Status Page

PROTOCOL 13-048

Closed to New Accrual

Closure Effective Date: 12/13/2016
No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Date Submitted: ***2/17/2015***
Date Posted: ***[02/18/2015]***

Alert Page

DF/HCC Protocol #: **13-048**

Protocol Clarifications (non-drug related e.g. eligibility criteria, study assessments)

Protocol Section 3: Laboratory tests required for eligibility must be completed within 14 days prior to study entry. History and exam must be performed within 28 days prior to study entry. Other non-laboratory tests (EKG and MUGA or echocardiogram) must be performed within 12 weeks of beginning study treatment as stated in Tables 5 and 6.

Protocol Version Date: *9/1/2017*

Local Protocol #:13-048
TBCRC#: TBCRC 033

Title: *A randomized Phase II study of adjuvant Trastuzumab emtansine (T-DM1) vs. Paclitaxel in combination with Trastuzumab for Stage I HER2-positive Breast Cancer (ATEMPT Trial)*

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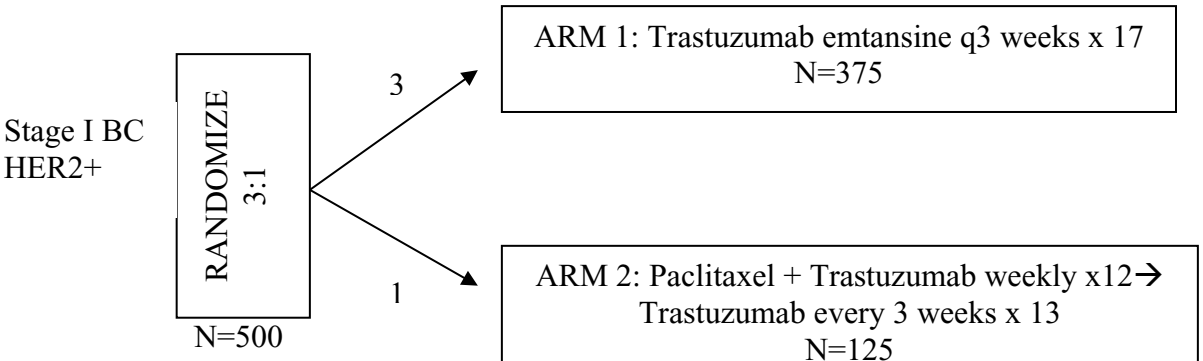
Agent(s): *Trastuzumab emtansine (IND# 116650)*

SCHEMA



Stratification by:

- Age (<55, ≥55)
- Planned Radiation (Yes/No)
- Planned Hormonal therapy (Yes/No)

*Hormonal therapy, when appropriate, should not be administered concurrently with paclitaxel and should only begin after 12 weeks of trastuzumab emtansine

Patients who undergo lumpectomy (breast conserving surgery) must receive breast radiation therapy according to local institutional standards. Patients undergoing mastectomy may receive chest wall and nodal radiation according to local institutional standards. Radiation therapy will begin after the conclusion of all study paclitaxel and after 12 weeks of trastuzumab emtansine

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1 OBJECTIVES

1.1 Study Design

This is a randomized phase 2 adjuvant study for women and men with Stage I HER2-positive invasive breast cancer. The goal enrollment is 500 patients. Patients will be randomized 3:1 to trastuzumab emtansine (n=375) or the Paclitaxel + Trastuzumab (TH) arm (n=125). If randomized to trastuzumab emtansine, patients will receive trastuzumab emtansine 3.6 mg/kg IV every 3 weeks for 17 doses, for a total of 51 weeks of treatment. If randomized to TH, patients will receive paclitaxel 80 mg/m2 IV weekly and trastuzumab 4 mg/kg IV load, followed by 2 mg/kg IV weekly for 12 weeks, followed by trastuzumab 6 mg/kg IV every 3 weeks for 13 treatments. Patients will receive additional adjuvant radiation therapy and/or endocrine therapy if deemed necessary per institutional practice. Endocrine therapy should not be administered concurrently with paclitaxel, and should begin after 12 weeks of trastuzumab emtansine. Patients will also participate in quality of life (QOL) surveys and symptom questionnaires at various time points through the course of study treatment and during follow-up. This study requires submission of tumor blocks or slides in order to perform biomarker analysis.

1.2 Primary Objectives

- Compare the incidence of clinically relevant toxicities in patients with Stage I HER2-positive breast cancer treated with adjuvant trastuzumab emtansine to the incidence in those treated with paclitaxel in combination with trastuzumab. We hypothesize that toxicity will be lower with trastuzumab emtansine than with paclitaxel and trastuzumab.
  Clinically relevant toxicities will include the composite incidence of grade 3 or higher non-hematologic toxicity, grade 2 or higher neurotoxicity, and grade 4 or higher hematologic toxicity. These toxicities will only be assessed at the pre-specified toxicity-assessment visits. In addition, the following events, regardless of timing of their occurrence, will also count towards the composite endpoint: febrile neutropenia, any toxicity requiring dose-delay, discontinuation of any study treatment (Paclitaxel, Trastuzumab, or T-DM1) for toxicity, , and any serious adverse event (SAE).

- Evaluate disease-free survival (DFS) in patients with Stage I HER2-positive breast cancer treated with trastuzumab emtansine

1.3 Secondary Objectives

1.3.1 Compare the incidence of all grade 3 and 4 adverse events in patients treated with adjuvant trastuzumab emtansine to the incidence in those receiving paclitaxel in combination with trastuzumab

1.3.2 Compare quality of life (QOL) in patients receiving trastuzumab emtansine to that experienced by patients receiving paclitaxel in combination with trastuzumab using FACT B

1.3.3 Evaluate symptoms related to therapy in patients receiving trastuzumab emtansine compared to those receiving Paclitaxel in combination with trastuzumab using the Rotterdam symptom checklist and Patient Neurotoxicity questionnaire (PNQ)

1.3.4 Evaluate effects of therapy on work productivity and activity using the Work Productivity and Activity Impairment Questionnaire (WPAI-SHP) in patients receiving trastuzumab emtansine compared to those receiving paclitaxel in combination with trastuzumab

1.3.5 Evaluate the effects of alopecia on patients receiving paclitaxel in combination with trastuzumab using an alopecia questionnaire

1.3.6 Describe DFS in patient groups defined by tumor size ($\leq$ 1 cm or > 1 cm) and hormone receptor status who are treated with trastuzumab emtansine

1.3.7 Evaluate the incidence of grade 3-4 cardiac left ventricular dysfunction from adjuvant trastuzumab emtansine and paclitaxel and trastuzumab

1.3.8 Evaluate the incidence of trastuzumab emtansine-induced grade 2-4 thrombocytopenia

1.3.9 Evaluate gene biomarkers predictive of trastuzumab emtansine-induced grade 2-4 thrombocytopenia

1.3.10 Investigate the percentage of patients with amenorrhea at various times after start of treatment in premenopausal women receiving treatment with trastuzumab emtansine and paclitaxel and trastuzumab for early stage breast cancer

1.3.11 Utilize a high-throughput mutation profiling system (Oncomap) to query a large panel of cancer gene mutations in patients with Stage I HER2-positive breast cancer

1.3.12 Describe overall survival in patients with Stage I HER2-positive breast cancer treated with trastuzumab emtansine.

2 BACKGROUND

2.1 Trastuzumab emtansine

Trastuzumab emtansine is a novel antibody-drug conjugate (ADC) that is specifically designed for the treatment of HER2-positive malignancies. Trastuzumab emtansine is composed of trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an anti-microtubule agent derived from maytansine; and SMCC, a thioether linker molecule used to conjugate DM1 to trastuzumab. Trastuzumab emtansine retains all of the modes of action of trastuzumab, which include a binding affinity to the HER2 extracellular domain (ECD) that is comparable to trastuzumab, inhibition of HER2-ECD shedding, inhibition of the HER2-activated PI3K/Akt signaling pathway, and mediation of antibody-dependent cellular toxicity (ADCC). Linkage of a cytotoxic agent to highly specific monoclonal antibodies targeting tumor-specific and/or overexpressed tumor-associated antigens focuses the delivery of such agents to tumor cells, which creates a more favorable therapeutic window than could be achieved by their administration as free drugs. Key steps in the production of trastuzumab emtansine include chemical linkage of DM1 to MCC, followed by linkage of the several MCC-DM1 complexes to trastuzumab through non-reducible thioether bonds on trastuzumab lysine residues, with a

drug-to-antibody ratio of approximately 3.5:1. After binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity.

Phase I and II studies of trastuzumab emtansine as a single agent have shown robust and clinically meaningful activity in patients with HER2-positive metastatic breast cancer (MBC) whose disease had progressed on trastuzumab-containing chemotherapy regimens. As of April 2010, over 600 patients have been treated with trastuzumab emtansine.

2.1.1 Trastuzumab emtansine in metastatic disease

Studies TDM4258g and TDM4374g

Two Phase II studies—TDM4258g and TDM4374g—evaluated the safety and efficacy of a trastuzumab emtansine administered at a dose of 3.6 mg/kg (maximum tolerated dose [MTD] in Phase I) every 3 weeks until progressive disease (PD) or unacceptable toxicity in HER2-positive MBC patients who had progressed on previous HER2-directed therapy and conventional chemotherapy. Although patients enrolled into both studies had received multiple agents for the treatment of breast cancer, patients enrolled onto Study TDM4374g were specifically required to have received an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine in the neoadjuvant, adjuvant, or metastatic setting or as treatment for locally advanced disease; additionally, patients must have been treated with two or more HER2-directed regimens in the metastatic or locally advanced setting and must have progressed on their most recent treatment. Patients were required to have known HER2 overexpression as previously determined by local laboratory testing with immunohistochemistry (IHC) or HER2 gene amplification by fluorescence in situ hybridization (FISH).

Study TDM4258g was activated on 20 July 2007 and was completed on 25 June 2009 after 112 patients were enrolled and treated. Study TDM4374g was activated on 2 May 2008, with a total of 110 patients enrolled and treated by 2 April 2009.

The clinical activity of trastuzumab emtansine was similar in the two studies. In Study TDM4258g, on the basis of the final analysis approximately 12 months after the last patient was enrolled, the overall response rate (ORR) in efficacy-evaluable patients was 38.9% (95% confidence interval [CI], 29.7%, 48.5%) by investigator and 26.9% (95% CI, 19.2%, 35.8%) by independent review. The clinical benefit rate (CBR) (defined as complete response [CR], partial response [PR], or stable disease for > 6 months) was 46.3% by investigator assessment (95% CI, 36.7%, 56.2%) and 40.7% by independent review (95% CI, 31.8%, 50.6%). The median progression-free survival (PFS) was 4.6 months by both the investigators and the independent review facility (IRF) assessment.

In Study TDM4374g, on the basis of clinical data collected through 1 January 2010, approximately 9 months after the last patient had enrolled, the ORR among all treated patients was 34.5% (95% CI, 26.1%, 43.9%) by IRF assessment and 32.7% (95% CI, 24.1%, 42.1%) by investigator assessment. The CBR was 48.2% (95% CI, 38.8%, 57.9%) by IRF assessment and 46.4% (95% CI, 37.1%, 56.1%) by investigator assessment. The median duration of response was not reached (95% CI, 4.6 months, not reached) by IRF assessment and 9.7 months (95% CI, 6.6 months, not reached) by investigator assessment. In this study population, there was a median PFS of 6.9 months (95% CI: 4.2, 9.5) as assessed by the IRF and 5.5 months (95% CI: 4.1, 7.5) by investigator review.

The safety profile of trastuzumab emtansine was also similar between the two studies. In Study TDM4258g, the five most common adverse events (AEs) were fatigue (65.2%), nausea (50.9%), headache (40.2%), epistaxis (35.7%), and pyrexia (34.8%). Most of these events were Grade 1–2. The three most common Grade 3–4 AEs observed in this trial were hypokalemia (8.9%), thrombocytopenia (TCP) (8.0%), and fatigue (4.5%). In Study TDM4374g, a total of 49 patients (44.5%) experienced at least one Grade ≥ 3 AE. The three most common Grade ≥ 3 adverse events (by Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) were TCP (7.3%), fatigue (4.5%), and cellulitis (3.6%). Serious adverse events (SAEs) were reported in 25 patients (22.7%). No single SAE was reported in more than 4 patients. No Grade ≥ 3 left ventricular systolic dysfunction (LVSD) events (symptomatic congestive heart failure [CHF] and/or left ventricular ejection fraction [LVEF] of < 40%) were reported in either study.

In Study TDM4258g, study treatment was discontinued in 4 patients because of AEs. Two of these events were considered by the investigator to be possibly related to study treatment: Grade 4 increase in transaminases and Grade 2 TCP.

In Study TDM4374g, two deaths on study within 30 days of trastuzumab emtansine administration were reported. One patient died following CNS progression, with the cause of death listed as PD. A second patient death following Grade 5 hepatotoxicity, reported to be possibly related to trastuzumab emtansine, occurred in a patient with preexisting non-alcoholic fatty liver disease and multiple other co-morbidities including renal insufficiency and heavy tumor burden. The patient died with multi-organ failure and biopsy-confirmed non-alcoholic steatohepatitis. Additional confounding factors including exposure to hepatotoxic drugs preclude making definitive conclusions regarding Trastuzumab emtansine attributability.

Study TDM4450g

This is a randomized, multicenter, Phase II study of the efficacy and safety of trastuzumab emtansine versus trastuzumab plus docetaxel (control arm) in patients with metastatic HER2-positive breast cancer who have not received prior chemotherapy for metastatic disease. This study completed enrollment in December 2009 (n = 137). The primary objectives are to assess the efficacy of trastuzumab emtansine compared with the combination of trastuzumab and docetaxel, as measured by PFS on the basis of investigator assessments, and to characterize the safety of trastuzumab emtansine compared with the combination of trastuzumab and docetaxel in this population. Secondary endpoints include ORR, survival, and duration of response.

No new trastuzumab emtansine safety signals were observed. The incidence of Grade ≥ 3 AE on the control arm (75.0%) was twice that of trastuzumab emtansine (37.3%). Efficacy data demonstrated a 47.8% ORR in the trastuzumab emtansine arm compared to 41.4% in the trastuzumab plus docetaxel arm.

Patients on trastuzumab emtansine had significantly longer progression-free survival compared with those on standard therapy (14.2 months vs 9.2 months), which amounted to a 41% relative risk reduction in progression (HR 0.59, p=0.035).

Nonclinical Safety Evaluation of trastuzumab emtansine

The nonclinical safety evaluation trastuzumab emtansine was performed in accordance with the International Conference on Harmonisation (ICH) S6 Guidance for Industry on the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (1997). The results of nonclinical safety studies with trastuzumab emtansine showed no evidence of direct cardiac toxicity in either acute or chronic studies conducted for up to 6 months in nonhuman primates. A review of the nonclinical studies of cynomolgus monkeys treated with multiple doses of trastuzumab emtansine revealed no significant electrocardiogram (ECG) findings or evidence of QT prolongation.

With consideration of the clinically observed phenomenon of trastuzumab-associated cardiotoxicity, a single-dose cardiovascular safety study of trastuzumab emtansine was conducted in conscious cynomolgus monkeys through use of radiotelemetry, and ECG evaluations were performed in the repeat-dose monkey studies. No cardiovascular abnormalities were observed in the single-dose cardiovascular study or the repeat-dose studies. DM1 was tested for its effects on the human ether-à-go-go–related gene (hERG) channel current at 3, 10, and 30 μM. No inhibition was observed at the concentrations tested. A DM1 concentration of 30 μM is 30-fold higher than the fraction of unbound DM1 in clinically relevant doses of trastuzumab emtansine and is considered an adequate safety margin in evaluating cardiovascular safety (Redfern et al. 2003). Hence, the combined in vivo and in vitro data did not identify trastuzumab emtansine – or DM1-related cardiotoxicity.

2.2 HER2+ Breast Cancer

Breast cancer is the second most commonly diagnosed cancer and is the second leading cause of cancer death among women in the United States. HER2/neu is a member of the erbB family of transmembrane tyrosine kinase receptors. This family includes the epidermal growth factor receptor (EGFR), HER2, HER3, and HER4. These receptors regulate cell growth, differentiation, and survival. Amplification of the HER2 gene occurs in 20-25% of breast cancers, and is associated with poorly differentiated, high-grade tumors, resistance to therapy, higher rates of recurrence, and a higher incidence of brain metastasis.[1, 2] However, among patients with small (T1a,T1b) tumors, the rate of HER2-positivity is lower, and around 10%. The diagnosis of these small HER2+ tumors appears to be rising, and is likely due to an increase in mammographic screening.

2.3 Rationale

Five randomized trials have established trastuzumab-based therapy as standard of care for patients with HER2-positive, early stage breast cancer.[3-6] However, most of the clinical trials excluded patients with small lymph node negative cancers, while others accrued few patients with node-negative disease. Recent data from a retrospective analysis found a 5 yr DFS of 86.4% for pts with T1a,bN0 HER2-positive breast cancer, compared to 97.2% in similar patients with HER2-negative breast cancer.[7] Also, when looking at the data from the BCIRG 006 study, and specifically looking at the node-negative cohort of patients on study, the estimated 3 yr DFS is approximately 95% in patients who received either ACTH or TCH chemotherapy[6]. This suggests patients with small HER2-positive tumor have a significant risk of relapse.

Because the absolute benefit of trastuzumab for Stage I HER2-positive tumors remains unknown, the role of trastuzumab in patients with small, node-negative tumors remains controversial. Current

consensus guidelines from the NCCN do not recommend adjuvant trastuzumab for tumors <1 cm in size, owing to the lack of data for safety and efficacy in this patient population (see www.nccn.org). Based on historical experience, it is reasonable to expect that the absolute benefit of chemotherapy and trastuzumab is more modest in node-negative breast cancer, as these tumors have in general a better prognosis and thus lower gains with adjuvant therapy. Thus, the decisions to use adjuvant chemotherapy with agents such as anthracyclines and taxanes, and the use of adjuvant trastuzumab, may be informed by different considerations of risk and benefit for this lower risk group than for higher risk early stage breast cancer.

We are conducting a single-arm phase II clinical trial using paclitaxel (T) with trastuzumab (H) for 12 weeks followed by 9 months of trastuzumab monotherapy (Study # 07-199). A total of 410 patients were enrolled from October 2007 to September 2010, and efficacy of TH is currently monitored by the DF/HCC Data Safety Monitoring Committee with a final analysis specified in the protocol to occur at 1600 total patient-years of follow-up. Interim analyses have found this regimen to be well tolerated. At the most recent reporting cycle, 31.3% of patients were recorded as having at least one of the following adverse events: febrile neutropenia, grade 2+ neurotoxicity, grade 3+ non-hematologic toxicity, or grade 4+ or higher hematologic toxicity (Tolaney, personal communication).
Since many patients who have developed resistance to trastuzumab in the metastatic setting appear to respond to trastuzumab emtansine, treating patients with early stage breast cancer with trastuzumab emtansine may result in fewer relapses than seen with trastuzumab-based regimens. In addition, this agent has been associated with a favorable toxicity profile, and therefore would provide a regimen with relatively few toxicities to patients with a relatively low-risk of recurrence.

In order to evaluate treatment regimen for this patient population, prospective trials are needed. Additionally, there is no current standard therapy approach for this group of patients, so a randomized study with a control arm is necessary. Furthermore, it would be difficult to compare to no therapy given the known benefits of herceptin therapy for HER2+ breast cancer. Given these limitations, we set out to determine the toxicity of this agent is significantly less than paclitaxel with trastuzumab, as a reasonable alternative regimen; and, to evaluate the efficacy of trastuzumab emtansine for this patient population. A definitive phase III could be designed and powered based on preliminary evidence from this study design.

Trastuzumab emtansine was recently FDA-approved for the treatment of patients with metastatic HER2+ breast cancer that have progressed on a prior taxane-containing regimen. A Phase 2 multicenter trial (TDM4874g) was conducted that evaluated patients in the neoadjuvant or adjuvant setting who received AC or FEC and then trastuzumab emtansine every 3 weeks for up to a total of 17 treatments. If radiation was indicated, it was performed. A total of 39 patients received radiation concurrently with trastuzumab emtansine and 77 patients received radiation sequentially. 38 of the 39 patients completed at least 95% of the planned radiation dose. One patient had a delay in radiation due to grade 3 skin erythema. There were no grade 4 AEs (special communication from Ian Krop). Patients were also allowed to receive concurrent hormonal therapy, and no significant increase in adverse events was noted.

This study is a randomized phase II trial in which patients undergo a 3:1 randomization to trastuzumab emtansine every 3 weeks for 1 year of therapy or to 12 weeks of paclitaxel in combination with trastuzumab, followed by 9 months of trastuzumab monotherapy. We would like to demonstrate that

trastuzumab emtansine is better tolerated than paclitaxel and trastuzumab, and also demonstrate that the DFS event rate in the trastuzumab emtansine arm is less than 5% at 3 years. The endpoint will be the incidence of clinically relevant toxicities. Specifically these will include the composite incidence of grade 3 and 4 non-hematologic toxicity, grade 2 neurotoxicity; grade 4 hematologic toxicity. These toxicities will only be assessed at the pre-specified toxicity-assessment visits. In addition, the following events will also count towards the composite endpoint: febrile neutropenia, anything requiring dose-delay, discontinuation of any study treatment (Paclitaxel, Trastuzumab, or T-DM1) for toxicity, and any serious adverse event (SAE).

The study design and sample size take into consideration the two primary objectives. The study will include a sequential monitoring of disease-free survival within the trastuzumab emtansine arm to monitor whether the data suggest that the disease-free survival rate is too high.

