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TITLE: ATOP TRIAL: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

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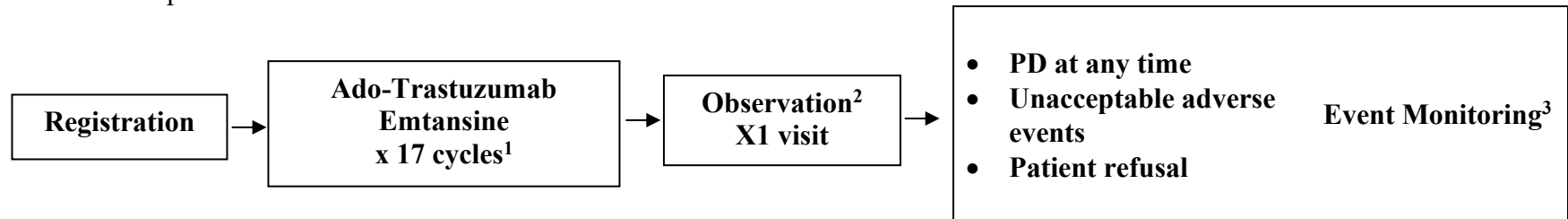
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SCHEMA

Confirmed HER2 positive disease



Note: If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

1. Cycle length=21 days; Multiple correlative studies occur longitudinally. See Study Calendar (Section 10) for details on schedule.
2. See section 5.9.
3. See section 13

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1. OBJECTIVES

1.1 Study Design

This is a single-arm Phase II to evaluate the efficacy and safety of T-DM1 in older patients with HER2-positive breast cancer. The primary endpoint is 5-year IDFS. The study plans to enroll up to 92 evaluable patients (and will be combined with data from consenting patients who have already been enrolled and treated on the companion protocol led by ACCRU [RU011301I]-DFCI protocol 15-019). We will be combining the cohorts of patients enrolled on the two trials into one analysis of 120 evaluable patients.

1.2 Primary Objectives

To evaluate invasive disease-free survival (IDFS) for patient receiving T-DM1, with an IDFS event defined as occurrence of any of the following ¹:

- Ipsilateral invasive breast cancer recurrence
- Regional invasive breast cancer recurrence
- Distant recurrence
- Death attributable to any cause
- Contralateral invasive breast cancer
- Second non-breast invasive cancer

Note: In-situ events are not included

1.3 Secondary Objectives

- 1.3.1 To evaluate overall survival (OS) for patient receiving T-DM1, defined as the time from study enrollment to death attributable to any cause (i.e. death from breast cancer, non-breast cancer cause, or from unknown cause).¹
- 1.3.2 To evaluate recurrence-free survival (RFS) for patient receiving T-DM1, defined as the time from study enrollment to disease recurrence and will not include death as an event.
- 1.3.3 To evaluate adverse events for patient receiving T-DM1, defined as adverse events of all grades
- 1.3.4 To evaluate cardiac function/adverse events for patient receiving T-DM1, defined as incidence of symptomatic left ventricular systolic dysfunction, cardiac death, and incidence of decrease in ejection fraction by at least 10 percentage points below baseline or to below 50%.
- 1.3.5 To evaluate site of first recurrence for patient receiving T-DM1, which will be tabulated as frequencies and relative frequencies.

1.4 Correlative Objectives

The associations of adverse events (grade 3 and higher) and outcomes (recurrence and survival) with each of the following will be examined (see statistical considerations for full information on analysis plan):

- 1.4.1 Geriatric assessment (GA)
- 1.4.2 Patient reported outcomes (PRO-CTCAE)
- 1.4.3 Quality of life (QOL)
- 1.4.4 Biomarkers of aging
- 1.4.5 Additional correlative goal: To determine whether clinician-reported CTCAEs are more accurate when PRO-CTCAE data are shared with the patient and clinician.
- 1.4.6 Utilize a high-throughput mutation profiling system (Oncomap) to query a large panel of cancer gene mutations in older patients with HER2-positive breast cancers

NOTE: Patients who cannot read and understand Spanish or English will not be included on the PRO-CTCAE, QOL, or Geriatric Assessment components of the study (but may be included in other study components) unless an interpreter is readily available to actively translate English documents and instructions to patients at each survey timepoint.

2. BACKGROUND

2.1 HER2-positive disease in the elderly

Rates of HER2-positive breast cancer in older populations have not been well described. This question was recently examined within the National Comprehensive Cancer Network (NCCN), and observed that approximately 26% of patients with stage I-III, HER2-positive disease with diagnoses during 2005-2008 were aged ≥ 60 ². Among these patients treated at NCCN centers, rates of initiation of trastuzumab-based adjuvant chemotherapy were 79% for women in the 60-69 age group and 54% for women ≥ 70 compared to 90% in women aged 50 or younger ². In addition, among women who started trastuzumab in the adjuvant setting within Surveillance, Epidemiology, and End Results (SEER)-Medicare, the oldest patients were less likely to complete at least 9 months of therapy ³.

2.2 Chemotherapy in Older Patients

Despite similar risk reductions with chemotherapy compared with younger women, many older women do not receive guideline-recommended chemotherapy, which likely impacts survival ⁴⁻⁸. This may be particularly important in the case of HER2-positive disease because of the 50% relative risk reduction for recurrence with improved survival provided by a course adjuvant

trastuzumab-based chemotherapy⁹⁻¹². The reasons for lower rates of chemotherapy administration in older women are likely multifactorial and include physician bias,¹³ patient and family preferences, or concerns for competing comorbidity¹⁴⁻¹⁶. In addition, robust prospective toxicity and benefit data for standard cancer-directed treatments are lacking for older patients because of their persistent underrepresentation in clinical trials. Although pooled analyses and cancer registry studies have suggested substantial benefits of chemotherapy for older women^{6, 7, 17, 18} the expected treatment benefits and toxicities in older patients are often extrapolated from observations in younger women. Decisions regarding adjuvant treatments can often be challenging with limited evidence-based recommendations for older patients with cancer.

2.3 T-DM1 in breast cancer

Ado-trastuzumab emtansine (T-DM1, KADCYLA®) is a novel, antibody-drug conjugate consisting of trastuzumab, a humanized antibody directed against the extracellular region of HER2, and DM1, an antimicrotubule agent derived from maytansine. These agents are linked via a thioether molecule, succinyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate. T-DM1 binds to HER2 and is hypothesized to undergo receptor-mediated internalization, resulting in a focused, directed intracellular release of DM1 and subsequent cell death^{19, 20}. Completed and ongoing phase I, II, and III studies of T-DM1 have demonstrated promising clinical activity with minimal toxicity when administered as a single agent in the metastatic, treatment-refractory, HER2-positive disease setting²¹⁻²⁴. In a phase II study in women with HER2-positive cancers who had progressed on a taxane, anthracycline, lapatinib, and capecitabine, single agent T-DM1 administration resulted in an objective response rate of 41.3% (95% CI, 30.4-52.8 months) with a median PFS of 7.3 months (95% CI 4.6-12.3 months). In this study, most adverse events were grades 1-2; the most frequent grade 3 or higher events were thrombocytopenia (9.1%), fatigue (4.5%), and cellulitis (3.6%)²². In the EMILIA study^{24, 25} 991 women who were previously treated with a taxane and trastuzumab were randomized to T-DM1 or lapatinib/capecitabine (lap/cape). In this study, the median PFS for women on the T-DM1 arm was 9.6 months vs. 6.4 months on the lap/cape arm (hazard ratio= 0.65, 95% confidence interval 0.55-0.77). Objective responses, progression of symptoms, and overall survival were also improved for women who received T-DM1, although the median overall survival has not yet been reached for these patients²⁴. T-DM1 had a favorable toxicity profile in this study, making its administration in older women appealing. The most common grade ≥ 3 adverse events for women receiving T-DM1 were thrombocytopenia (12.9%), increased AST (4.3%), and increased ALT (2.9%). Overall, 41% of women experienced a \geq grade 3 event with T-DM1 vs. 57% for women receiving lap/cape. Other studies have reported similar side effects for T-DM1, as above. Results from the EMILIA study led to approval for T-DM1 by the FDA on 2/22/2013. T-DM1 was approved specifically for use in women with metastatic, HER2-positive breast cancer who have been treated with a prior taxane and trastuzumab as per the eligibility criteria for EMILIA.

Results from protocols of T-DM1 in other settings have also confirmed its activity and tolerability in HER2-positive breast cancer, including FDA approval for adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant chemotherapy and trastuzumab-based treatments (KATHERINE trial, von Minckwitz NEJM 2019). Further, early results from the 'ATEMPT' Study (Tolaney et al SABCS 2019) demonstrated low recurrence rates for patients with early-stage HER2+ breast

cancer who received T-DM1. Currently, there are no adjuvant protocols dedicated to older women with HER2-positive breast cancer.

2.4 Summary of the rationale for adjuvant T-DM1 in older patients with HER2-positive disease

Because of the challenges mentioned with regard to treating older women with breast cancer who may have competing comorbidity and frailty but who would likely significantly benefit from HER2-directed therapy, T-DM1 is as a promising therapy option because of its favorable toxicity profile with proven efficacy in advanced disease.

2.5 Background for Correlative Studies

2.5.1 Geriatric Assessment:

In recent years, a greater emphasis has been put on functional age rather than chronological age given the vast heterogeneity of medical comorbidity and functional status for any given age. The geriatric assessment was designed with this in mind and identifies older adults who have diminished life expectancy and/or are at risk for hospitalization and functional decline^{26,27}. Data have also shown the value of a geriatric assessment in weighing risks and benefits for cancer treatment in older patients²⁸⁻³⁰, although a traditional assessment is time consuming and might be challenging to incorporate broadly. To overcome this, a brief assessment was designed by Dr. Hurria and colleagues which included validated and reliable measures which are primarily self-administered and require minimal resources and time by providers³¹. This assessment was tested for feasibility, and in the 93 patients enrolled on a CALGB trial, the median time to complete the geriatric assessment tool was 22 minutes and 87% of patients completed their portion without assistance. Patients were generally satisfied with questionnaire length and reported no difficult questions. All providers completed their portion of the assessment as well. This assessment is now being incorporated more widely across protocols in older patients with cancer and will be administered to participants longitudinally while on study.

We will examine factors that predict the risk for grade 3-5 adverse events in patients receiving T-DM1 on study and will also test how well Dr. Hurria's previously developed model predicts for adverse events to T-DM1³². The factors to be examined will include the following listed in Table 1 (per prior validation work by Arti Hurria)^{31,33}. Only patients who speak and read English and/or Spanish will be included in this component of the study; assessment can be completed for any patient if staff interpreter is present in-person for each survey timepoint.

Table 1. Components of Geriatric Assessment	
Domain assessed	Tests to be administered

Functional status	<ul style="list-style-type: none"> • OARS MFAQ (IADL) ^{34, 35} • MOS Physical Functioning ³⁶ • Karnofsky Performance Status Rated Healthcare Professional ^{37*} • Karnofsky Performance Status Rated by Patient ³⁸ • Timed “Up and Go” ^{39*} • Number of falls in last 6 months
Comorbidity	OARS Physical Health Section
Medication Review	Patient reports number and names of medications, herbs, or vitamins
Cognition	Blessed Orientation-Memory-Concentration Test*
Psychological Status	Mental Health Inventory (MHI)-17
Nutritional Status	<ul style="list-style-type: none"> • % Unintentional Weight Loss in last 6 months • Body Mass Index
Social Functioning and Social Support	<ul style="list-style-type: none"> • MOS Social Activity Limitation Scale • MOS Social Support Survey Subscale
Abbreviations: OARS, Older American Resources and Services; MFAQ, Multidimensional Functional Assessment Questionnaire; IADL, Instrumental Activities of Daily Living ; MOS, Medical Outcomes Study; *Items completed by the healthcare professional (Karnofsky performance status, Timed Up and Go, and Blessed Orientation-Memory-Concentration test).	

2.5.2 Biomarkers of Aging:

Biomarkers are an exciting new field of research. They have the potential to define “biological” age and identify patients at highest risk for toxicity and functional decline during chemotherapy ⁴⁰. Studies have shown that markers such as inflammatory markers or telomere length can be informative in this regard. In this study, we will examine the biomarkers in Table 2 for patients on study at the time points indicated in the Study Calendar (Section 10). These will all be collected using routine blood draws and can be performed as a single assay at Mayo Clinic. We will explore associations of each these markers with outcomes and adverse events overall and at each time point. We will also assess associations with each category of marker (i.e. inflammatory markers, coagulation, and senescence) with outcomes and adverse events.

Table 2. Candidate Biomarkers of Frailty to be Tested (all examined using routine blood draws at study visits)	
Chronic inflammatory markers	Cytokines: IL-6, IL-1Ra, TNFa, CXCL/GROa; Chemokines: IL-8, CCL2/MCP-1, CCL3/MIP-1a, CCL5/RANTES
Coagulation/vascular markers	D-dimer, PAI-1, s-VCAM
Markers of cellular senescence	HMGB1, Wnt-16

2.5.3 Patient-Reported Outcomes (PROs):

There are no published data on the specific toxicities of T-DM1 in an elderly population, and certainly none that incorporate patient-reported outcomes. Patient-reported outcomes (PRO) are an important part of new drug evaluation, and may play a role in regulatory approval of novel agents in oncology ⁴¹. PROs can be the consequences of disease and/or its treatment as reported by the patient. PROs are evaluated through the use of questionnaires developed to assess topics a patient can report about his or her own health and are often completed electronically. This includes symptoms, physical functioning, and mental health.

The current standard mechanism for reporting toxicities in cancer research is clinician-only reporting using items from the National Cancer Institute (NCI) CTCAEs. In multiple studies, PRO measures have improved the predictive accuracy of clinician CTCAE reporting. In a prospective study including lung cancer patients PRO measurements of toxicities better reflected patients' underlying state and functional status than clinician's evaluation⁴². Although PROs have been well validated⁴²⁻⁴⁴, these examinations have not specifically evaluated for feasibility and accuracy in an older patient group.

Based on prior experience with T-DM1, we will focus our PROs on ocular effects, myalgias, easy bruising, nail changes, anorexia, diarrhea, constipation, dry mouth, dyspnea, insomnia, fatigue, hair loss, headache, hives, mouth sores, nausea, vomiting, coughing, epistaxis, numbness/tingling, pain, and rash. Tablet computers will be shipped to each site in advance, and research coordinators will bring a tablet to each participating patient in-clinic prior to each scheduled visit. Patients will be asked to complete the online survey prior to the visit. Back-up paper surveys will also be available in case technical problems preclude tablet use (Note: if the back-up paper survey is used, patient responses should be entered by the site research coordinator into the PRO-CTCAE system). We will use the PRO-CTCAE items developed by the NCI (<https://healthcaresdelivery.cancer.gov/pro-ctcae/>) in order to allow patients to self-report the above symptomatic adverse events. The primary purpose of the inclusion of PRO-CTCAE is to evaluate the performance of an electronic-based system for patient self-reporting of adverse events in an elderly population with breast cancer, and to assess whether clinician-reported CTCAEs are enhanced when PRO-CTCAE data are available.

Only patients who speak and read English and/or Spanish will be included in this component of the study, which will utilize tablet computers at each clinic visit (see Section 9.2); assessment can be completed for any patient if staff interpreter is present in-person for each survey timepoint.

2.5.4 Quality of Life Assessments:

In addition to the reporting of symptoms, understanding how quality of life may be affected by T-DM1 in the adjuvant setting has not been evaluated previously and will add important information for older patients on study. Assessment of QOL will be brief and will use the EuroQol-5D-5L (EQ-5D)^{45, 46} and EQ VAS. Tablet computers will be used by each participating patient in order to minimize additional burden of questioning (see 1.53 above). Furthermore, assessments of function, mood, and symptoms will also be captured by the geriatric assessment and PRO-CTCAEs. Only patients who speak and read English and/or Spanish will be included in this component of the study (see Appendices A-E); assessment can be completed for any patient if staff interpreter is present in-person for each survey timepoint.

2.5.5 Evaluate Genetic Mutations in Archival Tumor Tissue

The pattern of mutations for older patients with HER2-positive breast cancer is not well described. To address this, archival tumor tissue from all patients on study will be assessed, likely using a high-throughput mutation profiling system (e.g. Oncopanel) 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.

2.6 Single-agent T-DM1 clinical experience in breast cancer

The following phase II and phase III studies have demonstrated clinical benefit of T-DM1 in women with metastatic breast cancer: TDM4450g, TDM5248g, and TDM 4370g/BO21977.

2.6.1 Phase II Studies with T-DM1

2.6.1.1 Study TDM4450g (Single-Agent T-DM1 in Previously Untreated Metastatic Breast Cancer Patients)

TDM4450 was a randomized, multicenter, Phase II study of the efficacy and safety of T-DM1 versus trastuzumab plus docetaxel in patients with metastatic HER2-positive breast cancer who have not received prior chemotherapy for metastatic disease⁴⁷. This study completed enrollment in December 2009 (n = 137). The primary objectives were to assess the efficacy of T-DM1 compared with the combination of trastuzumab and docetaxel, as measured by PFS based on investigator tumor assessments, and to characterize the safety of T-DM1 compared with the combination of trastuzumab and docetaxel in this population. Secondary endpoints included ORR, survival, and duration of response.

Information on the safety and efficacy of T-DM1 in the front-line setting is available based on a data cutoff date of November 15, 2010⁴⁷. Seventy patients were randomized to the control arm and 67 patients to the T-DM1 arm. The median duration of follow-up was 13.5 months and 13.8 months for the control arm and T-DM1 arm, respectively.

As of a report in November 15, 2010, the median PFS was 14.2 months in the T-DM1 arm versus 9.2 months in the trastuzumab plus docetaxel arm⁴⁷. The hazard ratio (HR) for PFS was 0.594 (95% CI: 0.364, 0.968; p = 0.0353). The ORR in the T-DM1 arm was 64.2% (95% CI: 51.8%, 74.8%) compared with 58.0% (95% CI: 45.5%, 69.2%) in the control arm (based on 69 evaluable patients). The clinical benefit rate was 74.6% (95% CI: 63.2%, 84.2%) in the T-DM1 arm versus 81.2% (95% CI: 70.7%, 89.1%) in the trastuzumab plus docetaxel arm (based on 69 evaluable patients).

Based on safety data analyzed at the data cutoff date, single-agent T-DM1 appears to have a favorable overall safety profile compared with trastuzumab and docetaxel in first-line MBC⁴⁷. The incidence of Grade ≥ 3 AEs in the control arm (89.4%; n = 66) was nearly twice that of T-DM1 (46.4%; n = 69). The rates of SAEs for both arms were similar (control arm 25.8% vs. T-DM1 18.8%). One patient in the T-DM1 group died as a result of an AE (sudden death). This patient was randomized to receive trastuzumab plus docetaxel but mistakenly received a single dose of 6 mg/kg T-DM1 instead of 6 mg/kg trastuzumab. (Data on File, Genentech) One patient in the trastuzumab plus docetaxel group died due to cardiopulmonary failure. With respect to cardiotoxicity, based on local assessments of LVEF, T-DM1 was not associated with an increase in cardiotoxicity compared with trastuzumab plus docetaxel⁴⁷.

