A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Neratinib and Ado-Trastuzumab Emtansine (T-DM1) for Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast cancer and Brain Metastases

Protocol Number	TBCRC 022
Sponsor-Investigator	Rachel A. Freedman, MD, MPH Dana-Farber Cancer Institute 450 Brookline Avenue, Boston, MA 02215 [redacted]
Study statistician	Nabihah Tayob, PhD Dana-Farber Cancer Institute Boston, MA 02215 [redacted]
Supporters	Translational Breast Cancer Research Consortium (TBCRC) Puma Biotechnology, Inc.
Coordinating Center	Dana-Farber Cancer Institute (Boston, MA) *Study Liaison:* Project Manager ([redacted]) *Study Coordinator:* Study Coordinator([redacted])

- Protocol Revision Record -

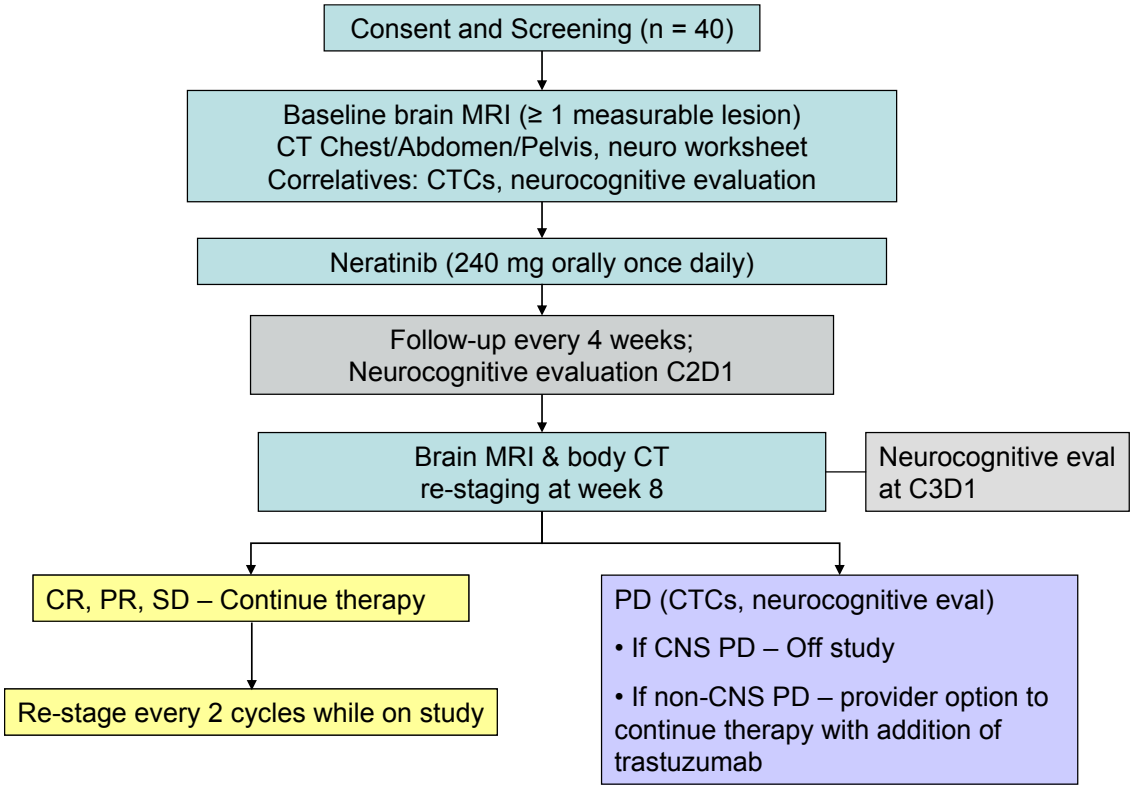
Original Protocol:	09/01/11
Amendment 1:	04/25/12
Amendment 2:	09/17/12
Amendment 3:	07/01/13
Amendment 4:	10/10/13
Amendment 5:	10/23/13
Amendment 6:	05/22/14

Amendment 7:	06/11/14
Amendment 8:	04/14/15
Amendment 9:	05/04/15
Amendment 10:	12/24/15
Amendment 11:	02/18/16
Amendment 12:	03/01/16
Amendment 12:	04/26/16
Amendment 13:	09/07/16
Amendment 14:	06/30/17
Amendment 15:	07/13/18
Amendment 16:	07/02/19
Amendment 17:	05/18/21
Amendment 18:	03/18/24

