ≥21 days to ≥14 days	Correction

SUMMARY OF CHANGES IN AMENDMENT 2

Section(s)	Change	Rationale
Sections 2 (Table 1), 6.4.1, 6.4.3, 6.5, 7.4, 9.2.4.2, 9.3.7, Appendix A, and Synopsis	Removed language regarding biomarkers as an exploratory endpoint and blood sample collection for biomarker analysis. Sections 7.4, 9.2.4.2 and 9.3.7 have been removed and the subsequent sections have been renumbered.	Exploratory biomarker analysis is no longer included in this study.
Section 3.2.3	Updated text in criterion #2: Information on study treatment assignment ~~should~~ must not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, the sponsor is to be notified within 24 hours of the occurrence.	Update
Section 3.2.3.1	Changed text from "sponsor safety" to "sponsor Global Safety and Risk Management"	Update
Section 4.1	Updated text in inclusion criterion 1 by removing the word "metastatic" Changed criterion 6 from "Age ≥18 years at time of consent" to "Age ≥18 years at time of consent or ≥ the age of majority in the geographic location" Changed absolute neutrophil count from ≥1.5 × 10^3/μL to ≥1.0 × 10^3/μL	Correction Provide clarification on age requirements Update absolute neutrophil count safe for subjects to enroll on study To align with CTCAE v4.03 criteria for Grade 1 ALT/AST elevation
Sections 4.1 and 10.1	Removal of language allowing a legally acceptable representative to provide consent on behalf of the subject. Updated contraception language for effective birth control methods in inclusion criteria 14d, 15b, and 15c and added Appendix K.	To disallow informed consent from a legally acceptable representative. Update, clarification, and addition
Section 4.1	Inclusion criterion 18: Added "or previously treated and progressing lesions found"	Update
Section 4.2	Exclusion criterion 12: Shortened window for avoiding sensitive CYP3A substrates from 2 to 1 week.	Update
Section 4.2	Exclusion criterion 1: Changed to exclude use of pryotinib	Update
Section 4.2	Clarified that left ventricular systolic dysfunction or decrease in ejection fraction to indicate that histories must be symptomatic.	Provided clarification of criterion

Section(s)	Change	Rationale
Section 4.2	Exclusion criterion 9: Updated text to clarify HIV-positive exclusion criteria	Clarification
Section 5.3	Added guidance regarding planned surgery.	Clarification
Section 5.3.2	Added routine prophylaxis with vaccines.	Clarification
Section 5.4	Removed “at the end of each cycle”.	Clarification
Section 6.2.1	Added requirement that subject must be reconsented if they remain in prescreening for more than 1 year. Added “In China, refer to the lab manual for details regarding HER2 testing.”	Clarification
Section 6.2.2	Updated text to the following: “All other safety labs and assessments will need to be repeated per the schedule of events ~~if outside the 28-day window~~ for these subjects.”	Correction
Section 6.2.3, etc.	Changed references from “serum chemistry” for laboratory testing to “chemistry”	Update
Section 6.4.1	Removed ECG	Update
Section 6.4.2	Added “blood pressure, heart rate, temperature, and respiration rate” after vital signs	Clarification
Section 6.4.3	Updated text: Administer the first cycle ~~morning~~ dose of tucatinib/placebo. (Subject will self-administer the evening dose, unless the cycle began in the afternoon)	Clarification
Section 6.4.5	Added ALP to blood samples for LFTs	Update
Section 6.5	Added the following text: The time of End of Treatment (EOT) visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy.	Clarification
Section 6.6	Added “Subsequent long-term follow-up scan windows are based on the most recent scan completed”.	Clarification
Sections Synopsis, 3.1, 7.1, 9.1, 9.3, 9.3.1.6	Revised to include language about China portion.	Update

Section(s)	Change	Rationale
Section 7.1.1	Removed requirement of 5 unstained charged slides for HER2 expression testing from the protocol. It will instead be specified in the lab manual. Removed requirement of "a minimum of 100 tumor cells" from the protocol. It will instead be specified in the lab manual.	Update
Section 7.1.2	Deleted "All such instances, with the exception of immediate local therapy to the CNS".	Clarification
Section 7.2	Added "and chosen as either target or non-target lesions".	Clarification
Section 7.2.1	Updated text: In subjects with baseline brain lesions, ~~at least one~~ all brain lesions should be included in the baseline RECIST lesion selection as either a target or non-target lesion. ~~As an exception, however,~~ When unsuspected brain metastases are discovered at screening and immediate CNS-directed therapy is administered, treated lesions should not be selected as target lesions but as non-target lesions for the purpose of disease assessment by RECIST v1.1.	To provide clarification and align with Response Assessment Manual v02
Section 7.8.1.1 (renumbered to 7.7.1.1)	Changed from "Adverse Events and Pre-existing Conditions CRF" to "Adverse Events CRF".	Clarification