2.4 Correlative Studies Background

2.4.1 Quality of Life Assessment: FACT B

We hypothesize that patients receiving trastuzumab emtansine will have superior health-related quality of life compared to patients receiving paclitaxel plus trastuzumab. We will explore quality of life measurements in several instruments that have also been used in other trials analyzing quality of life in patients who have received trastuzumab emtansine. These instruments include: FACT-B, Patient-Neurotoxicity Questionnaire (PNQ), Alopecia Patient Assessment, Rotterdam Symptom Checklist (RSCL), and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem. Scores will be analyzed using an appropriate longitudinal modeling approach (e.g., mixed-effects linear modeling assuming normality of scores) to compare patterns over time between treatment groups.

The FACT-B is a breast-cancer specific questionnaire, with demonstrated psychometric properties, that has been used extensively in oncology studies. This same questionnaire was administered to patients in TMD4450g, a randomized phase II of trastuzumab emtansine vs trastuzumab plus docetaxel in previously untreated human epidermal growth factor receptor 2-positive metastatic breast cancer. This study demonstrated that patients treated with trastuzumab emtansine had superior health-related quality of life compared with patients who received standard trastuzumab plus docetaxel. The phase III MARIANNE study (TDM4788g) will further explore these same instruments to assess patient related outcomes.

The FACT-B includes the FACT-G, a 27-item generic cancer questionnaire and a 10-item breast cancer specific module. Respondents rate each item on a 5-point scale ranging from "Not at all" to "Very much." Scores can be obtained for each domain (Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and Breast Cancer (BCS)). Each subscale is scored by summing the individual item scores and multiplying by the number of items in the scale and dividing by the number of items completed (all negatively worded items are reversed). Additionally a FACT-Breast total score, a FACT-G total score, and a FACT- Breast Trial Outcome Index (TOI) can also be calculated. The FACT-Breast total score is a sum of all domain scores. The FACT-G is a sum of all scales except BCS. The FACT-Breast TOI is the sum of the PWB, FWB, and BCS. The

range for each scale is as follows: PWB (0-28), SWB (0-28), EWB (0-24), FWB (0-28), BCS (0-36), FACT-B total (0-144), FACT-G (0-108), and TOI (0-92). Higher scores represent better quality of life.

The questionnaire will be administered to patients at pre-specified study visits in clinic: baseline, 3 weeks (+/- 1 weeks), 12 weeks (+/- 1week), 6 months (+/- 4 weeks), 12 months (+/- 8weeks), 18 months (+/- 8 weeks) , 24 months (+/- 8 weeks), and 36 months (+/- 8 weeks). The entire FACT-B will be administered. If possible, patients will be able to complete this electronically on a computer tablet. If a tablet is not available to patients at a particular study site, paper forms will be provided.

Treatment-induced neurotoxicity can negatively impact on a patient's health status and may lead to dose reductions or dose delays with paclitaxel therapy. The Patient-Neurotoxicity Questionnaire (PNQ) will be administered at pre-specified study visits: baseline, 3 weeks (+/- 1 week), 12 weeks (+/- 1 week), 6 months (+/- 4 weeks), 12 months (+/- 8 weeks), 18 months (+/- 8 weeks), 24 months (+/- 8 weeks), and 36 months (+/- 8 weeks). This questionnaire will allow for repeated measures of chemotherapy-induced peripheral neuropathy over time. Physicians have often been found to underreport and underestimate the severity of neuropathy symptoms compared with patients. This supports the importance of assessing patient-reported outcomes of neuropathy. If possible, patients will be able to complete this electronically on a computer tablet. If a tablet is not available to patients at a particular study site, paper forms will be provided. We will compare rates of neurotoxicity between the two arms of the study (trastuzumab emtansine vs TH) and will also assess time to resolution of neuropathy for those who develop any grade 1 or higher neuropathy.

An Alopecia Patient Assessment will be conducted for patients receiving paclitaxel and trastuzumab therapy. This is a 5-item questionnaire that will assess the impact alopecia has had on these patients and will be conducted electronically at pre-specified study visits. If electronic evaluation is not possible, paper evaluation will be conducted. This will be administered at baseline, 3 weeks (+/- 1 week), 12 weeks (+/- 1 week) , 6 months (+/- 4 weeks), 12 months (+/- 8 weeks) , and 18 months (+/- 8 weeks).

2.4.2 Evaluation of symptoms related to study treatment

The Rotterdam Symptom Checklist (RSCL) is a questionnaire that was originally designed to measure symptoms reported by cancer patients participating in clinical research. It has also been used to monitor levels of anxiety and depression and the presence of psychological illness. The Activity Level Scale Domain from the RSCL is an 8-item scale designed to measure whether the respondent can perform a series of activities at the present time. The recall period is the past week. Respondents rate each activity on a 4-point scale ranging from "unable" to "without help." Items are summed to produce an overall score, with higher scores representing better functioning. (NOTE: The items are frequently reversed for consistency with the scoring of the other RSCL domain scores: in this case, higher scores represent worse impairment.) This will be administered at pre-specified study visits: baseline, 3 weeks, 12 weeks, 6 months, 12 months, 18 months, 24 months, and 36 months.

2.4.3 Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

The WPAI was created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health (WPAI:GH) or a specific health problem (WPAI:SHP). The 6 questions in the WPAI questionnaire were generated from three main sources. First, a review of the work productivity literature suggested the type of items that should be tested in the questionnaire. A one-week recall period was selected on the basis of a study of interview data on chronic conditions compared with information derived from medical records which suggested that there could be a significant decrease in the accuracy of reporting work productivity data with a lengthy recall interval. Second, comments made by allergic rhinitis patients when responding to the interviewer- administered version of the WPAI items in a series of clinical studies and their responses to different work productivity questions were analyzed. For example, responses and reactions to questions about "bed days", "cut down days", "sick days" and "hours missed" were reviewed to assess what might be gained or lost by asking about work productivity in these ways. Third, cognitive debriefing of subjects following interviewer-administration and self-administration of a disease specific and general health version of the WPAI items and related work productivity questions helped to determine the final wording of the items. This will be administered at baseline, 3 weeks (+/- 1 week), 12 weeks (+/- 1 week), 6 months (+/- 4 weeks), 12 months (+/- 8 weeks), and 18 months (+/- 8 weeks).

2.4.4 Evaluation of gene predictors of trastuzumab emtansine -induced thrombocytopenia

One of the most common and troublesome toxicities specific to the therapeutic agent trastuzumab emtansine is thrombocytopenia. Although typically reversible, this toxicity can result in the need to delay or stop therapy. There are currently no predictive biomarkers to predict which patients will be most likely to incur this toxicity. Thus, an unbiased, genome wide assessment represents a reasonable approach to identify which patients may be at greatest risk. Additionally, this approach may provide critical hints to the underlying mechanism for the clinical heterogeneity observed with this toxicity.

DNA from the patients of this trial will be genotyped for SNPs and CNV markers using the Infinium Human Omni1 array (1.2 million SNP platform) from Illumina. The genotype calls will then undergo quality control (QC) assessment and be statistically correlated with the likelihood of thrombocytopenia in order to discover novel genetic variants that are predictive biomarkers for trastuzumab emtansine in breast cancer. Any provocative leads can be further validated in an independent trial using a selected candidate approach.

2.4.5 Evaluate Oncomap in archival tumor tissue

Archival tumor tissue from all patients will be assessed using a high-throughput mutation profiling system (Oncomap) to query a large panel of cancer gene mutations. Developing further understanding of gene mutations seen amongst patients with stage I HER2+ breast cancer may facilitate the development of rationale therapeutics for this population in the future. We will also explore profiles of tumors in patients that have a recurrence: we will compare mutational status at baseline to status in the recurrence, and will also explore if there are differences in profiles in

tumor tissue at baseline in patients who recur relative to those who do not. This will be done by Dr. Nikhil Wagel at the Broad Institute.

2.4.6 Evaluation of amenorrhea in premenopausal patients receiving trastuzumab emtansine

2.4.6.1 Objectives

- Investigate the percentage of patients with chemotherapy-related amenorrhea (CRA) at one year after start of treatment in premenopausal women treated with trastuzumab emtansine.
- To investigate the percentage of patients with CRA at other timepoints after start of treatment in premenopausal women treated with trastuzumab emtansine.
- To investigate the percentage of patients with CRA at various timepoints after start of treatment in premenopausal women treated with paclitaxel and trastuzumab.

2.4.6.2 Background and Significance

Many premenopausal women undergoing adjuvant chemotherapy for breast cancer are concerned about the risk of ovarian damage due to the treatment. Standard adjuvant breast cancer chemotherapy regimens are associated with chemotherapy-related amenorrhea (CRA) as well as with a risk of infertility. Menses may cease temporarily or permanently during or shortly after chemotherapy. Women may also continue menstruating normally (or resume menses after a period of amenorrhea) only to experience premature ovarian failure later on.

Risk of CRA is known to increase with older age and when greater cumulative dose of alkylating agents are used. [8] In the International Breast Cancer Study Group (IBCSG) Trial V, 31% of the 188 premenopausal women with node-positive disease who received only one cycle of perioperative cyclophosphamide-methotrexate-fluorouracil (CMF) reported at least three months of amenorrhea within the nine months after surgery, compared with 68% of the 387 similar patients who received 6-7 cycles of CMF. [9] A retrospective evaluation of long-term follow-up data from IBCSG Trials V and VI (which also administered variable numbers of CMF cycles) showed that the 227 women who remained premenopausal after 6 cycles of adjuvant CMF had high rates of menopause at five years after start of CMF, even in younger age cohorts. [10] In IBCSG V or VI, a woman who was 30 years old at time of diagnosis with continued menstruation after six cycles of CMF had a 37% risk of menopause at age 35 and an 84% risk at age 40. Thus, alkylating agents can induce both immediate amenorrhea and eventual premature ovarian failure. However, the occurrence of not immediate, but nevertheless premature menopause following adjuvant chemotherapy is not well studied as most studies of amenorrhea have focused on earlier endpoints.

For example, a prospective study of 25-40 year old women with breast cancer undergoing either doxorubicin-cyclophosphamide (AC, 120 pts), doxorubicin-cyclophosphamide-paclitaxel (ACT, 168 pts), CMF (83 pts), 5-FU-doxorubicin-cyclophosphamide (FAC, 38 pts), doxorubicin-cyclophosphamide-docetaxel (ACD, 19 pts), or another regimen (58 pts) found that menstrual cycles were more likely to persist

after the regimens that contained a lower cumulative dose of cyclophosphamide (AC, ACT, or ACD rather than FAC or CMF). [11] While women who were on CMF were more likely than those on AC, ACT, or ACD to bleed during the one month following chemotherapy (approx 50% vs. 20%, odds ratio 2.9, 95% CI 1.7-5), one year later the likelihood of menses was less in the CMF group (OR .37, 95% CI .37-.67).

A meta-analysis of twelve studies confirmed that amenorrhea occurred after CMF chemotherapy in approximately 40% of women younger than 40, and in 76% of women older than 40. [12] Anthracycline-containing regimens including cyclophosphamide-epirubicin-5-FU (CEF) may be even more gonadotoxic than CMF. In one study, premenopausal women who received CEF had a 51% risk of amenorrhea compared to a 42.6% risk in women who received CMF at the 6 month follow-up. [13] However, in this study, rates of amenorrhea were similar in the two groups at 12 months (76% in CEF group, 71% in CMF group), highlighting the importance of longer term follow-up.

Because paclitaxel-trastuzumab and trastuzumab emtansine do not contain anthracyclines or alkylating agents, and because of the targeted delivery mechanism of trastuzumab emtansine, we expect that CRA rates may be lower with these regimens. We are currently collecting data on amenorrhea after paclitaxel-trastuzumab in DFCI Protocol 07-199, but we do not have any data on amenorrhea after trastuzumab emtansine. Trastuzumab emtansine is an immunoconjugate between trastuzumab, a monoclonal antibody against Her2-expressing cells that has not been found to damage the ovaries, and maytansine, a chemotherapy that may be gonadotoxic (though this has not yet been studied).

In this study, it is important that data on menstrual history before treatment is begun be collected in order to establish a baseline, and then, for those who were premenopausal pre-chemotherapy, at each follow-up visit (every six months) in order to assess for duration of amenorrhea and also premature ovarian failure. Relevant data will be recorded at each time, as is the case for other standard toxicity and disease outcomes evaluation. This information will be valuable to physicians and premenopausal patients making decisions regarding adjuvant therapy, as well as in their follow-up care and concerns.
Each woman who enrolls will be asked to fill out a questionnaire regarding her baseline menstrual status at the time of initial study registration. Any woman who reports at least one menstrual period over the 12 months prior to filling out that form will be followed prospectively and queried regarding their menstrual frequency and last menstrual period every six months thereafter until the month 36 of the trial. The surveys will be administered to patients in clinic electronically (or as paper forms if electronic system is not available) or mailed to them to complete at home. If mailed, patients will both complete and mail back the survey or they will be contacted for collection of the information by phone. These surveys will ask about use of hormonal agents during the year prior to registration and during follow-up.

3 PARTICIPANT SELECTION

Laboratory tests required for eligibility must be completed within 14 days prior to study entry. History and exam must be performed within 28 days prior to study entry. Other non-laboratory tests (EKG and MUGA or echocardiogram) must be performed within 12 weeks of beginning study treatment as stated in Tables 5 and 6.

3.1 Inclusion Criteria

3.1.1 Patients must have HER2-positive Stage I histologically confirmed invasive carcinoma of the breast. Patients must have node-negative (N0) or micrometastases (N1mi) breast cancer according to the AJCC 7th edition.

3.1.1.1 If the patient has had a negative sentinel node biopsy, then no further axillary dissection is required, and the patient is determined to be node-negative. If an axillary dissection, without sentinel lymph node biopsy is performed to determine nodal status, at least 6 axillary lymph nodes must be removed and analyzed and negative for the patient to be considered node-negative. Axillary nodes with single cells or tumor clusters ≤ 0.2 mm by either H&E or immunohistochemistry (IHC) will be considered node-negative.

3.1.1.2 Any axillary lymph node with tumor clusters between 0.02 and 0.2cm is considered a micrometastasis. Patients with a micrometastasis are eligible. An axillary dissection is not required to be performed in patients with a micrometastasis found by sentinel node evaluation. In cases where the specific pathologic size of lymph node involvement is subject to interpretation, the principal investigator will make the final determination as to eligibility. The investigator must document approval in the patient medical record.

3.1.1.3 Patients who have an area of a T1aN0, ER+, HER2 negative cancer in addition to their primary Her2 positive tumor are eligible.

3.1.2 ER/PR determination is required. ER- and PR-assays should be performed by immunohistochemical methods according to the local institution standard protocol.

3.1.3 HER2-positive by ASCO CAP 2013 guidelines, confirmed by central testing (Clarient labs):

- IHC 3+ based on circumferential membrane staining that is complete, intense

-OR-

- FISH positive based on one of the three following criteria:
  - Single-probe average HER2 copy number ≥ 6.0 signals/cell; **OR**
  - Dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number ≥ 6.0 signals/cell; **OR**
  - Dual-probe HER2/CEP17 ratio ≥2.0

NOTE: DCIS components should not be counted in the determination of HER2 status

NOTE: HER-2 status must be confirmed to be positive by central review prior to patient starting protocol therapy. Patients previously having had HER2 testing at Clarient Laboratories do not need to undergo retesting for central confirmation of HER2 status. A pathology report documenting testing at Clarient should be provided at time of patient registration.

3.1.4 Bilateral breast cancers that individually meet eligibility criteria are allowed.

3.1.5 Patients with multifocal or multicentric disease are eligible as long as each tumor individually meets eligibility criteria. Central confirmation is needed for any site of disease that is tested to be HER2-positive by local testing (unless testing was done by Clarient).

3.1.6 Patients with a history of ipsilateral DCIS are eligible if they were treated with wide-excision alone, without radiation therapy. Patients with a history of contralateral DCIS are <u>not</u> eligible.

3.1.7 Patients should have tumor tissue available, and a tissue block of sufficient size to make 15 slides, which must be sent to DFCI for correlative research. If a tissue block is unavailable, sites may send one H&E stained slide and 15 unstained sections of paraffin-embedded tissue on uncharged slides. Slide sections should be 4-5 microns in thickness. It is also acceptable to submit 2 cores from a block of invasive tissue using a 1.2 mm diameter coring tool. If tumor is not available, the investigator must document why tissue is not available in the patient medical record, and that efforts have been made to obtain tissue.

3.1.8 ≤ 90 days between the planned treatment start date and the patient's most recent breast surgery for this breast cancer

3.1.9 All tumor should be removed by either a modified radical mastectomy or a segmental mastectomy (lumpectomy), with either a sentinel node biopsy or axillary dissection

3.1.9.1 All margins should be clear of invasive cancer or DCIS (i.e. no tumor on ink). The local pathologist must document negative margins of resection in the pathology report. If all other margins are clear, a positive posterior (deep) margin is permitted, provided the surgeon documents that the excision was performed down to the pectoral fascia and all tumor has been removed. Likewise, if all other margins are clear, a positive anterior (superficial; abutting skin) margin is permitted provided the surgeon documents that all tumor has been removed. Radiation therapy to the conserved breast is required.

3.1.10 Endocrine Therapy

3.1.10.1 May have received up to 4 weeks of tamoxifen therapy, or other hormonal therapy, for adjuvant therapy for this cancer. Patients cannot receive adjuvant hormonal therapy during protocol treatment for the first 12 weeks.

3.1.11 Prior oophorectomy for cancer prevention is allowed.

3.1.12 Patients who have undergone partial breast radiation (duration ≤ 7 days) prior to registration are eligible. Partial breast radiation must be completed prior to 2 weeks before starting protocol therapy. Patients who have undergone whole breast radiation are not eligible.

3.1.13 Patients who have participated in a window study (treatment with an investigational agent prior to surgery for ≤2 weeks) are eligible. Patients must have discontinued the investigational agent at least 14 days before participation.

3.1.14 ≥ 18 years of age with any menopausal status. Because no dosing or adverse event data are currently available on the use of trastuzumab emtansine in participants <18 years of age, children are excluded from this study.

3.1.15 ECOG Performance Status 0 or 1

3.1.16 Adequate bone marrow function: ANC ≥ 1000/mm^3, hemoglobin ≥ 9 g/dl, and platelets ≥ 100,000/mm^3

3.1.17 Adequate hepatic function: Total bilirubin ≤ 1.2mg/dL, AST and ALT ≤ 1.5x Institutional ULN. For patients with Gilbert syndrome, the direct bilirubin should be within the institutional normal range. Serum alkaline phosphatase should be ≤ 1.5x Institutional ULN.

3.1.18 Patients who have not been tested within 3 months prior to starting adjuvant therapy must be tested for hepatitis B and hepatitis C serologies during study screening.

Patients with positive Hepatitis B or C serologies without known active disease must meet the eligibility requirements for ALT, AST, total bilirubin, INR, aPTT, and alkaline phosphatase on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period.

3.1.19 Left ventricular ejection fraction (LVEF) ≥ 50%

3.1.20 Willingness to discontinue sex hormonal therapy, e.g. birth control pills, prior to registration and while on study

3.1.21 Premenopausal patients must have a negative serum or urine pregnancy test, including women who have had a tubal ligation and for women less than 12 months after the onset of menopause.

3.1.22 Women of childbearing potential and men with partners of childbearing potential must be willing to use one highly effective form on nonhormonal contraception or two effective forms of nonhormonal contraception by the patient and/or partner and continue its use for the duration of the study treatment and for 7 months after the last dose of study treatment.

3.1.23 Potent CYP3A4 inhibitors, such as ketoconazole and erythromycin, should be avoided during the study treatment period with trastuzumab emtansine.

3.1.24 Excessive alcohol intake (more than 3 alcoholic beverages per day) should be avoided (occasional use is permitted)

3.1.25 Patients undergoing breast conservation therapy (i.e. lumpectomy) must not have any contraindications to radiation therapy.

3.1.26 Willing and able to sign informed consent

3.1.27 Willing to provide tissue for research purposes

3.1.28 Must be able to read and understand English in order to participate in the quality of life surveys. If patient does not read and understand English, the patient is still eligible, but cannot participate in the quality of life surveys.

3.2 Exclusion Criteria

3.2.1 Any of the following due to teratogenic potential of the study drugs:

- Pregnant women
- Nursing women
- Women of childbearing potential who are unwilling to employ adequate contraception (condoms, diaphragms, IUDS, surgical sterilization, abstinence, etc). Hormonal birth control methods are not permitted.
- Men who are unwilling to employ adequate contraception (condoms, surgical sterilization, abstinence, etc).

3.2.2 Locally advanced tumors at diagnosis, including tumors fixed to the chest wall, peau d'orange, skin ulcerations/nodules, or clinical inflammatory changes (diffuse brawny cutaneous induration with an erysipeloid edge)

3.2.3 Patients with a history of previous invasive breast cancer.

3.2.4 History of prior chemotherapy in the past 5 years.

3.2.5 History of prior paclitaxel therapy

3.2.6 Active, unresolved infection

3.2.7 Patients with active liver disease, for example, due to hepatitis B virus, hepatitis C virus, autoimmune hepatic disorder, or sclerosing cholangitis

3.2.8 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. In addition, individuals with the following cancer are eligible regardless of when they were diagnosed and treated: cervical cancer in situ, basal cell or squamous cell carcinoma of the skin.

3.2.9 Active cardiac disease

- Any prior myocardial infarction (asymptomatic changes on EKG suggestive of old MI is not an exclusion)

- Documented congestive heart failure (CHF)
- Current use of any therapy specifically for CHF
- Current uncontrolled hypertension (diastolic >100 mmHg or systolic > 200 mmHg)
- Clinically significant pericardial effusion

3.2.10 Significant intercurrent illness including, but not limited to ongoing or active systemic infection, renal failure requiring dialysis, active cardiac disease as noted in Section 3.2.9, psychiatric illness/social situations, or other conditions that in the opinion of the investigator limit compliance with study requirements.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

This study will be open to patients of all ethnic backgrounds who meet eligibility criteria. Accrual targets will not be specific for ethnic groups.