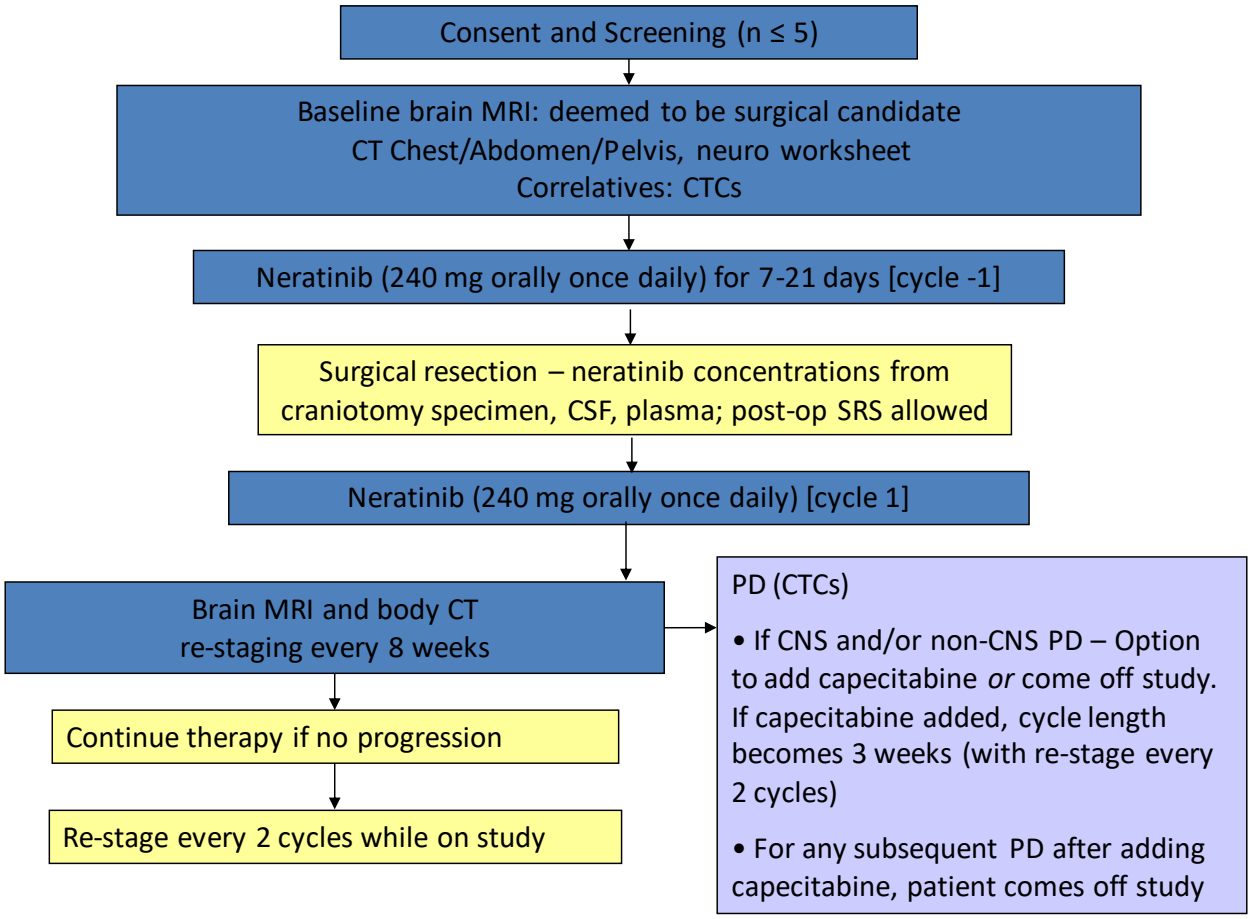
Table of Contents

SCHEMAS

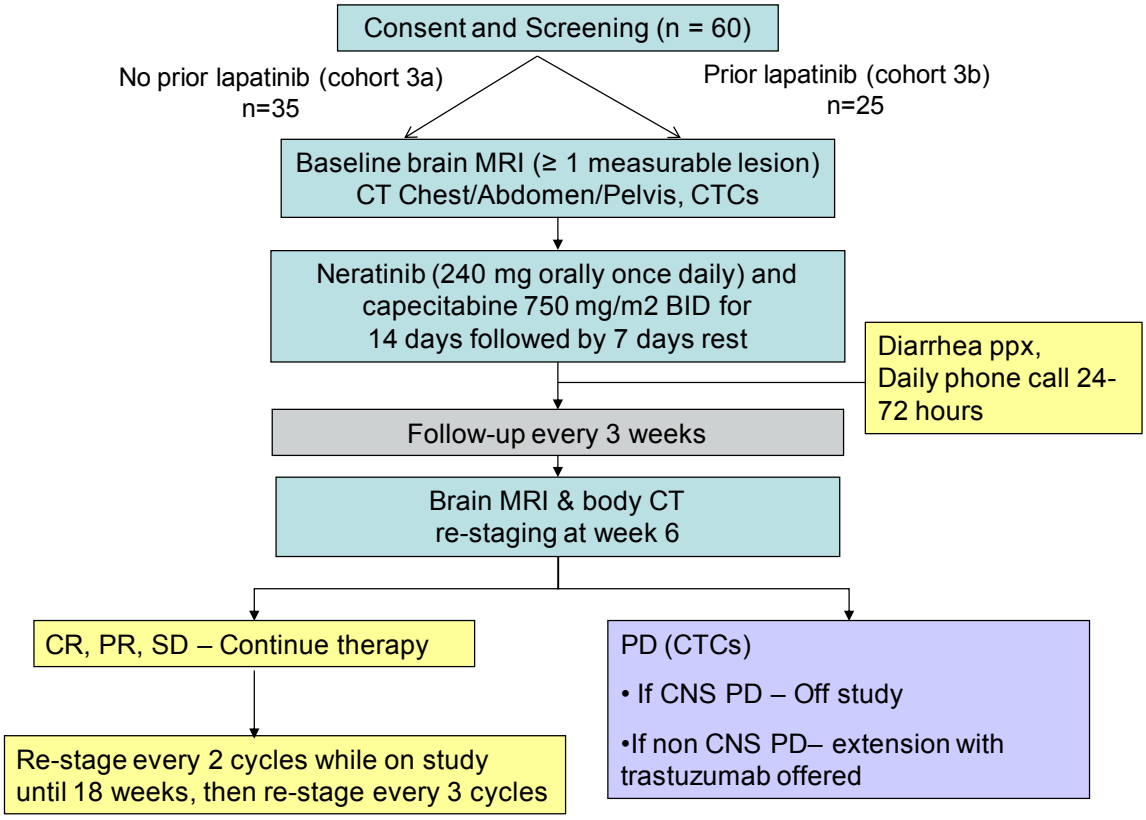
COHORT 1: PATIENTS WITH PROGRESSIVE BRAIN METASTASES



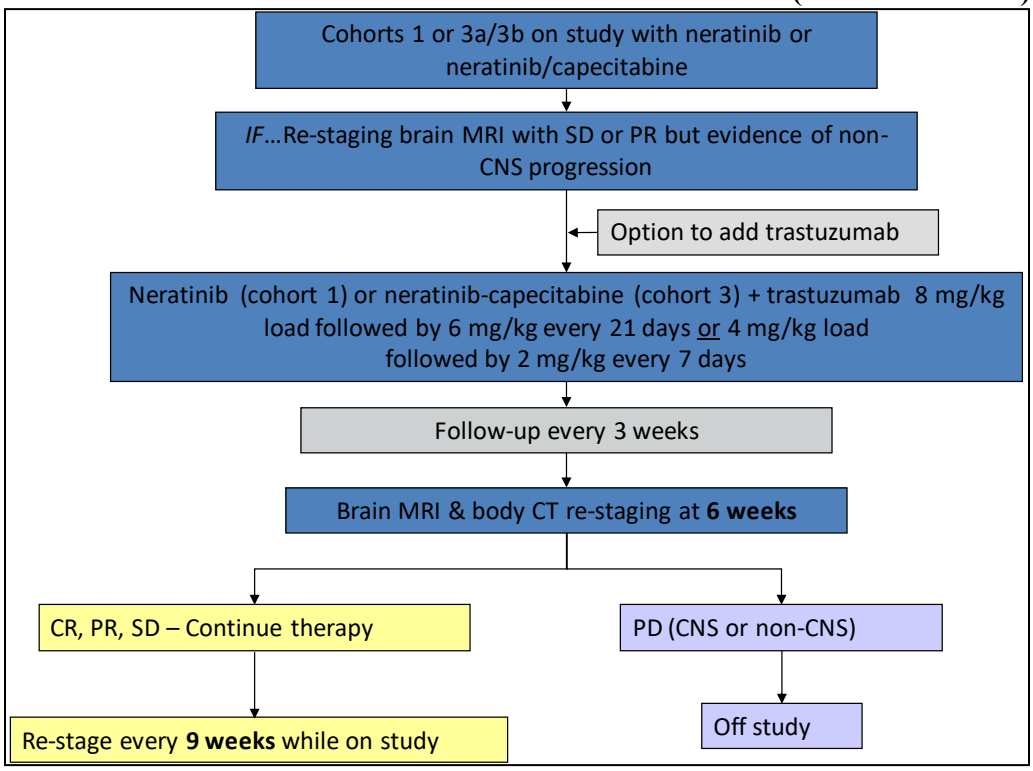
COHORT 2: PATIENTS WHO ARE CANDIDATES FOR CRANIOTOMY



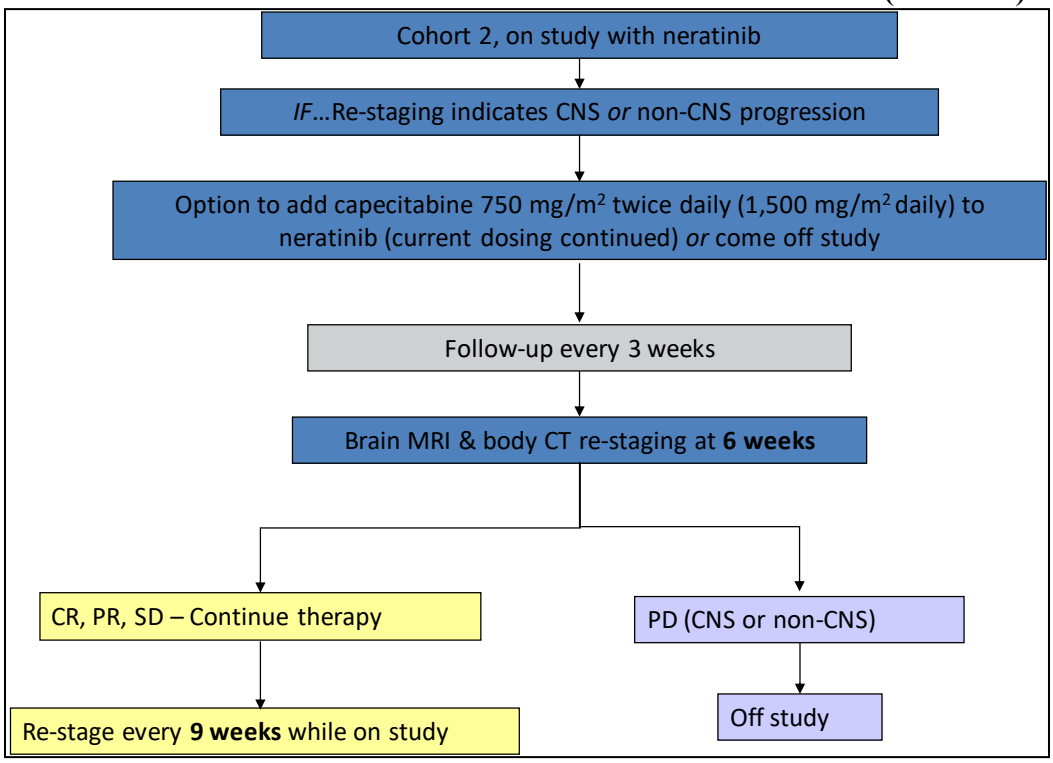
COHORTS 3A and 3B: PATIENTS WITH PROGRESSIVE BRAIN METASTASES



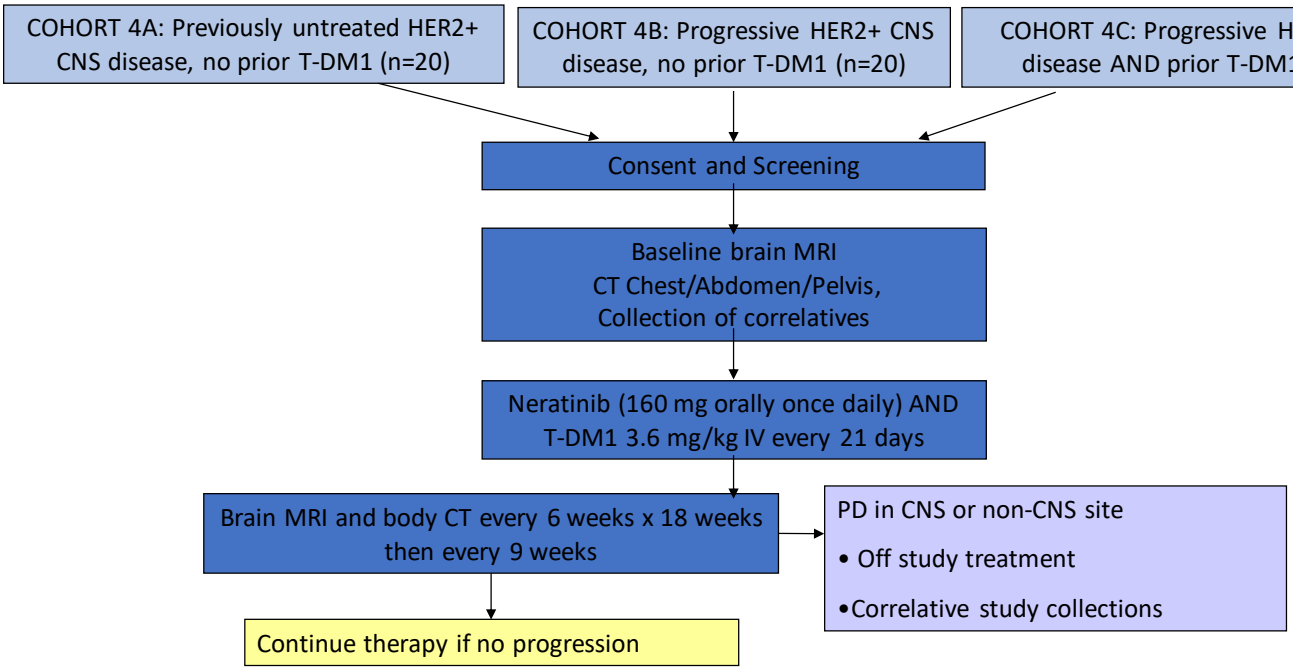
OPTIONAL EXTENSION PHASE: PATIENTS WHO PROGRESS OUTSIDE OF THE CNS (Cohorts 1 and 3)



OPTIONAL EXTENSION PHASE: PATIENTS WHO PROGESSS IN CNS OR NON-CNS SITES (Cohort 2)



COHORT 4A, 4B, 4C: PATIENTS WITH PREVIOUSLY UNTREATED HER2+ BRAIN METASTASES WITHOUT PRIOR T-DM1 (4A), PROGRESSIVE BRAIN METASTASES WITHOUT PRIOR T-DM1 (4B), AND PROGRESSIVE BRAIN METASTASES AND WITH PRIOR T-DM1 (4C)



1. STUDY DESIGN/SUMMARY

This is a multi-Cohort, phase II, open-label, single arm study with administration of neratinib-based treatments for patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer with brain metastases. Neratinib will be administered to participants with progressive brain metastases (Cohort 1) at a starting dose of 240 mg orally daily without breaks and cycle duration will be 4 weeks. In the ≤ 5 patients who are surgical candidates (Cohort 2), treatment with neratinib will continue for 7-21 days preoperatively and will then resume postoperatively (or after radiosurgery as appropriate). The decision to enter patients into Cohort 2 will be at the treating physician's discretion in collaboration with a local therapist (i.e. radiation oncology or neurosurgery). Patients on Cohort 2 who develop progressive disease in CNS or non-CNS sites will have the option to add capecitabine to their current neratinib dosing (and will then transition to q21 day cycles). Cohorts 3A (no prior lapatinib) and 3B (prior lapatinib) administer neratinib 240 mg once daily orally and capecitabine 1500 mg/m^2 (750 mg/m^2 orally, twice daily) for days 1-14 of each 21-day cycle to participants with progressive brain metastases. Cycle length for participants on Cohort 3 will be 21 days. Cohorts 4A and 4B will enroll 20 patients each; those with previously untreated CNS disease (4A) and those with progressive CNS disease (4B), both without prior ado-trastuzumab emtansine exposure (T-DM1). Cohort 4C will enroll up to 23 patients with progressive CNS disease who have had prior T-DM1 exposure.