Section(s)	Change	Rationale
Section 7.8.1.2 (renumbered to 7.7.1.2)	Updated subsection for Diagnosis vs. Signs or Symptoms: ~~If applicable:~~ Important exceptions for this study are adverse reactions associated with the infusion of study drug. ~~For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.' Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.~~ Record each sign or symptom as an individual AE in addition to the infusion-related reaction term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity. Added language to Progression of the Underlying Malignancy subsection: The events described above are the only protocol-defined events which do not need immediate reporting from the investigator to the sponsor for this study.	Clarification
Section 7.8.1.5 (renumbered to 7.7.1.5)	Added language to include reporting of SUSARs	Addition of SAE type for reporting to regulatory authorities
Section 7.8.4 (renumbered to 7.7.4)	Updated list of tests to be included in the chemistry panel, CBC with differential, and coagulation panel	Update
Section 9	Table 10 removed	Redundant information
Section 9.2.4.1	Language replaced as follows: The PK of tucatinib and T-DM1 will be evaluated. ~~Peripheral blood will be collected from subjects per Section 7.3. Exploratory, predictive, and prognostic biomarkers associated with response, resistance, or safety observations will be monitored before and during treatment with tucatinib. Correlative studies will be conducted to gain a better understanding of target response relationship, predictive biomarkers, MOA, and resistance mechanisms.~~	Update
Section 9.3.1	Revised for clarity	Administrative change
Section 9.3.1.5	Revised description of multiple comparisons and multiplicity	Update

Section(s)	Change	Rationale
Throughout protocol	Minor grammatical corrections, cross-reference updates, section renumbering, formatting, and sponsor name change	Administrative changes

SUMMARY OF CHANGES IN AMENDMENT 3

Section(s)	Change	Rationale
Title page	Updated name and contact information for the study's medical monitor.	Update due to change in study medical monitors
Synopsis	Modified text: Subjects must be >3 weeks post-treatment from any prior systemic anticancer therapy (including hormonal therapy), noncentral nervous system radiotherapy (palliative or therapeutic), or participation in another interventional clinical trial.	Clarification
	Modified text: If treatment for newly identified lesions or previously treated ~~or~~ and progressing lesions is initiated, subjects may still be eligible…"	Correction for consistency with Section 4.1, Criterion 18.c.ii
	Added text: Baseline disease assessments include measurement of all known sites of unresectable locally-advanced/metastatic disease through radiographic imaging. Assessment for brain metastases is performed with contrast MRI of the brain for all subjects, regardless of prior history of brain metastases.	Clarification that contrast MRI of the brain is required as a baseline assessment for all subjects in the study
	Modified text: These PRO instruments include the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L) instrument, 2 questions to capture global health status/quality of life from the European Organization for Research and Treatment of Cancer ~~(EORTC)~~ quality-of-life questionnaire (EORTC QLQ ~~C30~~ IL6), the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE) questionnaire customized to focus on adverse events (AEs) or symptoms of interest, and 1 question from the Functional Assessment of Cancer Therapy – Breast (~~FACTB~~FACT-B GP5) questionnaire to capture the patients' perceptions of side effects.	Clarification that the study uses the EORTC QLQ IL6 and FACT-B GP5 rather than the respective full scales.
	Added text: In addition, a summary of health care resource utilization (HCRU) will be presented.	