3.4 Central Testing for HER2 status

Central Testing for HER2 will be performed by Clarient Laboratories. IHC for HER2 will be performed on all samples. A result of HER2 3+ by IHC will be consistent with HER2-positivity. If a patient is HER2 2+ by IHC, a FISH test will be performed. If HER2/CEP17 ratio is <2.0 with an average HER2 copy number ≥ 6.0 signals/cell, or HER2/CEP17 ratio is ≥2.0, the tumor with be declared HER2-positive.

HER2 IHC will be assessed by HercepTest (Dako). HER2 FISH for HER-2 gene amplification will be assessed utilizing the PathVysion assay (Vysis Corp., Downers Grove, Illinois). The identification probes for the HER-2 (SpectrumOrange) and alpha satellite DNA sequence at the centromeric region of chromosome 17 (SpectrumGreen) were hybridized according to the manufacturer's guidelines. At least twenty non-overlapping nuclei containing at least one orange and one green signal were enumerated. The ratio of orange signals (HER-2 gene) to green signals (chromosome 17) was calculated. A HER2/CEP17 ratio greater than or equal to 2.0 is considered as amplified based on the FDA approval in this kit. The ASCO CAP 2013 guidelines suggest that a dual-probe HER2/CEP17 ratio of less than 2.0 be considered positive if an average HER2 copy number is greater than or equal to 6.0 signals/cell. HER2 is considered to be borderline (equivocal) if a single probe FISH average HER2 copy number is greater than or equal to 4.0 and less than 6.0 signals/cell, or if a dual-probe HER2/CEP17 ratio is less than 2.0 and has an average HER2 copy number of greater than or equal to 4.0 and less than 6.0 signals/cell. Intended Use: The PathVysion HER-2 DNA Probe Kit (PathVysion Kit) is designed to detect amplification of the HER-2/neu gene via fluorescence in situ hybridization (FISH) in formalin-fixed, paraffin-embedded human breast cancer tissue specimens.

All central testing will be performed at Clarient Laboratories. A minimum of 5 slides (and a maximum of 8 slides), each 4-5 µm thick, should be sent to:

Clarient Laboratories
Attn: BioPharma Services (Jorge Gottheil)
31 Columbia
Aliso Viejo, CA 92656

Clarient designated shippers will be provided. Included in the shipper will be the necessary supplies and instructions for shipment of slides, specimen/patient requisition forms, FedEx air bill. Slides should be labeled with the patient ID (preferably a printed label). No patient names on slides. Results of central review will be provided directly by email to sites within 7-10 days of receipt of tissue.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. Registration/Randomization cannot occur outside of regular business hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

4. The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. An email confirmation of the registration will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator, and registering person immediately following the registration and randomization. A fax confirming randomization will be sent to the pharmacy, if applicable.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be registered centrally at Dana-Farber Cancer Institute by a member of the study team. All sites should email DFCIBOCATEMPT@partners.org to verify slot availability.

It is recommended that participants begin protocol treatment within 7 business days, and no more than 30 days from registration. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. Notify DFCIBOCATEMPT@partners.org of cancellations as soon as possible.

4.4 Registration Process for Other Participating Institutions

To register a participant, the following documents should be faxed or emailed to the Lead Institution designee by fax at 617-632-5152 or by email at DFCIBOCATEMPT@partners.org or CTOPM@dfci.harvard.edu:

- Copy of required laboratory tests including: Hematology (CBC w/differential), Serum Chemistries (Sodium, potassium, chloride, bicarbonate, BUN, creatinine, total protein, albumin, total bilirubin, SGOT (AST), SGPT (ALT), and Alkaline Phosphatase, and pregnancy test (for women of child-bearing potential only).
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed QACT Eligibility Checklist
- Mammogram or Breast Ultrasound
- MUGA or Echocardiogram
- EKG
- Pathology report and documentation of ER/PR and HER2+ status
- Clinic visit note documenting consent process, history and physical exam
- Confirmation of request of archival tissue per inclusion criteria 3.1.7 (block or slides)

The Participating Institution will then call or e-mail the Lead Institution or designee to verify receipt of registration materials and eligibility.

To complete the registration process, the Lead Institution designee will:

- Register the participant on the study with the DF/HCC Quality Assurance Office for Clinical Trials (QACT)
- Fax or e-mail the participant case number and the treatment assignment to the Participating Institution

Registration/Randomization can only occur during QACT's normal business hours of 8:00 am to 5:00 PM Eastern Time.

4.5 Guidelines for End of Accrual Registration Process

At the time 480 patients are registered, a 2 week deadline will be provided to all participating sites for consent of patients. All patients consented within this 2 week deadline will be screened for the study. Consent of participants beyond the 2 week deadline will not be permitted. All patients consented within the 2 week window who are eligible for registration will be enrolled to the trial. This may result in accrual slightly under or beyond the target goal of 500.

5 TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for trastuzumab emtansine and for paclitaxel and trastuzumab are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Arm 1: Trastuzumab emtansine

In order to initiate each treatment every 3 weeks including Cycle 1, the following is needed (note: eligibility lab criteria intentionally differs from the criteria below, refer to Section 3):

- ANC $\geq 1000/mm^3$
- Platelets $\geq 75{,}000/mm^3$
- Total bilirubin $\leq$ 1.5 mg/dL, or direct bilirubin within the institutional normal range for patients with Gilbert syndrome
- ALT< 2.5x ULN

Trastuzumab emtansine will be administered on Day 1 (+/- 3 days) of a 3-week cycle at a dose of 3.6 mg/kg IV for up to a total of 17 cycles. The total dose will calculated based on the patient's weight on Day 1 of (or up to 3 days before) each cycle with no upper limit. The same total dose may be given in the subsequent infusions if the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) is within 10% of the subject weight obtained at the prior infusion. If the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) at a subsequent dosing visit is **not** within 10% of the subject weight compared to the previous infusion, the total dose must be recalculated based on the most recent subject weight for that dosing visit.

Trastuzumab emtansine doses may be reduced to as low as 2.4 mg/kg, according to the dose modification guidelines in section 7.2.1. Dose delays of up to 42 days from last dose are permitted. If the timing of a protocol-mandated procedure, such as administration of trastuzumab emtansine, coincides with a holiday that precludes the procedure, the procedure should be performed within 3 days of the scheduled date (unless otherwise specified in the protocol) and, when possible, on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly.

The first infusion of trastuzumab emtansine will be administered over 90 minutes (± 10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion associated symptoms. Vital signs must be assessed before and after the first dose administration. Following the initial dose, patients will be observed for at least 60 minutes for fever, chills, or other infusion associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of trastuzumab emtansine may be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period after infusion. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.

Premedication for nausea and infusion reactions are not commonly required but may be given at the investigator's discretion.

Trastuzumab emtansine will be continued up to 17 cycles, unless one of the following occurs: breast cancer recurrence, intolerable toxicity, initiation of another anti-cancer therapy, patient discontinuation, or 1 year of HER2-directed therapy has been reached. Therefore, if doses of therapy are missed, they are not made up.

5.2 Arm 2: Paclitaxel and Trastuzumab

Trastuzumab may be administered at a non-participating institution. The referring site is responsible for initiating contact with the provider at the non-participating institution and ensuring the local provider has all protocol-related instructions regarding administration of trastuzumab per protocol. The referring site is responsible for obtaining and reviewing all source documentation related to trastuzumab administration. This information should be placed in the participant's research file. Additionally, the referring site is responsible for collection of adverse events on dates of administration of trastuzumab; this information can be collected by phone and documented appropriately. If the patient's trastuzumab is held at an outside facility due to toxicity, then the patient must be reevaluated by the referring site before drugs are to resume.

5.2.1 Trastuzumab

Concurrent Phase with Paclitaxel

Patients will receive a 4 mg/kg IV loading dose on day 1 followed by 2 mg/kg IV dose weekly (+/- 3 days), for a total of 12 doses. The same total dose may be given in the subsequent infusions if the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) is within 10% of the subject weight obtained at the prior infusion. If the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) at a subsequent dosing visit is **not** within 10% of the subject weight compared to the previous

infusion, the total dose must be recalculated based on the most recent subject weight for that dosing visit. When trastuzumab is being administered concomitantly with paclitaxel, trastuzumab administration may occur prior to, or after, chemotherapy administration.

The initial dose of trastuzumab will be administered over 90 minutes. If this first dose is well tolerated, subsequent infusion times may be shortened to 30 minutes or given per participating site's institutional SOP for trastuzumab administration. If the initial or a subsequent dose is not well tolerated (i.e. fevers, chills, or rigors), subsequent infusion times may be shortened only after a dose is well tolerated.

If during the 12 weeks of paclitaxel and trastuzumab a dose of paclitaxel is missed, this dose should be made up. Trastuzumab should be administered if paclitaxel is being held. Up to 3 doses of paclitaxel can be made up, and all paclitaxel must be completed within 16 weeks from starting therapy. Weekly Trastuzumab is given until completion of Paclitaxel (up to 16 weeks).

Maintenance Phase after Paclitaxel

After completion of 12 weeks of concurrent trastuzumab and paclitaxel, trastuzumab should be administered 6 mg/kg IV every 3 weeks (+/- 7 days) (over 30 minutes or per local standard operating procedures) x 39 weeks. The same total dose may be given in the subsequent infusions if the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) is within 10% of the subject weight obtained at the prior infusion. If the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) at a subsequent dosing visit is **not** within 10% of the subject weight compared to the previous infusion, the total dose must be recalculated based on the most recent subject weight for that dosing visit. A total of 13 doses should be administered, unless there are missed doses or one of the following occurs: breast cancer recurrence, intolerable toxicity, initiation of another anti-cancer therapy, patient discontinuation, or 1 year of HER2-directed therapy has been reached

Trastuzumab monotherapy should begin no sooner than 1 week after the completion of combination therapy and no later than 3 weeks after the completion of combination therapy. If during the maintenance phase with trastuzumab monotherapy a dose of trastuzumab is delayed due to patient scheduling, patients may continue on study, until patients have received a total of 39 weeks of therapy (i.e. missed doses are not made up). Up to 3 missed doses of maintenance (every 3 week) trastuzumab is permissible. If greater than 3 missed doses of maintenance (every 3 week) trastuzumab are missed, permanently discontinue the patient from study treatment, and notify the overall principal investigator. Those patients permanently discontinued from the study treatment will still be followed for study endpoints. If a patient has been without a dose of trastuzumab for ≥ 28 days, they will require a reloading dose. The reloading dose is 8 mg/kg IV if given on the every 3 week schedule. This reloading dose should be infused over 90 minutes.

During the maintenance phase, trastuzumab should be administered every 3 weeks (+/- 7days). It is encouraged that patients stay on schedule +/- 1-3 days. Patients can receive maintenance trastuzumab at non-participating sites in between their scheduled every 9 week evaluations at the referring site.

5.2.2 Paclitaxel

Paclitaxel 80 mg/m^2 will be administered over 30 – 180 minutes or per local standard operating procedures. The same total dose may be given in the subsequent infusions if the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) is within 10% of the subject weight obtained at the prior infusion. If the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion) at a subsequent dosing visit is **not** within 10% of the subject weight compared to the previous infusion, the total dose must be recalculated based on the most recent subject weight for that dosing visit. It will be administered weekly (+/- 3 days) for 12 weeks.

Paclitaxel may be administered at a non-participating institution on days 8 and Day 15 of each cycle. Paclitaxel must be administered at a participating institution on day1 of each cycle of therapy. The referring site is responsible for initiating contact with the provider at the non-participating institution and ensuring the local provider has all protocol-related instructions regarding administration of paclitaxel and trastuzumab per protocol. The referring site should use the protocol instructions for guideline regarding dose modifications. The referring site is responsible for obtaining and reviewing all source documentation related to paclitaxel and trastuzumab administration. This information should be placed in the participant's research file. If the patient's paclitaxel and/or trastuzumab are held at an outside facility due to toxicity, then the patient must be reevaluated by the referring site before drugs are to resume.

The following premedication regimen is recommended for the initial dose of paclitaxel. If the patient does not experience an allergic reaction, the premedication regimen may be altered at the discretion of the treating physician.

- Benadryl 12.5-50 mg IV, 30-60 minutes pre-paclitaxel
- Ranitidine 50 mg IV, 30-60 minutes pre-paclitaxel (can be replaced with cimetidine 300 mg, or famotidine 20 mg)
- Dexamethasone 10 mg IV, <60 minutes pre-paclitaxel OR Dexamethasone 20 mg po 6 hours and 12 hrs pre-paclitaxel. Methylprednisolone (60 mg IV) may be used instead of dexamethasone.

In order to initiate each weekly treatment, the following is needed:

- ANC ≥ 800/mm^3
- Platelets ≥ 100,000/mm^3

If these criteria are not met, delay treatment with paclitaxel until counts recover to this level. Trastuzumab should be administered if paclitaxel is being held. Paclitaxel should be held for all instances of febrile neutropenia. Please refer to section 9.1.6 for more information. Missed doses of paclitaxel should be made-up. If a delay of >21 days is required, permanently discontinue patient from study treatment, and notify study chair. These patients permanently discontinued from the study treatment will still be followed for study endpoints. If Paclitaxel needs to be discontinued in a patient who has received at least 9 weeks of combined therapy

the patient may continue on study to receive the monotherapy Trastuzumab per physician discretion.

5.3 Radiation Therapy

- Patients who undergo lumpectomy (breast conserving surgery) must receive breast radiation therapy. This may be performed according to local institutional standards. Patients may be treated with conventional, post-chemotherapy, whole breast radiation, or partial breast radiation, administered by external beam or brachytherapy.

- For patients on Arm 1, radiation will begin after 12 weeks of therapy with trastuzumab emtansine. For patients on Arm 2, radiation therapy will begin after the conclusion of paclitaxel therapy.

- Patients undergoing mastectomy may receive chest wall and nodal radiation according to local institutional standards.

- Patients may receive adjuvant trastuzumab emtansine (Arm 1) or adjuvant trastuzumab (Arm 2) or as per protocol during radiotherapy.

5.4 Endocrine Therapy

Patients may have received up to 4 weeks of tamoxifen therapy, or other hormonal therapy, for adjuvant therapy for this malignancy prior to study enrollment. However, they must temporarily stop such therapy at time of entry to study. Patients may initiate adjuvant hormonal therapy per institutional standards after completion of 12 weeks of therapy with Trastuzumab emtansine (Arm 1) or after completion of paclitaxel (Arm 2).

5.5 Reconstructive Surgery

Patients on either Arm may undergo reconstructive surgery after completing 12 weeks of trastuzumab emtansine (Arm 1) or after completion of paclitaxel (Arm 2). Patients on Arm 1 (T-DM1) should have a CBC test to ensure adequate platelet counts prior to surgery.

6 FOLLOW-UP PLAN

6.1 Duration of Follow-up

Participants will be followed for 5 years after completion of study treatment or until death, whichever occurs first.

Participants taken off study treatment for unacceptable adverse events will continued to be followed for recurrence, and should still remain on study.

During the follow-up period, after completion of study treatment, all AEs that are related to study treatment should be recorded including: neurotoxicity, thrombocytopenia, cardiac toxicity.

6.2 Criteria for Removal from Study

Participants will be removed from study by patient choice, or they have completed the duration of follow-up required on study. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF).

Patients should still continue to be followed if a DFS event has occurred so they can be followed for survival.

If a patient is taken off study treatment, they should still be followed on study.

A QACT *Treatment Ended/Off Study Form* should be submitted out when a patient completes study treatment (or stops early for any reason) and again when they come off study. This form can be found in Appendix 8.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Dr. Sara Tolaney, by phone: 617-632-2335.

7. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit during the pre-specified toxicity assessment visits (please see Study Calendar). Participants continuing to experience toxicity at the off treatment visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Toxicities will only be assessed at the pre-specified toxicity-assessment visits: these will occur every 3 weeks during study treatment for the 51 week treatment period. In addition, the following events will also count as reported toxicities even if not occurring at a toxicity assessment visit: febrile neutropenia, any toxicity requiring dose-delay, and any serious adverse event (SAE).

Toxicities that should be followed after completion of study treatment will include: thrombocytopenia, neurotoxicity, cardiac toxicity.

7.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1. Adverse Event Lists for trastuzumab emtansine

Infusion-Associated Reaction, Hypersensitivity Reactions, and Severe Pulmonary Events
On the basis of experience with trastuzumab, an infusion reaction may include symptoms of dyspnea, hypotension, elevated blood pressure, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. Signs and symptoms of hypersensitivity reactions have included anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. Severe pulmonary events in trastuzumab-treated patients have included signs, symptoms, and clinical findings of dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and ARDS, which may or may not occur in conjunction with an infusion. In some cases, these reactions have been fatal. In trastuzumab-treated patients, those who are experiencing dyspnea at rest because of complications of advanced malignancy or comorbidities may be at increased risk of a fatal infusion reaction. Some severe trastuzumab reactions have been treated successfully with supportive therapy such as oxygen, IV fluids, β-agonists, and corticosteroids. Most serious infusion-associated reactions occurred within the first 2 hours following the start of the first trastuzumab infusion, but delayed post-infusion events with rapid clinical deterioration have also been reported.

Cardiac Adverse Events
Despite intensive monitoring of LVEF and cardiac troponin levels in studies TDM4258g and TDM4367g, no Grade 3 LVEF decreases or symptomatic CHF was observed, and no patients had treatment discontinuations because of cardiac toxicity. Two patients had asymptomatic decreases in LVEF to below 45%. No elevation in serum troponin I level was observed. Other potential risks associated with trastuzumab emtansine are based on nonclinical toxicities observed in rodents and cynomolgus monkeys, as well as the clinical toxicities related to its components trastuzumab and maytansine, and other DM1-containing ADCs. However, the majority of expected toxicities have been described in our early-phase clinical trials.

DM1 is a thiol-containing maytansinoid derived from the naturally occurring ester ansamitocin P-3. The related plant ester, maytansine, has been studied as a chemotherapeutic agent in approximately 800 patients, administered every 3 weeks either as a single dose or for 3 consecutive days (Issell and Crooke 1978). The gastrointestinal DLTs consisted of nausea, vomiting, and diarrhea (often followed by constipation). These toxicities were dose dependent but not schedule dependent. Peripheral neuropathy (predominantly sensory) was reported, which was most apparent in patients with preexisting neuropathy. Subclinical transient elevations of hepatic transaminases, alkaline phosphatase, and serum bilirubin have been reported. Constitutional toxicities, including weakness, lethargy, dysphoria, and insomnia, were common. Less common toxicities include infusion-site phlebitis and mild myelosuppression.

DM1-containing ADCs have been evaluated in clinical testing with varying schedules of administration (Tolcher et al. 2003; Helft et al. 2004). Toxicities common to more than one and thus likely to be unrelated to the antibody employed include non-cumulative, reversible elevations in hepatic transaminases, alkaline phosphatase and serum bilirubin, and peripheral neuropathy. Other toxicities include mild nausea, vomiting, diarrhea, fatigue, and arthralgias.

Hematologic Toxicities

Reversible Grade 1−4 thrombocytopenia has been observed in ongoing studies with trastuzumab emtansine. In the Phase I dose-finding Study TDM3569g, Grade 4 TCP was observed as the DLT in 2 of 3 patients treated with 4.8 mg/kg of trastuzumab emtansine. Mild reversible thrombocytopenia is a commonly reported event in clinical trials. Thrombocytopenia requiring transfusion or resulting in hemorrhage was uncommon. Severe hemorrhage with fatal outcomes including central nervous system bleeding has been reported in patients receiving T-DM1. Anti-coagulation therapy and anti-platelet therapy may increase the risk of bleeding. An update investigator brochure is forthcoming and the protocol will be amended to reflect the new information. Non-serious anemia has also been observed in patients receiving trastuzumab emtansine every 3 weeks.

Hepatic Toxicities

In preclinical toxicology studies, abnormalities consistent with reversible liver toxicity (increased ALT and AST) have been observed with trastuzumab emtansine. Additionally, patients treated with maytansines developed subclinical transient elevations of hepatic transaminases, alkaline phosphatase, and serum bilirubin. In clinical studies, liver function test abnormalities, including elevated hepatic transaminases, are commonly reported in the Phase I and Phase II trastuzumab emtansine trials. Most of the events are transient and mild and do not require either discontinuation or dose reduction of trastuzumab emtansine. However, SAEs of hepatotoxicity have occurred. Two events occurred in Study TDM4258g: Grade 4 hepatotoxicity and Grade 4 elevation of liver function tests. Both events were acute in nature, and neither patient had underlying liver disease; study drug was discontinued in both patients. In Study TDM3569g, a patient with underlying cirrhosis and liver metastases developed hepatic encephalopathy that responded to treatment and did not require discontinuation of trastuzumab emtansine. A patient with underlying steatohepatitis who participated in Study TDM4374g developed fatal hepatic function abnormality in the context of multiorgan failure.

Neurologic Toxicities

In preclinical toxicology studies of trastuzumab emtansine, axonal degeneration of large nerves was noted. Peripheral neuropathy (predominantly sensory) was reported in patients who have been treated with maytansines. These events were most apparent in patients with preexisting neuropathy. In clinical trials with trastuzumab emtansine, peripheral neuropathy has been reported, predominantly as a Grade 1 toxicity. There have been no serious events of neuropathy, but there has been 1 patient to date who experienced a Grade 3 peripheral neuropathy. Once the AE resolved, the patient continued on study drug. One additional patient required a dose reduction for a Grade 2 peripheral neuropathy. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

Developmental and Reproductive Toxicities

Trastuzumab emtansine should not be administered to patients who are pregnant. For women of childbearing potential (who have not undergone surgical sterilization), and the female partners of male participants; agreement must be obtained to use one highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

Highly Effective Non-Hormonal Contraception
Methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly-effective forms of contraception.
The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.