All patients on Cohorts 1 and 2 will be evaluated on day 1 of each cycle for toxicity and will be re-staged every 2 cycles (8 weeks) with Magnetic Resonance Imaging (MRI) of the brain and computed tomography (CT) scans (or MRI) of the chest, abdomen, and pelvis (and CT of brain if MRI is contraindicated). Re-staging scans can decrease in frequency to every 3 cycles after the completion of 12 cycles. For those patients who have non-CNS progression on Cohorts 1 and 3 (and who have not progressed within the CNS), there will be an option to continue therapy on protocol with the addition of trastuzumab (administered as 8 mg/kg bolus followed by 6 mg/kg every 21 days or 4 mg/kg bolus followed by 2 mg/kg every 7 days) (*Section 5.5*). Patients on Cohort 3A and 3B will be evaluated on day 1 of each cycle (every 21 days) and will have re-staging completed every 2 cycles until they reach 18 weeks on study treatment. At that point, re-staging will transition to every 3 cycles. Patients on Cohort 2 who have non-CNS or CNS progression will have the option to add capecitabine rather than trastuzumab. Patients on Cohorts 4A-4C will all receive neratinib 160 mg once daily (maximum tolerated dose from the phase 1 study) and standard-dose T-DM1 at 3.6 mg/kg every 21 days. Re-staging will occur every 6 weeks for all patients on Cohorts 4A-4C for 18 weeks and will then occur every 9 weeks thereafter.

Additional correlative studies will include research blood draws for banking (optional for all Cohorts), Circulating Tumor Cell (CTC) collection for cell enumeration (Cohort 1 and 3A/3B), neratinib concentration in the CNS (Cohort 2), neurocognitive function examinations (Cohort 1), and other CTC molecular studies (Cohorts 1 and 3A/3B). Correlative studies for participants

enrolled to Cohort 3 will also include collection of archival tissue for genomic analyses. Correlative studies for Cohorts 4A-4C will include circulating tumor (ct)DNA studies, genomics of available tissue, patient-reported outcomes and their agreement with traditional adverse event assessments, and evaluation of self-reported adherence to medications for diarrhea prophylaxis. Further details on proposed correlative studies are delineated in the body of the protocol below.

Cohorts 3A and 3B will enroll patients separately and will not serve as a crossover Cohort for those who have progression on neratinib alone. Participants on this Cohort will also have the option to extend protocol therapy with trastuzumab in the case of non-CNS progression. Cohorts 4A-4C will *not* have the option to enroll in an extension Cohort.

2. OBJECTIVES

2.1 Primary Objective

To evaluate the objective response rate (ORR) in the Central Nervous System (CNS) by composite response criteria separately in Cohort 1, Cohort 3A, and Cohort 3B (described in detail in *Section 12)*

To evaluate the ORR in the CNS by more modern criteria, namely the RANO-BM criteria,[1] separately in Cohorts 4A, 4B, and 4C (described in detail in *Section 12*).

2.2 Secondary Objectives [Cohort 3A/3B evaluated separately in relevant Cohorts]

- Progression-Free Survival (PFS) and Overall Survival (OS) (All Cohorts)
- CNS response by Macdonald criteria[2] (Cohort 1 only)
- CNS response by volumetric/composite criteria (secondary endpoint for Cohorts 4A-4C only as this is primary objective for Cohorts 1, 3A-3B)
- First site of disease progression (All Cohorts)
- Safety and tolerability of therapy (All Cohorts)
- Time to CNS radiation (Cohort 4A only)
- Assess clinical outcomes for patients who opt to receive trastuzumab and neratinib at the time of non-CNS progression (i.e. toxicity, CNS and non-CNS response, site of first progression, OS) [Cohort 1 only]

2.3 Exploratory Objectives

- PFS and OS in patients who undergo craniotomy [Cohort 2]
- PFS from the time of addition of capecitabine for Cohort 2 patients
- ORR in the CNS for lapatinib-naïve patients vs. lapatinib-treated patients [all Cohorts]
- Association of CTC count and OS [Cohort 1 only]
- Explore the association of MET (hepatocyte growth factor receptor) and HER2 co-amplification (in CTCs) with treatment response [Cohorts 1, 3A/3B]

- Explore the relationship between the HER2 status of a patient's primary breast cancer, metastatic lesions, and CTCs using fluorescence in situ hybridization (FISH) for HER2 gene amplification [Cohorts 1, 3A/3B]
- Explore the possible mechanisms of resistance driven by Epidermal Growth Factor Receptor (EGFR) using FISH for EGFR gene amplification in HER2-positive CTCs [Cohorts 1, 3A/3B]
- Assess neratinib concentrations and concentrations of its metabolites in CNS tumor, cerebrospinal fluid (CSF), and plasma at craniotomy in patients who receive neratinib prior to surgery [Cohort 2]
- Examine neurocognitive function for patients with varying previous therapies for CNS disease [Cohort 1]
- Explore primary archival samples and metastatic samples when able to evaluate for predictors of response and outcome (Cohorts 3A/3B)
- Perform molecular characterization of potential resistance mechanisms, predictive biomarkers, and immunological function by collecting blood and tumor specimens (Cohort 3A/3B, 4A/4B/4C).
- Examine changes in the mutational profiles of one's disease using circulating tumor (ct)DNA (all Cohort 4 patients) in blood and in CSF (for any Cohort 4 patient undergoing lumbar puncture)
- Evaluate patient-reported gastrointestinal (GI) toxicity and its impact on quality of life for patients receiving neratinib and T-DM1 (Cohort 4 patients only, cycles 1-3)
- Compare patient-reported and clinician-reported gastrointestinal adverse events during the first 3 cycles of T-DM1 and neratinib therapy (Cohort 4 patients)
- Evaluate self-reported adherence using the Voils measure[3] to anti-diarrheal prophylaxis during cycle 1 and anti-diarrheal medication diaries during T-DM1 and neratinib therapy (all Cohort 4 patients)
- Compare (exploratory endpoint) symptom reporting for PROMIS[4] and STIDAT[5] measures for diarrhea (Cohorts 4A-4C)

3. BACKGROUND

3.1 Investigational Agents – Neratinib (HKI-272) (administered in all Cohorts)

Neratinib is a potent, oral irreversible-binding inhibitor of the erbB family of receptor tyrosine kinases that inhibits signal transduction through erbB1 (EGFR), erbB2 (HER2), and erbB4. The irreversible binding of these receptors by neratinib results in sustained inhibition of growth pathways (autophosphorylation, signal transduction, and cell proliferation) and ultimate cell cycle arrest at the gap 1/DNA synthesis (G1/S) phase transition of the division cycle. This agent has demonstrated promising in vitro and in vivo activity in patients with HER2-positive breast cancers.[6] It was recently granted FDA approval for use in the post-trastuzumab (adjuvant) setting

due to the efficacy reported in the ExteNET Study.[7] There is no FDA approval for use of neratinib in the metastatic setting.

3.2 Capecitabine (administered in Cohorts 3A/3B)

Capecitabine (Xeloda, Hoffman La-Roche) is an oral fluoropyrimidine carbamate with antineoplastic activity in the breast cancer setting. It is approved by the FDA as monotherapy for patients with metastatic breast cancer that is resistant to paclitaxel and an anthracycline-containing chemotherapy regimen or for patients whose disease is resistant to paclitaxel and for whom further anthracycline therapy is not indicated. Capecitabine is also approved in the setting of metastatic breast cancer when combined with docetaxel. It is commercially available and used widely in patients with metastatic breast cancer.

3.3 Ado-trastuzumab-emtansine (T-DM1) (administered in Cohorts 4A-4C)

T-DM1 (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 antimicrotuble 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. 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 setting.[8-14] T-DM1 is FDA approved as single agent for patients with metastatic breast cancer that is resistant to trastuzumab-based regimens. It is commercially available and used widely in patients with metastatic breast cancer, with case reports and small case series suggesting it has activity in the setting of breast cancer metastasized to the brain.[10,12] and with pre-clinical data suggesting some CNS penetration of T-DM1 in mice with brain metastases [15] Further, in the EMILIA trial which compared T-DM1 to capecitabine-lapatinib in the setting of metastatic HER2+ breast cancer, although the rate of CNS progression was slightly higher in those receiving T-DM1, among those with CNS disease at baseline, an overall survival improvement was observed in those receiving T-DM1 over capecitabine-lapatinib.[16]

3.4 Study Disease

The HER2-positive breast cancer subtype accounts for approximately 20-30% of breast cancers. HER2 is a member of the EGFR family and is an important mediator of cell proliferation and differentiation.[17,18] Although numerous studies in the past have correlated HER2 over-expression with higher grade tumors and poor prognoses,[19] inclusion of trastuzumab (Herceptin®; Genentech, Inc) into adjuvant and metastatic treatment regimens has substantially improved outcomes. However, those with metastatic disease often face significant challenges once their disease progresses through standard trastuzumab-based regimens.

Approximately one-third of patients with HER2-positive, metastatic breast cancer will develop parenchymal brain metastases.[20] It is hypothesized that the high rate of CNS involvement, compared to historical controls, is related to a biological predilection of HER2-positive disease to spread to the CNS, in combination with the widespread use of trastuzumab. Despite trastuzumab's efficacy against extracranial disease, this agent is unable to penetrate the CNS due to its large molecular size.

Standard upfront therapy for newly diagnosed brain metastases includes either whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or both. A very small proportion of patients present with a single lesion, for which surgical resection may be considered. Historically, the survival from CNS diagnosis was poor and many patients died of progressive systemic disease. However, recent series from multiple institutions have suggested that median survival for patients with CNS disease may be improving, likely as a result of advances in systemic therapy.[21,22] For a subset of patients, the CNS has become the dominant site of disease progression. Unfortunately, standard therapies after CNS progression remain undefined, and this area represents an unmet medical need. Very few carefully conducted prospective clinical trials have been conducted in the modern era and many trials using novel agents have specifically excluded patients with CNS disease.

Two studies have evaluated the activity of lapatinib in the setting of progressive brain metastases.[23,24] Collectively, these studies have enrolled nearly 300 patients with an ORR in the CNS of approximately 6%. While the activity was modest, it was comparable to that observed on trials with lapatinib for the treatment of refractory, systemic (i.e. non-CNS) metastatic disease. In an optional extension phase of the multicenter trial, patients who had progressed on lapatinib were allowed to crossover to receive lapatinib plus capecitabine. Among 50 evaluable patients who participated in this study extension, the ORR in the CNS was 20%.[24] Beyond these specific trial results, the rapid accrual of these studies supports the medical need for new therapies for brain metastases and the feasibility of conducting trials in this patient population. Further study of potentially active CNS agents is crucial to improve the quality and duration of life for patients with progressive metastatic breast cancer to the brain.

3.5 Rationale for Neratinib (all Cohorts)

Multiple studies with neratinib have been conducted to date that have demonstrated substantial clinical activity and acceptable toxicity profile in patients with HER2-positive breast cancer. Neratinib is now approved for use by the FDA in the adjuvant setting given its efficacy in the ExteNET trial.[7] However, most prior evaluations of with neratinib have been in the setting of metastatic disease. In a phase I study of neratinib in patients with previously treated solid tumors, 8 of 25 patients with breast cancer had a partial response (32%) and another patient had prolonged stabilization of disease.[25] In a subsequent phase II trial for patients with HER2-positive, metastatic de-novo or pre-treated breast cancer, the ORR (defined as complete or partial responses) was 51% (95% Confidence Interval [CI]

16% to 39%) and 26% (95% CI 38% to 64%), respectively. At 16 weeks, 75% of first-line patients and 61% of previously treated patients were progression-free.[26] Of note, patients with active CNS disease were not eligible for this study.