Section(s)	Change	Rationale
		Update to indicate that health care resource utilization will be assessed.
Section 2, Synopsis	The following endpoint was revised and reclassified from 'other secondary endpoint' to a 'key secondary endpoint': ~~Evaluate~~Compare progression-free survival (PFS) by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms.	Update to include PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline as an alpha-controlled endpoint.
Section 3.1 (Figure 3), Section 6.6	Modified text to clarify that the description of one of the assessment schedules applies to subjects who discontinue treatment for any reason prior to documented disease progression.	Clarification because many investigative sites have asked about imaging requirements after end of treatment. Clarifying the text in the amendment may simplify site communications and ensure that all required imaging is obtained.
Section 3.2.3	Modified Items #2: Unblinding a subject's treatment assignment prior to study closure must be limited to safety emergency circumstances only where knowledge of the treatment assignment would affect decisions regarding the immediate clinical management of the subject. In the event of such an emergency circumstance, the investigator will assume full responsibility for unblinding the study treatment and a formal unblinding procedure, carried out by a third-party organization, will be followed to allow the investigator to immediately access a subject's treatment assignment (see study manual). Information on study treatment assignment must not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, the sponsor is to be notified within 24 hours of the occurrence.	Clarification
Section 4.2	Modified Item #4: Treatment with any systemic anticancer therapy (including hormonal therapy), non-CNS radiation (palliative or therapeutic), experimental agent or participation in another interventional clinical trial ≤3 weeks prior to first dose of study treatment. An exception for the washout of hormonal therapies is gonadotropin	Clarification

Section(s)	Change	Rationale
	releasing hormone agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications.	
Section 5.2.3.1, Table 4	Modified text: • Clinical Adverse Event column: All ≥ Grade 3 AEs ~~other than~~ except the following: Grade 3 fatigue lasting ≤3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities • T-DMI column: Do not administer until severity ≤ Grade 1 or pretreatment level. Reduce to next lowest dose level. Note: Dose reduction is not required for hematologic abnormalities (other than thrombocytopeniab) that recover to ≤ Grade 1 prior to dosing. Footnote b: Refer to Table 6 for thrombocytopenia dose reduction requirements	Clarification of which adverse events are not included in the category of all ≥ Grade 3 adverse events that require dose modification Update to address dose modifications in the event of hematologic laboratory abnormalities
Section 6.4.3	Added text: * Predose assessments do not need to be repeated if performed within 1 day prior to Day 1.	Clarification
Section 6.6	Added text: More frequent long-term follow-up may be conducted as needed for OS event tracking (eg, for subjects with clinical progression, OS event tracking may be conducted at the same time radiographic scans and PFS event tracking will be performed every 9 weeks, until PD per RECIST 1.1 is confirmed, at which time PFS tracking ends and OS event tracking may be performed starting 90 days [±7 days] from the date of the last imaging scan)	Clarification with an example of when more frequent long-term follow-up may be conducted as needed for OS event tracking
Section 7.6.1	Added a reference to Appendix G	Clarification
Section 7.6.2	Modified text: The questionnaire has been streamlined based on a patient-centric approach to minimize the number of questions being asked as part of the patient-reported outcome (PRO) data collection, therefore only Questions 29 and 30 of the questionnaire which make up the 'global health status/QoL' scale of the QLQ-C30 will be used for this study (Appendix H). The EORTC refers to	Clarification that Questions 29 and 30 of the EORTC QLQ-C30 make up the 'global health status/QoL' scale of this measure and is referred to as the EORTC QLQ IL6.

Section(s)	Change	Rationale
	~~the combination of questions used in~~ this ~~study~~ set of questions as the EORTC QLQ IL6. Added a reference to Appendix H.	 Clarification
Section 7.6.3	Modified text: ~~The FACT-B was created with an emphasis on patients' values and brevity. It is written at the sixth-grade reading level, takes approximately 10 minutes to complete, and is available in nine languages. Its psychometric properties, brevity, and relevance to patients' values make its suitable for use in both research and clinical settings. The FACT-B will be collected while subjects are receiving study treatment and until the EOT visit; the instrument has been customized to minimize the number of questions be asked as part of the PRO data collection, therefore only question 5 will be used (). The Functional Assessment of Chronic Illness Therapy (FACIT) organization referred to the combination of questions used in this study as the GP5.~~To minimize the number of questions to reduce patient burden, only Question 5 (ie, GP5) regarding patient's perception of bother due to treatment side effects will be used (Appendix I). Responses to this question will be collected while subjects are receiving study treatment and until the EOT visit. Added a reference to Appendix I	Update to focus on the FACT-B GP5 rather than the FACT-B overall because the study uses only the FACT-B for subject assessment. Clarification
Section 7.6.4	Modified text: The NCI ~~Patient Reported Outcomes Common Terminology Criteria for Adverse Events (~~PRO-CTCAE~~)~~ is a ~~new patient-reported outcome (~~validated PRO~~)~~ measurement system developed to characterize the frequency, severity, and interference of 78 symptomatic treatment toxicities (Smith 2016). These include symptomatic toxicities such as pain, fatigue, nausea, and cutaneous side effects such as rash and hand-foot syndrome, all toxicities that can be meaningfully reported from the patient perspective. The NCI PRO-CTCAE allows for customization; thus, symptomatic toxicities of interest (17 items) in both the control and experimental arms will be collected as part of the PRO data collection (Appendix J). ~~The PRO-CTCAE measurement system consists of an item library of adverse symptoms, and a prototype electronic platform with a variety of~~	Reduced length of text to focus on the purpose of implementing the NCI PRO-CTCAE in this study rather than on the measure's background information.