-OR-

Effective Non-Hormonal Contraception
Alternatively two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal intrauterine device (IUD) or intrauterine system (IUS). Consideration should be given to the type of device being used, as there is higher failure rates quoted for certain types, e.g., steel or copper wire.
- Condom with spermicidal foam/gel/film/cream/suppository.
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository.

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.

- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream /suppository.

Timing and duration of contraception

Based on PK considerations, contraception methods must continue for the duration of study treatment and for at least 7 months after the last dose of study treatment.

7.1.2 Adverse Event List for Trastuzumab

Cardiac Events
Most serious adverse reactions include cardiomyopathy, dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, or reduced EF, which are symptoms of cardiac dysfunction.

Infusion Reactions
Patients should be made aware of the possibility of severe delayed infusion reactions associated with trastuzumab and should be instructed to contact their treating physician with any concerns after dosing. If infusion-related symptoms occur, the patient will be monitored until symptoms completely resolve or are deemed clinically insignificant. Patients who experience infusion-related symptoms may be pre-medicated for subsequent infusions. On the basis of experience with trastuzumab, an infusion reaction may include symptoms of dyspnea, hypotension, elevated blood pressure, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. Signs and symptoms of hypersensitivity reactions have included anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. Severe pulmonary events in trastuzumab-treated patients have included signs, symptoms, and clinical findings of dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome (ARDS), which may or may not occur in conjunction with an infusion. In some cases, these reactions have been fatal. In trastuzumab-treated patients, those who are experiencing dyspnea at rest because of complications of advanced malignancy or comorbidities may be at increased risk of a fatal infusion reaction. Some severe trastuzumab reactions have been treated successfully with supportive therapy such as oxygen, IV fluids, β-agonists, and corticosteroids.

Other Adverse Events
Additional AEs that have been noted include fever, diarrhea, infections, chills, increased cough, headache, rash, and insomnia.

Developmental and Reproductive Toxicity
Trastuzumab should not be administered to patients who are pregnant. Trastuzumab is labeled as Pregnancy Category D drug in the U.S. Prescribing Information.

For additional information on trastuzumab that may not be described here, refer to the latest information provided in the trastuzumab prescribing information.

7.1.3 Adverse Event List for Paclitaxel

Myelosuppression, liver function test abnormalities (elevated SGOT, SGPT, bilirubin, alkaline phosphatase), nausea, vomiting, diarrhea, mucositis, peripheral neuropathy, transient asymptomatic bradycardia, and with much less frequency, arrhythmias, hypotension, hypersensitivity/anaphylaxis reactions (dyspnea, tachycardia, rash, urticaria, hypotension, or

hypertension), myalgias, arthralgias, and alopecia have been observed in patients receiving paclitaxel.

7.2 Dose Modifications Delays

Patients will be assessed for toxicity prior to each dose. Dosing will occur only if the clinical assessment and laboratory test values are acceptable.

Dose delays and reductions are to serve as guidelines to maximize treatment for those who derive clinical benefit from treatment while ensuring patient safety. Dose delays for specific toxicities are detailed in the following sections.

7.2.1 Dose Modifications for Patients Receiving Trastuzumab Emtansine

If significant trastuzumab emtansine –related toxicities have not recovered to Grade ≤ 1 or baseline grade, the next scheduled dose may be delayed for up to 42 days from the last administered dose. "Significant" and "related" will be based on the judgment of the investigator in consultation with the Sponsor, Dr. Sara Tolaney, when appropriate. For example, alopecia, even if considered related, would most likely not be considered significant. Fatigue may or may not be considered either related or significant.
In general, when the significant and related toxicity (or any other toxicity for which the investigator chooses to delay dosing) resolves to Grade ≤ 1 or baseline, the patient may resume trastuzumab emtansine if the delay has not exceeded 42 days from the last administered dose. Patients should be re-evaluated weekly during the delay whenever possible. If dosing resumes, the patient may receive trastuzumab emtansine either at the previous dose level or at one dose level lower (see Table 2) based on the specific instructions in the sections below. If possible, future cycle intervals should remain every 21 days.

If a patient requires a dose reduction for hematologic or hepatic toxicity as described in the following sections, dosing will be reduced by one dose level per Table 2. No re-escalation of the trastuzumab emtansine dose will be allowed.

Table 2. Dose Reduction for trastuzumab emtansine

Dose Level	Dose
0	3.6 mg/kg
–1	3.0 mg/kg
–2	2.4 mg/kg
Indication for further dose reduction	Off study treatment

a. Trastuzumab Emtansine Dose Modification/Management for Infusion Reactions and Hypersensitivity Reactions

No premedication for the first infusion of trastuzumab emtansine is specified or expected. Patients should be observed closely for infusion reactions and hypersensitivity reactions for a

minimum of 60 minutes after the first infusion and for a minimum of 30 minutes after subsequent infusions as described in section 8.1.3. Patients who experience trastuzumab emtansine infusion–related temperature elevations of > 38.5°C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen and/or H1 and H2 receptor antagonists (e.g., diphenhydramine or ranitidine). Serious infusion-related events (Grade ≥ 3 allergic reaction or ARDS) manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated according to standard clinical practice. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Patients who experience a Grade 3 allergic reaction or ARDS will be discontinued from study treatment and followed as described in section 6.0. Patients who have infusion-related symptoms and/or hypersensitivity reactions should be managed as specified in section 6.0.

b. Trastuzumab Emtansine Dose Modification/Modification for Hematologic Toxicity

In order to initiate each treatment every 3 weeks including Cycle 1, the following is needed (note: eligibility lab criteria intentionally differs from the criteria below, refer to Section 3):

- ANC ≥ 1000/mm^3
- Platelets ≥75,000/mm^3
- Total bilirubin ≤ 1.5 mg/dL, or direct bilirubin within the institutional normal range for patients with Gilbert syndrome
- ALT< 2.5 x ULN

Patients who experience Grade 2 TCP should have the next dose of trastuzumab emtansine held until the platelet count has recovered to Grade ≤ 1. Patients can then continue treatment with trastuzumab emtansine at the same dose or one dose level lower in subsequent treatment cycles at the discretion of the investigator. Patients who received trastuzumab emtansine and who experience a first Grade ≥3 TCP event may, after adequate recovery to a platelet count of Grade ≤ 1 or to the baseline grade, continue treatment with trastuzumab emtansine at one dose level lower in subsequent treatment cycles. Patients who experience a second Grade ≥3 TCP event may, after adequate recovery as defined above, continue treatment with trastuzumab emtansine at two dose levels lower (if that dose is not < 2.4 mg/kg) in subsequent treatment cycles. Patients who experience a Grade ≥3 TCP event at the 2.4–mg/kg dose level will be discontinued from study treatment. A dose delay of up to 42 days from the last administered dose is permitted. Patients who experience a Grade ≥2 hematologic AE should be checked weekly as medically indicated for recovery of platelet counts. If a patient's platelet count does not recover to baseline or Grade ≤ 1 within the allowable delay of 42 days from the last administered dose, the patient will be discontinued from all study treatments and will be followed as described in Section 6.0. No re-escalation of the trastuzumab emtansine dose will be allowed.

Patients who experience grade 4 neutropenia will have trastuzumab emtansine held until the neutrophil count recovers to grade 1, when the patient should be treated at one dose level lower in subsequent treatment cycles. For a second occurrence of grade 4 neutropenia, trastuzumab

emtansine will be held until the neutrophil count has recovered to grade 1; trastuzumab emtansine should then be given at two dose levels lower (if that dose is not < 2.4 mg/kg) in subsequent treatment cycles. Patients who experience a grade 4 neutropenia event at the 2.4 mg/kg dose level will be discontinued from study treatment and will be followed as described in Section 6.0.

A dose delay of 1 cycle (i.e., 42 days from the last trastuzumab emtansine dose) is permitted. Patients who experience a grade 3 or 4 hematologic adverse event should be checked weekly for recovery of platelet and/or neutrophil counts. If a patient's platelet and/or neutrophil count does not recover to baseline or grade 1 within the allowable delay of 42 days from the last administered dose, the patient will discontinue all study treatment, but will continue to be treated as described in Sections 6.0.

c. Trastuzumab emtansine Dose Modification/Management for Hepatotoxicity

In order to receive trastuzumab emtansine:

- Total bilirubin should be no greater than 1.5 mg/dL at time of dosing, or direct bilirubin within the institutional normal range for patients with Gilbert syndrome

  If the Total bilirubin is > 1.5 mg/dL and <2x institutional ULN, then trastuzumab emtansine should be held until it resolves to ≤ 1.5 mg/dL. After adequate recovery, trastuzumab emtansine can be continued at one dose level lower. Patients who experience a second event should, after adequate recovery, continue treatment with trastuzumab emtansine at two dose levels lower (if that dose is not < 2.4 mg/kg) in subsequent treatment cycles.

- ALT should be <2.5x institutional ULN at time of dosing

  If ALT is ≥2.5x institutional ULN, Grade 2, or Grade 3, then trastuzumab emtansine should be held until it resolves to ≤ Grade 1. After adequate recovery, trastuzumab emtansine can be continued at one dose level lower. Patients who experience a second event should, after adequate recovery, continue treatment with trastuzumab emtansine at two dose levels lower (if that dose is not < 2.4 mg/kg) in subsequent treatment cycles.

If a patient's liver enzymes and total bilirubin do not recover within the allowable dose delay of 42 days from the last administered dose, the patient will be discontinued from all study treatments and will continue to be followed as described in Section 6.0.

Patients who experience a grade 4 ALT or Total bilirubin >2x institutional ULN or higher must discontinue therapy with trastuzumab emtansine. Patients who experience an AE should be checked weekly as medically indicated for the recovery of liver enzymes and/or total bilirubin.

No re-escalation of the trastuzumab emtansine dose will be allowed.

d. Trastuzumab Emtansine Dose Modification/Management for Neurotoxicity

Grade 1 or 2 Neurotoxicity:

- There will be no dose modifications for grade 1 or 2 neurotoxicity.
- Treatment does not need to be delayed and previously administered doses can be continued.
- If the patient is experiencing significant distress from grade 2 toxicity or the treating physician is uncomfortable with continuing the same doses, a dose reduction at one se lower is acceptable in subsequent cycles.

Grade 3 Neurotoxicity:

- Patient should not receive additional treatment until the toxicity has resolved to ≤ grade 2.
- Patients who experience Grade ≥3 peripheral neuropathy that does not resolve to Grade ≤2 within the allowable dose delay of 42 days from the last administered dose will be discontinued from all study treatments and will be followed as described in section 6.0.

e. Trastuzumab emtansine Dose Modification for Cardiotoxicity

Please see the schedule of assessments for ECHO/MUGA requirements. ECHO/MUGAs should also be obtained as indicated on the basis of standard institutional practice. Any patient with symptomatic cardiac dysfunction or a significant decrease in LVEF (Grade ≥ 3 LVSD or Grade 3–4 heart failure or Grade 2 heart failure accompanied by an LVEF < 45% by CTCAE v4.0) will discontinue study treatment. Asymptomatic decreases in LVEF will be managed according to the algorithm in Table 3. Follow-up at 3, 6, 9, and 12 months with MUGA/echocardiogram from the time of decrease in EF is required in patients who come off study treatment. And records should be made if non-protocol therapy is received.

The patient should be discontinued if clinically significant cardiac dysfunction or cardiac failure develops or persists.

If toxicity does not resolve to allow retreatment within 42 days from the prior dose, the patient will be discontinued from study treatment and will be followed. If a patient experiences three intermittent holds for asymptomatic LVEF decrease, the patient will be discontinued from study treatment and will be followed.

Table 3. Asymptomatic Decrease in LVEF: Percentage Points from Baseline

Relationship of LVEF to radiology facility's LLN	Decrease of <10 percentage points	Decrease of 10 to 15 percentage points	Decrease of ≥16 percentage points
Within normal limits	Continue	Continue	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)

1-5 percentage points below LLN	Continue and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)
≥ 6 percentage points below LLN	Continue and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)

7.2.2 Dose modifications for patients receiving paclitaxel and trastuzumab

7.2.2.1 Paclitaxel

Dose modifications shall be considered optional when toxicities are deemed unrelated to treatment with Paclitaxel and do not adversely impact study drug administration. Patients permanently discontinued from the study treatment will still be followed for study endpoints

Dose levels for dose modifications of paclitaxel

Dose Level	**Dose**
0	80 mg/m^2
-1	60 mg/m^2

a. Anaphylaxis/Hypersensitivity

Below is a list of suggested guidelines for management of paclitaxel anaphylaxis/hypersensitivity reactions. It is also permissible for management to be in accordance with institutional standards.

Mild symptoms (Grade 1): mild flushing, rash, pruritis

- Complete infusion, observation in treatment area. No treatment required.

Moderate symptoms (Grade 2): moderate rash, flushing, mild dyspnea, chest discomfort

- Stop infusion.
- Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Methylprednisolone (60mg IV) may be used instead of dexamethasone.
- Resume paclitaxel infusion after recovery of symptoms, at a slower rate. 10 ml/hour for 15 minutes, then 25 ml/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.
- If moderate or severe symptoms recur after rechallenge, stop paclitaxel infusion, and report as an adverse event.
  Patient may be rechallenged after premedication with dexamethasone 8 mg po or IV q6hrs x 4 doses (moderate symptoms) or 20 mg po or IV q6hrs x 4 doses (severe symptoms) and diphenhydramine 25 mg po or IV q6hrs x 4 doses (moderate or severe symptoms).Methylprednisolone (60mg IV) may be used instead of dexamethasone.

The paclitaxel should be administered at a slower rate. 10 ml/hour for 15 minutes, then 25 ml/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.

Severe life-threatening symptoms (Grade 3): hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria.

- Stop paclitaxel infusion.
- Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Methylprednisolone (60mg IV) may be used instead of dexamethasone.
- Add epinephrine or bronchodilators if indicated.
- Report episode as an adverse event.
- Patient may be rechallenged after premedication with dexamethasone 20 mg po or IV q6hrs x 4 doses and diphenhydramine 25 mg po or IV q6hrs x4 doses. Methylprednisolone (60mg IV) may be used instead of dexamethasone.
- The paclitaxel should be administered at a slower rate, 10 ml/hour for 15 minutes, then 25 ml/hr for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.

b. Cardiac Arrhythmias

Asymptomatic, EKG-documented arrhythmias

- Stop paclitaxel, and manage arrhythmia according to standard practice.

Asymptomatic sinus bradycardia or tachycardia

- No intervention is necessary.

Sinus bradycardia or tachycardia associated with hypersensitivity reaction

- See management of hypersensitivity reaction in section 7.2.2.1A.

c. Hematologic Toxicity

Requirements to initiate any cycle of paclitaxel:

- ANC $\geq 800/mm^3$
- Platelets $\geq 100{,}000/mm^3$

If ANC<800

- Delay paclitaxel. Continue trastuzumab
- Check counts weekly until ANC ≥ 800 mm^3
- If a delay of greater than 21 days is required, permanently discontinue protocol therapy and notify study chair.

If platelets <100,000

- Delay paclitaxel. Continue trastuzumab.
- Check counts weekly until platelets $\geq 100{,}000/mm^3$

- If a delay of >21 days is required, permanently discontinue protocol therapy and notify study chair.

There will be no dose reductions for hematologic toxicity. Doses will not be reduced based on low nadir counts. Nadir blood counts are not required. Treatment with growth factor support (i.e. neupogen, neulasta) is allowed and is at the discretion of the treating physician.

d. Neurologic Toxicity: Neuropathy (motor and sensory)

Grade 1 or 2 Neurotoxicity

- There will be no dose modifications for grade 1 or 2 neurotoxicity.
- Treatment does not need to be delayed and previously administered doses can be continued.
- If the patient is experiencing significant distress from grade 2 toxicity or the treating physician is uncomfortable with continuing the same doses, a dose reduction of 20 mg/m^2 in the paclitaxel dose is acceptable.

Grade 3 Neurotoxicity

- Patient should not receive additional treatment until the toxicity has resolved to ≤ grade 2.
- The next infusion may be delayed up to 2 weeks to allow for neurologic toxicity to improve.
- If it does not resolve to ≤ grade 2 after 2 weeks, the patient will be permanently discontinued from protocol therapy.
- Re-treatment should be initiated with a dose of paclitaxel 60 mg/m^2 when the toxicity resolves to grade 2 or less. All subsequent infusions will be administered using the reduced dose.
- If grade 3 neurotoxicity develops with additional infusions, paclitaxel therapy should be discontinued. The patient can continue with trastuzumab monotherapy.

e. Gastrointestinal Toxicity

Nausea/Vomiting

- Grade 0-2 Nausea/Vomiting: No change
- ≥ Grade 3 despite maximal anti-emetic therapy: Hold paclitaxel until ≤ grade 2, then restart with 60 mg/m^2 and continue trastuzumab.
- If nausea/vomiting toxicity causes a dosing delay of >21 days, or if ≥ Grade 3 nausea/vomiting recurs despite dose reduction, permanently discontinue paclitaxel therapy. Patients can continue on trastuzumab monotherapy.
- Prophylactic antiemetics should be used at the discretion of the investigator. The specific regimen must be recorded in the patient's medical record.

Mucositis

- Grade 2 Mucositis

If grade 2 mucositis is present on the day of any treatment, the treatment should be delayed until the mucositis has resolved to a grade 1 or 0, and then resume paclitaxel at 80 mg/m^2.

- Grade 3 or 4 Mucositis
  Delay treatment until mucositis has resolved to grade 1 or 0, then the dose of paclitaxel should be reduced to 60 mg/m^2.

  If grade 3 or 4 mucositis recurs, treatment with paclitaxel should be discontinued. The patient should then complete trastuzumab monotherapy in order to receive a total of 51 weeks of trastuzumab.

If mucositis causes a delay of >21 days, paclitaxel therapy should be discontinued. The patient should then complete trastuzumab monotherapy in order to receive a total of 51 weeks of trastuzumab.

Once the paclitaxel dose has been decreased, it should not be re-escalated.

Diarrhea

- Grade 2
  If grade 2 diarrhea is present on the day of any treatment, the treatment should be delayed until the diarrhea has resolved to grade 1 or 0, and then resume paclitaxel at 80 mg/m^2

  Optimal use of anti-diarrheal agents is encouraged.

- Grade 3 or 4
  If grade 3 or 4 diarrhea occurs, delay treatment until the diarrhea has resolved to grade 1 or 0, then the dose of paclitaxel should be reduced to 60 mg/m^2.

  If grade 3 or 4 diarrhea recurs, treatment with paclitaxel therapy should be discontinued. The patient should then complete trastuzumab monotherapy in order to receive a total of 51 weeks of trastuzumab.

If diarrhea causes a delay of >21 days, the patient should be discontinue paclitaxel therapy. The patient should complete trastuzumab monotherapy in order to receive 51 weeks of trastuzumab.

Once the paclitaxel dose has been decreased, it should not be re-escalated.

Optimal use of anti-diarrheal agents is encouraged.

f. Hepatic Dysfunction

Because the plasma clearance of paclitaxel is reduced in patients with hepatic impairment, careful evaluation of liver enzymes in necessary before the administration of each new cycle of paclitaxel. For elevations in total bilirubin, SGOT (AST), SGPT(ALT), the following dose modifications will be applied:

- Grade 1
  No dose modifications

- Grade 2 or 3
  Hold paclitaxel for one week.

  If abnormal tests return to grade 0 or 1, paclitaxel should be continued at full dose.

  If the abnormal test does not return to grade 0 or 1 in one week, but remains at grade 2, continue paclitaxel at 60 mg/m^2. If the abnormal test result returns to grade 0 or 1, return to full dose, 80 mg/m^2.

- Grade 4
  Patient should be permanently discontinued paclitaxel therapy. The patient should complete trastuzumab monotherapy in order to receive 51 weeks of trastuzumab.

g. Febrile Neutropenia

- Fever ≥38°C (101.3°F) in the presence of neutropenia (ANC <1000)
  Paclitaxel should be held for all instances of febrile neutropenia.

  First episode: G-CSF or GM-CSF may be used for subsequent cycles at the discretion of the treating physician, but it is not required. There will be no dose reduction for the first episode of febrile neutropenia.

  Second episode: Remaining doses will be reduced to paclitaxel 60 mg/m^2 given with G-CSF or GM-CSF.

  Third episode: Patient should be permanently discontinued from paclitaxel therapy. The patient should complete trastuzumab monotherapy in order to receive 51 weeks of trastuzumab.

h. Infection with/without neutropenia

- Grade 3
  Paclitaxel should be held for all instances of Grade 3 infection with/without neutropenia.

  First episode: G-CSF may be used for subsequent cycles at the discretion of the treating physician, but it is not required. There will be no dose reduction for the first episode of febrile neutropenia.

Second episode: Remaining doses will be reduced to paclitaxel 60 mg/m^2. This should be given with G-CSF if infection occurred with neutropenia.

Third episode: Patient should be permanently discontinued from paclitaxel therapy. The patient should complete trastuzumab monotherapy in order to receive 51 weeks of trastuzumab.

i. Other Grade 3 or 4 Toxicities

Any patient experiencing grade 3 or 4 toxicity, other than those described above must be discussed with the study chair.

j. Dose Modifications for Obese Patients

- There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight.
- All dosing is to be determined solely by the patient's BSA as calculated from actual weight, OR actual weight without any modification unless explicitly described in the protocol.
- This will eliminate the risk of calculation error and the possible introduction of variability in dose administration.
- Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.
- Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on this protocol.

7.2.2.2 Trastuzumab

- No cardioprotective drugs are permitted. There are no data for the use of cardioprotective agents such as dexrazoxane (Zinecard®)

- No dose modifications of trastuzumab are permitted.