More recently, phase 1/2 studies have evaluated the administration of neratinib in addition to other agents and have been reported. Administration of neratinib and vinorelbine in 18 previously treated metastatic patients and demonstrated clinical activity in lapatinib-treated (ORR 25%, n=14) and lapatinib-naïve (ORR 43%, n=4) patients.[27] Neratinib in combination with paclitaxel was also an active and tolerable combination in a larger cohort of patients (n=198) with an overall ORR of 69% (95% CI 59% - 78%). In first-line patients, an ORR of 70% was observed (95% CI 51% - 84%).[28] A third study with a similar design administered capecitabine with neratinib and is currently underway. Results from this protocol are forthcoming.[29]

Although the CNS penetration of neratinib has not been well described, pre-clinical studies have been performed in male CD-1 mice who received neratinib in order to examine the potential brain penetration of this agent. These studies demonstrated plasma concentrations considerably higher than brain concentrations (brain-to-plasma exposure ratio of 0.04). Although these concentrations are low, they are similar to the brain concentrations observed in healthy animals who received lapatinib. Subsequent study of CNS penetration of lapatinib in human subjects with glioblastoma multiforme has demonstrated significantly higher levels (vs. previously observed levels in healthy mice) of lapatinib in CNS surgical specimens. After 7 days of pre-operative lapatinib administration the average tumor-to-plasma ratio was 11.4 (range 0.65 – 39.52), perhaps due to a disrupted blood-brain barrier or inhibition of efflux transporters.[30,31] Because lapatinib and neratinib are both small molecule inhibitors of HER2, and because of the increased systemic activity of neratinib monotherapy (vs. lapatinib monotherapy), these data demonstrate the potential for CNS penetration of neratinib in human subjects with brain metastases.

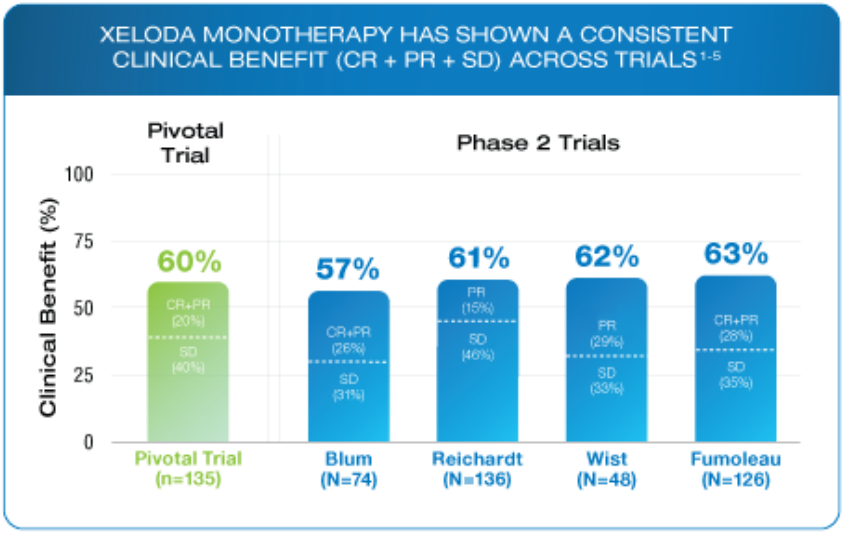
Although Cohorts 1 and 2 were initially designed for administration of neratinib alone, we have amended the protocol to build on these results, with the addition of capecitabine (Cohorts 3A/3B) and now T-DM1 (Cohorts 4A/B/C).

In addition to investigating the activity of neratinib and neratinib-based combinations in patients with CNS disease, we have been interested in developing and understanding predictors of clinical benefit and prognosis for these patients. In this protocol, we have included interesting scientific correlative studies with each enrolled cohort such as peripheral blood studies to examine potential correlations with response to treatment and survival (all Cohorts), neurocognitive function testing in Cohort 1-treated patients, and testing of neratinib concentrations in intracranial specimens and CSF at the time of craniotomy in Cohort 2-treated patients.

3.6 Rationale for capecitabine (Cohorts 3A/3B)

Multiple studies to date have demonstrated impressive efficacy and good tolerability of capecitabine in the treatment of extracranial and intracranial metastatic breast cancer. Approval for single-agent capecitabine for breast cancer was based on data from a single-arm, phase II trial that enrolled 162 patients with stage IV breast cancer and administered this at a dose of 1250 mg/m^2 twice daily for 14 days followed by a one week rest period, every 21 days. Results from this study showed an objective response rate of 20% (95% CI 14-28%) and a median duration of response of 8.1 months in a population with relatively refractory disease (i.e. all had to have failed prior taxane).[32] On this study, the most common treatment-related adverse events were hand-foot syndrome, diarrhea, nausea, vomiting, and fatigue. Diarrhea (14%) and hand-foot syndrome (10%) were the only treatment-related adverse events that occurred with grade 3 or 4 intensity in more than 10% of patients. Additional studies have also documented impressive efficacy of capecitabine in the metastatic breast cancer setting. A summary of the clinical benefit demonstrated in capecitabine monotherapy studies is shown below (taken directly from http://www.xeloda.com/hcp/overview/#):

Approximately 60% of patients resistant to paclitaxel and/or an anthracycline demonstrated a clinical benefit (CR + PR + SD) from XELODA treatment (n=135)[1*]



* In a subgroup of patients with measurable disease who were assessable for response (n=135) in a multicenter, open-label, single-arm phase 2 study (N=162).[1]

In addition, when capecitabine was combined with paclitaxel in women with metastatic breast cancer on a phase III study comparing this to docetaxel alone, the time to progression for the combination was 6.1 months vs. 4.2 months (p=.0001) and overall survival was also improved (14.5 months for combination vs. 11.5 months for docetaxel alone, p=0.0126).[33] All of these studies were completed in women without active CNS metastases.

With regard to treatment of breast cancer that is metastatic to the CNS, capecitabine has also been efficacious, particularly when combined with lapatinib for women with HER2-positive disease. Most recently, the LANDSCAPE study has reported a very high CNS response rate (67%; 95% CI 51-81%) with the use of lapatinib plus capecitabine in lieu of WBRT as upfront treatment of brain metastases.[34] In addition, in a study where 50 women who progressed in their CNS while on lapatinib monotherapy were offered addition of capecitabine, a 20% response rate was observed.[24] In addition, in a small study completed at MD Anderson for women with CNS metastases from breast cancer, an 18% response rate for capecitabine and temozolomide was observed.[35] Capecitabine is thus a promising chemotherapy partner for treatment both systemic and CNS disease in women with HER2-positive breast cancer. We saw activity of this combination in Cohort 3A of this protocol, as noted above.[36]

3.7 Rationale for combining neratinib and capecitabine (Cohorts 3A and 3B)

As above, both neratinib and capecitabine each have promising data with regard to their potential in treatment of CNS disease. Furthermore, capecitabine and neratinib have been tested in combination with encouraging results on a phase 1/2 study in the setting of non-CNS disease, adding further data to support that HER2-directed therapy may work best when partnered with chemotherapy. In a phase 1/2 study of neratinib and capecitabine, in 61 women who received prior taxane and trastuzumab but no prior lapatinib, the objective response rate (systemically) was 64% with clinical benefit rate of 72%.[29] Because of the efficacy of this regimen, a randomized study is currently underway ("NALA") which will compare the combination of lapatinib and capecitabine (standard HER2-based treatment in second line) to neratinib and capecitabine (NCT01808573). Because of these promising data, the combination of capecitabine and neratinib for women with metastatic breast cancer and CNS metastases is attractive. Furthermore, the toxicity profile of the planned combination is favorable per recent phase 1/2 data reported from the above study.[29]

3.8 Rationale for T-DM1 (Cohorts 4A-4C)

Prior studies have demonstrated impressive efficacy and good tolerability of T-DM1 in the treatment of extracranial metastatic, HER2-positive breast cancer. The EMILIA trial[14] was the landmark trial leading to the FDA approval of T-DM1 in the metastatic setting. This trial randomized 978 patients previously treated with trastuzumab and a taxane to receive T-DM1 (3.6 mg/kg intravenous [IV]) or the combination of capecitabine (1000 mg/m2 orally twice a day, days 1 to 14) plus lapatinib (1250 mg orally daily), with each regimen repeated every three weeks. Results from this study showed an improvement in overall survival for T-DM1 arm (OS; median, 31 versus 25 months; HR 0.68, 95% CI 0.55-0.85), even in the presence of crossover treatment. There was also an improvement in progression-free survival (PFS) (median, 10 versus 6 months, respectively; HR 0.65, 95% CI 0.55-0.77), and a significant improvement in the overall response rate by RECIST criteria (44 versus 31 percent). The TH3RESA[37] and MARIANNE[38] studies have also documented impressive efficacy of T-DM1 in the metastatic breast cancer setting.

In the setting of CNS disease, multiple studies have suggested activity of T-DM1 within the CNS. In one retrospective analysis of 5 French centers, T-DM1 demonstrated an response of 44% using RECIST criteria and clinical benefit in 59% in those with CNS and extra-CNS disease.[12] These data are supported by a small prospective trial which evaluated the activity of T-DM1 exclusively in brain metastasis, with 3/10 patients with partial response and 2/10 patients with stable disease lasting more than 6 months, by RANO-BM .[10] These results suggest that T-DM1 monotherapy offers relevant clinical activity in brain metastases and further investigation with larger prospective studies is warranted.

In a retrospective, exploratory analysis of EMILIA trial,[8] 2.0% (9/450) and 0.7% (3/446) of patients without baseline CNS metastasis developed CNS progression in the T-DM1 and capecitabine+lapatinib arms, respectively. Among 95 patients with baseline CNS metastases, 22.2% (10/45) and 16.0% (8/50), respectively, developed CNS progression in the study. Although the percentage of patients with CNS progression was similar between the two treatments, irrespective of whether patients had baseline CNS metastases, T-DM1 was associated with significantly improved median OS of 26.8 months versus 12.9 months with capecitabine and lapatinib [HR = 0.38; 95% CI 0.18–0.80; P = 0.008].

In summary, T-DM1 has emerged as a promising agent for treatment both systemic and CNS disease in women with HER2-positive breast cancer.

3.9 Rationale for combining neratinib and T-DM1 (Cohorts 4A-4C)

Neratinib, like other anti-HER2 agents has increased efficacy when combined with other agents, both extra-cranially and intra-cranially. Given the degree of diarrhea we observed on the combination of neratinib and capecitabine component of this study (Cohort 3), we have decided to move forward with an alternative combination in the next extension of this trial. With the activity of T-DM1 reported in the CNS and the previously reported extracranial activity of T-DM1 and neratinib in the NSABP FB-10 trial, we have decided to move forward with this treatment combination in Cohort 4.