2.6.1.2 Study TDM4258g (Single-Agent T-DM1 in Previously Treated Metastatic Breast Cancer Patients)

Study TDM4258g was a Phase II study that evaluated the safety and efficacy of T-DM1 administered at a dose of 3.6 mg/kg (intravenous [IV]) every 3 weeks in HER2-positive MBC patients who had progressed on previous HER2-directed therapy and conventional chemotherapy⁴⁸.

The primary objectives for this study were: 1) to assess ORR by independent radiologic review associated with T-DM1 3.6 mg/kg IV every 3 weeks, and 2) to characterize the safety and tolerability of T-DM1 at this dose⁴⁸. The study was activated on July 20, 2007, and enrollment was completed (n = 112) on July 31, 2008. The final analysis of ORR was performed with a data cutoff date of June 25, 2009, 11 months after the last patient was enrolled. The reported ORR in all patients was 25.9% (95% CI, 18.4%, 34.4%) by Independent Review Committee (IRC) and was 37.5% (95% confidence interval [CI], 28.6%, 46.6%) by investigator assessment. The clinical benefit rate (defined as complete response [CR], partial response [PR], or stable disease [SD] for >6 months) was 39.3% by independent review and 46.3% by investigator assessment. The median PFS was 4.6 months by both the IRC and the investigators. In the subset of patients whose archival primary tumors were retrospectively confirmed to be HER2-positive (74 of 95 patients with submitted tumor samples), the ORR was 33.8% by independent review and 47.3% based on investigator assessment.

The most common adverse events (AEs; occurring in ≥20% of patients) were fatigue (65.2%), nausea (50.9%), headache (40.2%), epistaxis (35.7%), pyrexia (34.8%), constipation (30.4%), cough (27.7%), hypokalemia (26.8%), diarrhea (25.9%), vomiting (24.1%), arthralgia (22.3%), pain in extremity (22.3%), anemia (20.5%), and dyspnea (20.5%)⁴⁸. Most of these AEs were Grade 1–2. The three most common Grade 3–4 AEs observed in this trial were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). There was one reported Grade 5 event in a patient who died of respiratory failure attributed by the investigator to underlying disease. (Data on File, Genentech) No Grade ≥3 left ventricular systolic dysfunction events (symptomatic congestive heart failure [CHF] and/or left ventricular ejection fraction [LVEF] of <40%) were observed.

2.6.2 Phase III Study

2.6.2.1 TDM 4370g/BO21977 (*EMILIA*)

TDM4370g/BO21977 was a randomized, Phase III study of T-DM1 versus lapatinib + capecitabine for the treatment of patients with HER2-positive unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane²⁵. Patients received T-DM1 (3.6 mg/kg IV on Day 1 of a 21-day cycle) or lapatinib (1250 mg orally once per day) plus capecitabine (1000 mg/m² orally twice daily on Days 1–14 of a 21-day cycle) until PD or unmanageable toxicity. Eligible patients must have confirmed HER2-positive MBC (immunohistochemistry have received prior therapy with trastuzumab and a taxane. Primary endpoints were PFS by independent review, overall survival (OS), and safety.

From February 2009 through October 2011, a total of 991 patients were enrolled; 496 were assigned to lapatinib + capecitabine, and 495 were assigned to trastuzumab emtansine ²⁵. Median duration of follow-up for the first and second interim analysis was approximately 13 months and 19 months, respectively. Baseline patient demographics, prior therapy, and disease characteristics were balanced. The study met the primary endpoint with an improvement in PFS by independent review with a HR = 0.65, (95% CI, 18.4%, 34.4%), p<0.001. The median PFS was 9.6 months in the T-DM1 arm and 6.4 months in the lapatinib + capecitabine arm. A strong trend in OS was observed in favor of the T-DM1 arm (HR = 0.62, [95% CI 0.48-0.81], p = 0.0005). At the first interim analysis, median OS was not reached in the T-DM1 arm and was 23.3 months in the lapatinib + capecitabine; the interim efficacy stopping boundary for OS was not crossed. However, at the second interim analysis, OS data crossed the pre-specified boundary that showed patients receiving T-DM1 (median OS = 30.9 months) survived significantly longer than the control group (median OS=25.1 months), with a HR=0.68, 95% CI, 0.55-0.85, p<0.001). The ORR was 43.6% for the T-DM1 arm versus 30.8% for the lapatinib + capecitabine arm, with a median duration of objective response (DOR) of 12.6 months versus 6.5 months, respectively.

T-DM1 was well tolerated, with no unexpected safety signals. The most common Grade ≥ 3 AEs in the T-DM1 arm were thrombocytopenia (12.9% vs. 0.2%), increased AST (4.3% vs. 0.8%), and increased ALT (2.9% vs. 1.4%); the most common Grade ≥ 3 AEs in the lapatinib + capecitabine arm were diarrhea (20.7% vs. 1.6%) palmar plantar erythrodysesthesia (16.4% vs. 0), and vomiting (4.5% vs. 0.8%). The incidence of Grade 3/4 AEs in the T-DM1 arm was 40.8% versus 57.0% in the lapatinib + capecitabine arm ²⁵.

2.6.3 Post-preoperative setting

2.6.3.1 The KATHERINE study (von Minckwitz et al NEJM 2019)

This phase 3 study randomized patients with HER2-positive early breast cancer who were found to have residual disease in the breast or axilla at surgery after completing neoadjuvant chemotherapy and trastuzumab-based therapy to the standard arm of trastuzumab only or T-DM1 x 14 cycles. In this study, T-DM1 was very well tolerated and improvement in the primary outcome of invasive disease-free survival was demonstrated in the T-DM1 arm, with an absolute improvement in invasive disease free survival at the interim analysis at three years (88.3% disease free in T-DM1 group vs. 77.0% in the trastuzumab-treated group, p<0.001), further demonstrating the efficacy of this agent but for the first time in the adjuvant setting.

2.6.3.2 The ‘ATEMPT’ study (Tolaney et al SABCS 2019)

This phase 2 study randomized patients with stage I HER2+ breast cancer to T-DM1 x 1 year vs. paclitaxel + trastuzumab x 12 weeks followed by trastuzumab maintenance to complete 1 year (3:1 randomization). The primary endpoint of this trial was toxicity. Early results from this trial also showed promising single agent activity with T-DM1 alone in the adjuvant setting (98% disease-free survival at 3 years). It was also tolerable and was without alopecia.

2.7 T-DM1 Clinical Safety

In clinical trials, T-DM1 has been evaluated as single-agent in 884 patients with HER2- positive metastatic breast cancer. The most common (frequency $\geq 25\%$) adverse drug reactions (ADRs) seen in 884 patients treated with T-DM1 were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.

Adverse events were identified in patients with HER2-positive metastatic breast cancer treated in the randomized trial described above (Section 7.1), TDM 4370g/BO21977 (EMILIA)²⁵. The study design and efficacy results are also described above. With regard to more detail on toxicity, while on study, 211 (43.1%) patients experienced \geq Grade 3 adverse events in the T-DM1 -treated group compared with 289 (59.2%) patients in the lapatinib plus capecitabine-treated group. Dose adjustments for T-DM1 were permitted. Thirty-two patients (6.5%) discontinued T-DM1 due to an adverse event, compared with 41 patients (8.4%) who discontinued lapatinib, and 51 patients (10.5%) who discontinued capecitabine due to an adverse event. The most common adverse events leading to T-DM1 withdrawal were thrombocytopenia and increased transaminases. Eighty patients (16.3%) treated with T-DM1 had adverse events leading to dose reductions. The most frequent adverse events leading to dose reduction of T-DM1 (in $\geq 1\%$ of patients) included thrombocytopenia, increased transaminases, and peripheral neuropathy. Adverse events that led to dose delays occurred in 116 (23.7%) of T-DM1 treated patients. The most frequent adverse events leading to a dose delay of T-DM1 (in $\geq 1\%$ of patients) were neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases and pyrexia²⁵.

The most common ADRs seen with T-DM1 in the randomized trial, EMILIA (frequency $>25\%$) were nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and constipation. The most common NCI-CTCAE (version 3) \geq Grade 3 ADRs (frequency $>2\%$) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue²⁵.

Although data for toxicities of T-DM1 specific to older patients are limited, recently published data from a safety-analysis using pooled data from T-DM1 monotherapy trials in the metastatic setting demonstrate good tolerance of therapy for all women. Toxicities consisted of mostly lab-based toxicities rather than symptomatic side effects. Sub-analyses restricted to older women showed similar toxicities in older women receiving T-DM1 compared with younger patients⁴⁹.

2.8 Clinical Pharmacokinetics of T-DM1

The recommended dose of T-DM1 for breast cancer is 3.6 mg/kg given as an IV infusion every 3 weeks. The PK analysis from the Phase I study (TDM3569g) following administration of 0.3 mg/kg to 4.8 mg/kg T-DM1 every 3 weeks showed that at the dose of 3.6 mg/kg every 3 weeks, the systemic clearance was approximately 12.7 mL/day/kg and the elimination half-life was approximately 3.1 days. The clearance of T-DM1 was nonlinear at doses less than or equal to 1.2 mg/kg. At all dose levels, clearance of T-DM1 was faster than that of trastuzumab. A weekly dosing regimen was also evaluated in Study TDM3569g, and 2.4 mg/kg weekly was identified as the MTD for weekly dosing. Key T-DM1 PK parameters (i.e., CL, Vss and t_{1/2}) at 2.4 mg/kg weekly were similar to those observed at 3.6 mg/kg every 3 weeks dosing.

There was no accumulation of T-DM1 when given every 3 weeks. The estimated volume of distribution was 30.7 to 58.4 mL/kg across all dose levels tested. Measurable levels of free DM1 were found, but are approximately 10,000 fold (by mass ratio) and approximately 50-fold (by molar ratio) lower than T-DM1 levels.

In the Phase II and III studies in MBC patients (TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976 and TDM4370g/BO21977), PK parameter values for T-DM1 after a 3.6 mg/kg dose given every 3 weeks were similar to those observed for the every 3 weeks dosing regimen in the Phase I study.

A robust population PK (popPK) model has been developed using the accumulated clinical data. The popPK model can predict T-DM1 exposure and interindividual variability in a large and representative patient population that has received prior trastuzumab-based therapy. The population parameter values for clearance and volume of distribution of the central compartment (Vc) for a typical person were estimated to be 0.68 L/day and 3.13 L, respectively. The popPK analysis showed a mean $t_{1/2}$ of 3.94 days for T-DM1. No adjustments in the starting dose of T-DM1 appear to be necessary in patient subpopulations based on data available to date, as it appears that dose adjustments would be unlikely to result in a meaningful reduction in inter-individual PK variability.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

- 3.1.1 Participants must have histologically or cytologically confirmed HER2-positive disease by local pathology, defined as immunohistochemistry (IHC) 3+ or amplification by FISH (HER2/CEP17 ratio ≥ 2 or an average of ≥ 6 HER2 gene copies per nucleus) AND confirmed by Central Pathology Review (Dr. Deborah Dillon at Brigham and Women's Hospital, Boston, MA) prior to patient being registered to begin protocol therapy. See section 3.4. <http://ascopubs.org/doi/full/10.1200/jco.2013.50.9984>. In cases where central review is prolonged, as per Section 3.4.8, a waiver may be granted by the Overall PI, Dr. Freedman.

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

- 3.1.2 Age ≥ 60 years at the time of study registration (men and women eligible)
- 3.1.3 Participants must have histologically or cytologically confirmed Stage I-III breast cancer with the following criteria met:
- If node-negative or if node status unknown (because it was not assessed), tumor size must be >5 mm of any hormone receptor subtype (document ER/PR status: if some ER/PR staining is present, ER and PR negative are defined as being positive in $<10\%$ cells [per local pathology read]).
 - If node-positive (N1-N3), T1mi, T1a, T1b, T1c, T2, or T3 tumors are eligible (see below for further details on defining node-negative disease)

Definition of node-negative disease (when node status known): If the patient has had a negative sentinel node biopsy and/or a negative axillary dissection, then the patient is determined to be node-negative. Axillary nodes with single cells or tumor clusters ≤ 0.2 mm by either H&E or IHC will be considered node-negative. Any axillary lymph node with tumor clusters between 0.02 and 0.2cm is considered a micrometastasis. Patients with a micrometastasis are eligible even if their tumor is ≤ 5 mm. An axillary dissection is not required to be performed in patients with a positive sentinel node and management of the axilla will be left up to the treating provider. 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. In these special situations, the investigator must document this approval in the patient medical record.

- 3.1.4 ER/PR determination assays performed by IHC methods according to the local institution standard protocol.
- 3.1.5 Standard chemotherapy/trastuzumab declined by patient OR patient is deemed by physician for any reason to not be a candidate for standard therapy (i.e. patient and/or provider choose not to pursue standard trastuzumab-based chemotherapy regimen because of concerns related to toxicity or provider/patient preference).
- 3.1.6 For patients with bilateral or multifocal/multicentric breast cancers, one of the following criteria must be met to enroll: (1) each cancer individually meets criteria for enrollment (only ONE tumor has to undergo central confirmation for HER2), (2) at least one tumor meets eligibility (per tumor size/nodes/subtype outlined above) and the other foci in the ipsilateral or contralateral breast are also HER2-positive but are too small for enrollment (e.g., a patient is eligible if a cancer is T2N0 and HER2-positive in one breast, but the contralateral breast has a T1a HER2+ cancer that isn't eligible on its own), (3) there is at least one qualifying tumor of >5 mm but there are other small foci of disease that are too small to test for ER/PR/HER2 and are felt to be a part of the same tumor or similar tumor, OR (4) at least one tumor meets eligibility and the other foci in the ipsilateral or contralateral breast are HER2-negative and do not meet criteria for adjuvant chemotherapy per provider discretion (e.g. if a patient has a HER2-positive tumor meeting eligibility but also has a second, HER2-negative, small, node-negative, ER+, low grade cancer present, she is still eligible for enrollment). However, in the specific case that a second breast cancer is stage III and HER2-negative, that patient is excluded (because the second cancer is high-risk and likely will require non-HER2-directed therapy).
- 3.1.7 All tumor removed by either a modified radical mastectomy or a segmental mastectomy (lumpectomy).

NOTE: Management of axillary lymph nodes is up to the treating provider; however, all surgical 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.

- 3.1.8 ≤ 90 days from the patient's most recent breast surgery for this breast cancer.
Note: In cases where registration will occur >90 days from surgery but within an acceptable time frame, patient may be eligible for enrollment with approval from the PI, Rachel Freedman MD, MPH.
- 3.1.9 ECOG Performance Status (PS) 0-2. See Appendix F.
- 3.1.10 Baseline ejection fraction $\geq 50\%$ by MUGA scan or echocardiogram performed ≤ 60 days prior to registration.
- 3.1.11 The following laboratory values obtained ≤ 14 days prior to registration:
- Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$ *
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Hemoglobin >9.0 g/dL
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN). If patient has known Gilbert's syndrome, the suggested threshold for treatment is a total bilirubin $\leq 2.0 \times$ ULN, but will be left to the treating provider's discretion.
 - AST and ALT $\leq 2.5 \times$ ULN, alkaline phosphatase $\leq 2.5 \times$ ULN
 - INR $<1.5 \times$ ULN for institution unless patient is on planned therapy with anticoagulants (i.e., warfarin) with higher target planned. In those cases, INR up to 3.5 is acceptable.
 - PTT $<1.5 \times$ ULN for institution unless patient is on planned therapy with heparin or heparin-like products

***NOTE:** In the case of longstanding ethnic neutropenia, patient may be eligible for enrollment with approval from the PI, Rachel Freedman MD, MPH.

- 3.1.12 Life expectancy >5 years per provider's assessment
- 3.1.13 Willing to employ adequate and appropriate birth control if applicable

NOTE: This study is for patients aged 60 and older, and most female patients will have entered menopause by this time; however patients should not become pregnant while on this study because T-DM1 can affect an unborn baby. Pre-menopausal women need to use birth control while on this study and women should not breastfeed a baby while on this study. Any man treated on this study will also need to use contraception if his partner is a premenopausal female. Patients should check with their health care provider about what kind of birth control methods to use and how long to use them.

- 3.1.14 Negative urine or serum pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only

NOTE: In the rare case that a woman enrolling on study is of childbearing potential, a pregnancy test is required prior to enrollment on study.

- 3.1.15 Able to provide informed written consent.
- 3.1.16 Willing to return to consenting institution for follow-up at 6 months
- 3.1.17 Willing to provide blood samples for mandatory correlative research purposes.
- 3.1.18 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- 3.2.1 Evidence of metastatic disease.

NOTE: Patients will not require baseline staging PET or CT chest, abdomen, pelvis or bone scan to rule out metastatic disease prior to enrollment. Any staging scans will be ordered at the treating provider's discretion. If metastatic disease is found on any staging studies done, patients will not be eligible for enrollment.

- 3.2.2 Locally advanced tumors at diagnosis (T4), including tumors fixed to the chest wall, peau d'orange, skin ulcerations/nodules, or clinical inflammatory changes (diffuse brawny cutaneous induration with an erysipeloid).
- 3.2.3 Patients with stage III, HER2-negative cancer in the contralateral breast (see 3.1.6 above).
- 3.2.4 Positive Hepatitis B (Hepatitis B surface antigen and antibody) and/or Hepatitis C (Hepatitis C antibody test) as indicated by serologies conducted ≤ 3 months prior to registration if liver function tests are outside of the normal institutional range.

NOTE: A hepatitis panel is required of all participants as part of screening (See Section 10: Study Calendar). Patients with positive Hepatitis B or C serologies indicating active infection without known active disease must meet the eligibility requirements for ALT, AST, total bilirubin, INR, PTT, and alkaline phosphatase on at least two consecutive occasions, separated by at least 1 week. Patients with laboratory evidence of vaccination to Hepatitis B (e.g., positive antibodies) are eligible.

- 3.2.5 Active liver disease, for example, due to autoimmune hepatic disorder, or sclerosing cholangitis.

- 3.2.6 Significant, active cardiopulmonary dysfunction (i.e. uncontrolled heart issues) as indicated by MUGA or echocardiogram performed ≤ 60 days prior to registration and/or by presence of any of the following:
- History of NCI CTCAE (Version 4.0) Grade ≥ 3 symptomatic congestive heart failure (CHF) or NYHA criteria Class \geq II
 - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
 - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate > 100 /min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second degree AV-block Type 2 [Mobitz 2] or third degree AV-block]); if adequately and safely treated, patient may be eligible.
 - Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
 - Myocardial infarction within 12 months prior to registration
 - Uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 100 mmHg)
 - Evidence of transmural infarction on ECG
 - Requirement for oxygen therapy
- 3.2.7 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
- 3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.9 Currently receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.
- 3.2.10 Concurrent second malignancy or past malignancy with $> 30\%$ estimated risk of relapse in next 5 years. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix in addition to smoldering pre-malignant or malignant conditions with minimized concern for clinical progression during treatment such as MGUS or CLL, based on treating provider's assessment. NOTE: If there is a history or prior malignancy, patient must not be receiving active treatment for this malignancy.
- 3.2.11 Any prior treatment with T-DM1 or any trastuzumab therapy.
- 3.2.12 Any neoadjuvant chemotherapy for this breast cancer.