- If more than 9 weeks of trastuzumab therapy have been missed, permanently discontinue patient from study treatment, and notify study chair. These patients permanently discontinued from the study treatment will still be followed for study endpoints.

- Trastuzumab may be administered at non-participating sites. The every 9 week evaluations must be conducted at a participating site.

- Trastuzumab monotherapy can be given locally when given in between the every 9 week required study visits, but adverse event assessments must be conducted by phone in those participants not being seen at a participating site for the required every 3 week adverse event assessments. If the patient's trastuzumab is held at an

outside facility due to toxicity, then the patient must be reevaluated by the referring site before drugs are to resume.

a. Infusion-associated symptoms

- During the first infusion, a symptom complex of fever and/or chills may occur. These are usually mild-to-moderate and may be accompanied by nausea, vomiting, headache, dizziness, rigors, pain, hypotension, rash, and asthenia. These symptoms occur infrequently during subsequent infusions.

b. Trastuzumab when paclitaxel is delayed or discontinued

- If paclitaxel is delayed for any reason other than cardiotoxicity or severe hypersensitivity reactions that occurred when both paclitaxel and trastuzumab were administered, trastuzumab may be continued.

c. Cardiac Dysfunction

- Patients with symptomatic CHF will permanently discontinue trastuzumab

- Individual patients should have their MUGA scans/echocardiograms performed at the same radiology facility to eliminate variability between facilities.

Asymptomatic decrease in LVEF:

- Decision to continue or stop is based on the measured ejection fraction as it relates to the radiology facility's LLN and change in ejection fraction from baseline. Guidelines for performing MUGA scan/echocardiogram and management of patients who have an asymptomatic decrease in LVEF from baseline are in Table 4 below.

Table 4. Management of Asymptomatic decrease in LVEF

Asymptomatic Decrease in LVEF: Percentage Points from Baseline			
Relationship of LVEF to radiology facility's LLN	**Decrease of <10 percentage points**	**Decrease of 10 to 15 percentage points**	**Decrease of ≥16 percentage points**
Within normal limits	Continue	Continue	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)
1-5 percentage points below LLN	Continue and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)
≥ 6 percentage points below LLN	Continue and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)	Hold and repeat MUGA/echocardiogram in 3 weeks (+/- 3 days)

- If trastuzumab is held or discontinued during therapy with paclitaxel, paclitaxel may be continued at the discretion of the investigator.

- If trastuzumab is not started or discontinued during therapy, MUGA scan/echocardiogram still needs to be done at 12 weeks, 6 months, 9 months, and at 1 year.

- Trastuzumab must be permanently discontinued when two consecutive "hold" categories occur.

- Trastuzumab must be permanently discontinued when three intermittent "hold" categories occur.

- At the discretion of the investigator, trastuzumab may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories.

- If LVEF is maintained at a "continue and repeat MUGA/echocardiogram" or improves from a "hold" to a "continue and repeat MUGA/echocardiogram" category, additional MUGA scans/echocardiogram prior to the next scheduled MUGA scan/echocardiogram will be at the discretion of the investigator.

Symptomatic decrease in LVEF

- Grade 3 CHF
  Monitor for signs and symptoms of CHF (i.e. dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc)

  If patient develop these signs and symptoms, hold treatment.

  If CHF occurs while on paclitaxel plus trastuzumab, resumption of paclitaxel is at the discretion of the investigator.

  Confirm diagnosis of CHF with either a MUGA scan/echocardiogram. A chest x-ray is also required. Once a diagnosis of CHF is confirmed, trastuzumab must be permanently discontinued and reported as an adverse event.

  Follow-up at 3, 6, 9, and 12 months from time of CHF diagnosis with MUGA scan/echocardiogram.

- Grade 4 CHF (severe refractory CHF or requiring intubation)
  Discontinue treatment, and report as an adverse event.

  Follow-up at 3, 6, 9, and 12 months with MUGA/echocardiogram from time of CHF diagnosis with MUGA scan/echocardiogram.

Ischemia

- Grade 1
  Continue treatment with frequent monitoring.

- Grade 2
  Hold treatment and conduct cardiac evaluation.
  Based on this evaluation, treatment may be continued at the discretion of the investigator.

- Grade 3 or 4
  Discontinue treatment.

Arrhythmia

- Grade 1
  Continue treatment with careful monitoring OR hold treatment (and paclitaxel if patient is receiving paclitaxel) and conduct cardiac evaluation.

  Based on cardiac evaluation, treatment with trastuzumab and paclitaxel or trastuzumab alone may continue or discontinue at the discretion of the investigator.

  If trastuzumab is discontinued, paclitaxel may also be discontinued at the discretion of the investigator, and patient removed from protocol therapy.

- Grade 2
  Hold treatment (and paclitaxel if patient is receiving paclitaxel) and conduct cardiac evaluation.

  Based on cardiac evaluation, treatment with trastuzumab and paclitaxel or trastuzumab alone may continue or discontinue at the discretion of the investigator.

- Grade 3 or 4
  Discontinue trastuzumab.
  Paclitaxel is not permitted.
  Patient should be removed from protocol therapy but should continue to be followed.

Myocardial Infarction

- Discontinue Treatment

d. General disorders

Fever

- Grade 1 (38°C - 39°C [100.4° - 102.2°F] OR Grade 2 (39.1°C - 40°C [102.3° - 104°F]
  Stop infusion and give antipyretics. Once temperature is <38°C, resume infusion at a slower rate.

- Grade 3 (>40°C [104°])
  Stop infusion immediately and give antipyretics
  Monitor patient for a minimum of one hour
  If temperature drops to <38°C within 3 hours, resume infusion at a slower rate.
  If fever does not resolve within 3 hours, inpatient monitoring is strongly recommended.
  If temperature drops to <38°C within 3 days, re-challenge at a slower rate.
  If temperature remains >38°C after 3 days, abandon this administration and subsequent administration is at the discretion of the investigator

- Grade 4 (40°C [104°F] for 24 hours)
  Stop infusion immediately and give antipyretics
  Monitor patient for a minimum of one hour
  If fever does not resolve within 3 hours, inpatient monitoring is strongly recommended.
  If temperature drops to <38°C within 3 days, re-challenge at a slower rate.
  If temperature remains >38°C after 3 days, abandon this administration and subsequent administration is at the discretion of the investigator

Chills

- Treat with acetaminophen and/or diphenhydramine hydrochloride.
- Meperidine may be given at the investigator's discretion.

e. Gastrointestinal

Diarrhea

- Any grade
  Any antidiarrheal medication may be given at the investigator's discretion.

f. Allergy/Immunology

Allergic reaction/hypersensitivity (including drug fever)

Stop the infusion and give diphenhydramine hydrochloride
If toxicity resolves within 3 hours, treatment in next dose is allowed at a slower rate and under close observation.

If toxicity does not resolve in 3 hours, overnight observation is recommended and treatment in the next dose under close observation is at the discretion of the investigator.

g. Pulmonary

Any (e.g. Adult Respiratory Distress Syndrome [ARDS], pneumonitis/pulmonary infiltrates, etc)

Delay trastuzumab until case is known.
If pneumonitis/fibrosis, or pulmonary infiltrate is confirmed, and the relationship to trastuzumab cannot be excluded, trastuzumab must be permanently discontinued.

8 DRUG FORMULATION AND ADMINISTRATION

8.1 Trastuzumab emtansine

8.1.1 Formulation, Preparation, and Storage

Trastuzumab-MCC-DM1 (trastuzumab emtansine) is provided as a single-use lyophilized formulation in a colorless 20-mL Type I glass vial closed by means of a FluroTec-coated stopper and an overseal with flip-off cap. Upon receipt of trastuzumab emtansine vials should be refrigerated at 2°C–8°C. All vials of trastuzumab emtansine should be handled by appropriately trained site staff wearing gloves and visually inspected upon receipt to ensure they are intact without exterior contamination. Drug from any vials that appear abnormal upon inspection should not be administered to patients.

The lyophilized product should be reconstituted using Sterile Water for Injection (SWFI). Using a new syringe, 8 mL SWFI should be added to the vial and the vial swirled gently until the product is completely dissolved. The vial should not be shaken. The resulting product contains 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 60 mg/mL sucrose, and 0.02% (w/v) polysorbate 20. Each 20 mL vial contains enough trastuzumab emtansine to allow delivery of 160 mg trastuzumab emtansine. The reconstituted product contains no preservative and is intended for single use only. The vial should be inspected to ensure the reconstituted product is a clear colorless solution, and is free of particulates before proceeding. Drug from any vial that appears abnormal upon inspection should not be administered to patients. Using a new syringe, the indicated volume of trastuzumab emtansine solution should be removed from the vial(s) and added to the IV bag containing at least 250 mL of 0.45% sodium chloride (preferred) or 0.9% sodium chloride injection and gently inverted to mix the solution. A 0.22 micron polyethersulfone (PES) in-line filter is recommended when using 0.45% sodium chloride and required when using 0.9% sodium chloride injection. The solution of trastuzumab emtansine should not be shaken.

The solution of trastuzumab emtansine for infusion should be used immediately. If not used immediately, storage times should not be longer than 24 hours at 2°C−8°C (36°F−46°F) for solutions of trastuzumab emtansine diluted in polyvinyl chloride (PVC) or latex-free PVC-free

polyolefin, polypropylene, or polyethylene bags containing 0.45% or 0.9% Sodium Chloride Injection, USP.

For additional details, please refer to the current version of the trastuzumab emtansine Investigator Brochure.

8.1.2 Availability

Trastuzumab emtansine is an investigational agent and will be supplied free-of-charge from Genentech.

8.1.3 Administration

The first infusion of trastuzumab emtansine will be administered over 90 minutes (±10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 60 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of trastuzumab emtansine may be administered over 30 minutes (±10 minutes), with a minimum 30-minute observation period after infusion.

8.1.4 Ordering

Each participating institution is responsible for completing the applicable drug supply forms to receive re-supply of trastuzumab emtansine for the duration of study. Except in very unusual circumstances, each participating institution will order the study agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the supplier.

8.1.5 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the trastuzumab emtansine.

8.1.6 Destruction and Return

At the end of the study, unused supplies of trastuzumab emtansine should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2 Trastuzumab

8.2.1 Formulation, Preparation, and Storage

Trastuzumab is a commercially available sterile, white to pale yellow, preservative-free-lyophilized powder for intravenous (IV) administration. Each vial of trastuzumab contains 440 or150 mg of trastuzumab (may vary based on availability). ,

Use appropriate aseptic technique. Each 440 mg vial of trastuzumab should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multidose solution containing 21 mg/mL trastuzumab. Immediately upon reconstitution with BWFI, the vial of trastuzumab must be labeled in the area marked "Do not use after" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, trastuzumab must be reconstituted with Sterile Water for Injection. Trastuzumab which has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided.

Each 150 mg vial is reconstituted with 7.4 ml of Sterile Water for Injection (SWFI). The reconstituted vial yields a single-dose solution containing 21mg/ml trastuzumab that delivers 7.15 mL (150 mg of trastuzumab).

Determine the dose of trastuzumab needed, based on a loading dose of 6 mg trastuzumab/kg body weight during q3wk dosing. Calculate the correct dose using 21 mg/mL trastuzumab solution. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Vials of trastuzumab are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of 440 mg trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. A vial of 150 mg trastuzumab once reconstituted with SWFI should be used immediately, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted trastuzumab solution for up to 24 hours at 2°C–8°C; discard any unused trastuzumab after 24 hours.

DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24

hours at room temperature 15°C–25°C; however, since diluted trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).

Treatment may be administered in an outpatient setting. The recommended initial loading dose for weekly administration is 4 mg/kg trastuzumab administered per institutional guidelines. The recommended maintenance weekly trastuzumab dose is 2 mg/kg and should be administered per institutional guidelines. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION).

The recommended loading dose for every 3-week administration is 8 mg/kg trastuzumab administered per institutional guidelines. The recommended every 3 week initial (not loading) and maintenance trastuzumab dose is 6 mg/kg q3wk and should be administered per institutional guidelines. Trastuzumab may be administered in an outpatient setting. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION).

The initial dose of trastuzumab should be infused over 90 minutes. If this first dose is well tolerated, subsequent infusion times may be shortened to 30 minutes or given per participating site's institutional SOP for trastuzumab administration. If the initial or a subsequent dose is not well tolerated (i.e. fevers, chills, or rigors), subsequent infusion times may be shortened only after a dose is well tolerated.

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8.3 Paclitaxel

8.3.1 Formulation, Preparation, and Storage

Paclitaxel is commercially available and must be diluted prior to administration with 0.9% sodium chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Paclitaxel should be prepared and stored in glass, polypropylene, or polyolefin containers due to leaching of DHEP [di-(2ethylhexyl)phthalate] plasticizer from polyvinyl chloride (PVC) containers. Non-PVC containing tubing and connectors such as the IV administration sets (polyethylene or polyolefin) used to infuse parenteral nitroglycerin should be used.

In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 micron (e.g. IVEX-2®) into the IV fluid pathway distal to the infusion pump. The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the paclitaxel solution.

Intact vials should be stored between 20° - 25° C (68° - 77° F) in the original package to protect from light, and remain stable until the expiration date on the label. Neither freezing nor

refrigeration adversely affects stability. Upon refrigeration components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

Paclitaxel will be administered per institutional guidelines as an IV infusion using an in-line 0.22 micron filter.

9 CORRELATIVE/SPECIAL STUDIES

9.1 Translational Research Blood Collection

Translational research blood collections are required for all sites unless the local IRB will not allow mandatory collection. Contact the Principal Investigator, Sara Tolaney, MD, to discuss institution-specific requirements for specimen collection. The following samples are required to be submitted to DFCI:

- At baseline, 1- 10 mL purple top tube and 1- 10 mL red top tube will be collected.
- At subsequent time points, only 1- 10 mL red top tube will be collected.

Blood from the 1- 10 mL purple top tube will be aliquoted into 5- 2mL cryovials and stored at -80° at the DFCI breast cancer core lab. Note that samples are shipped at ambient temperature (refer to Section 10.2 for processing and shipping details). This blood will be used for DNA extraction for GWAS analysis. All research blood samples that are collected for this protocol will be stored at Dana-Farber until the samples have been exhausted.

See section 10.2 for collection and shipment details.

9.2 Tumor Tissue for gene profiling

Submission of tumor tissue is required for all sites. The following specimens are required to be submitted to DFCI:

- Tumor blocks
- 1 H&E slide

A core sample will be performed on the block, and the remaining block will be returned to the original institution when processing is complete. If a tumor block is needed for clinical care purposes, the participating site should contact the coordinating center study coordinator to request that the applicable block be returned. All slides will be kept indefinitely. For all human breast cancer (BrCa) samples to be used in this project, the Center for Molecular Oncologic Pathology (CMOP) at Dana-Farber will prepare a fresh tissue section of 5µm thickness for subsequent staining with H&E. This will promote the most accurate assessment of both the epithelial and stromal tissue, in order to denote the areas to

be excised via macrodissection. Macrodissection of BrCa tissue samples will require pathological analysis to denote the relative enrichment (expressed as percent) with either cell type via circled H&Es. These circled slides will be used to direct tissue core punches from archival FFPE BrCa tissue blocks of 0.6mm in diameter. While tissue blocks will be stored at 4˚C, all tissue isolated via macrodissection will be stored at -20˚C prior to use.

For FFPE BrCa tissue samples obtained via macro dissected cores, DNA will be isolated using the QIAamp Investigator BioRobot Kit running on an automated high-throughput BioRobot (Qiagen). The samples will be deparaffinized using Citrisolv (ThermoFisher), prior to overnight tissue lysis. In the experience of CMOP, overnight digestion of archival FFPE samples is the most effective and efficient way to extract high-quality nucleotides. Post tissue digestion, following the manufacturer's protocol, the samples are incubated in RNase to remove contaminating RNA. Samples are then column purified to elute DNA. For all DNA extractions, concentration of double-stranded DNA (ng/µl) will be determined using the Quant-iT PicoGreen dsDNA Assay (Invitrogen), and all necessary quality control will be performed when required with the Bioanalyzer 2100 (Agilent), using DNA 7500 chips. DNA will then be used in SNP Genotyping. This methodology is one of the most cost-effective and error-free technologies for high throughput SNP typing. The system relies on MALDI-TOF (Matrix Assisted Laser Desorption/Ionization-Time-Of-Flight mass spectrometry). Mass spectrometry is used to identify alleles on the basis of mass, hence it is more reliable than other genotyping approaches. Briefly, the technology involves PCR amplification of the region containing the SNP of interest, an optimized primer extension reaction to generate allele-specific DNA products, and chip-based mass spectrometry for separation and analysis of the DNA analytes. A single post-PCR primer extension reaction generates diagnostic products that, based on their unique mass values, allow discrimination between two alleles.

Tumor blocks and slides will be analyzed by Tumor Infiltrating Lymphocyte (TIL) evaluation at Brigham & Women's Hospital Pathology according to the recommended standardized approach from the international TIL-working group (Salgado R, 2014). In brief it will consist of selecting an area of tumor and evaluating the stroma within the tumor borders for the presence of a mononuclear stromal TIL infiltrate (lymphocytes and plasma cells). Neutrophils and necrotic areas will not be scored. The percentage of stromal TILs will be estimated (between 0%-100%) for each case and recorded.

Tumor blocks and slides will also be evaluated for PDL1 immunohistochemistry at Brigham & Women's Hospital Pathology. Four-µm thick paraffin-embedded sections will be pre-baked at 60°C for 1 hour and subsequently dewaxed and rehydrated followed by heat-induced antigen retrieval. PD-L1 immunostaining will be performed (incubation period two hours) followed by Dako HRP Envision secondary antibodies (incubation period 30 minutes) and then slides will be developed using a 3,3'diaminobenzidine (DAB) chromogen (Dako) (5 minutes), counterstained with hematoxylin, dehydrated and cover-slipped following standard protocols. Staining will be evaluated by H-score (percentage and intensity of cells staining).

See section 10.2 for collection and shipment details.

9.3 GWAS for prediction of trastuzumab emtansine induced thrombocytopenia

DNA from the patients of this trial will be genotyped for SNPs and CNV markers using the Infinium Human Omni1 array (1.2 million SNP platform) from Illumina. This work will be performed in Dr. Brian Schneider's lab. The genotype calls will then undergo quality control (QC) assessment and be statistically correlated with the likelihood of thrombocytopenia in order to discover novel genetic variants that are predictive biomarkers for trastuzumab emtansine in breast cancer. Any provocative leads can be further validated in an independent trial using a selected candidate approach.

9.4 Specimen Banking

Any leftover study blood and tissue samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. Any samples will only be released for use in future studies after approval by the Principal Investigator and other regulatory bodies, as appropriate.

The study PI and collaborators have approval by the TBCRC to use all research bio-specimens collected during the conduct of this trial to address the research questions described in the protocol document. All future use of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the TBCRC according to its established policies, whether the specimens are stored in a central site or at a local institution in a virtual repository.

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

10 STUDY CALENDAR

10.1 Study Tests and Procedures

Table 5 describes the tests and procedures that are required for patients randomized to Arm1: Trastuzumab emtansine (T-DM1) and Table 6 describes the tests and procedures that are required for patients randomized to Arm 2: Paclitaxel and Trastuzumab. Tables 5 and 6 contain the same required screening/baseline tests and procedures so either can be referenced prior to randomization.

Table 5. Study calendar for patients randomized to Arm 1: Trastuzumab Emtansine

		TREATMENT			FOLLOW-UP		
Tests and procedures	**≤14 days prior to registration**	**During the first 12 weeks of T-DM1[6]**	**During weeks 13- 51 of T-DM1[6]**	**At 12 weeks, 6 months, 9 months and at 1 yr, or end of treatment[4]**	**Q6 months (+/-8 weeks) x 2 yrs and at progression[7]**	**Q12 months (+/-3 months) yrs 4, 5, 6 or until progression[8]**	**Yearly (+/- 3 months)**
History + exam, ECOG PS (ECOG at baseline only)	≤28 days prior to registration	Every 3 weeks	Every 9 weeks (+/- 3 weeks)		X	X	
Vital signs, weight, height (height at baseline only)	X	Every 3 weeks	Every 3 weeks		X	X	
Hematology (CBC with diff)	X	Every 3 weeks	Every 3 weeks				
Chemistry[1]	X	Every 3 weeks	Every 3 weeks				
Hepatitis B surface Antibody, Hepatitis B surface Ag, and Hepatitis C Antibody[2]	X						
EKG[2]	X						
Mammogram or breast US	X[3]						X[9]
MUGA or echocardiogram[4]	X			X[4]			
Pregnancy test[5]	X						
Clinically-relevant toxicity assessment		Every 3 weeks	Every 3 weeks		X		
Research Specimens (see section 10.2)		X (C1D1)	X (6 mos, 12 mos)		X (18 mos, 24 mos, progression)		
Quality of Life Assessments (see section 10.3)		X (C1D1, 3weeks, 12 weeks)	X (6 mos, 12 mos)		X		

[1] Sodium, potassium, chloride, bicarbonate, BUN, creatinine, total protein, albumin, total bilirubin, SGOT(AST), SGPT(ALT), Alkaline Phosphatase. Pts with positive Hepatitis B or C serologies should have an ALT, AST, total bilirubin, alkaline phosphatase, INR and aPTT, sample collected on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period. INR and PTT testing is not required for any other patients.

[2] Should be performed within 12 weeks of beginning study treatment.

[3] Mammograms obtained as part of the initial diagnosis, biopsy, and surgery will suffice (do not need to be repeated).