Section(s)	Change	Rationale
	~~features designed to promote integration of the PRO-CTCAE measurement system into clinical trials workflow. The system allows for data collection via the web, a hand-held computer, or an interactive voice response system, and includes features that allow for customized PRO-CTCAE questionnaires, tailoring the schedule for data collection, as well as patient reminders and clinician alerts for severe symptoms. Development and validation of PRO-CTCAE were consistent with well-established measurement principles as well as guidelines for PROs instrument development proposed by the FDA and EMA. The development process included patients with cancer as well as professionals from the US and Europe with expertise in oncology, instrument development, clinical research and the regulatory aspects of cancer therapy development. The NCI PRO-CTCAE will be customized to focus on symptomatic toxicities of interest in both the control and experimental arms.~~ Added a reference to Appendix J	 Clarification
Section 7.7.1.2	Modified text: Email or fax to the sponsor's Drug Safety Department within ~~48~~24 hours of becoming aware of a pregnancy.	Correction
Section 7.8	Modified text: The ~~QLQ-C30 (Version 3.0) is a validated questionnaire developed by the~~PROs included in this study (EORTC ~~to assess the QoL of cancer subjects . The~~QLQ IL6, EQ-5D-3L ~~is a validated instrument for use as a measure of health-related QoL. The ,~~ and FACT-B ~~is a sound instrument~~GP5) are validated questionnaires that ~~can be used to measure symptoms in subjects with breast cancer. These PROs~~ have been incorporated into previous clinical trials ~~that seek to quantify the QoL in subjects~~to assess global health status and quality of life as well as perception of side effects, respectively.	Simplified text for clarification
Section 9.1, Synopsis	Revised the final analysis of OS to take place approximately 30 months instead of 29 months after the primary analysis of PFS. Added text to describe the analyses related to PFS in subjects with brain metastases at baseline.	Update to accommodate one additional OS interim analysis Update

Section(s)	Change	Rationale
Section 9.1, Section 9.3.1.5, Section 9.3.1.8, Section 9.3.9, Synopsis	Increased the number of overall survival (OS) events required for the final OS analysis from 248 to 253	Update to accommodate one additional interim analysis of OS
Section 9.2.2.2 (new section), Section9.2.3.2	Reclassified the analysis related to the endpoint of PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms from other secondary endpoint to a key secondary endpoint.	Update
Section 9.2.4.1	Modified text: The pharmacokinetics of tucatinib and ~~T-~~DM1 will be evaluated.	Correction
Section 9.2.4.3, Synopsis	Replaced the words 'Quality of Life' and 'health-related quality of life' with 'Patient-Reported Outcomes' when referring to the PRO measures overall that are implemented in this study.	Correction
Section 9.3.1.5, Section9.3.1.8, Section 9.3.9, Synopsis	Updated text to reflect that an additional OS analysis (key secondary endpoint) is planned when approximately 202 (80%) OS events have been observed. Updated text to state that a formal statistical test of objective response rate (ORR) will only be performed if the results of the PFS, OS, and PFS.BM analyses are all statistically significant.	Update to accommodate one additional interim analysis of OS Update
Section 9.3.1.5, Section 9.3.9, Synopsis	Added text to describe 2 possible analyses of the key secondary endpoint of PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline if both PFS and OS (OS IA1, OS IA2, or OS FA) results are statistically significant.	Update
Section 9.3.1.8	Modified text related to the timing of analyses relative to the randomization of the first subject. Added text to describe the timing of the analyses of PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline	Update to accommodate one additional OS interim analysis Update
Section 9.3.7	Modified text: PRO assessments will be analyzed to determine if treatment affects PRO scores. ~~PRO scores will be analyzed using longitudinal models.~~ All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment timepoint may be presented. ~~Time to deterioration will be assessed in specific pre-specified single items from either the EORTC QLQ-C30 or FACT-B.~~	Removed statements related to PRO scores being analyzed using longitudinal models and assessment of time to deterioration. As time to deterioration may be difficult to interpret for regulatory purposes, it will be reserved as ad-hoc analysis. Additional detail of the PRO analyses will be included in the supplemental SAP for the prespecification.