In FB-10[39], T-DM1 and neratinib are being examined in combination on a phase 1B study in the setting of non-CNS disease. This study, recently presented at AACR in preliminary form, 22 patients with metastatic HER2-positive breast cancer with prior trastuzumab and pertuzumab were assigned to receive T-DM1 [3.6 mg/kg I.V. Day 1 every 21 days] plus neratinib daily beginning on Day 1 of T-DM1 and continuing until disease progression by RECIST 1.1 criteria. Neratinib dose escalation levels were 120mg, 160mg, 200mg and 240mg and the aim was to determine the safety and tolerability of the combination. On this trial, the recommended neratinib phase II dose was 160mg PO daily for the expansion Cohort. With regard to efficacy, among 16 evaluable patients, there was an objective (non-CNS) response by RECIST 1.1 in 9 of them [ORR (CR / PR) of 56%]. Diarrhea was the major dose-limiting toxicity in this dose-escalation trial, with overall grade 3 diarrhea in 19% of patients across all dose levels, similar to slightly better than the diarrhea

rate in prior neratinib-based studies. At the time of presentation, no grade 3 events were reported in the 160 mg neratinib dose level and this was thus selected as the dose for further study when given with T-DM1. We anticipate that the combination of T-DM1 and neratinib will be active in the CNS as well and will test this hypothesis in Cohorts 4A-4C.

The study population for Cohort 4A will include patients with HER2-positive, metastatic breast cancer with CNS involvement, who have not previously received local CNS therapy. Although many patients will receive local therapies to their brain as first treatment of CNS metastasis, multiple trials have shown responses to systemic therapy that are just as robust as the responses anticipated from local therapy alone[24,34,36] and with the ability to potentially delay WBRT,[34] a treatment associated with cognitive decline and significant toxicity. Developing novel systemic therapy combinations which may be able replace local therapy while also treating extra-cranial disease is of great interest, as is delaying the time to needing local therapy to the brain and WBRT. As a primary example of this, the LANDSCAPE trial demonstrated significant CNS responses to capecitabine and lapatinib in previously untreated patients with HER2-positive CNS disease and demonstrated a delayed time to WBRT.[34] Further, patients on Cohort 4A will be monitored every 6 weeks for response and will thus be watched closely for progression with the ability to transition to CNS-directed therapy with SRS, WBRT, or surgery as appropriate at the time of progression.

3.10 Correlative Science Background (All Cohorts)

3.10.1 CTC Enumeration Studies (Cohort 1 only)

An experimental method for following response to therapy and predicting prognosis is to measure microscopic disease burden, manifested as CTCs, which are present in the majority of patients with metastatic breast cancer, and can be detected upon collection of less than 10 mL of whole blood.[40] CTC counts before and after a single cycle of therapy have been shown in several prospective studies to be predictive of objective radiographic response, PFS, and OS.[40,41] This provides a potential opportunity to monitor metastatic disease, provide prognostic information, and provide a means to perform non-invasive molecular interrogation of cancers. CTCs can provide a molecular snapshot, or real-time biopsy, of tumor cells without the need for clinical biopsy. For these reasons, there is widespread clinical interest in examining the usefulness of these methods in subjects being treated on clinical trials in order to see whether more sensitive correlates of tumor response can be identified. The predictive ability of CTCs in patients with CNS disease is unknown and has not been previously studied.

We plan to collect CTCs at different time points in therapy to explore potential predictors of OS in patients with CNS disease. We hypothesize that patients with higher numbers of CTCs will have shorter OS times compared to patients with lower numbers of CTCs.

3.10.2 MET and HER2 Co-amplification Studies (Cohorts 1 and 3A/3B)

In a second set of correlative and exploratory analyses, we plan to explore MET proto-oncogene and HER2 co-amplification by FISH in CTCs to examine the correlation of co-amplification with treatment response. The MET proto-oncogene encodes a tyrosine kinase receptor for hepatocyte growth factor and is correlated with a poor prognosis when overexpressed in breast cancer. In lung cancer, amplification of MET is associated with resistance to EGFR targeted treatments by activating erbB3 signaling.[42] Erb3 signaling is also critical for HER2 function,[43] which suggests that MET amplification may play a significant role in resistance to HER2-directed therapies. This significant "cross talk" between MET and EGFR has been previously observed[44,45] and is of interest, but has not been extensively studied in patients with metastatic HER2-positive breast cancer, those with CNS disease, or those treated with novel therapies.

3.10.3 HER2 status of primary breast cancer, metastatic lesions, and CTCs (Cohorts 1 and 3A/3B)

In a third set of exploratory analyses, we will further explore the concordance in HER2 FISH status between primary breast tissue, metastatic lesions (when available for evaluation), and CTCs. Drs. Krop and Flores have previously completed work (manuscript submitted) in two groups of patients, demonstrating significant discordance in HER2 status among these sources of breast cancer tissue/cells. In 45 patients with known HER2-positive primary tumors, 44 patients were found to have HER2-positive CTCs and 1 patient had HER2-negative CTCs (2% discordance). In 30 patients with HER-negative primary tumor samples, 20 patients had HER2-negative CTCs while 10 patients had HER2-positive CTCs (33% discordance). Further studies are underway to further investigate concordance of HER2-positive samples, including the current protocol, which will collect blood samples at varying time points for these analyses. These studies may have significant treatment implications.

3.10.4 Possible Mechanisms of Resistance driven by EGFR (Cohorts 1 and 3A/3B)

In a final set of correlative analyses in CTCs, we will examine potential mechanisms of treatment resistance driven by EGFR. EGFR (HER-1, c-*erb*B1) is one of four transmembrane growth factor receptor proteins (HER1, HER2, HER3, HER4) that share similarities in structure and function. Together, this group comprises the human epidermal growth factor receptor (HER or c-*erb*B) family of receptor tyrosine kinases. Ligand binding to EGFR results in receptor homo- or hetero-dimerization (with one of the HER family of receptor tyrosine kinases) followed by autophosphorylation of the tyrosine kinase domain.[46] Phosphorylated tyrosine residues serve as binding sites for the recruitment of signal transducers and activators of intracellular substrates. The Ras–Raf mitogen-activated protein kinase pathway and the phosphatidyl inositol 3' kinase and Akt pathway are the major signaling routes for the HER family, including EGFR.[47-50] These pathways control several important biologic processes, including cellular proliferation, angiogenesis and inhibition of apoptosis.[51]

EGFR is expressed in a large number of breast cancers, with a positivity rate of 14–91% reported. Over-expression of EGFR has been linked to a more aggressive breast tumor phenotype, involving increased potential for invasiveness and metastasis. This has been linked to poorer patient prognosis, as extensively reviewed previously.[52] More recently, investigators have observed that EGFR expression was a significant prognostic factor in a large series of patients,[53] although this remains controversial.[54,55] There is also strong pre-clinical evidence linking EGFR expression and EGFR-mediated signaling to *de novo* and acquired anti-hormone resistance in estrogen receptor-positive, as well as estrogen receptor-negative , breast tumor growth. In addition, erbB receptor signal transduction has consistently been associated with resistance to anti-estrogens such as tamoxifen,[56] as well as to long-term estrogen deprivation in model systems.[57] One possible mechanism of resistance to EGFR tyrosine kinase inhibitors involves tyrosine phosphorylation in the absence of intrinsic EGFR tyrosine kinase activity. Tyrosine phosphorylation of EGFR provides docking sites for signaling proteins important for cell growth and survival. EGFR phosphorylation in some EGFR-expressing breast cancer cell lines lacking intrinsic EGFR tyrosine kinase activity appears to be mediated by MET.[58]

3.10.5 Neratinib Drug Concentrations in the CNS (Cohort 2)

Although CNS concentrations of neratinib have been tested in healthy mice (as described in *Section 2.3*), further work is required to better understand this drug's ability to cross the blood brain barrier. There has been no previous work to date that has examined drug concentrations in human tumor specimens or CSF and this additional information will greatly improve our understanding of neratinib's abilities. In this study, patients who undergo craniotomy will have plasma, tumor specimens, and CSF tested for neratinib concentrations. Other potential CSF correlatives may be added as a future study addendum and may include CTC enumeration in the CSF, neratinib concentration testing, as well as other molecular studies and HER2-testing.

3.10.6 Examination of Neurocognitive Function (Cohort 1)

For many years, there has been awareness and concern over the risk of cognitive deficits that may develop in patients receiving whole brain radiation therapy (WBRT) or even single or repeated treatments with stereotactic radiosurgery.[59-62] Neurocognitive function data are sparse for patients who have received various therapies for disease that is metastatic to the CNS. Although WBRT has been associated with cognitive deficits over time, the long term cognitive effects of a single or multiple episodes of SRS have not been well described. In addition, progressing brain metastases likely result in further cognitive decline but this is not well understood. These potential changes in neurocognitive function during treatment in the era of novel therapy is an important correlative outcome of treatment and is of great interest to patients, caregivers, and medical providers, particularly because our patients with CNS disease often survive for an extended period of time,

allowing for significant effects on quality of life. In this correlative study of patients who have received diverse previous treatment of CNS disease (Cohort 1), neurocognitive function will be assessed (at various time points) with a battery of previously validated tests. This correlative study will be led by Dr. Michelle Melisko at UCSF and Dr. Jeffrey Wefel at MD Anderson. Appendix O has detailed information on the test battery.

3.10.7 Archival samples (Cohorts 3A/3B)

We plan to collect primary, archived tumors and archived biopsies of metastases for additional correlative testing. Archival samples or fresh samples collected during scheduled diagnostic biopsies whenever possible. These archival samples will be banked for future research that will be used for state-of-the-art technologies such as DNA copy number, gene sequencing, and PI3 kinase, Akt and/or PTEN testing. These tests will be used to correlate with patient response and outcomes for participants with CNS disease. This material should be provided preferably as paraffin blocks, if not, at least ten 5micron sections on charged or coated slides and ten 5-7micron sections on regular non-coated slides (total of 20 slides from primary and metastatic sites) should be sent to the Dana-Farber Cancer Institute. See Appendix S for shipping instructions.

3.10.8 Blood sample collection for evaluation of ctDNA (Cohorts 3A/3B and 4A-4C)

For a number of reasons that include discomfort to the patient, logistics, and lack of clinical indication, serial tumor biopsies in individual patients in the metastatic setting are infrequently done. It has therefore been challenging to study the molecular evolution of tumors over time and through progression on serial treatment regimens. Both normal and malignant cells secrete cell-free DNA into plasma, generating an easily accessible repository of each cell's genetic signature. Emerging technology now permits whole exome sequencing from circulating tumor DNA (ctDNA) isolated from plasma.

Blood will be collected at baseline and at end of treatment for evaluation of ctDNA in addition to the end of cycle 2 for Cohorts 4A-4C. The ctDNA will be processed and banked in the DF/HCC Clinical Trials Core laboratory for future research purposes. The banked samples will be used to analyze DNA, RNA and protein in future studies and these samples are being collected across multiple DFCI protocols for pooled analyses. Specifically, we plan to assess changes in mutational profiles over time.