[4] MUGA or ECHO should be performed at baseline, 12 wks (+/- 3 wks), 6 months (+/- 3 wks), 9 months (+/- 3 wks), and 12 months (+/-4 wks). ECHO is the preferred method. Use the same method for each evaluation at the same facility where the baseline was done if possible. Baseline eval. must be within 12 weeks of beginning study treatment. Cardiac evaluation should still occur at these time points even if there has been a treatment delay. If a pt comes off study treatment early due to cardiac toxicity, cardiac imaging should be performed within 30 days of coming off study treatment. Asymptomatic decreases in LVEF will be managed according to the algorithm in Section 7.2.1e, Table 3. Follow-up at 3, 6, 9, and 12 months with MUGA or ECHO from the time of decrease in EF is required in patients who come off study treatment.

[5] For women of childbearing potential only. Serum or urine test. Must be done within 14 days of registration.

[6] May be performed up to 3 days prior to receiving each dose of T-DM1.

[7] Beginning 6 months after the final treatment, observation visits are required every 6 months for 2 yrs (+/- 8 weeks). (i.e., pts who complete 51 weeks of treatment: observation visits occur at 18, 24, 30, and 36 months; pts who do not complete treatment: observation visits occur q6 months for 2 yrs from the time of the final treatment). Visits may occur at the participating site or at the pt's local oncologist.
[8] Following 2 yrs of follow-up, annual visits are required for up to 3 yrs (+/- 3 months). Follow-up period is for a total of 5 yrs. (i.e., patients who complete 51 weeks of treatment: observation visits occur at 48, 60 and 72 months). Visits may occur at the participating site or at the patient's local oncologist.
[9] Mammograms should be performed at least annually in pts with any residual breast tissue. If a pt had bilateral mastectomies, no follow-up breast imaging is required.

Table 6: Study calendar for patients randomized to Arm 2: Paclitaxel and Trastuzumab

		TREATMENT			FOLLOW-UP		
Tests and procedures	**≤14 days prior to registration**	**During Paclitaxel and Trastuzumab combination therapy[7]**	**During trastuzumab monotherapy[7]**	**At 12 weeks, 6 months, 9 months and at 1 yr, or end of treatment[4]**	**Q6 months (+/-8 weeks) x 2 yrs and at progression[8]**	**Q12 months (+/-3 months) yrs 4, 5, 6 or until progression[9]**	**Yearly (+/- 3 months)**
History + exam, ECOG PS (ECOG at baseline only)	≤28 days prior to registration	Every 3 weeks	Every 9 weeks (+/- 3 weeks)		X	X	
Vital signs, weight, height (height at baseline only)	X	Weekly	Every 3 weeks		X	X	
Hematology (CBC with diff)	X	Weekly	Every 3 weeks				
Chemistry[1]	X	Every 3 weeks	Every 3 weeks				
Hepatitis B surface Antibody, Hepatitis B surface Ag, and Hepatitis C Antibody[2]	X						
EKG[2]	X						
Mammogram or breast US	X[3]						X[10]
MUGA or echocardiogram[4]	X			X[4]			
Pregnancy test[5]	X						
Clinically-relevant toxicity assessment[6]		Every 3 weeks	Every 3 weeks		X (+/- 3 weeks)		
Research Specimens (see section 10.2)		X (C1D1)	X (6 mos, 12 mos)		X (18 mos, 24 mos, progression)		
Quality of Life Assessments (see section 10.3)		X (C1D1, 3weeks, 12 weeks)	X (6 mos, 12 mos)		X		

[1] Sodium, potassium, chloride, bicarbonate, BUN, creatinine, total protein, albumin, total bilirubin, SGOT(AST), SGPT(ALT), Alkaline Phosphatase. Pts with positive Hepatitis B or C serologies should have an ALT, AST, total bilirubin, alkaline phosphatase, INR and aPTT, sample collected on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period. INR and aPTT testing is not required for any other patients.
[2] Should be performed within 12 weeks of beginning study treatment.
[3] Mammograms obtained as part of the initial diagnosis, biopsy, and surgery will suffice (do not need to be repeated).
[4] MUGA or ECHO should be performed at baseline, 12 wks (+/- 3 wks), 6 months (+/- 3 wks), 9 months (+/- 3 wks), and 12 months (+/- 4 wks). ECHO is the preferred method. Use the same method for each evaluation at the same facility where the baseline was done if possible. Baseline eval. must be within 12 weeks of beginning study treatment. Cardiac evaluation should still occur at these time points even if there has been a treatment delay. If a pt comes off study treatment early due to cardiac toxicity, cardiac imaging should be performed within 30 days of coming off study treatment. Asymptomatic decreases in LVEF will be managed according to the algorithm in Section 7.2.2.2c, Table 4. Follow-up at 3, 6, 9, and 12 months with MUGA or ECHO from the time of decrease in EF is required in patients who come off study treatment.
[5] For women of childbearing potential only. Serum or urine test. Must be done within 14 days of registration.
[6] AE assessments must be conducted by phone for pts not being seen at a participating site for the required q3 week AE assessments during Trastuzumab monotherapy phase.
[7] May be performed up to 3 days prior to receiving concurrent Paclitaxel/Trastuzumab or Trastuzumab monotherapy.

[8] Beginning 6 months after the final treatment, observation visits are required every 6 months for 2 yrs (+/- 8 weeks). (i.e., pts who complete 51 weeks of treatment: observation visits occur at 18, 24, 30, and 36 months; pts who do not complete treatment: observation visits occur q6 months for 2 yrs from the time of the final treatment). Visits may occur at the participating site or at the pt's local oncologist.

[9] Following 2 yrs of follow-up, annual visits are required for up to 3 yrs (+/- 3 months). Follow-up period is for a total of 5 yrs. (i.e., pts who complete 51 weeks of treatment: observation visits occur at 48, 60 and 72 months). Visits may occur at the participating site or at the pt's local oncologist.

[10] Mammograms should be performed at least annually (+/- 3 months) in pts with any residual breast tissue. If a pt had bilateral mastectomies, no follow-up breast imaging is required.

10.2 Specimen Submission Requirements

The following specimens are to be submitted to the indicated lab. Refer to the separate 13-048 Study Manual for additional processing and shipping instructions.

Table 7. Required Specimen Submissions

Specimen Type	Collection Time Point				Shipping Condition	Ship to
	Pre-study (Surgery)	Baseline[1] (Pre-treatment)	At 6, 12, 18, and 24[2] months, or end of treatment[3]	Progression		
5-8 Unstained slides (or 1 block) for central HER2 testing	X				Ambient temperature	Clarient Laboratories
Paraffin block (or 15 unstained slides)	X				Ambient temperature	ATEMPT study team
1 H&E stained slide	X				Ambient temperature	ATEMPT study team
10mL whole blood in Purple top tube		X			Ambient temperature	DFCI Laboratory
10mL whole blood in Red top tube		X	X (+/- 3 weeks)	X (+/- 3 weeks)	Ambient temperature	DFCI Laboratory

[1] Baseline samples should be drawn after the patient is randomized but prior to treatment start.
[2] If 18 and 24 month follow-up visits occur at local oncologist site, pt may opt out of research blood draws. Opt out must be documented in the pt's research chart.
[3] All pts coming off treatment will have research blood draws collected at the end of treatment, again at 6 months after the final treatment, and finally at 12 months after the final treatment (note: "after the final treatment" refers to the final day of treatment, not the time the decision was made to take the pt off treatment).

10.2.1 HER2 Confirmation testing

To confirm HER2 status for eligibility, submit:

- 5-8 unstained slides (4-5µm thick)

Slides are to be sent ambient temperature in a conventional slide shipper with Clarient patient ID on a printed label on the slide. Ship the slides along with documentation of the Clarient patient ID, Clarient site ID, and site contact to:

Clarient Laboratories
Attn: BioPharma Services (Jorge Gottheil)
31 Columbia
Aliso Viejo, CA 92656

Note: Patients previously having had HER2 testing at Clarient Laboratories do not need to undergo retesting for central confirmation of HER2 status. A pathology report documenting testing at Clarient should be provided at time of patient registration.

Contact the Coordinating Center at DFCI to obtain Clarient site ID and patient IDs.

10.2.2 Tumor Tissue from Surgical Resection

The following specimens are required for gene profiling:

- 1 paraffin block (or 15 unstained slides)
- 1 H&E slide

If there is insufficient tumor sample from the surgery submit 2 cores of invasive tissue using a 1.2 mm diameter coring tool. Label the block and slide with the DFCI Participant ID, site MRN, subject initials, site of collection, date of collection, and protocol number. Complete the Specimen Requisition form (found in the separate translational research specimen and tumor tissue procedures and shipping manual) and ship to:

Dana-Farber Cancer Institute
Breast Oncology
Attn: ATEMPT team
450 Brookline Avenue
Dana 157
Boston, MA 02215

The DFCI will take a core sample of the block and then return the block to the site. Any unused specimen may be stored for future use at DFCI. Confirmation of request of block or slides must be provided at the time of registration.

10.2.3 Translational Research Blood

Collect the following specimens after registration but prior to the start of protocol treatment:

- 10ml of whole blood in a red top tube (Fischer # 367820)
- 10ml of whole blood in a purple top tube

Collect the following specimen every 6 months for 2 years (from the start of treatment) and at progression:

- 10ml of whole blood in a red top tube (Fischer # 367820)

Label specimens with the assigned DFCI Participant ID, date of collection, time point of collection, and protocol number. Complete the requisition form found in separate study manual include in the shipment. Ship specimens overnight Monday-Thursday only by either FedEx or UPS to:

Dana-Farber Cancer Institute
DFCI Breast Bank
450 Brookline Ave.
Smith Building SM 956
Boston, MA 02215

Ph: 617-582-8189

Any unused specimen may be stored for future use at DFCI.

10.3 Quality of Life Assessments

The following Quality of Life (QOL) assessments are required for English speaking patients. The QOL assessments should be completed via the tablet provided by the study or on any available computer with an internet connection. If the participant cannot complete the assessments electronically, paper versions are available in Appendices 1-7. The site study team is responsible for submitting the paper completed assessments using the electronic forms and retaining the original paper forms as source documentation. Refer to the study manual for full instructions and the 13-048 QOL Assessment Guidelines and Completion Record (for optional use). The assessments are located at:

https://live.datstat.com/DFCI_PS-Collector/Survey.ashx?Name=Tolaney_Series

Password is: ***atempt***

Table 8. Required Quality of Life Assessments

Assessment	DURING TREATMENT					DURING FOLLOW-UP[3]			
	Baseline (C1 D1)[2]	**3 Weeks** (+/- 1 week)	**12 Weeks** (+/- 1 week)	**6 Months** (+/- 4 weeks)	**12 Months** (+/- 8 weeks)	**18 Months** (+/- 8 weeks)	**24 Months** (+/- 8 weeks)	**30 Months** (+/- 8 weeks)	**36 Months** (+/- 8 weeks)
Baseline Assessment of Menses[1]	X								
Follow-up Menses Assessment[1]				X	X	X	X	X	X
Alopecia Patient Assessment	X	X	X	X	X	X			
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)	X	X	X	X	X	X			
FACT B	X	X	X	X	X	X	X		X
PNQ	X	X	X	X	X	X	X		X
Rotterdam Symptom Checklist	X	X	X	X	X	X	X		X

[1] Baseline Assessment of Menses is to be filled out by all pts at baseline; pts deemed premenopausal at the time of study registration (i.e. having at least one menstrual period in 12 months prior to registration) need to complete Follow-up Menses Assessment.
[2] Baseline assessments should be filled out after registration but prior to initiation of chemotherapy.

[3] Beginning 6 months after the final treatment, questionnaires are completed q6 months for 2 yrs (+/- 8 weeks). (i.e., pts who complete 51 weeks of treatment: questionnaires are completed at 18, 24, 30, and 36 months; pts who do not complete treatment: questionnaires are completed q6 months for 2 yrs from the time of the final treatment). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point. Upon collection, the study team will submit the paper completed assessments using the electronic forms and retaining the original paper forms as source documentation.

11 MEASUREMENT OF EFFECT

11.1 Clinically-relevant toxicity

Clinically-relevant toxicity will include the occurrence of the following toxicities, as assessed at the pre-specified toxicity-assessment visits (Section 7: the every 3 weeks while receiving study treatment for the 51 week period) to ascertain consistency of reporting between the 2 treatment groups:

- grade 3 or higher non-hematologic toxicity,
- grade 2 or higher neurotoxicity, and
- grade 4 or higher hematologic toxicity.

In addition, the following events that occur at any time will also be considered as clinically-relevant toxicity:

- febrile neutropenia,
- any toxicity requiring dose delay
- any toxicity that requires discontinuation of any study treatment (paclitaxel, trastuumab, or T-DM1)
- any serious adverse event (SAE).

11.2 Disease-free survival event

Disease-free survival (DFS) will be defined from the time of randomization until the to the occurrence of the first of the following events:

- Local/regional recurrence: a recurrent or new invasive ipsilateral breast cancer, invasive breast cancer in the axilla, regional lymph nodes, chest wall, or skin of the ipsilateral breast.
- Contralateral invasive breast cancer,
- Distant recurrence: metastatic disease that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer. A single new lesion on a bone scan without evidence of lytic disease on x-ray and without symptoms does not in and of itself constitute distant recurrence, but multiple new bone lesions, or increased isotope uptake associated with new bone symptoms are more likely due to metastases. Bone metastases must be documented with x-rays and clinical description.
- Death from any cause

In situ cancer is not included as DFS event. If a patient has in situ breast cancer (on the ipsilateral or contralateral side) diagnosed during follow-up before any of the DFS events above, then the patient should continue to be followed for DFS on study (even if she is given hormonal therapy after the in situ diagnosis).

If a patient is diagnosed with a cancer of another site (i.e., other than a new breast cancer, a breast cancer recurrence, or breast cancer metastases) that is NOT a non-melanoma skin cancer or a vaginal carcinoma in situ, then the patient will be censored in the analysis for disease recurrence. They will remain on study and will be followed for survival.
If a patient is diagnosed with a non-melanoma skin cancer or any in situ carcinoma, she will continue on this study and continue to be followed for DFS.

12 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Definitions

12.1.1 Adverse Event (AE)

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

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests or require a dose modification. AEs will only be reported at the AE reporting visits (i.e. every 3 weeks for the first 12 weeks, then every 9 weeks for the subsequent 39 weeks).

12.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

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

12.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

12.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

12.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

12.1.4 Attribution

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

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

12.1.5 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means will be recorded in the participant's medical record. The following adverse events will be reported on the appropriate study specific case report forms:

- Toxicities that meet clinically significant criteria per section 11.1 (primary endpoint toxicities)
- Toxicities defined by Genentech as toxicities of special interest per section 12.6
- Any other toxicity grade 2 or higher (except for abnormal labs that do not meet reporting criteria defined in section 11.1 or 12.1.1)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.2 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

12.3 Reporting to the Study Sponsor

Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 12.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator and study team within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Dr. Sara Tolaney
Dana-Farber Cancer Institute
450 Brookline Ave.,
Floor 12, Room 1257
Boston, MA 02215
Tele: 617-632-2335
Fax: 617-632-1930
Email: DFCIBOCATEMPT@partners.org.

Within the following 24-48 business hours, the participating investigator must provide follow-up information on the serious adverse event if a full description of events was not included with the initial reporting of the event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation. This information should be submitted to Dr. Tolaney and the DFCI study team via email at: DFCIBOCATEMPT@partners.org.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

12.4 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Dr. Sara Tolaney
Dana-Farber Cancer Institute
450 Brookline Ave.,
Floor 12, Room 1257
Boston, MA 02215
Tele: 617-632-6876
Fax: 617-632-1930
Email: DFCIBOCATEMPT@partners.org

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

12.5 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

12.6 Reporting to Genentech, Inc.

Pregnancy
If a female subject becomes pregnant while receiving investigational therapy (trastuzumab emtansine) or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to trastuzumab emtansine should be reported as an SAE.

Post-Study Adverse Events
The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior trastuzumab emtansine exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a

subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

AEs of Special Interest (AESIs) for Trastuzumab Emtansine
AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of trastuzumab emtansine.

The trastuzumab emtansine Events of Special Interest are:

- LVEF < 40% or symptomatic CHF
- Grade ≥ 3 left ventricular systolic dysfunction
- Grade ≥ 3 AST, ALT or total bilirubin elevations
- Grade ≥ 3 thrombocytopenia
- Cardiac events
- Hepatic events
- Drug-Induced Liver Injury (non-serious and serious)
- Infusion Associated Reactions, Hypersensitivity
- Embryofetal Toxicity or Birth Defects

SAE Reporting
Investigators must report all SAEs deemed reasonably related to treatment with trastuzumab emtansine and AESIs for trastuzumab emtansine to Genentech within the timelines described below. The completed Medwatch form should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to trastuzumab emtansine and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to trastuzumab emtansine will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the trastuzumab emtansine will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Additional Reporting Requirements for IND Holders
For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

Calendar Day Telephone or Fax Report:
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of trastuzumab emtansine. An unexpected adverse event is one that is not already described in the trastuzumab emtansine Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

Calendar Day Written Report
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of trastuzumab emtansine. An unexpected adverse event is one that is not already described in the trastuzumab emtansine investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable.

FDA fax number for IND Safety Reports:

Fax: 301-796-9845

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-5288

IND Annual Reports
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

12.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

12.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

13 DATA AND SAFETY MONITORING

13.1 Data Reporting

13.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

13.1.2 Data Submission

The schedule for completion and submission of case report forms to the QACT is as follows:

Form	Submission Timeline

Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

13.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this trial. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed with the Principal Investigator, statistician and study team members. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet twice a year to review accrual, toxicity, primary endpoints, and reporting information. Information to be provided to the DSMB may include: participant accrual, treatment regimen information, adverse events and serious adverse events reported by category, summary of any deaths on study, audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

With regard to primary endpoints, the incidence of clinically-relevant toxicities and the number of DFS events will be summarized by treatment assignment; at specified times defined by person-years of follow-up, the number and rate of DFS events in the trastuzumab emtansine group will be summarized (Section 15.2.2).

13.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were

conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements.

14 REGULATORY CONSIDERATIONS.

14.1 Protocol Review and Amendments

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

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

14.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

14.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

14.4 Study Documentation

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

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

14.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the DF/HCC Overall Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix 9).

- The DF/HCC Overall Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

15 STATISTICAL CONSIDERATIONS

15.1 Study Design/ Objectives

This is a randomized phase II study of women and men with stage I HER2-positive invasive breast cancer where patients receive trastuzumab emtansine (T-DM1; q3weeks x 17) or paclitaxel + trastuzumab (TH; weekly x 12 then trastuzumab q3 weeks x 13) for a total of 51 weeks of treatment. All patients will be randomized in a 3:1 ratio stratified by age (<55yr / ≥55yr) and planned use of radiation therapy (yes / no), and planned use of hormonal therapy (y/n).

The two primary objectives of this trial are

1. To compare incidence of clinically-relevant toxicity between the two arms; and
2. To evaluate disease-free survival in patients treated with T-DM1.

Each objective will be testing using a 5% Type I error.

15.2 Endpoints

The endpoint for primary objective 1 (safety) is clinically-relevant toxicity (defined in section 11.1). Briefly, the composite endpoint is the occurrence of any of the following: grade 3 or higher non-hematologic toxicity; grade 2 or higher neurotoxicity; grade 4 or higher hematologic toxicity; febrile neutropenia; any toxicity requiring dose delay; discontinuation of any study treatment (Paclitaxel, Trastuzumab, or T-DM1) for toxicity, and any serious adverse event (SAE).
The endpoint for primary objective 2 (efficacy) is disease-free survival (DFS, defined in section 11.2). Briefly, it is defined as the time from randomization to first DFS event; surviving patients who are disease free will be censored at: the date of last disease assessment, diagnosis of a cancer at another site, or withdrawal of consent to be followed, whichever occurs first.

Secondary endpoints include overall survival (OS); quality-of-life instruments and patient reported outcomes: FACT B, Rotterdam symptom checklist, PNQ, WPAI-SHP, and an alopecia questionnaire; and all grade 3 and 4 adverse events, grade 3-4 cardiac left ventricular dysfunction, grade 2-4 thrombocytopenia, and amenorrhea in patients premenopausal at the time of study entry.

15.3 Sample Size / Accrual Rate

15.4 The target accrual is 500 patients (375 to T-DM1 and 125 to TH). Accrual is estimated to reach a maximum of 16 patients per month, though we expect that it will take 12 months to reach this accrual rate from the time of first patient enrollment. For planning purposes and the anticipated timeline for interim monitoring of efficacy, we assume a linear increase

from 0 to 16 patients in the first 12 months. This would result in approximately 3 years of patient accession. Once target accrual is met, there will be an additional follow-up period of 3 years before the final analysis, so that the anticipated total length of this trial is 6 years.Power Considerations

The determinations of sample size and power are based on the co-primary endpoints of clinically-relevant toxicity (comparing the two arms) and DFS (for the T-DM1 arm only). For the comparison of clinically-relevant toxicities between T-DM1 and TH arms, we assume an incidence of 31.3% in the control arm based on preliminary safety information to an ongoing study of TH in this patient population (Tolaney, personal communication). A 40% reduction in the rate of clinically-relevant toxicity would be considered clinically meaningful. With 125 and 375 patients randomized to the TH and T-DM1 arms, respectively, there is 81% power to detect this level of decrease in the T-DM1 arm to a rate of 18.8% (Fisher's exact test, two-sided Type I error of 0.05).

For the evaluation of DFS in patients treated on the T-DM1 arm, we assume that a 3-year DFS $\geq$ 95% would be will be considered worthy of further study of the regimen in this patient population, based on the imputed 3-year DFS rates on the trastuzumab+chemotherapy arms of BCIRG[6]. Conversely, a 3-year DFS $\leq$ 91% would be an unacceptable level of efficacy in this patient population. Thus, our study is designed to have a high probability (0.95) of declaring T-DM1to be effective with a true 3-yr DFS of 95%, while controlling the probability of falsely declaring T-DM1 effective with a true 3-yr DFS of 91% or worse to be less than 0.05 (i.e. one-sided Type I error). The sequential monitoring and analysis plan (see section 15.5) uses a Poisson model for DFS events, and operating characteristics are calculated under assumption of a constant hazard rate and no loss-to-follow-up.