3.2.13 > 90 days of tamoxifen therapy, or other hormonal therapy, for adjuvant therapy for this malignancy

NOTE: If the patient has received <90 days of such therapy but is still receiving it at the time of entry into the study, patient must temporarily stop the therapy prior to Cycle 1 Day 1. The therapy can re-start only after at least 6 weeks of T-DM1 have been administered (any time after C3D1).

3.2.14 History of exposure at any time to the following cumulative doses of anthracyclines:

- Doxorubicin or liposomal doxorubicin >500mg/m².
- Epirubicin >900mg/m².
- Mitoxantrone >120 mg/m².
- Another anthracycline, or more than one anthracycline used in a cumulative dose exceeding the equivalent of doxorubicin 500mg/m².

3.2.15 History of intolerance (including Grade 3 or 4 infusion reactions) to murine proteins.

3.2.16 History of previous invasive breast cancer ≤5 years.

NOTE: History of DCIS, LCIS is allowed.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Central Testing for HER2 Status

Mandatory Central Pathology Review is required as part of eligibility to confirm HER2-positive status. All central testing will be performed at the [REDACTED]

3.4.1 As soon as possible after consent is signed, notify the Coordinating Center [REDACTED] and DFCI CRC to obtain a screening number for HER2 Central Review. Pathology reports from both the biopsy and excision (with histology included, i.e. HER2 by IHC and/ or FISH) should be sent along for review. The Coordinating Center may provide guidance on which tissue is best to send for the central review.

3.4.2 Submit the below materials to the Coordinating Center for HER2 Central Review. These are mandatory (unless indicated otherwise):

- Original HER2 IHC slide with positive and negative controls
Note: some hospitals will not release the original HER2 IHC slide. If that is the case, please send the 5 unstained slides and a new IHC slides will need to be stained.
- 5 charged unstained slides (not baked) of invasive cancer for HER2 IHC/FISH each 5 µm thick for central testing (surgical and/or biopsy specimens).

- One corresponding H&E slide from the representative block
Note: Some hospitals will not release the original H&E. If that's the case, please send an additional unstained slide (total 6 USS)
- Redacted pathology reports from biopsy and excision
- Operative Report (Optional)
- HER2 Central Testing Requisition Form (Appendix K)
- Consider also shipping the additional tissue for banking at the same time as per Section 9.3 (15 additional unstained slides/FFPE block)

Please clearly label all materials listed above with patient initials, date of birth, screening number, and accession numbers. Official study ID will not yet be available at time of central testing.

- 3.4.3 If slides are unavailable or insufficient for tissue banking as below in Section 9, priority should be taken for central HER2 testing to be completed before any additional slides are sent. In addition, if slides are not available, sites may instead submit two cores taken from the block with invasive tissue (taken with a 1.2mm coring tool). If there isn't sufficient tissue for this collection, patients will still be deemed eligible for trial participation per local HER2-positive read.
- 3.4.4 The unstained slide(s) must be appropriately packed to prevent damage (i.e., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, patient screening number, and patient initials
- 3.4.5 Review is being performed at [REDACTED]
Ship all slides and accompanying materials to:

[REDACTED]

[REDACTED]

- 3.4.6 The Coordinating Center/ATOP Team will facilitate central HER2 review with BWH pathology. In some cases, HER2 IHC and/or HER2 FISH will need to be repeated.
- 3.4.7 The Coordinating Center/ATOP Team will forward the expedited results from central review to sites within 7-10 business days of receipt of tissue. Additional time may be required if IHC or FISH is repeated at the Coordinating Center. If significant delay exists because of difficulty obtaining tissue or because of logistical delays, a waiver of central HER2 status review can be made on a case by case basis by the study PI (Rachel Freedman; [REDACTED]) only.

- 3.4.8 After results are received from central review, if the patient is eligible, the patient will be registered per protocol section 4.
- 3.4.9 Submitted tissue samples will be analyzed as follows:

[REDACTED] If available, the original outside HER2 IHC slide will be reviewed and scored. If the result is HER2 3+ upon central review, the case will be classified as positive and repeat testing will not be performed. If the result is not HER2 3+ on central review, repeat HER2 IHC testing will be performed. A result of HER2 3+ on central IHC testing will be classified as HER2-positive. If HER2 IHC result is not 3+, a FISH test will be performed. Results will be interpreted according to ASCO/CAP guidelines, including the 2018 update to the guidelines and subsequent updates ⁵⁰.

HER2 IHC will be assessed by immunohistochemistry with NeoMarkers HER2 (clone SP3) order number 913-SO-A. performed on the Leica Bond III platform with a 1:40 dilution of the primary antibody. FISH to detect HER2 gene amplification will be assessed utilizing the PathVysion assay (Abbott Molecular, Abbott Park, Illinois). The selection of tissue and the identification of target areas on the hematoxylin and eosin (H and E)-stained slide are performed by [REDACTED] or her designate. Using the H and E slide as a reference, target areas are etched with a diamond-tipped etcher on the back of the unstained slide to be assayed. The HER2 probe (labelled with SpectrumOrange) and D17Z1 probe (alpha satellite DNA sequence at the centromeric region of chromosome 17 labeled with SpectrumGreen) are hybridized following the laboratory validated protocol. Two technologists each analyze 15 interphase nuclei (30 total) with the results expressed as the average ratio of HER2 signals to D17Z1 signals and the average number of HER2 and D17Z1 signals per nucleus. Results will be interpreted based on the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines, including the 2018 update to the guidelines and subsequent updates.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention 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 protocol-specific eligibility checklist.

An email confirmation of the registration be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. The required forms in Section 4.4 should be emailed or faxed to the Project Manager.

Following registration, participants should begin protocol therapy within 7 business days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

- Clinic visit note documenting history and physical exam
- Copy of required laboratory testing including: Hematology (CBC with differential), chemistries (SGOT (AST), SGPT (ALT), alkaline phosphatase, Total bilirubin, chloride, creatinine, bicarbonate, calcium, glucose, sodium, potassium), PT, INR, hepatitis testing, and pregnancy test report if necessary.
- MUGA or Echocardiogram report
- Pathology reports and documentation of ER/PR and HER2 status
- HER2 results report from central confirmation (see Section 3.4)
- Signed participant consent form
- HIPAA authorization form
- Completed Eligibility Checklist

The Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. Project Manager will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site.

5. TREATMENT PLAN

5.1 Treatment Regimen

T-DM1 will be administered every 3 weeks, with 21 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Regimen Description						
Agent	Premedications; Precautions	Dose	Route*	Observation**	Schedule	Cycle Length
T-DM1	None required; per institutional standards	3.6 mg/kg	IV over 90 mins (+/- 10 mins) for the first infusion, then over 30 mins (+/- 10 mins) for C2-C17	Per institutional policy.	Day 1 (-2/+7)	21 days (3 weeks)

* If patient tolerates longer infusion rate better, C2-C17 can be administered over longer than 30 min (+/- 10 min) with approval from the PI, [REDACTED]

** Per institutional policies and package insert instructions (Section 2.1 of Kadcyla package insert), participants should be observed for at least 90 minutes after the initial dose of T-DM1 for fever, chills, or other infusion associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), participants will be observed for at least 30 minutes for subsequent doses of T-DM1. Observation times are reflective of standard of care for T-DM1 administration. Over the course of treatment on study, if treating providers wish to manually allow for less observation time, after the first infusion has occurred, ordering providers may lessen the observation time in line with their institutional policy by providing direct nursing communication and ordering for that patient.

5.2 Pre-Treatment Criteria

5.2.1 The following must be confirmed ≤ 2 days of Day 1 of each cycle:

- $ANC \geq 1000/mm^3$ *
- $Platelets \geq 75,000/mm^3$
- Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) [For patients with Gilbert's syndrome, the suggested threshold for treatment is a total bilirubin $\leq 2.0 \times$ ULN, but will be left to the treating provider's discretion] (refer to protocol Table 5 for hyperbilirubinemia dose modifications);
- ALT and AST $\leq 5.0 \times$ ULN (refer to protocol Table 4).

C1D1 results need to re-meet eligibility parameters to start treatment if drawn again after screening evaluations.

*Note: for participants enrolled with longstanding ethnic neutropenia, ANC pre-treatment targets may be left to the discretion of the treatment provider

5.3 T-DM1 Agent Administration

TDM1 will be administered every 21 days (3 weeks), up to 2 days early or up to 7 days late (-2/+7). Use actual weight or estimated dry weight if fluid retention (no change in dose required for <5% weight change; per institutional policies, dose will be recalculated for >5% change in body weight).

During the treatment phase, patients will be seen every 21 days for symptom review and adverse event grading (at the start of each cycle). PRO-CTCAEs and QOL will be assessed at each time point and multiple other correlatives will be completed longitudinally as delineated (see Section 9.2)

Cardiac evaluation (echo or MUGA) will be completed at baseline, cycles 4, 8, and 17, and one time during the 6month follow-up visit after completion of therapy for patients on study. This will be billed to commercial insurance as standard of care practice. If patients come off study treatment early, they will have their final cardiac evaluation at the follow-up (6months) Observation visit only.

5.4 Hormonal Therapy (Non-Investigational Product)

Any patient deemed to be a candidate for hormonal therapy will be able to initiate this treatment at their provider's discretion, after at least 6 weeks of T-DM1 have been administered (anytime after C3D1). Any hormonal therapy started before clinical trial enrollment should be stopped prior to Cycle 1 Day 1 and then may be re-started after at least 6 weeks of T-DM1 treatment (any time after C3D1).

5.5 Radiation Therapy (Non-Investigational)

Any patient deemed to be candidate for radiation therapy will be able to initiate this treatment at their provider's discretion, at any time during T-DM1 treatment on this protocol (the protocol initially mandated at least 12 weeks of protocol therapy before radiation). Patients who have received previous intraoperative/partial breast radiation are eligible. Patients undergoing mastectomy may receive chest wall and nodal radiation according to local institutional standards. Patients may receive T-DM1 during radiotherapy.

5.6 Reconstructive Surgery and Other Surgery

Patients may undergo reconstructive surgery (and any other necessary elective surgery) after completing at least 12 weeks of protocol therapy. Patients should have a CBC test to ensure adequate platelet counts prior to any surgery. Although patients requiring elective surgery for any other reason should ideally wait until treatment completes, surgery is permitted after at least 12 weeks of protocol therapy. Urgent/emergent surgery can occur at any time that is necessary.

5.7 General Concomitant Medication and Supportive Care Guidelines

Antiemetics, NSAIDS, and acetaminophen may be used at the discretion of the attending physician. Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of ASCO 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline ⁵¹.

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Potent CYP3A4 inhibitors, such as ketoconazole and erythromycin, should be avoided if possible during the study treatment period with T-DM1; however, there are no specifically-contraindicated medications.

Medications known to potentially affect platelet counts and liver function should be used with caution at the treating providers' discretion.

Excessive alcohol intake should be avoided (occasional use is permitted, and there is no specific limit on the amount of intake).

5.8 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 17 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.9 Duration of Follow Up

Participants will be followed for 5 years after completion of protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Once patients complete a year of treatment (or once a patient comes off treatment for toxicity or progression), they will be followed according to usual clinical guidelines with regard to testing and lab draws. No routine staging examinations or blood work will be recommended after therapy completes unless symptoms arise and providers feel tests are necessary. However, a one-time in person, post treatment follow-up will occur 6 months (+/- 2 weeks) after treatment is completed (or after patients come off study treatment) with a physical exam, adverse event evaluation, cardiac examination, basic blood work, and correlative testing. Otherwise protocol-related follow-up for follow-up and DFS events may occur by phone, mail, fax, or email over time if patients return to their local, treating physicians. Patients will continue screening mammography at their providers' discretion.

5.10 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The safety plan for patients in the T-DM1 treatment arm is based on nonclinical toxicities of T-DM1, the clinical experience with this molecule in completed and ongoing studies, and clinical

toxicities related to its components (trastuzumab and maytansine, the parent drug of DM1).

The following section summarizes the important risks associated with T-DM1 identified in multiple breast cancer studies to date. Please refer to the T-DM1 Investigator's Brochure for the most recent comprehensive information on the safety profile of T-DM1.

Table 3. Recommended Dose Reduction Schedule for Adverse Events

Dose Reduction Schedule	Dose Level
Starting dose (dose level 0) *	3.6 mg/kg
First dose reduction	3.0 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

* Dose level 0 refers to the starting dose.

Use the following terminology to describe dose modification actions:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

6.1 Recommended dose modifications and toxicity

NOTE: No re-escalation of the T-DM1 dose will be allowed after a dose reduction occurs.

Patients will be assessed for adverse events 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.

If a planned dose is delayed or missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion may be administered at the dose and rate the patient tolerated in the most recent infusion.

The infusion rate of T-DM1 should be slowed or interrupted if the patient develops an infusion-related reaction. Permanently discontinue T-DM1 for life-threatening infusion related reactions.

Specific management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary interruption, dose reduction or treatment discontinuation of T-DM1 as per guidelines provided in Tables 4 to 10.

If any significant T-DM1-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. If delay of more than 42 days is necessary, patient will go off study treatment and proceed to Event Monitoring. "Significant" and "related" will be based on the judgment of the investigator in

consultation with the Study Chair, Dr. Rachel Freedman, 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 adverse event (or any other adverse event for which the investigator chooses to delay dosing) resolves to Grade ≤ 1 or baseline, the patient may resume T-DM1 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 T-DM1 either at the previous dose level or at one dose level lower (see Table 3) based on the specific instructions in the sections below. If possible, future cycle intervals should remain every 21 days.

If the treating provider feels strongly that the delay in therapy is not related to T-DM1 and wants to resume treatment after 42 days, the study chair, Dr. Rachel Freedman, will need to approve continuation of therapy (e.g. if a patient has elective surgery with a complication of surgery and can't resume treatment on schedule, etc.)

As per Section 5.9, T-DM1 will be continued up to 17 cycles, unless the following occur: Breast cancer recurrence, intolerable toxicity, initiation of another anti-cancer therapy (other than hormonal therapy or radiation), patient discontinuation, >42 days elapsed since the last dose, or 1 year of T-DM1 therapy has been reached. If treatment is delayed and reason for the treatment delay is resolved, T-DM1 therapy should continue until 17 cycles are reached (per MD discretion).

6.2 Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic transient increases in the concentrations of serum transaminases (Grade 1- 4 transaminitis), has been observed while on treatment with ado-trastuzumab emtansine in clinical trials (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). A cumulative effect of ado-trastuzumab emtansine on transaminases has been observed (Data on File. Genentech, Inc.)

Cases of severe hepatotoxicity, including death due to drug-induced liver injury (DILI) and hepatic encephalopathy, have been observed in patients treated with ado-trastuzumab emtansine (Trastuzumab Emtansine. Investigator's Brochure Version 7). While there is evidence of drug-induced liver toxicity (predominantly in the form of asymptomatic increases in the concentrations of serum transaminases) in patients treated with ado-trastuzumab emtansine, its potential to cause liver injury with clinically meaningful changes in liver function is unclear as the observed cases were confounded by concomitant medications with known hepatotoxic potential and/or underlying conditions. Nevertheless, a contributory role of ado-trastuzumab emtansine in these cases cannot be excluded.

Monitor serum transaminases and bilirubin prior to initiation of ado-trastuzumab emtansine treatment and prior to each ado-trastuzumab emtansine dose (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Patients with known active hepatitis B virus or hepatitis C virus were excluded from TDM 4370g/BO21977 (EMILIA).²⁵ Reduce the dose or discontinue ado-

trastuzumab emtansine as appropriate in cases of increased serum transaminases and/or total bilirubin. Permanently discontinue ado-trastuzumab emtansine treatment in patients with serum transaminases $\geq 5.0 \times \text{ULN}$ and concomitant total bilirubin $\geq 3.0 \times \text{ULN}$. Ado-trastuzumab emtansine has not been studied in patients with serum transaminases $> 2.5 \times \text{ULN}$ or bilirubin $> 1.5 \times \text{ULN}$ prior to the initiation of treatment.

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with ado-trastuzumab emtansine (Kadcyla® Prescribing Information, Genentech, Inc. February 2013). NRH was also observed in one fatal case of hepatic failure. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. NRH should be considered in all patients with clinical symptoms of portal hypertension and/or a cirrhosis-like pattern seen on computed tomography (CT) scan of the liver but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with ado-trastuzumab emtansine but with normal transaminases and no manifestations of cirrhosis. Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, ado-trastuzumab emtansine treatment must be permanently discontinued.

Serious hepatotoxicity has been reported, including liver failure and rare deaths in patients treated with T-DM1. Nodular regenerative hyperplasia is also a known and very rare condition that has been reported in patients receiving T-DM1. Monitor serum transaminases and bilirubin prior to initiation of T-DM1 treatment and prior to each T-DM1 dose. A reduction in the dose of T-DM1 is recommended in the case of hepatotoxicity exhibited as increases in serum transaminases and/or hyperbilirubinemia (see Tables 4 and 5).

Table 4. Dose Modification Guidelines for Increased Serum Transaminases* (AST/ALT)

Adverse Event	Grade 2 (>3.0 to $\leq 5 \times$ ULN*)	Grade 3 (>5 to $\leq 20 \times$ ULN*)	Grade 4 ($>20 \times \text{ULN}^*$)
Alanine aminotransferase (ALT)/ Aspartate aminotransferase (AST) increased	Treat at same dose level.	Hold T-DM1 until AST/ALT recovers to Grade ≤ 2 , and then reduce one dose level.	Permanently discontinue T- DM1. Patient goes to Observation and then to Event Monitoring.

* Upper limit of normal

Table 5. Dose Modification Guidelines for Hyperbilirubinemia

Adverse Event	Grade 2 (>1.5 to $\leq 3 \times \text{ULN}$)	Grade 3 (>3 to $\leq 10 \times \text{ULN}$)	Grade 4 ($>10 \times \text{ULN}$)
Blood bilirubin increased	Hold T-DM1 until total bilirubin recovers to Grade ≤ 1 , and then treat at same dose level.	Hold T-DM1 until total bilirubin recovers to Grade ≤ 1 , and then reduce one dose level.	Permanently discontinue T-DM1. Observation and then to Event Monitoring.

* For patient who have abnormalities in AST/ALT and bilirubin, permanently discontinue T-DM1 treatment in patients with serum transaminases $\geq 5.0 \times \text{ULN}$ and concomitant total bilirubin $\geq 3.0 \times \text{ULN}$. Permanently discontinue T-DM1 in patients diagnosed with nodular regenerative hyperplasia (NRH).