3.10.9 CSF collections for ctDNA (Cohorts 4A-4C only)

The implications of detecting tumor-derived ctDNA in the CSF are not clear, but prior work has shown the ability to detect ctDNA in the CSF readily in the setting of CNS tumors.[63-65] In this study, any patient undergoing a lumbar puncture for clinical reasons and up to 5 additional patients will be asked to consent to having a portion of their CSF sample banked and later tested for ctDNA. We will explore the mutational profiles ctDNA in these patients and how it may correlate to response and outcome.

3.10.10 Patient-Reported Assessment of Gastrointestinal (GI) Toxicity (Cohorts 4A-4C)

NOTE: If a patient needs assistance with surveys, and/or a survey(s) is not available in the necessary language, a family member and/or interpreter can assist with answering them.

To date, no prior study has examined patient-reported outcomes (PRO) with regard to neratinib exposure, yet PROs have become an important part of new drug evaluation, potentially playing a future role in regulatory approval of novel agents in oncology.[66] PROs represent 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. 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, collection of PRO measures has been shown to more completely assess toxicities than clinician CTCAE reporting.[67] For example in a prospective study including lung cancer patients, PRO measurements of toxicities better reflected patients' underlying state and functional status than clinician's evaluation.[67] Furthermore, studies have demonstrated that collection of PRO measures within the context of multi-center clinical trials is feasible.[68]

With regard to the evaluation of diarrhea in particular, clinician-reported CTCAE toxicity assessment is limited to quantification of the frequency of stools each day in comparison to baseline. This may lead to incomplete assessment of associated symptoms and does not incorporate assessment of the impact of diarrhea on quality of life. In addition, although many PRO measures have been well validated,[67,69,70] none have specifically been evaluated for feasibility and accuracy in patients taking neratinib or in patients with brain metastases in whom changes in cognition may be at play. In addition, few studies to date have utilized PRO measures to assess the impact of treatment-associated diarrhea on quality of life in cancer patients. Given the extent of diarrhea associated with neratinib in studies to date, it is important to characterize the patient experience with regard to GI symptoms.

A patient-reported version of the CTCAE measurement system (PRO-CTCAE) has recently been developed. [71] Validity and reliability for this tool have been demonstrated in cancer patients. The majority of the questions utilize a 5 point Likert-type scale and address components of symptomatology such as frequency, severity and interference with activities[71] with a 7 day recall period. We will administer 20 PRO-CTCAE questions regarding gastrointestinal toxicities (nausea, decreased appetite, vomiting, heartburn, bloating. flatulence, diarrhea, abdominal pain, hiccups, constipation and incontinence) on paper on Day 1 of Cycles 1-4 for all patients enrolled to Cohort 4 (Appendix W). This approach will allow for evaluation of baseline patient-reported GI symptoms plus GI toxicities experienced during cycles 1-3, with the final assessment performed on cycle 4 day 1 reflecting symptoms at the end of cycle 3. In addition, we will contact patients by

phone day 10 (+/- 4 days) of cycle 1 to complete the same 20 PRO-CTCAE questions regarding gastrointestinal toxicities in order to more comprehensively characterize the course of diarrhea soon after initiating therapy. The research staff will read the questions to the patient by phone and note the answers. We will include these time points as most of the toxicity of neratinib occurs early and patients remaining on therapy longer than 3 cycles are likely tolerating treatment well without new onset side effects. Further, the number of cycles a patient will receive will be highly variable in the setting of brain metastases and we want to ensure a high rate of data capture for all patients. Other than the mid-cycle PRO-CTCAE assessment by phone during cycle 1, these PRO-CTCAE assessments will be performed on the same day as standard clinician assessment of toxicity using the CTCAE system on the first day of cycles 1-4. In addition to characterizing the patient-reported gastrointestinal symptoms using the PRO-CTCAE questions at baseline and during the first 3 cycles of therapy, we plan to compare patient-reported and clinician-assessed gastrointestinal symptoms on day 1 of cycles 2-4.

In order to gain more in depth information about the extent of diarrhea and its impact on our patient's lives, we plan to administer two additional questionnaires. These will both be administered on paper on day 1 of cycles 1-4, coinciding with the PRO-CTCAE assessments and allowing for measurement of baseline symptoms and those occurring during cycles 1-3. The PROMIS Scale v1.0-Gastrointestinal Diarrhea 6a (Appendix Y) is a publicly available 6-question measure assessing bother, frequency and interference of loose stool and urgency. This measure has a 7 day recall period and utilizes a 5 point Likert-type response scale. To date, this measure has primarily been validated in patients with inflammatory bowel disease.[4] Given that this PROMIS measure has not previously been validated in cancer patients, we intend to also administer the recently developed Systemic Treatment-Induced Diarrhea Assessment Tool (STIDAT) questionnaire, a tool developed to characterize systemic therapy-induced diarrhea and its associated symptoms and management in cancer patients receiving systemic therapy in particular. This 12-question measure assesses onset and duration of diarrhea, diarrhea frequency, interventions to manage diarrhea, associated symptoms and impact of diarrhea on quality of life. The STIDAT has a 7 day recall period. The response format is a combination of yes/no answers and visual analog scale answers (with a range from 1-10).[5] One question on the STIDAT asks patients to report the type(s) of anti-diarrheal medications they have taken. We will modify the STIDAT questionnaire slightly to include the anti-diarrheal medications prescribed in this protocol in addition to other commonly used anti-diarrheal medications. (Appendix X). We have been given permission to use the STIDAT from Michelle Lui (email communication). We will describe the patient experience associated with diarrhea using these two measures in order to further enhance what has previously been reported which has essentially been limited to timing of onset and grading.

Finally, we recognize that some patients may not take neratinib due to diarrhea. Neratinib administration will be tracked by patient-completed pill diaries (Section 5.3.1, Appendix C). In addition, we will ask patients on day 1 of cycles 2-4 whether they skipped any doses of neratinib during the previous cycle due to diarrhea. This question will be incorporated into their anti-diarrheal medication and diarrhea diary (described in Section, 2.10.11, Appendices Za and Zb).

3.10.11 Adherence to anti-diarrheal prophylaxis (Cohorts 4A-4C)

Although diarrhea is commonly reported in every clinical trial with neratinib and diarrhea prophylaxis has been mandated early during therapy in almost every neratinib-based trial to date, no study has clearly evaluated the degree to which patients adhere to prophylaxis and whether this correlates with the grade of diarrhea experienced. We will ask about prophylaxis using a daily diariy (Appendix Za) during cycle 1 of therapy when anti-diarrheal medication is mandated. Thus diary will be collected D1 C2. In addition, we will ask patients to complete diaries documenting any anti-diarrheal medication they choose to take during Cycles 2 and 3 of therapy (when anti-diarrheal medications are no longer mandated), and these additional diaries will be collected on D1 of C3 and C4 respectively (Appendix Zb). We anticipate this approach will cover the time period during which patients are most likely to have diarrhea and to use prophylaxis (i.e. early in their treatment course). Patients will also document the number of episodes of diarrhea per day in the diaries (Appendices Za and Zb).

Adherence to the required anti-diarrheal medication during cycle 1 will also be assessed on an exploratory basis on day 1 of cycle 2 using the 3-question Voils Extent of Adherence questionnaire. This questionnaire has a 7-day recall period and uses a 5 point Likert-type scale (never-always). Questions address whether patients miss or skip any doses of medication.[3] Given that this measure has previously been validated in patients prescribed anti-hypertensive medication, we will modify the questions slightly to reflect use in patients prescribed anti-diarrhea medication (Appendix Zc).

Although diarrhea is the primary concern with this study, it is possible that some patients will experience side effects such as constipation from the anti-diarrheal medications. We hope to capture constipation using the PRO-CTCAE questions (Section 2.10.10, Appendix W). However, we also want to determine whether patients stop the mandatory anti-diarrheal medications during cycle 1 because of constipation or because of any other side effects. To address this, we will ask two questions about skipped doses of the mandatory anti-diarrheal medications during cycle 1. These questions will be incorporated into the anti-diarrheal medication and diarrhea diary for cycle 1 (Appendix Za).

A Table summarizing all of the patient-reported outcomes is summarized below and is also delineated in the study calendars for Cohorts 4A, 4B, 4C.

Table of Patient-reported surveys and diaries

Measure	Time point				
	C1 D1	**C1 day 10 (+/1 4 days)**	**C2 D1**	**C3 D1**	**C4 D1**
PRO-CTCAE[71] Appendix W	X	X (by phone)	X	X	X
Modified STIDAT[5] Appendix X	X		X	X	X
PROMIS[4] Appendix Y	X		X	X	X
Anti-diarrheal medication and diarrhea diary	Provide diary for cycle 1 to patients (Appendix Za)		Collect diary for cycle 1. Provide diary for cycle 2 to patients (Appendix Zb).	Collect diary for cycle 2. Provide diary for cycle 3 to patients (Appendix Zb).	Collect diary for cycle 3
Voils Extent of Adherence to for anti-diarrheal medications[3] Appendix Zc			X		

3.11 Primary Pharmacology

Neratinib is highly active in cell lines that over-express HER2 or erbB1 and blocks receptor autophosphorylation in cells at doses consistent with inhibition of proliferation. This is thought to occur because neratinib inhibits tyrosine kinase activity by irreversibly binding to cysteine residues in the adenosine triphosphate (ATP) binding site of erbB family receptors. In erbB1 and HER2-positive tumor xenograft models, neratinib has demonstrated significant activity with daily oral administration.[6]

Capecitabine was designed to generate 5-fluorouracil (5-FU) preferentially in tumor tissues and to mimic continuous infusion 5-FU. Capecitabine is readily absorbed from the gastrointestinal tract and subsequently undergoes hydrolysis in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR). The enzyme cytidine deaminase, which is found in most tissues, including tumors, converts 5'-DFCR

to 5'-deoxy-5-fluorouridine (5'-DUFR), the prodrug of 5-FU. Thymidine phosphorylase hydrolyzes 5'-DUFR to 5'-FU (XELODA package insert).

T-DM1 is an antibody-drug conjugate incorporating the monoclonal antibody trastuzumab and emtansine. The emtansine moiety is comprised of two components, DM1, a microtubule inhibitor, and MCC, a thioether linker. T-DM1 binds to human epidermal growth factor 2 (HER2) receptors and undergoes internalization and lysosomal degradation, resulting in increased targeted delivery of DM1 to malignant cells that overexpress HER2. The trastuzumab moiety binds to HER2 receptors on the tumor surface and inhibits shedding of the HER2 extracellular domain, inhibits HER2 signaling, and mediates antibody-dependent cell-mediated cytotoxicity. Once internalized, the emtansine moiety binds to tubulin, resulting in cell cycle arrest in the G2/M phase and apoptosis.