15.5 Interim Monitoring

Monitoring of safety and efficacy will be conducted on a semiannual basis by a Data and Safety Monitoring Board (DSMB), and the exact timing of interim analyses will be determined by the meeting schedule of the DSMB.

The DSMB will evaluate safety from the start of patient enrollment through the entire follow-up period of the study. All adverse events will be reported to the DSMB in terms of the maximum grade observed in each patient for each type of toxicity. The incidence of clinically-relevant toxicities will be summarized in terms of the components of the composite endpoint. No formal stopping rules will be given to the DSMB, but in each report an odds ratio and 95% confidence interval will estimated, and provided with a two-sided p-value from a Fisher's exact test. In addition, observation of any of the following events will trigger the DSMB to make a decision whether the trial should be closed to further treatment and enrollment of patients:

- Any confirmed Hy's law cases
- $\geq$ 3% absolute difference in deaths (from any cause) between arms
- $\geq$ 10% absolute difference in grade 3+ ALT/AST elevation
- $\geq$ 3% absolute difference in grade 3+ cardiac toxicity, including the occurrence of "heart failure" OR Left Ventricular Systolic Dysfunction (LVSD) as defined by CTCAE v. 4.0.

The study will include sequential monitoring of DFS within the T-DM1 arm using a Poisson model for the failure rate. Stopping rules are specified below under conditions that that the failure rate is unacceptably high. No early-stopping is planned for low failure rates on T-DM1, because there would be insufficient clinical information to conclude the regimen is worthy of further investigation.

Monitoring of efficacy is scheduled to begin once there are at least 186 patient-years of follow-up (approximately 12% of information in the Poisson model), so if our assumption of accrual rate is correct, the first interim analysis will occur while still enrolling patients to the study (24 months after first patient enrollment; 234 assigned to T-DM1). Subsequently, the DSMB would review efficacy on an annual basis until the final analysis scheduled to occur 36 months after target accrual is met. Stopping rules to the Poisson model are calculated using Pocock-style error spending functions that limit the probability of stopping and concluding lack of efficacy to less than 5% when the true 3-year DFS is 95%. Actual stopping bounds will be computed at each reporting period using the exact number of patient-years of follow-up. For illustration purposes, stopping bounds are tabulated below under the anticipated accrual rate and study calendar; the Pocock nominal alpha threshold for these decision criteria is 0.021.

Interim	Months from first enrollment	Patient-years of follow-up	Number of DFS events
1	24 (N = 234)	186	≥ 8
2	36 (N = 375)	486	≥ 16
3	48 (N = 375)	861	≥ 24
4	60 (N = 375)	1236	≥ 32
FINAL	72 (N = 375)	1600	≤ 39

The following table provides the operating characteristics of sequential monitoring under a Poisson distribution for different target and unacceptable rates of 3-year DFS. This demonstrates the large chance (0.95) of declaring the regimen worthy of further research if the true 3-year DFS is as high as 95%, and the small chance (<0.05) of falsely declaring the regimen worthy of further research if the true 3-year DFS is as low as 91%. Further, the probability of stopping during enrollment (interim 1 or 2), is 0.50 with the unacceptable 3-year DFS of 91%, and increases to 0.89 if the true 3-year DFS were as low as 88%.

		Prob. study will be stopped early and T-DM1 declared ineffective				Prob. T-DM1 declared effective
3-year DFS %	**True DFS event rate**	**1st Interim**	**2nd Interim**	**3rd Interim**	**4th Interim**	**Final analysis**
95%	0.0171	0.016	0.024	0.035	0.043	0.951
91%	0.0314	0.24	0.50	0.78	0.91	0.039
88%	0.0426	0.54	0.89	0.99	1.00	0.000

15.6 Data Analysis and Primary Objectives

For this phase II trial, the analysis population for both safety and efficacy is a modified intention-to-treat population of all patients who initiate therapy after randomization. All participants who receive

at least one dose of protocol therapy will be evaluable for toxicity from the time of their first treatment.

An interim analysis will be performed for the comparison of clinically-relevant toxicity (CRT) when two-thirds of participants have completed therapy. The following statistics will be reported to the DSMB as a descriptive summary of CRTs across the two arms :

- Point estimates and 95% confidence intervals for the absolute difference (using the Binomial distribution) and relative difference (using odds ratios and the logistic regression model) between the T-DM1 and TH arms
- Conditional power, using the definition from Jennison and Turnbull (2000), of rejecting the null hypothesis under the following assumptions for the unobserved patients:
    - The null hypothesis is true (OR = 1.0)
    - The targeted alternative hypothesis is true (OR = 0.508)
- Predictive power, using the definition from Jennison and Turnbull (2000),
- Prediction interval plots, using the methods of Li, Evans, Wei, to display the potential effect sizes and corresponding confidence intervals with trial continuation to completion.

The final analysis for the comparison of clinically-relevant toxicity between the TH and T-DM1 arms will be based on a Fisher's exact test using an unadjusted two-sided α=0.05.

The primary analysis of DFS in patients treated with T-DM1 will occur once (a) there are 36-months of additional follow-up after reaching target accrual, and (b) a minimum of 1600 patient-years of follow-up are collected. If 40 or more DFS events are observed, or if the study is stopped at an interim analysis, T-DM1 will be declared not worthy of further study in this patient population. If less than 40 events are observed at the final analysis then T-DM1 will be declared worthy of further study.

Secondarily, the distribution of the survival function and cumulative hazard for DFS will be summarized using the Kaplan Meier product limit estimator and 95% confidence interval (CI) for each treatment arm. No comparison of treatment arms will be made.

15.7 Statistical Considerations for Secondary Objectives

15.7.1 Compare the incidence of all grade 3 and higher AEs, and specifically of grade 3 and higher cardiac left ventricular dysfunction and of grade 2 and higher thrombocytopenia in patients receiving trastuzumab emtansine compared to those receiving TH.

Per patient, each toxicity will be summarized over follow-up as maximum recorded grade of the toxicity. Incidence overall and by grade will be summarized according to treatment group. Ever-occurrence of grade 3-5 AE and incidence of specific AEs will be compared between treatment groups using Fisher's exact test (two-sided test). For the trastuzumab emtansine arm, with 375 patients the maximum half-width of an exact binomial 95% CI would be approximately ±0.05. The detectable difference in incidence will be an absolute difference in the range of about 0.09 to 0.15 (e.g., 0.05 vs. 0.14 or 0.3 vs. 0.45 with trastuzumab emtansine

vs. TH).

15.7.2 Compare quality of life (QOL) in patients receiving trastuzumab emtansine to that experienced by patients receiving TH using FACT B. Evaluate symptoms related to therapy in patients receiving trastuzumab emtansine compared to those receiving TH using the Rotterdam symptom checklist (RSCL) and Patient Neurotoxicity questionnaire (PNQ).

FACT B, RSCL and PNQ will be administered to all trial patients prior to, during and after treatment (See Study Calendar). Scores will be analyzed using an appropriate longitudinal modeling approach (e.g., mixed-effects linear modeling assuming normality of scores) to compare patterns over time between treatment groups. For comparing scores between the treatment groups, at any one time point there is 82% power to detect a standardized effect size of 0.30 (two-sample t-test, two-sided α=0.05, n=375:125).

15.7.3 Evaluate effects of therapy on work productivity and activity using the Work Productivity and Activity Impairment Questionnaire (WPAI-SHP) in patients receiving trastuzumab emtansine compared to those receiving TH.

WPAI-SHP will be administered to all trial patients at multiple time points during the trial (See Study Calendar). Data collected using the WPAI-SHP will be summarized descriptively over time according to treatment group.

15.7.4 Evaluate the effects of alopecia on patients receiving TH using an alopecia questionnaire.

The Alopecia Patient Assessment will be administered to patients randomized to receive TH at multiple time points during the trial (See Study Calendar). Data will be summarized descriptively over time.

15.7.5 Describe DFS in patient groups defined by tumor size ($\leq$ 1 cm or > 1 cm) and hormone receptor status who are treated with trastuzumab emtansine.

The distribution of DFS and 3-year DFS (with 95%CI) will be summarized using the Kaplan-Meier method among trastuzumab emtansine patients in subgroups defined by tumor size ($\leq$1cm vs. >1cm) and by hormone receptor status (positive vs. negative).

If trastuzumab emtansine is deemed to be worthy of further research, then there will be at most 40 DFS events at the time of final analysis, and if the hypothesis of a true 5% 3-year DFS event percentage is correct, then it is expected that there will be approximately 26 DFS events, or about 6.9% of the 375 patients at about 5.5 years after the study opens. With 6.9% events of 375 patients, there is 80% power (two-sided α=0.05) to detect only very large differences between subgroups, for example, HR of 3.0 if prevalence of a characteristic is 50% of patients, about HR~3.25 if prevalence of a characteristic is 33% and HR~3.6 if prevalence is 25%. Therefore these subgroup analyses will focus on estimates and CIs rather than testing.

15.7.6 Evaluate gene biomarkers predictive trastuzumab emtansine-induced grade 2 and higher thrombocytopenia

DNA will be genotyped for SNPs and CNV markers using the Infinium Human Omni1 array (1.2 million SNP platform) from Illumina. After quality control assessment of genotype calls, the association of genotypes and time to first onset of grade 2 or higher thrombocytopenia among patients treated with trastuzumab emtansine will be assessed using logrank tests with adjustment for multiple comparisons. Assuming that about 7% of 375 patients experience trastuzumab emtansine-induced thrombocytopenia, there is 80% power (nominal two-sided α=0.05) to detect only very large differences between genotype groups [assumed dichotomous], for example, HR of 3.0 if prevalence of a characteristic is 50% of patients, about HR~3.25 if prevalence of a characteristic is 33% and HR~3.6 if prevalence is 25%.

15.7.7 Evaluate Oncomap in archival tumor tissue

Archival tumor tissue from all patients will be assessed using a high-throughput mutation profiling system (Oncomap) to query a large panel of cancer gene mutations. Prevalence and exact binomial 95% CI will be summarized for each mutation.
For estimating prevalence among 500 trial patients, the half-width of an asymptotic 95% CI would be ±0.035, ±0.026 and ±0.019 when prevalence is 20%, 10% and 5% respectively.

15.7.8 Investigate the percentage of patients with amenorrhea at various times after start of treatment in premenopausal women receiving treatment with trastuzumab emtansine and paclitaxel-trastuzumab for early stage breast cancer.

Each woman who enrolls will be asked to fill out a questionnaire regarding her baseline menstrual status at the time of initial study registration (Baseline Assessment of Menses, Appendix 6). Any woman who reports at least one menstrual period over the 12 months prior to filling out that form will be followed prospectively and queried regarding their menstrual frequency and last menstrual period every 6 months thereafter (Follow-Up Menses Assessment, Appendix 7) until the month 36 of the trial. Those who reported no periods over the prior 12 months on the Baseline Assessment will not need to fill out the Follow-Up Assessments.

The primary objective will be to estimate the proportion of pre-chemotherapy premenopausal women who have menstruated at least once in the time period between 6 and 12 months after randomization in the trastuzumab emtansine group. The secondary objectives will be to estimate the proportions of women who have menstruated at least once in the 6 months prior to each of the other post-chemotherapy timepoints in the trastuzumab emtansine and TH groups (through 36 months). Women who are actively receiving ovarian suppression at any given timepoint will be excluded from these analyses at that time.

Assuming that 25% of enrolled patients are premenopausal and that approximately 70% of premenopausal patients do not receive ovarian suppression, we estimate that 88 premenopausal patients (66/375 on trastuzumab emtansine and 22/125 on TH) will be enrolled and assessable for amenorrhea at 1 year after start of therapy and subsequent timepoints. With 88 patients, then the largest half-width of the exact binomial 95% CI for the proportion still menstruating at 1 year will be approx ± 0.11 (and ±0.13 and 0.22 in the trastuzumab emtansine and TH treatment groups respectively).

The percent of patients still menstruating over time will be summarized overall and by treatment group as proportion and exact binomial 95% CI. For the trastuzumab emtansine group this will also be summarized, as feasible, in exploratory analysis by age group (<40y vs ≥40y), BMI (<30 vs ≥30), tamoxifen use.

The number of premenopausal patients accrued will be small, which means that the CIs on percent still menstruating at any time point will be large and exploratory analysis of factors associated with continued menstruation will be interpreted with caution. Also, if the study ceases accrual early, there will be fewer patients available for estimating amenorrhea. However, data resulting from this assessment will provide preliminary estimates of rates of amenorrhea in the population receiving trastuzumab emtansine, and will serve as a check of the rates in those receiving TH, currently under investigation in protocol 07-199.

15.7.9 Describe overall survival in patients with Stage I HER2-positive breast cancer treated with trastuzumab emtansine.

The distribution of OS and 3-year OS (with 95% CI), defined as the time from randomization to death from any cause or censored at the date last known alive, will be summarized using the Kaplan-Meier method according to treatment group. Few deaths are expected, and OS is described for completeness.

15.8 Reporting and Exclusions

15.8.1 For this phase II trial, the analysis population is a modified intention-to-treat population of all patients who initiate therapy.

15.8.2 Evaluation of toxicity. All participants will be evaluable for toxicity from the time of their first treatment.

15.8.3 Any exclusions from analysis will be documented and summarized in a CONSORT diagram.

16 PUBLICATION PLAN

The results should be made public within 24 months of the end of data collection. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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18 APPENDICES

Appendix 1: Patient Neurotoxicity Questionnaire (PNQ) Patient ID#_____Date ____

Patient Neurotoxicity Questionnaire (PNQ)©

Taxanes, Cisplatin and Carboplatin

Item 1.

☐ A	☐ B	☐ C	☐ D*	☐ E*
I have no numbness, pain, burning or tingling in my hands or feet.	I have mild numbness, pain, burning or tingling in my hands or feet. This does not interfere with my activities of daily living.	I have moderate numbness, pain, burning or tingling in my hands or feet. This does not interfere with my activities of daily living.	I have moderate to severe numbness, pain, burning or tingling in my hands or feet. This interferes with my activities of daily living.	I have severe numbness, pain, burning or tingling in my hands or feet. It completely prevents me from doing most activities of daily living.

Item 2.

☐ A	☐ B	☐ C	☐ D*	☐ E*
I have no weakness in my arms or legs	I have a mild weakness in my arms or legs. This does not interfere with my activities of daily living.	I have moderate weakness in my arms or legs. This does not interfere of my activities of daily living.	I have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living.	I have severe weakness in my arms or legs. It completely prevents me from doing most activities of daily living.

* Please indicate by placing an X in the box or writing in the space provided which activity or activities have been interfered with as a result of therapy.

My ability to:

☐ Button clothes	☐ Open doors	☐ Fasten buckles	☐ Write	☐ Sew
☐ Use a knife	☐ Put in or remove contact lenses	☐ Sleep	☐ Walk	☐ Work
☐ Use a fork	☐ Dial or use telephone	☐ Climb stairs	☐ Put on jewelry	☐ Tie shoes
☐ Use a spoon	☐ Operate a remote control	☐ Type on a keyboard	☐ Knit	☐ Drive
	☐ Other eating utensils, etc	☐ Perform activities of importance to me, specify: _____		

Signature **Date**

FACT B, PNQ, and the Rotterdam Symptom Checklist should be completed at baseline (after registration and prior to initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment) at: 18 months (+/- 8 weeks) , 24 months(+/- 8 weeks), and 36 months (+/- 8 weeks). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

Appendix 2: Alopecia Patient Assessment **Patient ID#_____Date:_____**

Alopecia Patient Assessment

The next questions ask about how much hair loss has impacted you.

If you did not have any hair loss during the past week, please check this box ☐ and proceed to the next page *(or next section).*

During the <u>past week</u>, how much has your hair loss…

	Not at all	A little bit	Some-what	Quite a bit	Very Much
a. Prevented you from spending time with others including family and friends?					
b. Affected your performance at work?					
c. Kept you from leaving the house?					
d. Affected your self image?					
e. Made you feel embarrassed?					

The Alopecia Patient Assessment and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) should be completed at baseline (after registration, and prior to initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment)at 18 months (+/- 8 weeks). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

Appendix 3: FACT B Patient ID#_____Date:_____

Below is a list of statements that other people with your illness have said are important**. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

FACT B, PNQ, and the Rotterdam Symptom Checklist should be completed at baseline (after registration and prior to initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment) at: 18 months (+/- 8 weeks) , 24 months(+/- 8 weeks), and 36 months (+/- 8 weeks). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient ID# _____Date:_____

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.

FACT B, PNQ, and the Rotterdam Symptom Checklist should be completed at baseline (after registration and prior to initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment) at: 18 months (+/- 8 weeks) , 24 months(+/- 8 weeks), and 36 months (+/- 8 weeks). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4

GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Patient ID#_____Date:_____

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

FACT B, PNQ, and the Rotterdam Symptom Checklist should be completed at baseline (after registration and prior to initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment) at: 18 months (+/- 8 weeks) , 24 months(+/- 8 weeks), and 36 months (+/- 8 weeks). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix 4: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

Patient ID#_____Date:_____

The following questions ask about the effect of your breast cancer on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your breast cancer? *Include hours you missed on sick days, times you went in late, left early, etc., because of your breast cancer. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your breast cancer affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If breast cancer affected your work only a little, choose a low number. Choose a high number if breast cancer affected your work a great deal.

Consider only how much breast cancer affected productivity while you were working.

CIRCLE A NUMBER

Problem had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Problem completely Prevented me from working

6. During the past seven days, how much did your breast cancer affect your ability to do your regular daily activities, other than work at a job?

CIRCLE A NUMBER

Problem had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Problem completely Prevented me from my daily activities

Note: By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal. Consider only how much breast cancer affected your ability to do your regular daily activities, other than work at a job.

The Alopecia Patient Assessment and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) should be completed at baseline (after registration, and prior to initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment) at: 18 months (+/- 8 weeks). If follow-up visits occur at local

oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

Patient ID#

Rotterdam Symptom Checklist — Confidential

date of completion _____ 19 _____

In this questionnaire you will be asked about your symptoms. Would you please, for all symptoms mentioned, indicate to what extent you have been bothered by it, by circling the answer most applicable to you. The questions are related to the past week.

Example: Have you been bothered, during the past week, by

headaches	not at all	(a little)	quite a bit	very much

Have you, during the past week, been bothered by

lack of appetite	not at all	a little	quite a bit	very much
irritability	not at all	a little	quite a bit	very much
tiredness	not at all	a little	quite a bit	very much
worrying	not at all	a little	quite a bit	very much
sore muscles	not at all	a little	quite a bit	very much
depressed mood	not at all	a little	quite a bit	very much
lack of energy	not at all	a little	quite a bit	very much
low back pain	not at all	a little	quite a bit	very much
nervousness	not at all	a little	quite a bit	very much
nausea	not at all	a little	quite a bit	very much
despairing about the future	not at all	a little	quite a bit	very much
difficulty sleeping	not at all	a little	quite a bit	very much
headaches	not at all	a little	quite a bit	very much
vomiting	not at all	a little	quite a bit	very much
dizziness	not at all	a little	quite a bit	very much
decreased sexual interest	not at all	a little	quite a bit	very much
tension	not at all	a little	quite a bit	very much
abdominal (stomach) aches	not at all	a little	quite a bit	very much
anxiety	not at all	a little	quite a bit	very much
constipation	not at all	a little	quite a bit	very much

FACT B, PNQ, and the Rotterdam Symptom Checklist should be completed at baseline (after registration and prior to

initiation of study treatment), during treatment at: 3 weeks (+/- 1week), 12 weeks (+/-1 week), 6 months (+/- 4 weeks), and 12 months (+/- 8 weeks), and during follow-up (starting 6 months from the final treatment) at: 18 months (+/- 8 weeks) , 24 months(+/- 8 weeks), and 36 months (+/- 8 weeks). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

Sep

diarrhoea	not at all	a little	quite a bit	very much
acid indigestion	not at all	a little	quite a bit	very much
shivering	not at all	a little	quite a bit	very much
tingling hands or feet	not at all	a little	quite a bit	very much
difficulty concentrating	not at all	a little	quite a bit	very much
sore mouth/pain when swallowing	not at all	a little	quite a bit	very much
loss of hair	not at all	a little	quite a bit	very much
burning/sore eyes	not at all	a little	quite a bit	very much
shortness of breath	not at all	a little	quite a bit	very much
dry mouth	not at all	a little	quite a bit	very much

A number of activities is listed below. We do not want to know whether you actually do these, but only whether you are able to perform them presently. Would you please mark the answer that applies most to your condition of the past week.

	unable	only with help	without help, with difficulty	without help
care for myself (wash etc.)	0	0	0	0
walk about the house	0	0	0	0
light housework/household jobs	0	0	0	0
climb stairs	0	0	0	0
heavy housework/household jobs	0	0	0	0
walk out of doors	0	0	0	0
go shopping	0	0	0	0
go to work	0	0	0	0

All things considered, how would you describe your quality of life during the past week?

0 excellent
0 good
0 moderately good
0 neither good nor bad
0 rather poor
0 poor
0 extremely poor

Would you please check whether you answered all questions?

Thank you for your help.

Patient ID #:

Date:

Appendix 6: Baseline Assessment of Menses

Patient ID#: _____

Date Today: _____

1) Have you menstruated in the past 12 months?

☐ Yes ☐ No

2) Have you taken any hormonal agents (e.g., birth control pills, fertility drugs, or tamoxifen) in the past 12 months?
If yes, please explain: _____

3) Have your ovaries been removed or radiated?