6.3 Thrombocytopenia

Thrombocytopenia, or decreased platelet count, was reported in clinical trials of ado-trastuzumab emtansine (103 of 884 treated patients with \geq Grade 3; 283 of 884 treated patients with any Grade) (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). The majority of these patients had Grade 1 or 2 events ($< \text{LLN}$ to $\geq 50,000/\text{mm}^3$) with the nadir occurring by day 8 and generally improving to Grade 0 or 1 ($\geq 75,000/\text{mm}^3$) by the next scheduled dose. In clinical trials of ado-trastuzumab emtansine, the incidence and severity of thrombocytopenia were higher in Asian patients. Independent of race, the incidence of severe hemorrhagic events in patients treated with ado-trastuzumab emtansine was low.

In the randomized trial, TDM 4370g/BO21977 (EMILIA), the overall frequency of thrombocytopenia was 31.2% in the ado-trastuzumab emtansine -treated group and 3.3% in the lapatinib plus capecitabine-treated group (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). The incidence of \geq Grade 3 thrombocytopenia was 14.5% in the ado-trastuzumab emtansine treated group and 0.4% in the lapatinib plus capecitabine-treated group. In Asian patients, the incidence of $>$ Grade 3 thrombocytopenia was 45.1% in the ado-trastuzumab emtansine -treated group and 1.3% in the lapatinib plus capecitabine-treated group.

Monitor platelet counts prior to initiation of ado-trastuzumab emtansine and prior to each ado-trastuzumab emtansine dose (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Ado-trastuzumab emtansine has not been studied in patients with platelet counts $< 100,000/\text{mm}^3$ prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater ($< 50,000/\text{mm}^3$) do not administer ado-trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq 75,000/\text{mm}^3$). Patients with thrombocytopenia ($< 100,000/\text{mm}^3$) and patients on anti-coagulant treatment should be closely monitored during treatment with ado-trastuzumab emtansine.

A reduction in dose is recommended in the case of Grade 2-4 thrombocytopenia (see Table 6).

Table 6 Dose Modification Guidelines for Thrombocytopenia

Adverse Event	Grade 2 <75,000/mm ³ - 50,000/mm ³ ; <75-50.0 x 10 ⁹ /L	Grade 3 <50,000/mm ³ - 25,000/mm ³ ; <50-25.0 x 10 ⁹ /L	Grade 4 <25,000/mm ³ ; <25.0 x 10 ⁹ /L
Platelet count decreased	<p>Hold T-DM1 until platelet count recovers to \leq grade 1 ($\geq 75,000/\text{mm}^3$) then continue T-DM1 at SAME dose. If platelets do not recover within 21 days from the last dose, then reduce one dose level.</p> <p>If a second occurrence of grade 2 platelets occurs, T-DM1 will be held until \leq grade 1, then re-started at next dose level (provided that dose isn't <2.4 mg/kg) for subsequent cycles. Patients with grade 2 platelets at 2.4 mg/kg may continue treatment but this needs to first be discussed with the study PI.</p> <p>However, if no recovery of platelets to \leq grade 1 occurs within the allowable delay of 42 days from last dose, the patient will discontinue T-DM1.</p>	<p>Hold T-DM1 until platelet count recovers to \leq grade 1 ($\geq 75,000/\text{mm}^3$) then continue T-DM1 at SAME dose. If platelets do not recover within 21 days from the last dose, reduce one dose level.</p> <p>If a second occurrence of grade 3 platelets occurs, T-DM1 will be held until \leq grade 1, then re-started at next dose level (provided that dose isn't <2.4 mg/kg) for subsequent cycles. Patients with grade 3 platelets at 2.4 mg/kg may continue treatment but this needs to first be discussed with the study PI.</p> <p>However, if no recovery of platelets to \leq grade 1 occurs within the allowable delay of 42 days from last dose, the patient will discontinue T-DM1.</p>	<p>Hold T-DM1 until platelet count recovers to \leq grade 1 ($\geq 75,000$), then REDUCE T-DM1 one dose level.</p> <p>If a second occurrence of grade 4 platelets occurs, T-DM1 will be held until \leq grade 1, then re-started at next dose level (provided that dose isn't <2.4 mg/kg) for subsequent cycles.</p> <p>Patients with grade 4 platelets at 2.4 mg/kg will discontinue T-DM1.</p>

6.4 Neutropenia

Note: Neutropenia is a rare event observed with T-DM1 monotherapy.

Table 7 Dose Modifications for Neutropenia

Adverse Event	Grade 3* (ANC <1000 – 500 mm ³)	Grade 4 (ANC <500/mm ³)**
Neutrophil count decreased (neutropenia) *The study PI can assist with management of dose reductions in the rare case of ethnic neutropenia at baseline and how to approach dose modification	HOLD T-DM1 until neutrophil count recovers to ≤ grade 1 then continue T-DM1 at SAME dose. If neutrophil count does not recover to baseline or ≤ grade 1 within 21 days from last administered dose, then REDUCE one dose level. If second occurrence of grade 3 neutropenia, T-DM1 will be held until neutrophil count ≤ grade 1, then re-started at two dose levels lower (provided that dose is not <2.4 mg/kg) for subsequent cycles. If no recovery of neutrophils within the allowable delay of 42 days from last dose, the patient will discontinue T-DM1. Patients with grade 3 neutropenia at 2.4 mg/kg may continue treatment, but this needs to be discussed with the study PI first. Growth factor is allowed per provider discretion.	HOLD T-DM1 until neutrophil count recovers to ≤ grade 1 then REDUCE one dose level. If second occurrence of grade 4 neutropenia, T-DM1 will be held until neutrophil count ≤ grade 1 and then re-started at two dose levels lower (provided that dose is not <2.4 mg/kg) for subsequent cycles. Patients with grade 4 neutropenia at 2.4 mg/kg will discontinue study treatment.

* No dose change for Grade 2

** It is recommended (but not mandatory) that patients who experience grade 4 hematologic adverse events of any kind should be checked weekly for recovery

6.5 Left Ventricular Dysfunction (LVEF)

Patients treated with ado-trastuzumab emtansine are at increased risk of developing left ventricular dysfunction (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). A decrease of LVEF to < 40% has been observed in patients treated with ado-trastuzumab emtansine. In the randomized trial, TDM 4370g/BO21977 (EMILIA), left ventricular dysfunction occurred in 1.8% of patients in the ado-trastuzumab emtansine -treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group.

Assess LVEF prior to initiation of ado-trastuzumab emtansine and at regular intervals (e.g. every three months) during treatment to ensure the LVEF is within the institution's normal limits (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Treatment with ado-trastuzumab emtansine has not been studied in patients with LVEF < 50% prior to initiation of

treatment. If, at routine monitoring, LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold ado-trastuzumab emtansine and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue ado-trastuzumab emtansine if the LVEF has not improved or has declined further. Patients with a history of symptomatic congestive heart failure (CHF), serious cardiac arrhythmia, or history of myocardial infarction or unstable angina within 6 months were excluded from TDM 4370g/BO21977 (EMILIA).

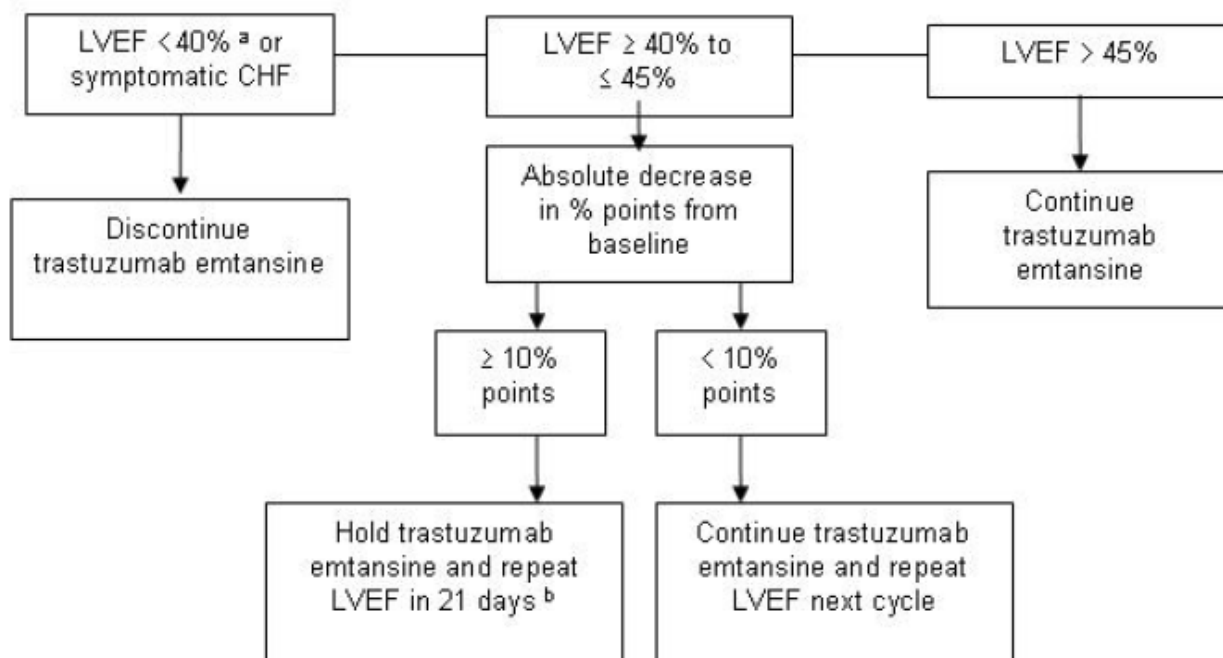
LVEF will be assessed prior to initiation of T-DM1 and at regular intervals (baseline, cycle 4, 8, 17) during treatment to ensure the LVEF is within the institution's normal limits. Treatment with T-DM1 has not been studied in patients with LVEF < 50%. If, at routine monitoring, LVEF is <40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold T-DM1 and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue T-DM1 if the LVEF has not improved or has declined further. Patients will then proceed to Observation and Event Monitoring (see Table 8 and figure below).

Table 8 Dose Modifications for Left Ventricular Dysfunction

Adverse Event	LVEF >45%	Resting ejection fraction (EF) ≥40 to 45% AND <10% points from baseline	Resting EF ≥40 to 45% AND ≥10% points drop from baseline	LVEF <40%	Symptomatic CHF
Ejection fraction decreased	Continue treatment with T-DM1. Treatment may be held at the discretion of the provider if felt to be in patient's best interest.	Continue treatment with T-DM1. Treatment may be held at the discretion of the provider if felt to be in patient's best interest. Repeat LVEF assessment within 3 weeks.	Hold T-DM1. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to <10% points from baseline, discontinue T-DM1. Patient goes to Observation and then Event Monitoring.	Hold T-DM1. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue T-DM1. If EF is ≥40, follow corresponding management for that EF. Patient goes to Observation and then Event Monitoring.	Discontinue T-DM1.

CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

Algorithm for Continuation and Discontinuation of T-DM1 Based on Left Ventricular Ejection Fraction Assessments in Patients



CHF = congestive heart failure; LVEF = left ventricular ejection fraction.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

^a LVEF can be repeated within 21 days, and trastuzumab emtansine should be discontinued if LVEF < 40% is confirmed. Trastuzumab emtansine should be held while the repeat LVEF is obtained.

^b After a second consecutive confirmatory result, trastuzumab emtansine should be discontinued if the LVEF is confirmed to be ≥ 10% points below baseline or if medical management was required to correct the LVEF.

6.6 Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome have been reported in clinical trials with ado-trastuzumab emtansine (Kadcyla® [ado-trastuzumab emtansine]. Genentech, Inc. February 2013).

Pneumonitis at an incidence of 0.8% (7 out of 884 treated patients) has been reported, with one case of grade 3 pneumonitis. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. In the randomized trial TDM 4370g/BO21977 (EMILIA) the overall frequency of pneumonitis was 1.2%. Treatment included administration of steroids, oxygen, and study drug discontinuation (Data on File. Genentech, Inc.).

Permanently discontinue treatment with ado-trastuzumab emtansine in patients diagnosed with ILD or pneumonitis (Kadcyla® [ado-trastuzumab emtansine]. Genentech, Inc. February 2013). Patients with dyspnea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary toxicity.

Table 9 Dose Modifications for Pulmonary Toxicity

Adverse Event	Any Grade
Hypoxia	Permanently discontinue T-DM1. Patient goes to Observation and then Event Monitoring
Pneumonitis	

6.7 Peripheral Neuropathy

Table 10 Dose Modifications for Peripheral Neuropathy

Adverse Event	Grade 3 or 4
Peripheral motor neuropathy	Hold T-DM1 in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2.*
Peripheral sensory neuropathy	

* Refer to protocol section 6.1 for re-initiation guidelines. A dose reduction or dose hold is not mandatory in the setting of grade 2 symptoms; however, if a provider feels a reduction in dose is warranted for grade 2 symptoms and is in the best interest of the patient, dose may be reduced one level for each adverse event.

6.8 Diarrhea

This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). Loperamide is not supplied by the study.

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

6.9 T-DM1 Overdosage

There is no known antidote for overdose of T-DM1. In clinical trials, overdose of T-DM1 has been reported at approximately two times the recommended dose which resulted in Grade 2 thrombocytopenia (resolved 4 days later) and one death. In the fatal case, the patient incorrectly received T-DM1 at 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to T-DM1 were not established.

6.10 Infusion Reactions

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. 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.

Serious reactions to trastuzumab are rare and are mild if they occur. No premedication for the first infusion of trastuzumab emtansine is specified or expected. Patients who experience trastuzumab emtansine infusion-related temperature elevations of $>38.5^{\circ}\text{C}$ 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. Patients who experience a Grade 3 allergic reaction or ARDS will be discontinued from study treatment and followed.

6.11 Embryo-Fetal Toxicity

Ado-trastuzumab emtansine can cause fetal harm when administered to a pregnant woman (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). There are no adequate and well-controlled studies of ado-trastuzumab emtansine in pregnant women and no reproductive and developmental toxicology studies have been conducted with ado-trastuzumab emtansine. Nevertheless, treatment with trastuzumab, the antibody component of ado-trastuzumab emtansine, during pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. DM1, the cytotoxic component of ado-trastuzumab emtansine, can be expected to cause embryo-fetal toxicity based on its mechanism of action.

If ado-trastuzumab emtansine is used during pregnancy, or if the patient becomes pregnant while receiving ado-trastuzumab emtansine, apprise the patient of the potential hazard to the fetus (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Verify pregnancy status prior to the initiation of ado-trastuzumab emtansine. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. If ado-trastuzumab emtansine is administered during pregnancy or if a patient becomes pregnant while receiving ado-trastuzumab emtansine, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MoTHER Pregnancy Registry by contacting 1-800-690-6720.

It is not known whether ado-trastuzumab emtansine, specifically, is excreted in human milk, but IgG is known to be excreted in human milk (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). In lactating monkeys, trastuzumab was excreted in small amounts (about 0.3% of maternal serum concentrations) in breast milk after post-partum doses of 25 mg/kg (about 7

times the clinical dose of ado-trastuzumab emtansine). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ado-trastuzumab emtansine, a decision should be made whether to discontinue nursing or discontinue ado-trastuzumab emtansine, taking into account the importance of the drug to the mother.

6.12 Neurotoxicity

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of ado-trastuzumab emtansine (14 of 884 treated patients with \geq Grade 3; 196 of 884 treated patients with any Grade) (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). In the randomized trial (Study 1), the overall frequency of peripheral neuropathy was 21.2% in the ado-trastuzumab emtansine-treated group and 13.5% in the lapatinib plus capecitabine-treated group. The incidence of \geq Grade 3 peripheral neuropathy was 2.2% in the ado-trastuzumab emtansine -treated group and 0.2% in the lapatinib plus capecitabine-treated group. Ado-trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to \leq Grade 2. Patients should be clinically monitored on an ongoing basis for signs or symptoms of neurotoxicity.

6.13 Extravasation

In ado-trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). These reactions, observed more frequently within 24 hours of infusion, were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Specific treatment for ado-trastuzumab emtansine extravasation is unknown. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List for T-DM1

Serious Adverse Effects:

Hepatotoxicity [U.S. Boxed Warning]: Serious hepatotoxicity has been reported, including liver failure and death in patients treated with Ado-trastuzumab emtansine. Monitor serum transaminases and bilirubin prior to initiation of treatment.

Cardiac Toxicity [U.S. Boxed Warning]: Ado-trastuzumab emtansine administration may lead to reductions in the left ventricular ejection fraction (LVEF). Evaluate left

ventricular function in all patients prior to and during treatment.

Embryo-Fetal Toxicity [U.S. Boxed Warning]: Exposure to ado-trastuzumab emtansine can result in embryo-fetal death or birth defects.

Injection site extravasation, anemia, neutropenia, thrombocytopenia, anaphylactoid reaction, peripheral nerve disease, dyspnea, interstitial lung disease and pneumonitis.

Most Common Adverse Events, >10%

Central nervous system: Fatigue, headache, fever, insomnia
Dermatologic: Skin rash
Gastrointestinal: Nausea, constipation, diarrhea, abdominal pain, vomiting, xerostomia, stomatitis
Hematologic: Thrombocytopenia, anemia
Hepatic: Increased serum aspartate aminotransferase, increased serum alanine aminotransferase, increased serum transaminases, increased serum bilirubin
Neuromuscular & skeletal: Musculoskeletal pain, peripheral neuropathy, arthralgia, weakness, myalgia
Respiratory: Epistaxis, cough, dyspnea

Less Common Adverse Events, 1% - 10%

Cardiovascular: Peripheral edema, hypertension, left ventricular systolic dysfunction
Central nervous system: Dizziness, chills
Dermatologic: Pruritus
Endocrine & metabolic: Hypokalemia
Gastrointestinal: Dyspepsia, dysgeusia
Genitourinary: Urinary tract infection
Hematologic: Neutropenia
Hepatic: Increased serum alkaline phosphatase
Local: Infusion related reaction
Ocular: Blurred vision, conjunctivitis, dry eye syndrome, lacrimation
Respiratory: Pneumonitis
Miscellaneous: Antibody development, hypersensitivity

Rare Adverse Events (Important or life-threatening), <1%

Anaphylaxis, hepatic encephalopathy, hepatic nodular regenerative hyperplasia, hepatotoxicity, portal hypertension

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
 - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
 - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.
- **Attribution of the AE:**
 - 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.

7.3 Adverse Event Reporting

- 7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.
- 7.3.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.
- 7.3.3 For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.
- 7.3.4 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report serious AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes

detailed in the table below.

Table 11. Reportable AEs

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 calendar days [#]	5 calendar days	24 hours [*]
Possible Probable Definite	Not required	5 calendar days	5 calendar days [#]	5 calendar days	24 hours [*]
[#] If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
[*] For participants enrolled and actively participating in the study or for AEs occurring within 30 days of the last intervention, the AE should be reported within <u>1 business day</u> of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Expedited Reporting to Genentech

7.4.1 Assessment of Safety

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to T-DM1, all events of death, any pregnancy that occurs during treatment of within seven months following the last dose of T-DM1, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.4.2 Methods and timing for assessing and recording safety variables

The investigator is responsible for ensuring that all AEs and SAEs observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period, during which AEs and SAEs must be reported begins after initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to study treatment. See Section 7.4.3 for additional reporting requirements.