3.12 Pre-clinical Studies with Neratinib, Capecitabine, and T-DM1

3.12.1 Neratinib

The in vivo activity of neratinib has been evaluated in cell lines grown as xenografts in athymic (nude) mice (RPT-49430). In these initial experiments, neratinib was observed to inhibit the growth of several HER2-dependent tumor xenograft models with anti-tumor activity observed in 3T3/neu, BT474 and SK-OV-3 (ovarian cancer) xenografts after oral administration of neratinib (10 mg/kg/day and 80 mg/kg/day). Neratinib was well tolerated by the animals and no weight loss or other compound-related toxicity was observed. The minimum efficacious dose was estimated at 10 mg/kg/day, and neratinib inhibited the growth of erbB1-overexpressing A431 tumor xenografts, consistent with its effects on cells in vitro (RPT-49430). Maximum inhibition of tumor growth occurred at doses of 40 mg/kg/day (76% inhibition on Day 15) but inhibition was also seen at doses as low as 5 m/kg/day (32% inhibition). However, regression was less than that seen with comparable doses in HER2-positive tumors in vivo, even though neratinib has equivalent activity against the two kinases in vitro. The in vivo activity of neratinib requires expression of HER2 or erbB1, as no significant anti-tumor effects were observed in xenografts of MCF-7 and MX-1 cells that express low levels of these receptors (RPT-49430).

The inhibition of tumor growth in vivo by neratinib has been observed to be associated with a blockade of HER2 receptor activation (RPT-49272). In BT474 xenografts, phosphorylation of HER2 was inhibited by 84% within 1 hour of a 40 mg/kg single (oral) dose of neratinib. This inhibition was sustained at 6 hours (97%) and then decreased to 43% over 24 hours. This prolonged reduction in phosphorylation is consistent with irreversible binding to the target, since the terminal half-life of neratinib after a single dose (20 mg/kg) in nude mice is < 4 hours. In addition, the persistent effects of neratinib support a once-daily dosing in animal models.

3.12.2 Capecitabine

Capecitabine is an approved chemotherapy for use in metastatic breast cancer and preclinical data is available on the FDA. For full prescribing information, please see package insert or FDA for additional information: www.accessdata.fda.gov/drugsatfda_docs/label/2000/20896lbl.pdf). Studies in animals to evaluate the carcinogenic potential of capecitabine have not been conducted. However, capecitabine was not mutagenic in vitro to bacteria or mammalian cells (hamster). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow. Fluorouracil causes mutations in bacteria and yeast and also causes chromosomal abnormalities in the mouse micronucleus test in vivo. In studies of fertility and reproductive performance in mice, oral capecitabine disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, fetuses did not survive the tested dose (760 mg/day). The disturbance of estrus was reversible.

3.12.3 T-DM1

In vitro studies demonstrate that the anti-proliferative activity of T-DM1 is most pronounced against tumor cells with high HER2 expression. T-DM1 activity was observed in vivo in all four breast cancer xenograft models tested with a maximum efficacious dose range of 3-15 mg/kg, depending on the sensitivity of the particular model. In a trastuzumab-insensitive model, anti-tumor activity was observed only with T-DM1 compared to the individual components trastuzumab and DM1, confirming the selective activity of T-DM1. Single-agent T-DM1 demonstrated anti-tumor activity in five out of six HER2-positive gastric cancer xenograft models at doses ranging from 5-15 mg/kg, with complete regressions occurring at 5 mg/kg in a highly sensitive model, vs. tumor growth delay observed in a less-sensitive model at a dose of 15 mg/kg. This information is taken directly from the investigator's brochure for T-DM1 and additional pre-clinical data details are available at length in the brochure. However, this section has been abbreviated for this protocol.

3.13 Clinical Experience

3.13.1 Neratinib – Clinical Experience

At least 30 clinical studies have been initiated with neratinib as a single agent or in combination with other therapies. Completed studies include nine phase I, clinical pharmacology studies conducted in healthy subjects, two phase I studies conducted in patients with metastatic or locally advanced solid cancers, and two phase II studies in patients with lung and HER2-positive, advanced breast cancer. Ongoing studies include multiple phase 1/2 protocols of neratinib in combination with other agents and a phase III study of neratinib with or without paclitaxel. The results of studies with administration of neratinib to date have demonstrated an acceptable toxicity profile (in healthy subjects and in those with cancer) and promising clinical activity, particularly in patients with HER2-

positive breast cancer. These results support the continued, clinical development of neratinib.

3.13.2 Neratinib Studies in Healthy Subjects

Approximately 9 clinical studies have been completed with neratinib in healthy subjects. Pharmacokinetic [PK] findings from these evaluations are discussed in detail in *Section 7.1.3* and include the following studies: (1) 3144A1-107-US (examined tolerability and safety of ascending doses of neratinib and the effect of a fatty meal on the PK at varying neratinib doses), (2) 3144A1-106 US (examined effect of ketoconazole on the PK profile of neratinib), (3) 3144A1-1109-US (examined the comparative bioavailability of 2 new formulation tablets of neratinib with a reference capsule), and (4) 3144A1-105-US (examined the effect of neratinib on QTc interval).

Findings from the above-mentioned studies demonstrated that (1) food appears to increase neratinib exposure by 2-fold (after oral administration of 240 mg), (2) neratinib exposure increased by 3-5 folds when it was co-administered with ketoconazole, (3) all tested formulations of neratinib have equivalent bioavailability, and (4) neratinib does not result in QTc prolongation. Other studies that have been completed in healthy subjects but are not yet reported include protocol 3144A1-1108-US (examined mass balance, metabolic disposition, and identification of metabolites after dose administration) and 3144A1-1116-US (examined the occurrence of mild to moderate diarrhea after administration of neratinib 240 mg once daily or neratinib 120 mg twice daily for 14 days). Results from 3144A1-1116-US did not demonstrate improved rates of diarrhea with twice daily dosing of neratinib. A clinical drug interaction study in healthy subjects showed that systemic exposure to digoxin, a P-glycoprotein (P-gp) substrate, increased by 54% for C_{max} and 32% for area under the concentration-versus-time curve (AUC) when a single oral dose of 0.5 mg of digoxin was co-administered with multiple oral doses of 240 mg of neratinib compared with the digoxin administered alone. Results from a drug interaction study of a single oral dose of neratinib with multiple doses of rifampin, a potent CYP3A4 inducer, in healthy subjects indicated that when co-administered with rifampin, neratinib exposures were significantly decreased, with mean values that were 24.05%, 6.87%, and 12.69%, of reference values (neratinib alone) for C_{max}, AUC_T, and AUC, respectively

3.13.3 Neratinib Studies in Cancer Patients

The clinical development plan for neratinib included multiple clinical studies, including one phase 1 study, two phase 1 studies in Japan, two phase 2 single-agent studies, and four phase 1/2 combination studies (some still ongoing). In addition, phase 3 studies have been designed and are currently enrolling patients with HER2-positive breast cancer with various stages of disease, as mentioned above. Highlights from completed studies in cancer patients are described below and were adapted from data provided in Pfizer's Investigator's Brochure for neratinib:

Study 3144A1-102-US: This was a phase I study with ascending, single and multiple oral dose regimens of neratinib (40 - 400 mg) administered to subjects with HER2-positive or erbB1 positive solid tumors. The PK results from this study are described in *Section 7.1.3.2* and support a once-a-day dosing regimen for neratinib. Among the 25 evaluable patients with stage IV breast cancer (all had received prior anthracycline and trastuzumab therapy) in this phase I study, 8 patients had a partial response (32%; 95% CI 14.9% to 53.5%) and 7 of these 8 patients had HER2 immunohistochemistry staining scores of 3+. An additional 6 patients with breast cancer had stable disease, including 1 subject with a prolonged duration of stable disease (≥ 24 weeks). The clinical benefit rate in this study was 36% (95% CI 18% to 57.5%).[25]

Study 3144A1-104-JA: This study was an open-label, phase 2 protocol of ascending single and oral doses of neratinib (80 mg or 320 mg), administered to patients with advanced solid tumors in Japan. The PK results from this study are described in *Section 7.1.3.2.*

Study 3144A1-200-WW: This study was an open label, phase 2, non-randomized, 3-arm study of neratinib (240 mg) for patients with previously treated, advanced non-small cell lung cancer (note: original recommended dose of 320 mg was reduced to 240 mg because of high rates of diarrhea and other gastrointestinal toxicities). This study has completed accrual and clinical results are forthcoming, although the toxicity data from this study are presented in the toxicity tables below.

Study 3144A1-201-WW: This study was an open-label, phase 2, two-arm study of neratinib 240 mg given daily to patients with HER2-positive breast cancer (Arm A: previously treated with trastuzumab; Arm B: no previous treatment with trastuzumab). Patients on study most commonly reported diarrhea (all grades, 89%), nausea (29%), vomiting (23%), fatigue (16%), and anorexia (15%). Diarrhea was the only grade 3 or 4 adverse event that occurred in at least 5% of patients. Dose reductions occurred in 27% of patients, most commonly because of diarrhea. ORR and PFS data from this trial were encouraging and these results are summarized in *Section 2.2*.[26,72]

Study 3144A1-202-WW: This was a phase 1/2 combination therapy study of patients with stage IV, HER2-positive breast cancer who were treated with neratinib in combination with trastuzumab. Preliminary results from this study also suggest clinical activity of neratinib with a 16-week PFS of 47.2% (95% CI 29.4% to 63.1%), a median PFS of 19.4 weeks (95% CI 15.3 to 31.6 weeks, with data censored for 10 patients), and an ORR of 27.3% (95% CI 13.3% to 45.5%).[73]

Of note, multiple future studies with administration of neratinib in HER2-positive breast cancer patients are planned and ongoing with results forthcoming.

Capecitabine – Clinical Experience (adapted from FDA brochure: www.accessdata.fda.gov/drugsatfda_docs/label/2000/20896lbl.pdf)

3.13.4 Phase I Study

In a phase I study with capecitabine in patients with solid tumors, the maximum tolerated dose (MTD) was 3000 mg/m2 when given as a single agent daily for 2 weeks, followed by 1 week of rest. The DLTs were diarrhea and leukopenia. In breast cancer, the antitumor activity of capecitabine has been evaluated in multiple studies.

This includes an open-label, single arm trial conducted in 24 centers in the U.S. and Canada. Here a total of 162 patients with stage IV breast cancer were enrolled with a primary endpoint of tumor response rate in patients who had measurable disease, with response defined as at least a 50% decrease in the sum of projects of the perpendicular diameters bi-dimensionally measurable disease for at least one month. Capecitabine was administered at a daily dose of 2510 mg/m2 for 2 weeks followed by 7 days rest, given as 21 day cycles. For the subgroup of 43 patients who were resistant to taxanes and anthracyclines, the median time to progression was 102 days and the median survival was 255 days. The ORR in this population was supported by the ORR of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with measurable disease, who were less resistant to chemotherapy. The median time to progression was 90 days and the median survival was 306 days. Multiple other studies in the metastatic breast cancer setting have also confirmed its activity. Anti-tumor responses from this protocol are summarized in the table below:

Table: Response rates to capecitabine in heavily pre-treated patient population

Table 2. Response Rates in Doubly-Resistant Patients

	Resistance to Both Paclitaxel and an Anthracycline (n=43)
CR	0
PR[1]	11
CR + PR[1]	11
Response Rate[1] (95% C.I.)	25.6% (13.5, 41.2)
Duration of Response,[1] Median in days[2] (Range)	154 (63 to 233)

[1]Includes 2 patients treated with an anthracenedione
[2]From date of first response

Capecitabine is indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and anthracycline-containing chemotherapy regimens or resistant to paclitaxel and for whom further anthracycline therapy is not indicated. This indication is based on demonstrated ORR. No results are available from controlled studies that demonstrate clinical benefit resulting from treatment, such as improvement in symptoms, progression, or survival.