☐ Yes ☐ No

4) Approximately how often did you have a menstrual period in the past 12 months?

☐ once every month ☐ once every 2 months ☐ 2 or more times a month
☐ once every 3-6 months ☐ less often than once every 6 months

Note - Baseline Assessment of Menses is to be filled out prior to initiation of study treatment.

Appendix 7: Follow-Up Menses Assessment

Patient ID#: _____

Date Today:_____

1) Have you menstruated in the past 6 months?

☐ Yes ☐ No

2) Approximately how often have you had your menstrual period over the past six months?

☐ once every month ☐ once every 2 months ☐ 2 or more times a month
☐ once every 3-6 months ☐ less often than every 6 months

3) Have your ovaries been removed or radiated?

☐ Yes (date:___/_____MM/YYYY) ☐ No

4) Are you currently taking any of the following?

☐ Tamoxifen (date started:___/_____MM/YYYY)

☐ Ovarian suppression shots (date started:___/_____MM/YYYY)

☐ Birth control pill (date started:____/_____MM/YYYY)

☐ Aromatase inhibitor (date started:___/_____MM/YYYY)

☐ Other hormonal drug (_____date started:__/_____MM/YYYY)

Menses assessment survey is to be filled out by all patients at baseline (after registration and prior to initiation of study treatment); if a patient is deemed premenopausal at the time of study registration (i.e. having at least one menstrual period in 12 months prior to registration), they then need to complete follow up menses assessments during treatment at 6 months and 12 months, and during follow-up (starting 6 months from the final treatment) at 18 months, 24 months, 30 months, and 36 months (+/- 2 months). If follow-up visits occur at local oncologist site, the study team is responsible for mailing and collecting paper copies of the questionnaires due for that time point as per Section 10.3, Table 8.

Appendix 8: Treatment Completion/Off-Study Form

QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS, OS-200
Dana-Farber/Harvard Cancer Center, 44 Binney Street (OS 200), Boston, MA 02115
TEL: (617) 632-3761
Email: qcc@partners.org

TREATMENT ENDED/OFF STUDY FORM INSTRUCTIONS: To be completed when a subject completes protocol treatment and/or when the subject comes off-study. Please fill out all the information requested below and email to the QACT registrars at **qcc@partners.org**

STUDY SUBJECT INFORMATION

Subject Name (Last, First) _____

Hospital I.D. #

Protocol Number or Name

****

Date Treatment Ended
(Last day of protocol treatment; i.e., chemotherapy, radiotherapy)

Reason

***If Reason 3* – Specify Toxicity Phase I DLT Y/N**

***If Reason 4* – Date of Death**

***If Reason 98* – Other (please describe)**

Will the subject continue on follow-up? (Y/N)
****

Date Off Study
(Last day patient was being followed on protocol) Leave blank if patient remains in follow-up.

Reason

***If Reason 4* – Date of Death**

***If Reason 5* – Specify Toxicity Phase I DLT Y/N**

***If Reason 98* – Other (please describe)**

****

Completed By Phone# Date

Guidance for Selecting Treatment Ended Reason

DATE TREATMENT ENDED is when protocol treatment for a subject (i.e. chemotherapy, radiation, surgery etc) is stopped due to the various reasons listed below. The date treatment ended is linked to Chemo-order entry as applicable. Therefore, it is critical that as subjects complete protocol therapy that this is documented in the QACT registration system.

Reason Codes	***Definitions***
Treatment Completed per Protocol Criteria	This is selected when a subject has finished the protocol requirements.
Disease Progression/Relapse During Active Treatment	This is selected when a subject's disease worsens and meets the criteria in the protocol for progression; i.e. the tumor is measured and evaluated according to the tumor evaluation criteria written in the protocol (RECIST, WHO, etc) and it is deemed "progressive" (the tumor has grown larger or the disease has spread to other parts of the body).
Adverse Events/Side Effects/Complications	This is selected when a subject is removed from treatment because of treatment side effects (either physician directed or subject choice) or because of treatment complications (e.g. infection from placement of catheter)
Death On Study	This is selected when a subject died during active treatment. If this is selected for Off Treatment reason then "Death" should be selected for the Off Study reason. *Note: CTEP defines "active treatment" as any form of therapy identified in the schema of the protocol (e.g., surgery; radiation; commercial chemotherapy agents, investigational agents).*
Patient Withdrawal/Refusal After Beginning Protocol Therapy	This is selected when a subject refused to continue protocol therapy for reasons other than side effects, Adverse Event or complications (e.g., cost, travel)
Subject Withdrawal/Refusal Prior to Protocol Therapy	This is selected when a subject decides not to receive participate in the protocol after screening/registration but before beginning protocol therapy
Alternative Therapy	This is selected when the subject is removed from protocol therapy in order to receive an alternative therapy, in spite of not meeting criteria for progression/relapse or experiencing unacceptable Adverse Event
Other Complicating Disease	This is selected when the subject is removed from protocol therapy due to other complicating disease.
Lost to Follow Up	This is selected when the subject cannot be located during the treatment or follow-up portion of the protocol and all communication is lost. Subject must be off treatment and off protocol.
Cytogenetic Resistance	This is selected when there is resistance to the treatment by the tissue or tumor due to a genetic trait in the subject
Disease Progression Prior to Active Treatment	This is selected when a subject meets eligibility requirements and is registered, but experiences disease progression before beginning active protocol treatment
No Treatment, per Protocol Criteria	This is selected when a subject has received no treatment per the protocol requirements.
Other	This is only selected if the subject's Off Treatment reason is not one of the reasons specified above.

Guidance for Selecting Off Study Reason

DATE OFF STUDY is when the subject will no longer be followed on the protocol due to the reasons listed below. Subjects can come off treatment before they come off study if they are still being followed on protocol or, they may come off treatment at the same time. This often is protocol dependent.

The use of data and samples collected when a subject comes off-study should be communicated via the informed consent document. For FDA regulated trials, including correlative studies associated with the FDA regulated trial, any information collected up to the point of the subjects withdrawal cannot be removed from the study. Typically, for non-FDA regulated research, all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study cannot be removed.

Reason Codes	*Definitions*
Protocol-defined Follow-up Completed	This is selected when a subject has finished the protocol requirements.
Lost to Follow Up	This is selected when the subject cannot be located during the treatment or follow-up portion of the protocol and all communication is lost. Subject must be off treatment and off protocol.
Refused Follow-up	This is selected when the subject has withdrawn consent to be followed.
Death	This is selected when a subject died either during active treatment or while in follow-up. If this is selected for Off Treatment reason then “Death” should be selected for the Off Study reason. *Of note, data and samples collected may continue to be used.*
Adverse Events/Side Effects/Complications	This is selected when a subject is removed from follow-up because of side effects (either physician directed or subject choice) or because of complications (e.g. infection from placement of catheter)
Other	This is only selected if the subject’s Off Study reason is not one of the reasons specified above.

Appendix 9: Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CHB, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.). The Lead Institution is the home of the Overall PI.

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A Participating Institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The Participating Institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative

support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

Clinical Trials Office: The clinical trials offices of the DF/HCC consortium members support investigators and their study teams with the coordination, submission and ongoing conduct of research protocols involving human subjects. Specifically, these offices support four core service areas including; pre-review of PI initiated protocols; assistance in the preparation and management of Investigational New Drug (IND) applications and subsequent required reporting to the FDA; regulatory consultation and guidance in the interpretation of local and federal policies; and the orientation and ongoing training support of clinical research personnel.

DF/HCC Quality Assurance Office for Clinical Trials: The DF/HCC QACT is a unit that has been developed to computerize, manage, and QC & QA data and DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to audit DF/HCC trials.

2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair, Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Dr. Sara Tolaney, will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling subjects.
- For international trials, assure that the protocol is provided to Participating Institutions in the primary language spoken at the site.

- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. CTEP, FDA, OBA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with CTEP/PIO Office (CTEP trials) or FDA (investigator-held IND trials) or OBA (gene therapy trials), as applicable.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e. Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution, Dana-Farber Cancer Institute, will ensure that all Participating Institutions within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, and HIPAA requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of FWA and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain CTEP, FDA or OBA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute Serious Adverse Event safety reports (both IND Safety reports and protocol specific SAEs).
- Monitor at Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Verify that eligibility has been confirmed by the investigator and that appropriate consent has been obtained.

- Provide auditing services (funding and QACT approval required).

2.3 Participating Institution

Each Participating Institution will provide to the Coordinating Center a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.
The general responsibilities for each Participating Institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event reports to local IRB and directly to the Coordinating Center. For CTEP trials, submit SAE reports directly to CTEP and provide copies to the Coordinating Center
- Submit deviations and violations to local IRB and the Coordinating Center.
- Secure investigational agents per federal guidelines and protocol requirements.
- For protocols using investigational agents, the Participating Institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company)

3.0 PROTOCOL DEVELOPMENT

3.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and if applicable CTEP Multi-center, FDA or OBA Guidelines. Further, the Protocol Chair will be the single liaison with the CTEP/PIO, the FDA or OBA, as applicable.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify, qualify and initiate Participating Institutions and obtain accrual commitments.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

3.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Maintain Regulatory documents for all Participating Institutions.
- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all Participating Institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Conduct regular communications with all Participating Institutions (conference call, emails, etc)
- Maintain documentation of all communications.

4.0 PROTOCOL MANAGEMENT

The Coordinating Center is responsible for assuring that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Coordinating Center must maintain copies of all IRB approvals, for each Participating Institution.

4.1 Protocol Distribution

The Coordinating Center will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

4.2 Protocol Revisions and Closures

The Participating Institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating Institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

Protocol Closures and Temporary Holds: Participating Institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

4.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for participating institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. **It is DF/HCC policy that only attending physicians can obtain informed consent and re-consent to drug and/or device trials.**

4.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee and must be submitted and approved by the DFCI IRB prior to participant registration:

- Approval Letter of the institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution's IRB
- IRB approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the DF/HCC Lead Institution their IRB approval for Amendments to a protocol.

4.5 IRB Re-Approval

Annual IRB re-approval from the Participating Institution is required in order to continue research and register participants onto a protocol. There is no grace period for continuing approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution from the Participating Institutions on or before the anniversary of the previous approval date.

4.6 Participant Confidentiality and Authorization Statement

The HIPPA of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol, the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol Participating Institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

4.7 Participant Registration and Randomization

Please refer to Protocol section 4 for participant Registration and Randomization Information. Treatment cannot begin until site has received confirmation that participant has been registered with DFCI QACT.

4.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

4.9 DF/HCC Multi-center Protocol Registration Policy

4.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy**.**

4.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval.

4.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

4.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

4.10 Schedule of Data Submission

The DF/HCC QACT develops a set of either paper or electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. QACT provides a web based training for eCRF users. These forms are designed to collect data for each study. Note: It is necessary to send only ONE copy of all paper Case Report Forms, if applicable.

4.10.1 Eligibility Checklist

Purpose - Outlines protocol-specific eligibility criteria and includes the following:

Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)

1) Parameters for eligibility
2) Parameters for exclusion
3) Parameters for stratifications

If a time frame is not specified in the protocol, tests must be completed as follows:

- Lab tests required for eligibility must be completed within 14 days prior to study enrollment by the QACT.
- Non-lab tests required for eligibility must be performed within 30 days prior to study entry. Example: radiological scans

4.10.2 On-study Form(s)

Purpose - documents the following items:

- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant's physical status at protocol registration
- Disease site specific data

4.10.3 Baseline Assessment Form(s)

Purpose – Documents objective and subjective disease status as defined by the protocol**.** Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

4.10.4 Treatment Form(s)

Purpose - Records the following information related to the time the participant receives protocol treatment:

- Participant, Protocol information
- Protocol treatment and supportive therapy per treatment cycle
- Protocol specific laboratory values per treatment cycle
- All medications other than protocol chemotherapy agents used to treat concomitant diagnoses, if applicable

4.10.5 Adverse Event Report Form(s)

Purpose – Documents adverse events that occur while the participant is receiving treatment and for up to 30 days after the last dose of treatment. All adverse events are to be graded by number using the toxicity grading scale required by the protocol. This form is not for IRB submission, but for recording the AE in the research database.

4.10.6 Response Assessment Form(s)

Not applicable

4.10.7Off Treatment and Off Study Form(s)

Purpose - The Off Treatment and Off Study Forms are submitted when the participant is removed from the study or has completed all protocol treatment. Note: If the participant dies while on protocol**,** the Off Study Form is the last form submitted.

4.10.8 Follow up / Survival Form

Purpose - Summarizes participant status at a given point in time after being removed from treatment.

4.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Completeness:
Is all the information provided as required per protocol?

Protocol Treatment Compliance:
Are the body surface area (BSA) and drug dosage calculations correct? The dose must be within 10% of the calculated protocol dose.

Adverse Events (Toxicities):

Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

4.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

5.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in protocol section 8.1.4.

Participating Institutions should order their own agent regardless of the supplier (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB. If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal guidelines. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

6.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

6.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

6.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol in section 11.4**.**

The Lead Institution will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating all SAEs to all sites conducting the trial.

Participating Institutions must report the AEs to the Protocol Chair and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

6.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The Protocol Chair will review all IND Safety Reports and is ultimately responsible for forwarding the IND Safety Reports to the Participating Institutions. The Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

7.0 PROTOCOL VIOLATIONS AND DEVIATIONS

FDA guidelines do not define the terms “protocol violation” or “protocol deviation.” All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all Institutions Participating in the DF/HCC Multi-center Protocol.

7.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

7.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations.

The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the Participating Institution's own IRB, per its institutional policy.
A copy of the Participating Institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

8.0 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality control oversight for the DF/HCC Multi-center Protocol.

8.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

The DF/HCC Lead Institution will implement on-going monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management.

Additionally, a plan will be formulated to provide regular and ongoing communication to Participating Institutions about study related information which will include participation in regular Lead Institution initiated teleconferences. Teleconferences will occur every 2 weeks and will continue regularly until completion of accrual. Upon completion of accrual, teleconferences will occur monthly until all patients complete protocol therapy. Upon completion of protocol therapy, teleconferences will occur every 3 months for 3 years and then every 6 months thereafter until study completion. Additional communication may be distributed via "Newsletter" or email as deemed appropriate by the protocol chair.

Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion. Data will be reviewed for completeness, timeliness of submission, quality, and adherence to the protocol requirements. The DF/HCC Lead Institution will utilize both on-site and remote monitoring. At a minimum, the Clinical Trial Monitor, will monitor each participating site once a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits additional monitoring may not be required. Additional monitoring visits (on-site or remote) may occur at the discretion of the Principal Investigator if there are significant findings or discrepancies.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the visit. In addition, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating Site. On-site monitoring visits can be substituted with remote (virtual) monitoring visits at the discretion of the Principal Investigator.

Remote Monitoring: Remote monitoring will be performed on an as-needed basis by the Clinical Trial Monitor. Sites will be asked to provide source documentation via fax, email, or mail as specified by the Clinical Trial Monitor for virtual monitoring.

8.2 Evaluation of Participating Institution Performance

8.2.1 Eligibility Checklist:

Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist

and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

8.2.2 Accrual of Eligible Participants:

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

A minimum of 3 participants per site annually is recommended for Phase II trials. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

9.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. The main focus in auditing is to measure if the standards and procedures set are being followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and the data were generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations.

9.1 DF/HCC Sponsored Trials

One on-site audit will be conducted by QACT in years 1 and 7 assuming at least three subjects have been treated on protocol at a site. Approximately 3-4 subjects would be audited at the site over a 2 day period. If violations which impact subject safety or the integrity of the study are found, more subject records may be audited. In years 2-6, QACT will audit 3 sites each year based on the rate of accrual and data compliance.

9.2 Participating Institution

It is the Participating Institution's responsibility to notify the DF/HCC Lead Institution of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.3 Coordinating Center (Lead Institution or designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

9.4 Sub-Standard Performance

The Protocol Chair, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal guidelines, will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

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Appendix 10: SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Study Number	ML28160
Principal Investigator	Sara Tolaney, MD, MPH
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**13-048**
Protocol Name:	**A randomized Phase II study of Trastuzumab emtansine (T-DM1) vs. Paclitaxel in combination with Trastuzumab for Stage I HER2-positive breast cancer (ATEMPT Trial)**
DFCI Site PI:	Sara Tolaney, MD, MPH
DFCI Research Nurse:	Peg Haldoupis, RN; Liz Kasparian, RN; Mary O'Driscoll, RN; Kathy Roche, RN; Myra St. Amand, RN, Beth Tiani, RN

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	***Trastuzumab emtansine*** is a novel antibody-drug conjugate that is specifically designed for the treatment of HER2-positive malignancies. ***Study Design:*** Participants will be randomized 3:1 to trastuzumab or paclitaxel + trastuzumab – Section 1.1; **Study Rationale** – Section 2.3. *Cycle length is cohort specific.*
Dose Calc.	• Trastuzumab emtansine dose is calculated in mg/kg based on the participant's weight on day 1 of each cycle; please see Section 5.1 for complete details on dose determination. • Trastuzumab dose is calculated in mg/kg; please see Section 5.2.1 for complete details on dose determination. • Paclitaxel dose is calculated in mg/m^2. All dosing will be determined solely by the participant's BSA as calculated from actual weight OR actual weight – see Sections 5.2.2 and 7.2.2.1 (j). Please review Section 5.2.2 for complete details on dose determination.
Study Drug Administration	***ARM 1: Trastuzumab emtansine*** – Sections 5.1 and 8.1 • IV,via a 0.22 micron non-protein adsorptive polyethersulfone in-line filter, administered on Day 1 (+/- 3 days) of a 3-week cycle, up to a total of 17 cycles. • Can be diluted in either 250mL of 0.45% (preferred) or 0.9% sodium chloride. • 1st infusion is administered over 90 min (+/- 10 min). Infusions may be slowed or interrupted for participants experiencing If initial infusion was well tolerated, then subsequent infusions may be administered over 30 min (+/-10 min). • **Vital signs** must be assessed before and after the FIRST infusion. • ***Criteria to treat*** – Section 5.1 • 1st infusion: Participants must be **observed** for at least 60 min for fever, chills or other infusion-associated symptoms. • If initial infusion was well tolerated, observation may be at least 30 min for subsequent infusions • See Section 7.2.a for management of **hypersensitivity** reactions • Missed doses are not made up. ***ARM 2: Trastuzumab and paclitaxel*** – Section 5.2 **Trastuzumab** – Section 5.2.1 and 8.2 • IV,with a loading dose on Day 1 followed by a weekly (+/- 2 days) dose for a total of 12 doses. After completion of 12 weeks, trastuzumab will be administered every 3 weeks (+/-7 days) x 39 weeks for a total of 13 doses. **NOTE:** If a participant has been without a dose of trastuzumab for ≥ 28 days, they will require a reloading dose. • Diluted in 250mL of 0.9% sodium chloride. **Dextrose (5%) solution MUST NOT be used**. • May be administered either before or after paclitaxel and should be administered if paclitaxel is held. • 1st infusion is administered over 90 min. If the first infusion was well tolerated, subsequent infusion times may be shortened to 30 minutes or given per the institutional standard. • DO NOT administer as an IV push or bolus. • See Section 7.2.2.2 for management of **hypersensitivity** reactions, **fevers** and **chills** • Missed doses during the 12 week combination therapy with paclitaxel should be made up. ***Paclitaxel*** – Section 5.2.2 • IV, administered weekly (+/-2 days) for 12 weeks. May be administered per institutional standard. • **Premeds** are recommended for the first dose – please see Section 5.2.2 for a list of meds and guidance. • See Section 7.2.2.1 for management of **hypersensitivity** reactions, including RATE adjustments and meds • ***Criteria to treat:*** ANC ≥ 800/mm^3 and platelets ≥ 100,000/mm^3 • Missed doses should be made up. • May be administered in some circumstances if trastuzumab is held – see Section 7.2.2.2 (#2) for guidance

Dose Mods & Toxicity	*Dose Modifications*/*Dosing Delay for Toxicity* are outlined in Section 7.2 • This protocol uses NCI CTCAE criteria, version 4.0 – Section 7 • Anticipated toxicities are outlined in Section 7.1 • See Section 7.2.1 for trastuzumab emtansine • See Section 7.2.2.1 for paclitaxel • See Section 7.2.2.2 for trastuzumab
Con Meds	*Concomitant Therapy* Guidelines are in Section 3.1.20 • Please review this section for permitted, prohibited and "use with caution" medications.
Required Data	*Study Calendar and Assessment Required data* are outlined in Sections 9.1 and 10 • Research blood collections – Section 9.1 • Please review the Study Calendars in Section 10
Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or the infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please be sure to also DOCUMENT additional vital signs, observation times for trastuzumab emtansine and injection sites.

Reproductive Risks and Recommendations

For Women of Childbearing Potential on TDM1 or Men on TDM1 with Partners of Childbearing Potential

DF/HCC Protocol #: **13-048**

The drug you are receiving in this research study, Trastuzumab emtansine (T-DM1), may affect a fetus. While participating in this research study, you should not become pregnant or father a baby and should not nurse a baby. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants.

It is recommended participants of child-bearing potential use one highly effective form of birth control or two effective forms of birth control for at least 7 months after their last study treatment.

- Highly effective forms of birth control which can be considered include:
  - True abstinence
  - Partner with a previous vasectomy
  - Oophrectomy/hysterectomy
- Effective forms of birth control which can be considered include:
  - Placement of an non-hormonal intrauterine device (IUD) with spermicidal foam/gel/film/cream/suppository
  - Condom with spermicidal foam/gel/film/cream/suppository.

It is also recommended nursing mothers discontinue nursing prior to starting study treatment. Nursing mothers should wait to re-start or begin breastfeeding for at least 7 months following the completion of study treatment.