The following adverse events will be reported on the appropriate study specific case report forms:

- Toxicities defined by Genentech as AEs of Special Interest (AESI) per section 7.4.3

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be assessed and reported, when appropriate. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to T-DM1 (see following guidance), expectedness, and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline for reporting to Genentech:

- Yes: There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study medication; and/or the AE abates or resolves upon discontinuation of the study medication or dose reduction/dose delay and, if applicable, reappears upon re-challenge. Events attributed to be definitely, probably, possibly, or unlikely related to the study treatment per Section 7.2 are considered "yes" when reporting to Genentech.
- No: Evidence exists that the AE has an etiology other than the study medication (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study medication administration (e.g., cancer diagnosed 2 days after first dose of study drug). Events attributed to be unrelated to the study treatment per Section 7.2 are considered "no" when reporting to Genentech.

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

7.4.3 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 7.4.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 7 months after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech. 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 the T-DM1 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 T-DM1 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)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid

communication by the trial Sponsor to other parties may also be warranted.

The T-DM1 Events of Special Interest are:

- Cardiac events
- Thrombocytopenia (Grade ≥ 3)
- Hepatic events (Grade ≥ 3 AST, ALT or total bilirubin elevations or Drug-Induced Liver injury (non-serious and serious))
- Infusion Associated Reactions, Hypersensitivity
- Embryofetal Toxicity or Birth Defects
- Suspected transmission of an infectious agent by the study drug, as defined below:
 - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
 - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
 - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

Product Complaint

A Product Complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial. Notify the Coordinating Center of any product complaints at [REDACTED]

7.4.4 Procedures for Reporting AEs to Genentech

Investigators must report all AEs of Special Interest (AESIs) and SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed by the site with the Safety Reporting Fax Cover Sheet (Appendix G) immediately upon completion to the Genentech Drug Safety at:

- [REDACTED]
- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
 - Serious AE reports that are related to the T-DM1 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 the T-DM1 will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- AESIs and Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Additional Reporting Requirements to Genentech include the following:

- Pregnancy reports: While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to T-DM1, shall be transmitted to Genentech/Roche within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Special situation reports

In addition to all SAEs, product complaints (with or without an AE), pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Drug interaction
- Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

MedWatch 3500A (Mandatory Reporting) form is available at
<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>

7.5 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Ado-trastuzumab emtansine (T-DM1, KADCYLA®)

8.1.1 Description

Ado-trastuzumab emtansine is a HER2-targeted antibody-drug conjugate. The antibody is the humanized anti-HER2 IgG1, Trastuzumab. Ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

Pharmacokinetic information:

- Distribution – V_d – 3.13 L
- Protein binding – DM1: 93%
- Metabolism – The DM1 component undergoes metabolism of CYP3A4/5. DM1 did not inhibit or induce major CYP450 enzymes.
- Elimination – The clearance was 0.68 L/day and the elimination half-life was approximately 4 days.

8.1.2 Form

Ado-trastuzumab emtansine single-use vials contain 160 mg per vial of ado-trastuzumab emtansine as lyophilized powder.

8.1.3 Preparation and Storage

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution. Do not freeze or shake. Protect the vials from light.

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is ado-trastuzumab emtansine and not trastuzumab.

Reconstitute the 160 mg vial with 8.0 mL of Sterile Water for Injection to a concentration of 20 mg/mL. Do not shake. The reconstituted vials should be used within 1 hour of reconstitution. If not used within this time frame, the reconstituted vials can be stored for up to 8 hours at ambient temperatures (20°C -25°C) or 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F). Discard unused vials after 24 hours. Do not freeze.

Determine the correct volume for the ado-trastuzumab emtansine dose and add it to a minimum volume of 250 mL 0.45% or 0.9% Sodium Chloride Injection in polyvinyl chloride (PVC), latex-free PVC-free polyolefin bags (PO), polypropylene (PP) or polyethylene (PE) bags. The 0.45% sodium chloride solution may be used without a 0.22 micron in-line (non-protein adsorptive) filter. If 0.9% sodium chloride is used for infusion, a 0.22 micron in-line filter is required. Do not use Dextrose (5%) solution. The diluted ado-trastuzumab emtansine infusion should be used immediately. If not used immediately the solution may be stored in a refrigerator for up to 24 hours prior to use. Do not freeze or shake.

8.1.4 Compatibility

DM1, the cytotoxic component of ado-trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) with ado-trastuzumab emtansine should be avoided due to the potential for an increase in DM1 exposure and toxicity.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

T-DM1 will be supplied free of charge by the study.

8.1.7 Administration

Administration should occur according to institutional guidelines. We recommend the following based on the package insert:

Administer ado-trastuzumab emtansine as an intravenous infusion with a 0.22 micron in-line non-protein adsorptive polyethersulfone (PES) filter if 0.9% sodium chloride is used as the final dilution solution. Loading doses are infused over 90 minutes (+/- 10 minutes) and subsequent doses over 30 minutes (+/- 10 minutes) if prior infusions were well tolerated. Flush IV line with saline after drug is administered. Do not administer with D₅W. Do not administer as an intravenous push or bolus.

Do not mix ado-trastuzumab emtansine, or administer as an infusion, with other medicinal products.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.

The recommended dose of T-DM1 is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. *Do not administer T-DM1 at doses greater than 3.6 mg/kg.*

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

Per institutional guidelines and/or package insert instructions (Section 2.1 of Kadcyla package insert), participants should be observed for at least 90 minutes after the initial dose of T-DM1 for fever, chills, or other infusion associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), participants will be observed for at least 30 minutes for subsequent doses of T-DM1. Please see Section 5.1 for further details regarding observation periods, including observation per institutional policies.

8.1.8 Ordering

Qualified personnel at participating sites will order drug from McKesson.

8.1.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.10 Destruction

Expired T-DM1 should be destroyed according to institutional policies. At the end of the study, unused supplies of T-DM1 should be destroyed. Destruction of all T-DM1 supplies, expired and unused, will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Summary of Blood Specimens

Table 12. Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Mandatory or optional	Tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being submitted by participating site	Baseline prior to treatment ***	Cycle 8 prior to treatment	Cycle 17 prior to tx or at off study treatment	Follow-up: 6 month visit after treatment ends (+/- 2 weeks)	Additional processing required at site after blood draw?	Storage / shipping conditions ¹	Lab Recipient
Mandatory (biomarkers) See Section 9.1.1	None (red)	10 mL (2)	Whole Blood**	X (all patients)	X (first 15 patients enrolled after Sp Am 2)*	X (all patients)	X (first 15 patients enrolled after Sp Am 2)*	No	Refrigerate / cold pack (DO NOT FREEZE)	Mayo Lab
Mandatory (biomarkers) See Section 9.1.1	EDTA (purple)	10 mL (2)	Whole blood	X (all patients)	X (first 15 patients enrolled after Sp Am 2)*	X (all patients)	X (first 15 patients enrolled after Sp Am 2)*	No	Refrigerate / cold pack (DO NOT FREEZE)	Mayo Lab
Mandatory (banking) See Section 9.1.2	EDTA (purple)	10 mL (2)	Whole blood	X (all patients)				No	Refrigerate / cold pack (DO NOT FREEZE)	DFCI Lab

*so that total number of patients with this time point = 50 including those treated on prior T-DM1 protocol (RU011301I). These time points originally applied to the first 12 patients enrolled on 18-124. Sponsor Amendment 2 added an additional 15 patients for these two timepoints to ensure at least 50 patients collected samples at Cycle 8 and 6 month follow-up between RU011301I and 18-124.

**red top tubes processed at Mayo for serum

***Bloods should be drawn after registration, preferably on Cycle 1 Day 1 prior to treatment start. If drawn during screening, this is not a violation.

9.1.1 Blood for biomarkers

Two 10 mL red top tubes for serum and two 10 mL purple top EDTA tubes for whole blood at the following time points:

- Baseline (preferably on Cycle 1 Day 1 prior to treatment start)
- Cycle 8, Day 1 (For the first 15 patients enrolled after activation of Sponsor Amendment 2)
- Cycle 17, Day 1 or at time off study treatment
- Follow-up visit 6 months after completing therapy (For the first 15 patients enrolled after activation of Sponsor Amendment 2). If the Cycle 17, Day 1/off study treatment sample is missed for patients not included in the first 12, the sample can be drawn at the 6 month follow up visit.

The first 12 patients (and an additional 15 patients with Sponsor Amendment 2) will have biomarkers drawn at 4 timepoints:

- Baseline (preferably on Cycle 1 Day 1 prior to treatment start)

- Cycle 8, Day 1
- Cycle 17, Day 1 or at Off Study Treatment
- 6 month follow up visit

The remaining patients will have biomarkers drawn at 2 timepoints:

- Baseline (preferably on Cycle 1 Day 1 prior to treatment start)
- Cycle 17, Day 1 or at Off Study Treatment (OR if missed, at 6 month follow up visit)

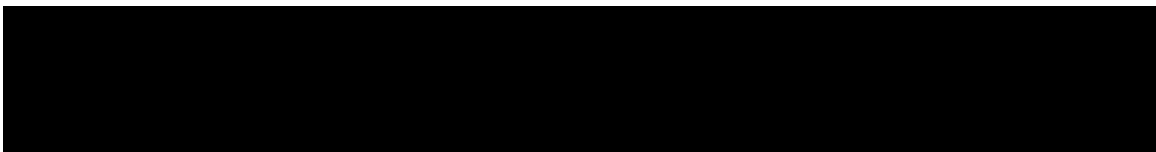
After all samples have been processed according to kit instructions (inverting gently), ship all specimens according to shipping instructions. Refrigerate / cold pack (DO NOT FREEZE).

Kits (from Mayo Clinic) are required for this collection and must be used. If a sample collection is missed at any time point, patients should be drawn at the next possible clinic visit and cycle number should be marked clearly on the study tube label.

Biomarker blood samples will be shipped to Mayo Clinic.

Verify ALL sections of the BAP Requisition Form (provided in kit & Appendix H), and specimen collection labels are completed and filled in correctly.

Specimens must be shipped the same day they are drawn. Samples should be shipped to:



Ship EDTA and red top tubes (no additive) with a properly prepared cold pack. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.

Ship specimens via Priority Overnight service, Monday – Thursday, to BAP Freezer according to kit instructions. Do not send samples on weekends or just prior to federal holidays. If a patient can only be seen on Fridays, email the Biospecimen Manager (found on resource page) with the sample information and FedEx tracking number.

The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an air bill. **Shipping costs will be covered by DFCI** if the shipping box provided with the BAP kit is used for shipping specimens to BAP Freezer.

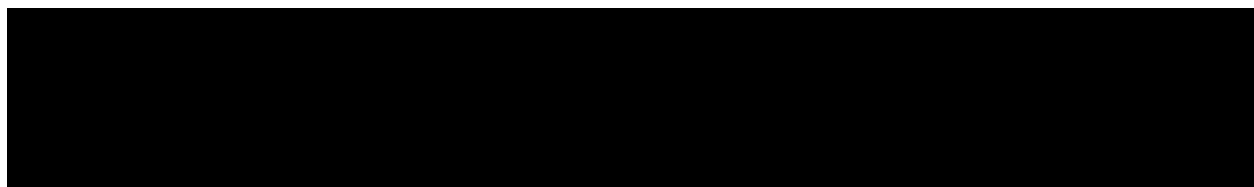
BAP Freezer will receive the samples and immediately forward specimens to the Mayo lab for storage.

9.1.2 Blood for future research

Two 10 mL purple top EDTA tubes at the following time points:

- Baseline (preferably on Cycle 1 Day 1 prior to treatment start)

No processing of tubes is required before shipment. Refrigerate / cold pack (DO NOT FREEZE). Complete the requisition form in Appendix I and ship tubes to Dana-Farber.:



All samples will be de-identified and assigned a unique sample ID number on arrival.

Please email the DF/HCC Core Blood and Tissue Bank and DFCI Coordinating Center with the sample information and tracking information the day before shipping specimens.



9.1.3 Study Methodology and Storage Information

Blood/blood product samples will be collected for the following research

Biomarkers of aging: We will examine the biomarkers of aging for patients on study at the time points indicated in the Study Calendar (Section 10). We will explore associations of each these markers with outcomes and adverse events overall and at each time point. We will also assess associations with each category of marker (i.e. inflammatory markers, coagulation, and senescence).

Table 13.

Candidate Biomarkers of Frailty to be Tested* (all examined using routine blood draws at study visits)	
Chronic inflammatory markers	Cytokines: IL-6, IL-1Ra, TNFa, CXCL/GROa; Chemokines: IL-8, CCL2/MCP-1, CCL3/MIP-1a, CCL5/RANTES
Coagulation/vascular markers	D-dimer, PAI-1, s-VCAM
Markers of cellular senescence	HMGB1, Wnt-16

*From Section 2.5.2

As part of ongoing research, we will collect and bank blood for future research studies. Samples will be stored by BAP until specific analyses are identified.

Return of Genetic Testing Research Results

Genetic testing is being done for the purposes of research only, and specific patient results will not be returned to patients or providers.

9.1.4 Sites performing correlative analysis

The Broad Institute of MIT
Mayo Clinic (Jolene Hubbard, MD)
Dana-Farber Cancer Institute

9.2 Summary of Questionnaires

Table 14. Questionnaires

Tests and procedures	Baseline (Cycle 1, Day 1) ¹	Day 1 of each cycle	Cycle 17 Day 1 or at time off study treatment	Follow-up: 6 months (+/- 2 weeks) after completing therapy (one time visit required)
Mandatory Geriatric Assessment (GA) (patient and Healthcare provider) – See section 9.2.1	X		X	X
Mandatory Quality of Life (QOL) Assessments using EQ-5D form and Visual Analog Scale (VAS) – See section 9.2.2	X	X	X	X
Mandatory Patient Reported Outcomes (PRO-CTCAE) – See section 9.2.3	X	X	X	X

¹ Baseline questionnaires (GA, QOL, and PRO-CTCAE) should be done after registration and preferably on Cycle 1 Day 1. This ensures the participant has a study ID assigned to include on the questionnaires. If completed during screening, this is not a violation.

Geriatric Assessments are completed using hard copies on paper (Appendix A-B).

PRO-CTCAE and QOL assessments (EQ-5D form and Visual Analog Scale (VAS)) are completed electronically on tablet computers.

See Appendix C for information about PRO-CTCAE/QOL procedures, including site credentialing and training. To obtain credentialing and access to the PRO-CTCAE/QOL system (REDCap), [REDACTED]

Participating sites need to be aware of their site randomization to PRO-CTCAE Shared Reporting vs. Traditional Reporting.

If a patient misses a questionnaire (GA, PRO-CTCAE, QOL), due to timing of appointment or institutional error, the site staff should contact the patient to complete over the phone whenever possible. Missed questionnaires are not considered protocol violations.

9.2.1 Mandatory Geriatric Assessment (GA): Patient and Healthcare provider

Mandatory **only** for patients who speak and read English and/or Spanish; assessment can be completed for any patient if staff interpreter is present in-person for each survey timepoint.

The Geriatric Assessment (GA) should be conducted in-clinic at the below timepoints:

- Baseline (preferably on C1D1)
- Cycle 17 (or at the time patient goes off study if >1 month since last assessment)
- 6 month follow-up visit (see Section 5.9).

The Geriatric Assessment will include a hard copy of both patient and healthcare professional questionnaires to be completed at each time point. Results will be submitted electronically via the Inform edc system to DFCI.

We will examine factors that predict the risk for grade 3-5 Adverse Events in patients receiving T-DM1 on study and will validate Dr. Arti Hurria's toxicity prediction model for T-DM1³². Patients will take the assessment using a hard copy of the GA (Appendix A and B) that will include all measures^{31,33}. Patients and providers will complete the components as listed in Table 15 (also see Appendices B-C for forms and instructions).

Table 15 (repeated from Section 2.5.1): Components of Geriatric Assessment	
Domain assessed	Tests to be administered
Functional status	<ul style="list-style-type: none"> • OARS MFAQ (IADL)^{34, 35} • MOS Physical Functioning³⁶ • Karnofsky Performance Status Rated Healthcare Professional^{37*} • Karnofsky Performance Status Rated by Patient³⁸ • Timed "Up and Go"^{39*} • Number of falls in last 6 months
Comorbidity	OARS Physical Health Section
Medication Review	Patient reports number and names of medications, herbs, or vitamins
Cognition	Blessed Orientation-Memory-Concentration Test*
Psychological Status	Mental Health Inventory (MHI)-17
Nutritional Status	<ul style="list-style-type: none"> • % Unintentional Weight Loss in last 6 months • Body Mass Index
Social Functioning and Social Support	<ul style="list-style-type: none"> • MOS Social Activity Limitation Scale • MOS Social Support Survey Subscale
Abbreviations: OARS, Older American Resources and Services; MFAQ, Multidimensional Functional Assessment Questionnaire; IADL, Instrumental Activities of Daily Living ; MOS, Medical Outcomes Study; *Items completed by the healthcare professional (Karnofsky performance status, Timed Up and Go, and Blessed Orientation-Memory-Concentration test).	

9.2.2 Mandatory Quality of Life (QOL) Assessments using EQ-5D form and Visual Analog Scale (VAS)

Mandatory **only** for patients who speak and read English and/or Spanish. Quality of Life (QOL) assessments will be obtained in-clinic on a tablet computer prior to treatment at the below timepoints:

- Baseline (preferably C1D1)
- At the start of every cycle
- At the time a patient goes off study if >1 month since last assessment
- 6-month follow-up

Back-up paper surveys will also be available to print in case technical problems preclude tablet use.

Site Randomization: For providers at sites that are randomized to receive the PRO-CTCAE results, patient PRO-CTCAE responses should be printed from the PRO-CTCAE system and provided to the clinician at the time of clinical grading of adverse events during treatment and at end of treatment.

The EQ-5D includes 5 items, one for each of the following dimensions of health-related quality of life: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression.^{44,45} Patients are asked to choose between five levels of severity (“no,” “slight,” “moderate,” “severe,” or “extreme”) for each dimension, and also to rate their overall health on a 20 cm vertical visual analogue scale. We plan to assess whether the EQ-5D quality of life scores correlate with certain patient-reported symptoms. The QOL assessments will be limited because QOL information will be captured by the PRO-CTCAEs and by the geriatric assessments. We want to minimize the degree of burden of questionnaires for patients on study. See Appendix D.

9.2.3 Mandatory Patient Reported Outcomes (PRO-CTCAE)

Mandatory **only** for patients who speak and read English and/or Spanish; assessment can be completed for any patient if staff interpreter is present in-person for each survey timepoint. Patient Reported Outcomes (PRO-CTCAE) assessments will be obtained in-clinic on a tablet computer at the below timepoints:

- Baseline (preferably C1D1)
- At the start of every cycle
- At the time a patient goes off study if >1 month since last assessment
- 6-month follow-up

Back-up paper surveys will also be available to print in case technical problems preclude tablet use.

Site Randomization: For providers at sites that are randomized to receive the PRO-CTCAE results, patient PRO-CTCAE responses should be printed from the PRO-CTCAE system and provided to the clinician at the time of clinical grading of adverse events during treatment and at end of treatment.