Section(s)	Change	Rationale
Appendix A	Added an 'X' for assessment HRCU at the 'End of Treatment (EOT)' visit. Added Footnote I to the following assessments at Day 1 in the 'Subsequent 21-Day Cycles' column: physical examination, weight, and ECOG performance status. Modified text under Footnote M: Predose laboratory testing ~~can~~ must be done within 1 day prior to study visit. Confirm laboratory results prior to continuing study treatment dosing. Added text under Footnote R: Subject should complete questionnaires prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days (ie, within 1 day prior to study treatment).	Correction to be consistent with text in Section 6.5. Update to indicate that these assessments do not need to be repeated, if already done within 1 day of study visit Correction to be consistent with text in Section 6.4.3 Clarification
Appendix C	Modified text: ~~Posoconazole~~Posaconazole Added text: Antivirals Boceprevir 3–4 hours Indinavir 1–2 hours Nelfinavir 3–5 hours Ritonavir 3–5 hours Telaprevir 9–11 hours Removed text (Footnote c): Strong CYP3A inhibitors are defined as those drugs that increase the area under the concentration-time curve (AUC) of oral midazolam or other CYP3A substrates ≥ 5-fold. ~~Ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir are also strong CYP3A3 inhibitors, but would not be used in this study as subjects with known human immunodeficiency virus are excluded.~~	Spelling correction Added antiviral drugs under the category of 'Strong Inhibitors' Modified footnote c because the study allows now enrollment of patients who were diagnosed as HIV positive.
Appendix K	Added text: **Acceptable methods for preventing secondary exposure to seminal fluid**	Update to describe acceptable methods for preventing secondary exposure to seminal fluid and unacceptable methods of contraception

Section(s)	Change	Rationale
	Subjects born male and who are sexually active with a pregnant person must use a male condom (even if the subject has had a vasectomy). Subjects born male and who are sexually active with a breastfeeding person must use a male condom (even if the subject has had a vasectomy). In addition, it is recommended that the breastfeeding partner use a highly effective female contraceptive method as listed in the section titled "Acceptable combinations of contraceptive methods". **Unacceptable methods of contraception** • Periodic abstinence • Spermicide only • No method • Progestin-only pills • Withdrawal • Concomitant use of female and male condoms • Rhythm • Barrier methods alone, including double-barrier methods	
Throughout protocol	Changed the name of the patient-reported outcome measure 'EORTC IL6' to 'EORTC QLQ IL6' when referring only to 2 items on global health status and quality of life. Changed the name of the patient-reported outcome measure 'FACT-B' to 'FACT-B GP5' when referring only to Item GP5 of the measure. Minor grammatical and spelling corrections, and formatting	Correction Correction Administrative changes

SUMMARY OF CHANGES IN AMENDMENT 4

Section(s)	Change	Rationale
Cover page	EU clinical trial (CT) number 2023-506418-30 added	EU CT number was available
Synopsis, Key Secondary Endpoints, Section 2 , Section 9.2.2.4	Added text to include key secondary endpoint "compare overall survival in subjects with brain metastases at baseline (OS.BM) between treatment arms"	Update for consistency with existing statistical analysis plan (SAP).
Synopsis, Study Population	Adjusted text to specify subjects must have histologically confirmed HER2+ breast carcinoma (previously the word 'breast' was not present).	Addition of inadvertently omitted word
Synopsis, Study Population, Section 4.1 inclusion criterion 2	Added parenthetical reference to Appendix L which specifies eligible study population in France	Direct to Appendix L for France specific language related to eligible study population
Synopsis, Sample Size Considerations	Adjusted wording about final OS analysis to be consistent with wording in Section 9.1	Consistency across the document.
Synopsis, Analysis Methods, Section 9.3.1.8	Added text about hierarchical testing and graphic to illustrate hierarchical testing strategy	More clearly present hierarchical testing strategy given multiple endpoints and analyses planned.
Section 1.2 , Section 1.3, Section 1.4	Updated text to be consistent with current standard of care	Update to reflect current standard of care
Section 3.1 , Figure 3	Updated footnote d to be consistent with updates made to Section 6.6.	Consistency across the document.
Section 4.2	Added bullet to exclusion criterion (EC) 6 as follows: "For France and Italy only: Any history of interstitial lung disease or pneumonitis." Added information to EC 8 to clarify Hepatitis B, Hepatitis C, and other known chronic liver disease exclusion criteria for subjects in Italy.	France and Italy specific language being consolidated in this global amendment Italy specific language being consolidated in this global amendment
Section 5.1.1.5	Updated storage information to refer to the tucatinib pharmacy instructions.	Provide source of most up to date storage information
Section 5.3	For France and Italy, added guidance about subjects being required to suspend treatment prior to surgery and when treatment can resume postoperatively in France and Italy.	France and Italy specific language being consolidated in this global amendment
Section 6.2.1	Changed FISH to ISH.	Make ISH method more general.