9.2.4 Sites performing correlative analysis

[REDACTED]

9.3 Tumor banking:

In addition to sending tissue for central testing of HER2 (see Section 3.4), we will bank additional tissue at Dana-Farber collected from cancer-directed surgery for genomic analyses.

Tumor Tissue from Surgical Resection: The following specimens are required for gene profiling:

- 1 paraffin block (or 15 unstained slides)

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 in Appendix J and ship to:

[REDACTED]

Please email the DFCI Coordinating Center with the sample information and tracking information the day before shipping specimens.

[REDACTED]

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.

9.3.1 Sites performing correlative analysis

[REDACTED]

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to registration except where noted in Table 16. C1D1 results need to re-meet eligibility parameters to start treatment if drawn again after screening evaluations. If baseline/screening exam and labs are completed within 2 days of treatment start, they do not need to be repeated on C1D1. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within -2 days or + 7 days of the protocol-specified date, unless otherwise noted.

Table 16. Study Calendar

Tests and procedures	Screening, ≤14 days prior to registration	Treatment ¹				Follow-up ²	
		Cycle 1 Day 1*	Day 1 of each cycle for one year	Cycle 8 Day 1	Cycle 17 Day 1 or off study treatment	Follow-up: 6 months (+/- 2 weeks) after completing therapy (one time visit required)	Yearly
History and exam, weight, ECOG PS	X	X	X	X	X	X	
Height	X						
Adverse event assessment		X	X	X	X	X	
Urine or serum pregnancy test ³	≤7 days prior to registration						
Hematology: CBC/ differential	X	X	X	X	X	X	
Chemistry ⁴	X	X	X	X	X	X	
INR, PTT	X						
Hepatitis panel ⁵	X						
MUGA or echocardiogram ⁶	≤60 days prior to study registration		Cycle 4, 8, 17			X	
Documentation of reason for enrolling on study ⁷	X						
Blood Samples – See section 9.1		X ⁹		X	X	X	
Mandatory Geriatric Assessment (GA) (patient and Healthcare provider) – Section 9.2.1		X ⁹			X	X	
Mandatory Quality of Life (QOL) Assessments using EQ-5D form and Visual Analog Scale (VAS) —Section 9.2.2		X ⁹	X	X	X	X	
Mandatory Patient Reported Outcomes (PRO- CTCAE) ⁸ —Section 9.2.3		X ⁹	X	X	X	X	
Survival and DFS Events ²							X

* If baseline/screening history, physical exam, ECOG and labs completed within 2 days of treatment start, they do not need to be repeated on C1D1 (if within 7 days of treatment start, they do not need to be repeated on C1D1 with prior PI approval)

1. Cycle length = 21 days; treatment administration may be given up to 2 days early or up to 7 days late for scheduling purposes/conflicts, weather, etc. However, subsequent cycles should resume a 21-day schedule.
2. See section 5.9.
3. Urine or serum pregnancy test, for women of childbearing potential only.

4. Chemistry includes: SGOT (AST), SGPT (ALT), alkaline phosphatase, Total bilirubin, chloride, creatinine, bicarbonate, calcium, glucose, Na, K.
5. Hepatitis panel required of all participants. Panel includes: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis C antibody. See section 3.2.4.
6. Studies can be done on day 1 or at any point during that treatment cycle, i.e., if cardiac examination is missed at dedicated time point, treatment teams should do this at next available time. If this is done within 30 days after the requested assessment (i.e. Day 1 of that cycle +30 days window), this will not count as protocol deviation. If patients come off study treatment early (i.e., before cycle 17), final cardiac evaluation will be at the follow-up (6 month) visit only.
7. Documentation on why participants enrolled on study rather than receive standard treatment is requested (i.e. frailty, disease risk, etc.).
8. For providers at sites that are randomized to PRO-CTCAE feedback, AE form should be printed from PRO-CTCAE system
9. Research bloods and questionnaires (GA, QOL, PRO-CTCAEs) should be done any time after registration occurs and a study ID is assigned. It is recommended to complete these on C1D1. If completed during screening, this is not a violation.

11. MEASUREMENT OF EFFECT

Patients will be followed for invasive-disease-free survival (IDFS). An IDFS event is defined as occurrence of any of the following events: ipsilateral invasive breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or a second primary non-breast invasive cancer. Note that in-situ events are not included as disease events in IDFS under the STEEP system.

11.1.1 Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory

values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix L.

- The Overall PI/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 study agent(s) directly from 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.

12.4 Collaborative Research and Future Use of Data and Samples

Tissue, blood, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one of more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study may be shared with these public databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Endpoint

The primary endpoint is the 5-year IDFS rate. An IDFS event is defined as occurrence of any of the following events ipsilateral invasive breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or a second primary non-breast invasive cancer. Note that in-situ events are not included as disease events in IDFS under the STEEP system. The primary efficacy analysis will be the entire IDFS experience of evaluable patients which will be summarized with a Kaplan-Meier curve. An evaluable patient is defined as anyone who receives at least one dose of T-DM1. The 5-year IDFS landmark will be estimated from the K-M curve, and a 2-sided 90% confidence interval will be provided. Patients who have not had an IDFS event at the time of data analysis will be censored at the date last known to be alive and event-free. A secondary efficacy analysis will use the log-rank test to compare the IDFS experience of this trial population with a similar population of older patients in a historical control cohort that received adjuvant chemotherapy + trastuzumab (unpublished data for older patients from ¹¹). Additional goals are to better characterize the toxicity profile of T-DM1 in this patient population.

13.1.2 Secondary Clinical Endpoints

Secondary clinical endpoints include OS, recurrence-free survival, safety/adverse events, cardiac function, and site of first recurrence. OS will be defined as the time from study enrollment to death attributable to any cause (i.e. death from breast cancer, non-breast cancer cause, or from unknown cause) ¹. Patients who are alive (including those lost to follow-up) at the time of data analysis will be censored at the last known alive date. A Kaplan-Meier curve will be used to summarize the OS experience of this patient cohort. Recurrence-free survival will be defined as the time from study enrollment to disease recurrence and will not include death as an event. Safety/adverse events data will be tabulated, including adverse events of all grades, in addition to cardiac dysfunction. Cardiac dysfunction will be defined as incidence of symptomatic left ventricular systolic dysfunction, cardiac death, and incidence of decrease in ejection fraction by at least 10 percentage points below baseline or to below 50%. The site of first recurrences will be tabulated as frequencies and relative frequencies. Recurrence-free survival will be summarized with a Kaplan-Meier curve.

13.2 Sample Size, Accrual Rate and Study Duration

This is a single-arm Phase II to evaluate the efficacy and safety of T-DM1 in older patients with HER2-positive breast cancer. The primary endpoint is 5-year IDFS. The study initially planned to enroll 82 evaluable patients (to be combined with data from 38 patients who have already been enrolled and treated on the companion protocol led by ACCRU- DFCI protocol 15-019). We will be combining the cohorts of patients enrolled on the two trials into one analysis. Since 10

patients on RU011301I/ DFCI 15-019 could not be reached for re-consent for ongoing follow-up and event monitoring at DFCI per this protocol, we now plan to enroll up to 92 patients so that the total sample is 120 evaluable patients. If a patient fails screening or registers and never starts study treatment, this patient will also be replaced.

As of Sponsor Amendment 2, the study will enroll up to 10 additional patients (up to 92 evaluable on 18-124) to reach the 120 evaluable patients across the two trials.

We project that the accrual rate on this protocol will be about 8-10 patients per month. Therefore, the study is expected to take about 12-15 months to complete accrual. With a maximum 5 years of follow-up after the last patient is enrolled, the study will take roughly 6 years to complete from after the first patient is enrolled on this protocol.

Assuming that 5-year IDFS follows a binomial distribution and no loss to follow-up, Table 17 below gives the 2-sided 90% confidence interval for various observed 5-year IDFS rates with 200 patients (original sample size) and 120 patients (new sample size, including patients from this protocol and from 15-019). For example, if the observed 5-year IDFS is 78%, the 2-sided 90% CI would be (0.70, 0.85). This means that with the planned sample size, we will be able to rule out an IDFS rate of 70% with 90% confidence if we observe a 5-year IDFS of 78%. Note that at the conclusion of this study, the IDFS rate will be estimated from the Kaplan-Meier curve. The Greenwood's formula will be used to estimate the variance of the K-M estimate and to construct the confidence interval. The primary analysis will be conducted when all patients have completed their 5-year IDFS evaluations.

Table 17:

Observed 5-yr IDFS	2-sided 90% CI (n = 200)	2-sided 90% CI (n = 120)
0.70	(0.65, 0.75)	(0.61, 0.78)
0.72	(0.67, 0.77)	(0.63, 0.80)
0.74	(0.69, 0.79)	(0.65, 0.82)
0.76	(0.71, 0.81)	(0.67, 0.83)
0.78	(0.73, 0.83)	(0.70, 0.85)
0.80	(0.75, 0.85)	(0.72, 0.87)
0.85	(0.80, 0.89)	(0.78, 0.90)
0.90	(0.86, 0.93)	(0.84, 0.94)

As a secondary efficacy analysis, we will compare the IDFS experience of this trial population to a similar population in a historical control cohort that received adjuvant chemotherapy + trastuzumab. This historical cohort is described by Perez and colleagues¹¹, which has been updated for the purpose of this analysis to provide 5-year disease-free survival for women aged 60 and older (data are confidential and unpublished for this age group). The observed 5-year

DFS for that patient group was 75.5% (95% CI: 71.0% to 80.4%). While it is the expectation that the IDFS experience in this study cohort would be comparable (or slightly worse given presumed higher comorbidity of current trial population) to that of the historical control, powering the study for a formal statistical comparison (e.g. to assess non-inferiority) is not feasible due to the rarity and the relatively favorable prognosis of this study population. We will use the log-rank test to compare the IDFS experience between the two study cohorts, with additional goals being to compare the toxicity between the two cohorts and to better characterize the toxicity profile of T-DM1 in this patient population. In addition, the Cox Proportional Hazards model will be used to adjust for potential differences in patient and disease characteristics between the two cohorts.

One concern is that there will be too many “low risk” patients enrolled on the trial. To this end, we will define patient risk groups by the number of positive lymph nodes a patient has: 0-3, 4-9 and ≥ 10 positive nodes.* For the Perez et al. N9831 study the percent of patients in each group was 54.9% for 0-3, 29.6% for 4-9, and 15.5% for ≥ 10 . We intend to monitor the percent of women who have been entered into each risk group. If we have enrolled 70% of the patients in the 0-3 positive node group and the study is still open for enrollment, we will consider amending the study so that only women who have 4 or more positive lymph nodes are allowed to enroll from that point forward.

*Note: Patients with unknown node status (as this is allowed per eligibility criteria 3.1.3) will be assumed to be clinically node negative and included in the 0-3 positive node risk group.

13.3 Stratification Factors – not relevant for a single-arm study nor implemented in the primary analysis

13.4 Interim Monitoring Plan

This study will be monitored by the DF/HCC Data Safety Monitoring Committee (DSMC). Reports containing patient characteristics, toxicity, and administrative information will be provided to the DSMC every six months, with the first report due at the first reporting period after study initiation.

Under the revised target sample size, no interim testing for inferiority will be conducted during the study. However, were a hypothesis test to be conducted as a single-stage Poisson test after 600 patient-years of follow-up (one-sided $\alpha = 0.05$) and a null hypothesis of a 70% 5-year IDFS rate, the null would be rejected with 31 or fewer IDFS events. Thus, if 32 or more IDFS events are observed at any point during the study, the DSMC may consider early termination of the trial and reporting of the unacceptable IDFS rate under the estimation-only analysis plan.

13.5 Analysis of Primary Endpoints

See Section 13.1.1.

13.6 Analysis of Secondary Endpoints

See Section 13.1.2.

13.6.1 Analysis of Questionnaires: Geriatric assessment:

We anticipate that at least 90% of the 120 total evaluable patients (n=108) accrued to this arm of the trial will provide viable assessment information at baseline. From prior data with T-DM1, we estimate that the overall rate of grade 3+ adverse events in patients receiving T-DM1 will be 30-35%²⁵.

The primary aim is to determine whether the baseline geriatric assessment (GA) grade 3+ adverse event prediction model developed by Dr. Hurria³² validates in this patient population. To do this, we will calculate the risk score for a 3+ adverse event using the baseline GA measures. A score of 0 to 5 will be considered low risk, a score of 6 to 9 will be considered intermediate risk and a score of 10 to 19 will be considered high risk. A chi-square test will be done to determine if the rates of grade 3+ adverse events differ for these categories. In addition, the grade 3+ adverse event rates will be estimated for each category with a binomial estimator and corresponding 95% CI and compared to the values obtained by Dr. Hurria.

We will also examine the associations between the occurrences of grade 3+ adverse events with the geriatric measurements at the different timepoints. For the continuous factors (MOS Physical Functioning, Karnofsky Performance Status Rated Healthcare Professional, Timed “Up and Go”, OARS Physical Health Section), we will use logistic regression to determine the odds ratio of adverse events. With 108 patients with complete data, and a two-sided $p = 0.05$, a univariable test will have approximately 80% power to detect a odds ratio of 1.61 between one standard deviation change in the continuous factor. Under the assumption of normality and that the 50th percentile of the population has a 35% probability of having an adverse event, this odds ratio equates to the 50th percentile having a 48% probability of adverse event. In further exploratory analyses, we will examine associations of components of the Geriatric assessment with biomarkers of aging, quality of life, prominent toxicities observed, and disease outcomes/survival.

Finally, we will also perform a longitudinal analysis using linear mixed models of changes in the geriatric assessment over time. We will also use these models to determine the association of changes in the geriatric assessment measures over time and other outcome variables such as QOL, PRO-CTCAEs and IDFS.

13.6.2 Analysis of Questionnaires: PRO-CTCAE/Quality of Life:

For the evaluation of the performance of an electronic-based system for patient self-reporting of adverse events (PRO-CTCAE), it is anticipated there will be a sample size of approximately 120 total patients. The data presentation and analysis will be descriptive and exploratory. If at least 80% of the patients can successfully complete 75% of the required PRO-CTCAE assessments, we will consider this type of assessment feasible in this population. To determine whether this is deemed feasible or not, a patient will be deemed a ‘success’ if they completed >75% of all required PRO-CTCAE assessments.

The proportion of successes out of 120 (or the number of evaluable patients in the trial) will be computed with a binomial estimate (number of ‘successes’ divided by 120 or the number of evaluable patients). An exact binomial, one-sided 95% confidence interval will be computed. If the interval contains 0.80 or lies entirely above 0.80, we will declare it feasible to do this type of an assessment in a population of elderly breast cancer patients. When the sample size is 120 patients, a one-sided 95% confidence interval for a single proportion will extend between 0.05 to 0.06 from the observed proportion if the true proportion is between 0.70 and 0.80. If the true proportion is greater than 0.80, the interval will have a smaller extension.

To determine whether clinician-reported CTCAEs are enhanced when PRO-CTCAE data are shared with the clinician, sites will be randomized 1:1 to either share the PRO-CTCAE assessments with the clinician or not share the PRO-CTCAE data with the clinician. It is anticipated there will be roughly 100 patients in each group: a group where the PRO-CTCAE data is shared with the clinician and a group where the PRO-CTCAE data is not shared. For each patient visit, a score will be determined that is the sum of the magnitudes of differences between the patient PRO-CTCAE grade and the clinician assigned grade for each item. The greater this value, the greater the difference between the clinician and patient are with respect to grading the AEs. The average score between the two groups (PRO-CTCAE shared versus PRO-CTCAE not shared) will be compared. Specifically, a linear mixed model will be used, to account for repeated measurements (multiple assessment times per patient) and a site effect, to determine if there is a difference in average score between the groups. In addition, the data will be summarized by group and timepoints. Plots over time will be generated that show differences in score at the individual level over time as well as by group. Analysis and graphics may also be generated for individual AEs. It is difficult to determine the power for the proposed linear mixed model. However, power can be determined for a comparison of average difference in scores at a given time point. With 60 patients in each group, there is 80% power to detect an effect size of 0.57 with a 0.05 two-sided significance level. There is 70% power to detect an effect size of 0.51 standard deviations. Hence, the more complex model, using more information from across timepoints will likely have sufficient power to detect a clinically meaningful difference, assuming that a 0.5 standard deviation is meaningful as in QOL data.

Finally, we will determine whether PRO-CTCAE assessments are associated with the QOL measure or the geriatric assessment score. Several different analyses will be done. The first will be to generate boxplots for each score for a particular PRO-CTCAE item for the geriatric assessment score. The average QOL score or geriatric assessment score will be compared across the PRO-CTCAE item scores using a repeated measure ANOVA. It is likely that there will be few patients reporting high scores for the PRO-CTCAE. Given this, another analysis will be to determine whether the baseline geriatric score is associated with a patient reporting a score of 3 or higher for PRO-CTCAE. This will be assessed using logistic regression and will be done for individual PRO-CTCAE or by grouping all the PRO-CTCAE and determining if the patient reports at least one score of 3 or higher across all items. The outcome variable will be that the patient reported a score of 3 or higher (either for an individual item or across all items) or not and the

explanatory variable will be the baseline geriatric assessment score. Compliance with PRO-CTCAE reporting, over time will be assessed in relation to baseline geriatric assessment scores. For the QOL data, it will be determined whether there is an association between the QOL score and if a patient reports a score of 3 or higher on PRO-CTCAE (either for an individual item or across all items) across the multiple timepoints. A linear mixed model will be used to account for the repeated measures. It is anticipated there will be approximately 120 patients for this analysis.

PRO-CTCAE data from this study may also be used to test alternative scoring approaches for the PRO-CTCAE overall. An interim analysis of PRO-CTCAE data will be conducted in June/July 2015 or after 60 patients are enrolled.

13.6.3 Biomarkers of aging:

This analysis will be exploratory. We will examine the biomarkers for patients on study at designated time points and will explore associations of each these markers with outcomes and adverse events overall and at each time point. We will also assess associations with each category of marker (i.e. inflammatory markers, coagulation, and senescence). Boxplots will be used to summarize the biomarker values at each timepoint and spaghetti plots will be used to display changes in biomarker values over time for each patient. Because the analysis is exploratory, we will determine whether a marker is associated with outcome (e.g. a grade 3+ AE, DFS, etc.) for each individual timepoint using the appropriate model: a logistic regression model will be used for binary outcomes and cox proportional hazards model will be used for time-to-event outcomes. We will also analyze if changes in marker values over time are associated with outcome using an appropriate linear mixed model.

13.6.4 Genetic alterations in archival tissue:

Archival tumor tissue from all patients will be assessed using a high-throughput mutation profiling system (e.g. OncoPanel) or similar genetic analysis 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 120 trial patients, the half-width of an asymptotic 95% CI would be ± 0.07 , ± 0.05 and ± 0.04 when prevalence is 20%, 10% and 5% respectively.

13.7 Reporting and Exclusions

Evaluable patients include those who have at least started treatment. Patients who withdraw consent prior to starting treatment may be replaced. In addition, if less than 38 patients consent to having their data transferred on the extension protocol of ACCRU [RU011301I]-DFCI protocol 15-019), we can replace these patients so that the total sample size across trials is 120. As of Sponsor Amendment 2, up to 10 additional patients (up to 92 evaluable on 18-124) will be enrolled to 18-124 to reach 120 evaluable patients across the two trials.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A. GERIATRIC ASSESSMENT – PATIENT QUESTIONNAIRE

Participant Study ID/Initials_____

Responsible person name (Physician, Nurse, or CRA)_____

Date assessment was completed _____

Assessment Period) ☐ Baseline/C1D1 ☐ Cycle # ☐ End of Treatment

Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

☐ **Mark box with an “X”, if form was not completed at specified timepoint and specify reason:**

(Mark one with an X): ☐ Patient refused ☐ Patient withdrew consent ☐ Not done
☐ Other, specify: _____

(For assessment date, record approximate date form was to be completed.)

A. BACKGROUND INFORMATION

1. What is the highest grade you finished in school? (Mark one with an X.)

<input type="checkbox"/> Less than 9 years of school	<input type="checkbox"/> Some college or technical school	<input type="checkbox"/> Post graduate education, but no higher degree
<input type="checkbox"/> Some high school (9-11 years)	<input type="checkbox"/> College degree graduate	
<input type="checkbox"/> High school graduate, or GED	<input type="checkbox"/> Graduate degree	<input type="checkbox"/> I prefer not to answer

2. What is your marital status? (Mark one with an X.)

<input type="checkbox"/> Married	<input type="checkbox"/> Divorced	<input type="checkbox"/> I prefer not to answer
<input type="checkbox"/> Domestic partnership	<input type="checkbox"/> Separated	
<input type="checkbox"/> Widowed	<input type="checkbox"/> Never married	

3. With whom do you live? (Mark all that apply with an X.)

<input type="checkbox"/> Spouse / partner	<input type="checkbox"/> Parents/ parents-in-law
<input type="checkbox"/> Girlfriend / boyfriend	<input type="checkbox"/> Live alone
<input type="checkbox"/> Children aged 18 years or younger	<input type="checkbox"/> Others, specify: _____
<input type="checkbox"/> Children aged 18 years or older	<input type="checkbox"/> Other relative, specify: _____

4. What is your current employment status? (*Mark one with an X.*)

- ☐ Employed \geq 32 hours per week
 - ☐ Employed \leq 32 hours per week
 - ☐ Homemaker
 - ☐ Disabled
 - ☐ On medical leave
-

- ☐ Unemployed
- ☐ Retired
- ☐ Student full-time
- ☐ Student part-time
- ☐ Other, specify:

B. DAILY ACTIVITIES*

PATIENT INSTRUCTIONS: Indicate your response by marking an X in one box per question.

1. Can you use the telephone...

- ☐ without help, including looking up and dialing;
- ☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or
- ☐ are you completely unable to use the telephone?

2. Can you get to places out of walking distance...

- ☐ without help (can travel alone on buses, taxis, or drive your own car);
- ☐ with some help (need someone to help you or go with you when traveling) ; or
- ☐ are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes (assuming you have transportation)...

- ☐ without help (taking care of all shopping needs yourself, assuming you have transportation);
- ☐ with some help (need someone to go with you on all shopping trips); or
- ☐ are you completely unable to do any shopping?

4. Can you prepare your own meals...

- ☐ without help (plan and cook full meals yourself);
- ☐ with some help (can prepare some things but unable to cook full meals yourself) ; or
- ☐ are you completely unable to prepare any meals?

5. Can you do your housework...

- ☐ without help (can clean floors, etc);
- ☐ with some help (can do light housework but need help with heavy work); or
- ☐ are you completely unable to do any housework?

6. Can you take your own medicines...

- ☐ without help (in the right doses at the right time);
☐ with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
☐ are you completely unable to take your medicines?

7. Can you handle your own money...

- ☐ without help (write checks, pay bills, etc.);
☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
☐ are you completely unable to handle money?

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

C. PHYSICAL ACTIVITIES*

1. The following items are activities you might do during a typical day. Does your health limit you in these activities? (*Mark an X in the box on each line that best reflects your situation.*)

Activities	Limited a lot	Limited a little	Not limited at all
A. <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
B. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
C. Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
D. Climbing <u>several</u> flights of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
E. Climbing <u>one</u> flight of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
F. Bending, kneeling, or stooping	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
G. Walking <u>more than a mile</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
H. Walking <u>several blocks</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
I. Walking <u>one block</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
J. Bathing or dressing yourself	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

* MOS, Physical Functioning Scale – Stewart, A.L. and Ware, J.E., 1992

D. CURRENT HEALTH RATING*

Which one of the following phrases best describes you at this time? (*Mark one with an X.*)

- ☐ Normal, no complaints, no symptoms of disease
- ☐ Able to carry on normal activity, minor symptoms of disease
- ☐ Normal activity with effort, some symptoms of disease
- ☐ Care for self, unable to carry on normal activity or do active work
- ☐ Require occasional assistance but able to care for most of personal needs
- ☐ Require considerable assistance for personal care
- ☐ Disabled, require special care and assistance
- ☐ Severely disabled, require continuous nursing care

* Patient KPS – Loprinzi, C.L., et al., 1994

E. FALLS

How many times have you fallen in the last 6 months? ☐☐☐

F. YOUR HEALTH

1. Your General Health*

Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at All, A Little or A Great Deal?** (*Mark an X in the box that best reflects your answer.*)

<u>Illness</u>	<u>No</u>	<u>If you have this illness:</u> How much does it interfere with your activities?				
		<u>Yes</u>		<u>Not at all</u>	<u>A little</u>	<u>A great deal</u>
A. Other cancers or leukemia	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B. Arthritis or rheumatism	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C. Glaucoma	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
D. Emphysema or chronic bronchitis	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E. High blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F. Heart trouble	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
G. Circulation trouble in arms or legs	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
H. Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I. Stomach or intestinal disorders	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
J. Osteoporosis	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
K. Liver disease	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L. Kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
M. Stroke	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
N. Depression	<input type="checkbox"/>	<input type="checkbox"/>	→	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

2. How is your eyesight (with glasses or contacts)? *(Mark one with an X.)*

- ☐ 1 Excellent
- ☐ 2 Good
- ☐ 3 Fair
- ☐ 4 Poor
- ☐ 5 Totally blind

3. How is your hearing (with a hearing aid, if needed)? *(Mark one with an X.)*

- ☐ 1 Excellent
☐ 2 Good
☐ 3 Fair
☐ 4 Poor
☐ 5 Totally deaf

4. Do you have any other physical problems or illnesses (other than listed in questions 1-4) at the present time that seriously affect your health?

- ☐ No
☐ Yes, specify: _____

If yes, how much does this interfere with your activities? *(Mark one with an X.)*

- ☐ Not at all ☐ Somewhat ☐ A great deal

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

5. How many medications (either prescribed or over-the-counter), herbs, or vitamins do you currently take? ☐☐☐

Please list all prescribed or over-the-counter medicines, herbs, or vitamins you are currently taking (doses not necessary).

1.	
2.	
3.	
4.	
5.	
6.	

7.	
8.	
9.	
10.	
11.	
12.	

G. HEALTH QUESTIONNAIRE*

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please mark an “X” in the box on each line that best reflects your situation.

<u>How much of the time during the past month:</u>	<u>All of the Time</u>	<u>Most of the Time</u>	<u>A Good Bit of the Time</u>	<u>Some of the Time</u>	<u>A Little of the Time</u>	<u>None of the Time</u>
1. has your daily life been full of things that were interesting to you?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
2. did you feel depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
3. have you felt loved and wanted?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
4. have you been a very nervous person?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
6. have you felt tense or high-strung?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
7. have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
8. have you felt emotionally stable?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
9. have you felt downhearted and blue?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

<u>How much of the time during the past month:</u>	<u>All of the Time</u>	<u>Most of the Time</u>	<u>A Good Bit of the Time</u>	<u>Some of the Time</u>	<u>A Little of the Time</u>	<u>None of the Time</u>
10. have you felt restless, fidgety, or impatient?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
11. have you been moody, or brooded about things?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
12. have you felt cheerful, light-hearted?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
13. have you been in low or very low spirits?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
14. were you a happy person?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
15. did you feel you had nothing to look forward to?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
16. have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
17. have you been anxious or worried?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

* MHI-17 – Stewart, A.L. and Ware, J.E., 1992

H. SOCIAL ACTIVITIES*

- During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? *(Mark one with an X.)*
 - ☐ 1 All of the time
 - ☐ 2 Most of the time
 - ☐ 3 Some of the time
 - ☐ 4 A little of the time
 - ☐ 5 None of the time
- Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? *(Mark one with an X.)*
 - ☐ 1 Much less socially active than before
 - ☐ 2 Somewhat less socially active than before
 - ☐ 3 About as socially active as before
 - ☐ 4 Somewhat more socially active as before
 - ☐ 5 Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? (Mark one with an X.)

- ☐ 1 Much more limited than others
☐ 2 Somewhat more limited than others
☐ 3 About the same as others
☐ 4 Somewhat less limited than others
☐ 5 Much less limited than others

* MOS, Social Activities – Stewart, A.L. and Ware, J.E., 1992

I. SOCIAL SUPPORT*

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (Mark an X in the box on each line that best reflects your situation.)

	<u>None of the Time</u>	<u>A Little of the Time</u>	<u>Some of the Time</u>	<u>Most of the Time</u>	<u>All of the Time</u>
1. Someone to help you if you were confined to bed.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. Someone you can count on to listen to you when you need to talk.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Someone to give you good advice about a crisis.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. Someone to take you to the doctor if you needed it.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5. Someone to give you information to help you understand a situation.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6. Someone to confide in or talk to about yourself or your problem.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
7. Someone to prepare your meals if you were unable to do it yourself.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
8. Someone whose advice you really want.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
9. Someone to help you with daily chores if you were sick.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
10. Someone to share your most private worries and fears with.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
11. Someone to turn to for suggestions about how to deal with a personal problem.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
12. Someone who understands your problems.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

* MOS Social Support Survey – Sherbourne, C.D. and Stewart, A.L., 1991

J. SPIRITUALITY/RELIGION*

Directions: Please answer the following questions about your religious beliefs and/or involvement. (Please mark an “X” in the box on each line that best reflects your situation.)

1. How often do you attend church or other religious meetings? *(Mark one with an X.)*
 - ☐ 1 More than once/wk
 - ☐ 2 Once a week
 - ☐ 3 A few times a month
 - ☐ 4 A few times a year
 - ☐ 5 Once a year or less
 - ☐ 6 Never

2. How often do you spend time in private religious activities, such as prayer, meditation or Bible study? *(Mark one with an X.)*
 - ☐ 1 More than once a day
 - ☐ 2 Daily
 - ☐ 3 Two or more times/week
 - ☐ 4 Once a week
 - ☐ 5 A few times a month
 - ☐ 6 Rarely or never

The following section contains 3 statements about religious belief or experience. Please mark the extent to which each statement is true or not true for you.

3. In my life, I experience the presence of the Divine (i.e., God). *(Mark one with an X.)*
 - ☐ 1 Definitely true of me
 - ☐ 2 Tends to be true
 - ☐ 3 Unsure
 - ☐ 4 Tends *not* to be true
 - ☐ 5 Definitely *not* true

4. My religious beliefs are what really lie behind my whole approach to life. *(Mark one with an X.)*
 - ☐ 1 Definitely true of me
 - ☐ 2 Tends to be true
 - ☐ 3 Unsure
 - ☐ 4 Tends *not* to be true
 - ☐ 5 Definitely *not* true

5. I tried hard to carry my religion over into all other dealings in my life. *(Mark one with an X.)*

- ☐ 1 Definitely true of me
☐ 2 Tends to be true
☐ 3 Unsure
☐ 4 Tends *not* to be true
☐ 5 Definitely *not* true

* DUREL: Duke University Religion Index – Koenig et al., 1997

K. YOUR FEELINGS*

1. Do you often feel sad or depressed?

- ☐ No ☐ Yes

2. How would you describe your level of anxiety, on the average?

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

0	1	2	3	4	5	6	7	8	9	10
No anxiety										Anxiety as bad as it can be

* Mahoney et al., 1994; LASA – Locke et al., 2007

L. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were there any questions difficult to understand?

- ☐ No ☐ Yes

If Yes, which questions were they?

2. Was the time it took to answer all the questions too long, just right or too short?

- ☐ Too short → How long would you have liked the questionnaire to be? minutes
☐ Just right
☐ Too long → How long would you have liked the questionnaire to be? minutes

Which items would you remove?

3. Did you find any of the questions upsetting?

- ☐ No ☐ Yes

If Yes, which questions were they?

Could you tell me why they were upsetting?

4. Do you think the questionnaire left out any questions that were important to ask?

Thank you for your participation.

REFERENCES FOR APPENDIX A

- Fillenbaum, G. G. and M. A. Smyer (1981). "The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire." *J Gerontol* **36**(4): 428-34.
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- Mahoney, J., T. J. Drinka, et al. (1994). "Screening for depression: single question versus GDS." *J Am Geriatr Soc* **42**(9): 1006-1008.
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- Stewart, A. L. and J. E. Ware, Jr., Eds. (1992). *Measuring functioning and well-being: the medical outcomes study approach*. Durham, Duke University Press.

APPENDIX B. GERIATRIC ASSESSMENT – HEALTHCARE PROFESSIONAL QUESTIONNAIRE

I. This form completed by: *(Mark all that apply with an X.)*

☐ Physician ☐ Nurse ☐ CRA

Participant Study ID/initials _____

Assessment Period (as applicable to this study)

☐ Baseline/C1D1 ☐ Cycle # ☐ End of Treatment

Mark box with an “X”, if form was not completed at specified timepoint and specify reason:
(Mark one with an X.)

☐ Patient refused ☐ Patient withdrew consent ☐ Not done

☐ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

II. FUNCTIONAL STATUS

A. KPS (Healthcare professional rated*)

Please rate your assessment of patient’s Karnofsky Performance Status as of date this form is completed. *(Scale is listed below.)* ☐☐☐ %

%	CRITERIA
100	Normal: no complaints; no evidence of disease
90	Able to carry on normal activity; only minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self, but unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very sick; hospitalization necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

* Physician KPS – Karnofsky, D.A., et al., 1948

B. Timed “Up and Go”*

INSTRUCTIONS: The timed “Up and Go” measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair’s arm, and his walking aid in hand. He is instructed that on the word “go”, he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform “Up and Go” □□.□ seconds

* Timed “Up and Go” – Podsiadlo, D. and Richardson, S., 1991

III. COGNITION *This section is only completed Pretreatment and at the end of treatment*

ORIENTATION-MEMORY-CONCENTRATION TEST**			
	Patient’s Response	Maximum errors	Final Score Weight score
1. What <u>year</u> is it now? [without looking at a calendar]	□□□□	1	□□ x 4 = □□
2. What <u>month</u> is it now? [without looking at a calendar] Memory Phrase: Repeat this phrase after me: ‘John Brown, 42 Market Street, Chicago’	□□	1	□□ x 3 = □□
3. About what <u>time</u> is it? [within 1 hour – without looking at your watch]	□□:□□	1	□□ x 3 = □□
4. <u>Count</u> backwards 20 to 1.		2	□□ x 2 = □□
5. Say the months in reverse order.		2	□□ x 2 = □□
6. Repeat the Memory Phrase.		5	□□ x 2 = □□
			TOTAL SCORE: □□

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in “Final Score” column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥ 11 will be excluded from the analysis. Maximum score = 28.

** OMC – Katzman, R., et al., 1983

IV. SCORING *This section is only applicable if BOMC-Test is completed Pretreatment and Post treatment*

Did the patient score ≥ 11 on the Orientation-Memory-Concentration Test?

- ☐ No
☐ Yes (If yes, notify the patient's treating physician.)

V. NUTRITION

What is the patient's height? (*from patient's chart*) cm

What is the patient's current weight? (*from patient's chart*) kg

What was the patient's weight approximately 6 months ago? (*from patient's chart or patients self-report*) kg

VI. QUESTIONS REGARDING THE QUESTIONNAIRES

- A. Were any of the questionnaires in the "Geriatric Assessment – Healthcare Professional Questionnaire" difficult for you to administer?

☐ Yes ☐ No

If no, please proceed to the next question.

If yes, please indicate which questionnaire was difficult to administer? (*Mark all that apply with an X.*)

- ☐ KPS Healthcare Professional Rated (page 1)
☐ Timed Up and Go (page 2)
☐ Orientation-Memory-Concentration Test (page 2)
☐ Other: Please specify _____

- B. Were any of the questionnaires in the "Geriatric Assessment – Patient Questionnaire" difficult for the patient to complete?

☐ Yes ☐ No

If no, please proceed to the next question.

If yes, please indicate which questionnaire(s) was difficult for the patient to complete? (*Mark all that apply with an X.*)

- ☐ Background Information (page 1)
- ☐ Daily Activities (page 2-3)
- ☐ Physical Activities (page 3)
- ☐ Current Health Rating (page 4)
- ☐ Falls (page 4)
- ☐ Your Health (page 5-7) *(Mark all that apply with an X.)*
 - ☐ 1. Your general health (page 5-6)
 - ☐ 2. Medications (page 7)
- ☐ Your Mood (page 8)
- ☐ Social Activity (page 9)
- ☐ Social Support (page 10)

C. Was the patient able to complete “Geriatric Assessment – Patient Questionnaire” on his/her own?

☐ Yes ☐ No

If no, why? *(Mark all that apply with an X.)*

- ☐ Not literate (does not read or write)
- ☐ Visual problem
- ☐ Fatigue
- ☐ Questions too difficult (above the patient’s reading ability)
- ☐ Other: specify _____

D. Length of time to complete both the Patient and Healthcare Professional Questionnaires

Length of time to complete healthcare professional questionnaire ☐☐☐ minutes

Length of time to complete patient questionnaire ☐☐☐ minutes

Total length of time to complete both questionnaires ☐☐☐ minutes

Completed by: _____
(Last name, First name)

Date form completed: ☐☐ / ☐☐ / ☐☐ ☐☐
MM / DD / YYYY

References for Appendix B Geriatric Assessment

- Sherbourne, C. D. and A. L. Stewart (1991). "The MOS social support survey." *Soc Sci Med* **32**(6): 705-14.
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APPENDIX C. PATIENT REPORTED OUTCOMES (PRO-CTCAE)/QOL PROCEDURES

NOTE: Patients may not be registered to this study until at least one staff person from the site study team has been credentialed to perform patient PRO-CTCAE/QOL training and registration.

We will collect Patient Reported Outcomes (PRO-CTCAEs) and Quality of Life (QOL) assessments (EQ-5D form and Visual Analog Scale (VAS)) at the timepoints listed in Section 9.2 (Summary of Questionnaires).

The PRO-CTCAE team (based at Memorial Sloan Kettering) in collaboration with the Coordinating Center (DFCI) will be training all sites for the PRO-CTCAE/QOL sections.