Section(s)	Change	Rationale
Section 6.2.2	Added bullet for Hepatitis B and C testing in Italy	Italy specific language being consolidated in this global amendment
Section 6.6, Appendix A Footnote F	Updated language to more clearly indicate after the last imaging scan is completed, the follow up visits much be scheduled every 90 days ± 7 days from the date of the last imaging scan or 90 days from the last study visit, whichever is later, and continuing every 90 days (±7 days) until death, withdrawal of consent, lost to follow up, or study closure. Added text to indicate data for OS will be collected from public records if allowed per local regulations. Updated Footnote F in Appendix A to align with the changes to text in Section 6.6.	Clarification about collection of follow up information after last imaging scan is completed and to indicate public records may be used as allowed per local regulations Addition of medical record review as a method of assessing survival status
Section 7.1.1	Adjusted language as follows: • "(most recent tumor tissue sample ~~preferred~~ requested)" … • "The central laboratory will require sufficient tumor tissue to generate unstained, positively-charged slides for HER2 expression testing." • "HER2 expression will be analyzed using ~~F~~ISH (DAKO IQFISH pharmDx)…"	Clarification of requirements for HER2 expression confirmation and consistency across document.
Section 7.2	Removed specification of measurable disease for imaging: "At the investigator's discretion, other appropriate imaging (eg, skin lesion photography for skin lesions, nuclear bone scan imaging for bone lesions) should be used to assess known sites of ~~measurable~~ disease"	Clarification to clearly indicate these would be non-target lesions and not allowed as target lesions
Section 7.6.2	Adjusted PRO measurement tool title to "EORTC QLC IL6" instead of "EORTC QLQ-C30".	Clarification to be consistent across document and with protocol text description of PRO measurement tool being used
Section 7.7.4	Updated clinical laboratory tests serum chemistry section to: "The chemistry panel is to include the following tests: blood urea nitrogen or urea,…."	Clarification that either blood urea nitrogen or urea are acceptable.

Section(s)	Change	Rationale
	Added bullet about blood samples for Hepatitis B and C related testing specific to Italy.	Italy specific language being consolidated in this global amendment
Synopsis, Analysis Methods, Section 9.3.1.5, Section 9.3.1.8, Section 9.3.9	Updated text to include OS.BM statistical analysis details	Update for consistency with existing statistical analysis plan (SAP).
Section 9.3.1.5, Section 9.3.9	Updated 2-sided alpha value from 0.0499 to 0.05	Update to alpha spend in statistical approach
Appendix A	Added safety assessment to table for Hepatitis B and C screening in Italy and added footnote X about requirement for Hepatitis B and C screening as a Safety Assessment in Italy.	Italy specific assessment being consolidated in this global amendment
Appendix D	Updated to indicate that clopidogrel is a moderate CYP2C8 inhibitor (previously listed as strong CYP2C8 inhibitor)	Update based on most relevant classifications of CYP2C8 inhibitors
Appendix K	Added parenthetical phrase “see unacceptable methods of contraception”	Added reference to unacceptable methods of contraception
Appendix L (new Appendix)	Added appendix with France-specific protocol requirements. As a result, subsequent appendix alphabetized titles have been shifted by 1 letter.	France specific language being consolidated in this global amendment
Throughout protocol	Minor grammatical corrections, cross-reference updates, section formatting, addition of abbreviations to minimize wordiness, etc.	Administrative updates