Tablet computers will be shipped to participating sites automatically in advance of patient enrollment. Some sites will already have tablets ready for this component of the study from their involvement in RU011301I / DFCI protocol 15-019. Research coordinators will provide a tablet computer to each participating patient in-clinic prior to each scheduled visit. Patients will be asked to complete the online survey prior to the visit with their provider. Back-up paper surveys, printed from the PRO-CTCAE system, will also be available in case technical problems preclude tablet use. NOTE: If the back-up paper survey is used, patient responses should be entered by the research coordinator into the PRO-CTCAE system.

Any PRO-CTCAE data collected prior to September 1, 2019 utilized the National Cancer Institute (NCI) PRO-CTCAE web platform. As of September 1, 2019, PRO-CTCAE data are captured through a REDCap system. Any data collected on the NCI system from ACCRU [RU011301I]/DFCI protocol 15-019 and 18-124 will be merged with data collected through REDCap.

1.0 Site Staff PRO-CTCAE Credentialing

- 1.1 Previously credentialed staff:** Members of site study teams previously credentialed to perform patient PRO-CTCAE training do not need to be re-certified for this study but **are required** to send an email to notify the central PRO-CTCAE coordinator at [REDACTED] of the prior certification. Be certain to include the prior study and the approximate date of training. [REDACTED]

The central PRO-CTCAE coordinator will determine if any additional training is needed. The central PRO-CTCAE coordinator will send notice of the certification to DFCI for documentation that training has been completed. To check the status of this, sites should contact: [REDACTED]

- 1.2 To obtain new credentialing:** All research staff, not previously credentialed, must be trained before enrolling their first patient to this study. To obtain credentialing to perform PRO-CTCAE patient training, sites should send an email request to the central PRO-CTCAE coordinator at [REDACTED]. The coordinator will contact the site to schedule a date and time for live interactive training using the telephone. The training does not require viewing of an instructional video. Training will require about 45 minutes and is required only once.

Training will include 1) how to register a patient to the PRO-CTCAE system, in order to report symptoms by computer; 2) how to explain and demonstrate the PRO-CTCAE computer system to patients; 3) how to monitor your patients' PRO-CTCAE reporting, 4) how to enter in responses if a paper back up of the questionnaire is used and 5) for applicable sites, how to print a shared AE report from the PRO-CTCAE system.

The central PRO-CTCAE Coordinator will email notice of the certification to the site and to the Coordinating Center. [REDACTED]
[REDACTED]

For any questions or concerns, please send email to [REDACTED]
[REDACTED]

2.0 Patient PRO-CTCAE

NOTE: Site study staff must clearly convey to the patient that the information regarding symptoms collected by the PRO-CTCAE self-report are for research purposes only and are not routinely monitored by a physician. Study staff must advise patients to directly contact their doctor for any concerning symptoms.

2.1 Patient PRO-CTCAE Training: All patients who can read and speak English and/or Spanish will be required to participate in PRO-CTCAE reporting by computer using the PRO-CTCAE system (REDCap database). Site study staff will train the patient how to use the system. This training will require about 10 to 20 minutes per patient at the first visit.

Each site will have a tablet computer that has internet access which will be brought to the patient in a private area either in the waiting room or an examination room in the clinic on Day 1 of each cycle before each regularly scheduled office visit.

Patients will use this tablet computer (or another computer at the clinic if the tablet is broken or in use by another patient) to go to the PRO-CTCAE system, **enter username and password**, and then answer the questions. This will require about 10 minutes. If the tablet computer is broken or not available, paper copies of the survey will be available by printing them. Site staff will be taught how to do this in their initial training.

2.2 Patient PRO-CTCAE Reporting: Patients will be asked to use the electronic system (REDCap) to self-report symptoms at baseline, at the start of each chemotherapy cycle (every 3 weeks), and one time during the 6 month Observation period. This reporting should require about 10 minutes.

Data reported by patients into the PRO-CTCAE electronic platform will be stored in a secure RedCap database. This database will be available electronically on an ongoing basis to the coordinating center for remote access with password protection.

3.0 Study Site PRO-CTCAE Reporting (Site Randomization)

3.1 Sites will be randomly assigned (1:1) at the time of training (or at the time that the site notifies

the PRO-CTCAE Coordinator of previous credentialing) by the central PRO-CTCAE Coordinator to report adverse events using either:

- **Traditional Reporting:** The AEs captured per standard practice in the participant's medical record.
- **Shared PRO-CTCAE Reporting:** The AEs generated from the PRO-CTCAE system which contains the patient's PRO-CTCAE scores, reported earlier the same day.

- 3.11 For sites assigned to Traditional Reporting (Unshared), AEs will be captured per standard practice in the participant's medical record.
- 3.12 For sites assigned to Shared PRO-CTCAE Reporting: the AE Form generated from the PRO-CTCAE system should be sent/printed from the PRO-CTCAE system and provided to the clinician that will be assessing Adverse Events ("Shared" site instructions will be provided during PRO-CTCAE training). The purpose of this approach is to assess whether viewing patient-reported symptom information influences clinical staff CTCAE reporting. Appendix E is a blank copy of the Provider Responses to PRO-CTCAEs form that is completed as part of Shared PRO-CTCAE Reporting.

Note: Sites will be told which group they are randomized to at the time of their PRO-CTCAE training by the central PRO-CTCAE coordinator. Any questions regarding the randomization group or the related processes, should be directed towards the central [REDACTED]

If a patient transfers to another participating site, the patient will keep the initial site randomization to traditional vs shared pro-ctcae reporting.

APPENDIX D. PATIENT-REPORTED OUTCOMES (PRO) CTCAE ITEMS

NOTE: This Appendix should not be used in place of the web platform. If a paper copy is needed, it can be printed from the PRO-CTCAE web platform (RedCap) or provided by the Coordinating Center in Spanish or English. This is a list of the questions (as they are exactly worded on the web platform).

1. Please think back over the past 3 weeks, what was the SEVERITY of your **FATIGUE, TIREDNESS, OR LACK OF ENERGY** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
2. Please think back over the past 3 weeks, how much did **FATIGUE, TIREDNESS, OR LACK OF ENERGY** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
3. Please think back over the past 3 weeks, what was the SEVERITY of your **INSOMNIA (INCLUDING DIFFICULTLY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY)** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
4. Please think back over the past 3 weeks, how much did **INSOMNIA (INCLUDING DIFFICULTLY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY)** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
5. Please think back over the past 3 weeks, what was the SEVERITY of your **DECREASED APPETITE** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
6. Please think back over the past 3 weeks, how much did **DECREASED APPETITE** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
7. Please think back over the past 3 weeks, how OFTEN did you have **NAUSEA**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly
8. Please think back over the past 3 weeks, what was the SEVERITY of your **NAUSEA** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
9. Please think back over the past 3 weeks, how OFTEN did you have **VOMITING**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly
10. Please think back over the past 3 weeks, what was the SEVERITY of your **VOMITING** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
11. Please think back over the past 3 weeks, how OFTEN did you have **LOOSE OR WATERY STOOLS (DIARRHEA)**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly

12. Please think back over the past 3 weeks, what was the SEVERITY of your **CONSTIPATION** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
13. Please think back over the past 3 weeks, how OFTEN did you have a **HEADACHE**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly
14. Please think back over the past 3 weeks, what was the SEVERITY of your **HEADACHE** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
15. Please think back over the past 3 weeks, how much did your **HEADACHE** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
16. Please think back over the past 3 weeks, how OFTEN did you have **PAIN**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly
17. Please think back over the past 3 weeks, what was the SEVERITY of your **PAIN** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
18. Please think back over the past 3 weeks, how much did **PAIN** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
19. Please think back over the past 3 weeks, how OFTEN did you have **ACHING MUSCLES**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly
20. Please think back over the past 3 weeks, what was the SEVERITY of your **ACHING MUSCLES** at their WORST:
 - None / Mild / Moderate / Severe / Very severe
21. Please think back over the past 3 weeks, how much did **ACHING MUSCLES** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
22. Please think back over the past 3 weeks, what was the SEVERITY of your **NUMBNESS OR TINGLING IN YOUR HANDS OR FEET** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
23. Please think back over the past 3 weeks, how much did **NUMBNESS OR TINGLING IN YOUR HANDS OR FEET** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
24. Please think back over the past 3 weeks, what was the SEVERITY of your **MOUTH OR THROAT SORES** at their WORST:
 - None / Mild / Moderate / Severe / Very severe

25. Please think back over the past 3 weeks, how much did **MOUTH OR THROAT SORES** INTERFERE with your usual or daily activities:
 - Not at all / A little bit / Somewhat / Quite a bit / Very much
26. Please think back over the past 3 weeks, what was the SEVERITY of your **DRY MOUTH** at its WORST:
 - None / Mild / Moderate / Severe / Very severe
27. Please think back over the past 3 weeks, how OFTEN did you have **NOSEBLEEDS**:
 - Never / Rarely / Occasionally / Frequently / Almost constantly
28. Please think back over the past 3 weeks, what was the SEVERITY of your **NOSEBLEEDS** at their WORST:
 - None / Mild / Moderate / Severe / Very severe
29. Please think back over the past 3 weeks, did you **BRUISE EASILY (BLACK AND BLUE MARKS)**:
 - Yes / No
30. Please think back over the past 3 weeks, did you have any **RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS**:
 - Yes / No
31. Please think back over the past 3 weeks, did you have any **CHANGE IN THE COLOR OF YOUR FINGERNAILS OR TOENAILS**:
 - Yes / No
32. Please think back over the past 3 weeks, did you **LOSE ANY FINGERNAILS OR TOENAILS**:
 - Yes / No
33. Please think back over the past 3 weeks, did you have any **HIVES (ITCHY RED BUMPS ON THE SKIN)**:
 - Yes / No
34. Please think back over the past 3 weeks, did you have any **RASH**:
 - Yes / No
35. Please think back over the past 3 weeks, did you have any **HAIR LOSS**:
 - Not at all/A little bit /Somewhat/ Quite a bit/ Very much
36. Please think back over the past 3 weeks, did you have any **FLASHING LIGHTS IN FRONT OF YOUR EYES**:
 - Yes / No
37. Please think back over the past 3 weeks, did you have any **SPOTS OR LINES (FLOATERS) THAT DRIFT IN FRONT OF YOUR EYES**:
 - Yes / No

38. Please think back over the past 3 weeks, what was the SEVERITY of your **WATERY EYES (TEARING)** at their WORST:
- None / Mild / Moderate / Severe / Very severe
39. Please think back over the past 3 weeks, how much did **WATERY EYES (TEARING)** INTERFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much
40. Please think back over the past 3 weeks, what was the SEVERITY of your **BLURRY VISION** at its WORST:
- None / Mild / Moderate / Severe / Very severe
41. Please think back over the past 3 weeks, how much did **BLURRY VISION** INTERFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much
42. Please think back over the past 3 weeks, what was the SEVERITY of your **SHORTNESS OF BREATH** at its WORST:
- None / Mild / Moderate / Severe / Very severe
43. Please think back over the past 3 weeks, how much did **SHORTNESS OF BREATH** INTERFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much
44. Please think back over the past 3 weeks, what was the SEVERITY of your **COUGH** at its WORST:
- None / Mild / Moderate / Severe / Very severe
45. Please think back over the past 3 weeks, how much did **COUGH** INTERFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much
46. Please indicate any additional symptoms you have experienced over the last 3 weeks that you were not asked about.

Quality of Life Forms (including EQ-5D and Visual Analog Scale (VAS))

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ☐
- I have slight problems walking ☐
- I have moderate problems walking ☐
- I have severe problems walking ☐
- I am unable to walk ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

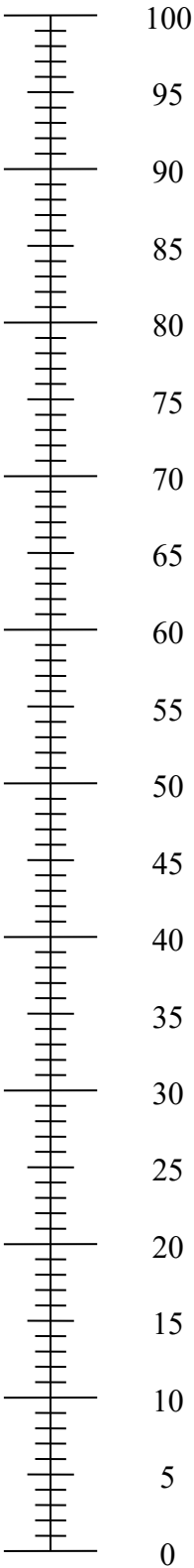
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is

**The best health
you can imagine**



**The worst health
you can imagine**

TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

APPENDIX E. PRO-CTCAE PROVIDER RESPONSES FOR SHARED REPORTING

This appendix is only applicable to sites randomized to PRO-CTCAE Shared Reporting.

NOTE: This appendix should not be used in place of the web platform, but may be utilized if a hard copy is needed.

PLACE LABEL HERE

Protocol Number: 18-124

Patient ID: _____ Patient Initials: _____
L F M

Institution Number: _____

Institution: _____

**ATOP TRIAL: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients
with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer
Adverse Event Form**

ALL ITEMS MUST BE COMPLETED

Are data amended? (check one) ☐ Yes ☐ No
(if data amended, please circle in red when using paper forms)

Current Cycle Number (adverse events associated with this cycle): _____

Date of evaluation: (mm/dd/yyyy) ____/____/____

CTC Adverse Event Term (CTCAE v.4.0)	MedDRA Code (v.12.0) <i>(must be completed)</i>	Patient Self-Reported AE Grades			CTC Adverse Event Grade (highest grade this cycle) INCLUDE GRADE 0's					CTCAE Attribution Code (If Grade >0) Enter a # below: 1=Unrelated 2=Unlikely 3=Possible 4=Probable 5=Definite	Has an adverse event expedited report been submitted?*
		Severity	Frequency	Interference with Activities of Daily Life							
Aspartate Aminotransferase increased	10001551				0	1	2	3	4	5 (death)	_____
Alanine Aminotransferase increased	10001551				0	1	2	3	4	5 (death)	_____
Blood bilirubin increased	10005364				0	1	2	3	4	5 (death)	_____
Platelets count decreased	10035528				0	1	2	3	4	5 (death)	_____
Hypoxia	10021143				0	1	2	3	4	5 (death)	_____
Pneumonitis	10035742				0	1	2	3	4	5 (death)	_____
Peripheral motor neuropathy	10034580				0	1	2	3	4	5 (death)	_____
Peripheral sensory neuropathy	10034620				0	1	2	3			_____
Alopecia	10001760				0	1	2				_____
Anorexia	10002646				0	1	2	3			_____
Blurred vision	10005886				0	1	2	3	4	5 (death)	_____
Bruising	10006504				0	1	2	3			_____
Constipation	10010774				0	1	2	3			_____
Cough	10011224				0	1	2	3	4	5 (death)	_____

PLACE LABEL HERE

Protocol Number: 18-124

Patient ID: _____ Patient Initials: _____
L F M

Institution Number: _____

Institution: _____

**ATOP TRIAL: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients
with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer
Adverse Event Form**

ALL ITEMS MUST BE COMPLETED

Are data amended? (check one) ☐ Yes ☐ No
(if data amended, please circle in red when using paper forms)

CTC Adverse Event Term (CTCAE v.4.0)	MedDRA Code (v.12.0) <i>(must be completed)</i>	Patient Self-Reported AE Grades			CTC Adverse Event Grade (highest grade this cycle) INCLUDE GRADE 0's						CTCAE Attribution Code (If Grade > 0) Enter a # below: 1=Unrelated 2=Unlikely 3=Possible 4=Probable 5=Definite	Has an adverse event expedited report been submitted?*
		Severity	Frequency	Interference with Activities of Daily Life								
Diarrhea	10012727				0	1	2	3			—	—
Dry Mouth	10013781				0	1	2	3	4	5 (death)	—	—
Dyspnea	10013963				0	1	2	3	4	5 (death)	—	—
Epistaxis	10015090				0	1	2	3	4	5 (death)	—	—
Fatigue	10016256				0	1	2	3			—	—
Flashing lights	10016757				0	1	2	3			—	—
Floaters	10016778				0	1	2	3			—	—
Headache	10019211				0	1	2	3			—	—
Insomnia	10022437				0	1	2	3			—	—
Myalgia	10028411				0	1	2	3			—	—
Mucositis oral	10028130				0	1	2	3	4	5 (death)	—	—
Nail discoloration	10028691				0	1					—	—
Nail loss	10049281				0	1	2				—	—
Nail ridging	10062283				0	2					—	—
Nausea	10028813				0	1	2	3			—	—

PLACE LABEL HERE
Protocol Number: 18-124
Patient ID: _____ Patient Initials: _____
L F M
Institution Number: _____
Institution: _____

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Adverse Event Form**

ALL ITEMS MUST BE COMPLETED

Are data amended? (check one) ☐ Yes ☐ No
(if data amended, please circle in red when using paper forms)

CTC Adverse Event Term (CTCAE v.4.0)	MedDRA Code (v.12.0) <i>(must be completed)</i>	Patient Self-Reported AE Grades			CTC Adverse Event Grade (highest grade this cycle) INCLUDE GRADE 0's						CTCAE Attribution Code (If Grade >0) Enter a # below: 1=Unrelated 2=Unlikely 3=Possible 4=Probable 5=Definite	Has an adverse event expedited report been submitted?*
		Severity	Frequency	Interference with Activities of Daily Life								
Pain	10033371				0	1	2	3			—	—
Rash maculo-papular	10037868				0	1	2	3			—	—
Urticaria	10046735				0	1	2	3			—	—
Vomiting	10047700				0	1	2	3	4	5 (death)	—	—
Watering eyes	10047848				0	1	2	3			—	—

Is the person who filled out the above form the same person who assigned the actual CTCAE grades for this patient: (check one)

1 ☐ Yes 2 ☐ No

Did the person who assigned the CTCAE grades for this patient have access to the patient's self-reported AE grades at the time they assigned the CTCAE grades: (check one)

1 ☐ Yes 2 ☐ No (If No, proceed to Other Adverse Events question)

Were any of the assigned CTCAE grades in the above form different than they would have been in the absence to the patient's self-reported AE responses? (check one)

1 ☐ Yes 2 ☐ No

Protocol Number: 18-124

Institution Number: _____

**ATOP TRIAL: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients
with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer
Adverse Event Form**

Are data amended? (check one) ☐ Yes ☐ No
(if data amended, please circle in red when using paper forms)

1 ☐ Yes, and reportable adverse events occurred
3 ☐ Yes, but no reportable adverse events occurred (*stop here*)
2 ☐ No (*stop here*)

(Other) CTC Adverse Event Term Not Listed (CTCAE v.4.0)	MedDRA Code (v.12.0) (must be completed)	CTC Adverse Event Grade (highest grade this cycle)				CTC AE Attribution Code (If Grade >0) Enter a # below: 1=Unrelated 2=Unlikely 3=Possible 4=Probable 5=Definite	Has an adverse event expedited report been submitted?*		
Adverse Events** beyond those required in Section 10.0 of the protocol. Record grade 2 with attribution of possible, probable or definite and all grade 3, 4, and 5 regardless of attribution.									
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____
	_____			2	3	4	5 (death)	_____	_____

APPENDIX F. PERFORMANCE STATUS CRITERIA

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