3.13.5 T-DM1 – Clinical Experience

Among several other studies in the phase I-III setting, the following relevant 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.

Phase II Studies with T-DM1:

Study TDM4450g (*Single-Agent T-DM1 in Previously Untreated Metastatic Breast Cancer Patients)* is a randomized, multicenter, Phase II study of the efficacy and safety of T-DM1versus trastuzumab plus docetaxel in patients with metastatic HER2-positive breast cancer who did not receive prior chemotherapy for metastatic disease [74]. 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, 2010 [74]. 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 November 15, 2010, the median PFS was 14.2 months in the T-DM1 arm versus 9.2 months in the trastuzumab plus docetaxel arm [74]. 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 MBC [74]. 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 docetaxel [74].

Study TDM4258g *(Single-Agent T-DM1 in Previously Treated* Metastatic Breast Cancer *Patients)* 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 inHER2-positive MBC patients who had progressed on previous HER2-directed therapy and conventional chemotherapy. [75] 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 dose [75]. 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%) [75]. 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.

Phase III Studies:
TDM4370g/BO21977 (EMILIA) 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 taxane [76]. 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 T-DM1[76]. 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[76].

The MARIANNE trial enrolled over 1000 women with progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer (provided they had at least a six-month treatment-free interval from neoadjuvant or adjuvant treatment). Patients were randomly assigned to trastuzumab plus a taxane (docetaxel or paclitaxel, arm 1), T-DM1 plus placebo (arm 2), or T-DM1 plus pertuzumab (arm 3).The median PFS for arms 1, 2, and 3 was 13.7, 14.1, and 15.2 months, respectively. There was no significant difference in PFS in arm 2 compared with arm 1 (HR 0.91, 97.5% CI 0.73-1.13), arm 3 compared with arm 1 (HR 0.87, 97.5% CI 0.69-1.08), or between arm 3 and arm 2 (HR

0.91, 97.5% CI 0.73-1.13). The ORR in the three arms was 68, 60, and 64 percent, respectively.

Some toxicities, including neutropenia, neuropathy, and peripheral edema, were less frequently reported in the nontaxane arms. In particular, alopecia was numerically much less common in the nontaxane arms (60 percent with taxane versus 7 percent with T-DM1 and 9 percent with T-DM1 plus pertuzumab). Liver function test (LFT) abnormalities and thrombocytopenia were more commonly reported in the T-DM1 arms.

3.14 Safety Pharmacology

The safety pharmacology of neratinib was initially evaluated in the CNS, an in-vitro hERG study, respiratory studies in rats, and in a cardiovascular telemetry study in dogs. Neratinib did not produce any effects on the CNS, respiratory system, or cardiovascular system of rats at oral doses of 5, 25, or 100 mg/kg. In the hERG assay, the concentration at which there was 50% inhibition (IC50) of the rapidly-activating, delayed-rectifier cardiac potassium current (IKr) was 1.9 μM or 1058 ng/mL. The human peak concentration (Cmax) was 0.76 ng/mL at the clinical dose of neratinib 240 mg. Based on the human free non-protein bound fraction, the exposure ratio of the hERG assay IC50 to the human free Cmax was 1392. This ratio greatly exceeded the generally accepted exposure ratio of 30 to 100, indicating that neratinib was not likely to prolong the corrected QT interval (QTc) interval at this exposure. In the single-dose cardiovascular safety pharmacology study in dogs, neratinib did not produce any significant toxic effects on the cardiovascular system of dogs at varying oral doses (5, 10, 20 mg/kg). In repeat-dose toxicity studies in mice, rats, and dogs, neratinib did not produce any changes in heart weight, and no macroscopic or microscopic findings were observed in the heart. Furthermore, in the 1-month and 9-month repeat-dose toxicity studies in dogs, no changes were seen in the electrocardiograms.

The pharmacokinetics of capecitabine and its metabolites have been evaluated in approximately 200 patients with cancer over a dosage range of 500 to 3500 mg/m2/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¾ of an hour. The inter-patient variability in the Cmax and AUC of 5-FU was greater than 85%.

The pharmacology of T-DM1 has been demonstrated in pre-clinical and phase I trials, which recommend initial 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 t1/2) 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 t½ 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.

3.15 Drug Interactions

3.15.1 Neratinib

As a substrate of CYP3A4, is susceptible to interactions with potent inhibitors or inducers of CYP3A4. A drug interaction study of a single oral dose of neratinib with multiple oral doses of ketoconazole (potent CYP3A4 inhibitor) in healthy subjects demonstrated that neratinib exposure increased by 3-5 fold when it was co-administered with ketoconazole. Results from a drug interaction study of a single oral dose of neratinib with multiple oral doses of rifampin (potent CYP3A4 inducer) in healthy subjects indicated that when co-administered with rifampin, neratinib exposures were significantly decreased, with mean values that were 24.05%, 6.87%, and 12.69%, of reference values (neratinib alone) for C_{max}, AUC_T, and AUC, respectively.

To prevent any potential drug interactions, patients should avoid taking any known CYP3A4 inhibitors or inducers while on study when possible. For a full list of these medications, see Appendix J. Recommendations for medications to avoid/minimize are discussed in more detail in *Section 5.4.1*.

In addition, an in vitro study indicated that neratinib is an inhibitor of P-glycoprotein (P-gp). A clinical drug interaction study in healthy subjects showed that systemic exposure of digoxin, a P-gp substrate, increased by 54% for C_{max} and 32% AUC when a single oral dose of 0.5 mg of digoxin was co-administered with multiple oral doses of 240 mg of neratinib compared with the digoxin administered alone. Co-administration of neratinib and digoxin, P-gp substrate with a narrow therapeutic window, could result in increased plasma concentrations of digoxin and associated digoxin toxicity. Subjects receiving digoxin should be monitored closely, and the digoxin dosage should be adjusted as needed.

3.15.2 Capecitabine

Drugs metabolized by the Cytochrome P450 enzyme: In vitro enzymatic studies with human liver microsomes indicated that capecitabine and 5'-DFUR had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9, 2D6, and 2E1, suggesting low likelihood of interactions with drugs metabolized by cytochrome P450 enzymes. Patients taking concurrent anticoagulants should have their PT monitored per clinical protocol. In addition when Maalox, an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine (1250 mg/m2, n=12 cancer patients), AUC and Cmax increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed o the other three major metabolites (5'-DFUR, 5-FU, FBAL) of capecitabine.
In addition, capecitabine has been found to have low potential for pharmacokinetic interactions related to plasma binding.

3.15.3 T-DM1

DM1, the cytotoxic component of T-DM1, 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 T-DM1 should be avoided if possible due to the potential for an increase in DM1 exposure and toxicity.

3.16 Route of Elimination

In pre-clinical models with rats and dogs, fecal excretion was the major route of elimination of neratinib. A single dose of radio-labeled neratinib at 20 mg/kg resulted in a recovery (mean ± standard deviation [SD]) in urine and feces after 5 days of 1.6 ± 0.9% and 90.7% ± 4.0%, respectively. Total recovery was 92.3% ± 3.2% and ranged from 88.7% to 95.0%. Excretion was rapid, with 89.2% ± 3.0% of the dose eliminated within the first 48 hours and < 4% eliminated over the following 3 days. Similar studies in dogs with 10 mg/kg of radio-labeled neratinib administration demonstrated recovery (mean ± SD) in urine and feces of 0.80% ± .26% and 66.2% ± 10.9%, respectively. Total recovery of radioactivity after 7 days was low (67% ± 10.8%) and

consistent among animals. Urinary and fecal excretion of radioactivity on day 7 was 0.5% of the administered dose. A ^{14C}-ADME study in healthy subjects indicated that the major route of neratinib excretion in humans is also feces, about 97% of the total radioactivity excreted in feces, and about 1% of total radioactivity excretes in urine, following single oral dose administration of 200 mg ^{14C}-labeled neratinib in healthy subjects.

Absorption, Distribution, Metabolism and Excretion of capecitabine: Capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean Cmax and AUC0-8 decreased by 60% and 35%, respectively. The Cmax and AUC0-8 of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed Tmax of both parent and 5-FU by 1.5 hours.

Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%). Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5,6-dihydro-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, ß-ureido-propionase cleaves FUPA to a-fluoro-ß-alanine (FBAL) which is cleared in the urine.

Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Special Populations (capecitabine):

Age, Gender and Ethnicity: No formal studies were conducted to examine the effect of age or gender or ethnicity on the pharmacokinetics of capecitabine and its metabolites.

Hepatic Insufficiency: Capecitabine has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase following a single 1255 mg/m2 dose of capecitabine. Both AUC0-8 and Cmax of capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The AUC0-8 and Cmax of 5-FU was not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when capecitabine is administered. The effect of severe hepatic dysfunction on capecitabine is not known.

Elimination of T-DM1: Biliary excretion is the predominant route of elimination for DM1-containing catabolites or DM1 metabolites following T-DM1 dosing in rats. Urinary elimination is a minor route. Following T-DM1 dosing, up to 80% of radioactivity was recovered in rat bile and less than 5% in rat urine mainly as DM1 and DM1-containing catabolites such as MCC-DM1, Lys-MCC-DM1 and DM1 adducts. Following [^{3}H] dosing, nearly 100% of radioactivity was recovered in bile. For additional pharmacology on T-DM1, see below in 2.5.6.

3.17 Rationale for Proposed Starting Doses

Neratinib:
The phase I study mentioned above, 3144A1-102-US, administered once-daily neratinib to patients with solid tumors in a planned dose escalation of 40, 80, 120, 180, 240, 320, 400 and 500 mg. Patients were given one dose of neratinib, followed by a 1 week observation period and then continuation of study drug daily. The dose-limiting toxicity was grade 3 diarrhea, which occurred in 1 patient treated at 180 mg and in 4 patients treated at 400 mg, resulting in a maximum-tolerated dose (MTD) of 320 mg. Exposure to neratinib was dose-dependent and the PK profile supported once-daily dosing. Significant clinical activity was observed on this trial at the 320 mg dose in patients who had received multiple prior therapies for metastatic breast cancer, as described above.[25] Since that time, follow-up studies have shown increased rates of diarrhea with the 320 mg dose, and because the 240 mg dose is well above the minimum effective dose, subsequent protocols have administered a regimen of 240 mg once daily. In this study, we also plan on a starting dose of 240 mg once daily in Cohorts 1-3 but will administer 160 mg in those receiving concurrent T-DM1 given the results of the phase 1/2 NSAPB FB-10 study.[39]

Capecitabine (when given in combination with neratinib):
Although the recommended dose of capecitabine monotherapy is 2500 mg/m^2 orally daily with food for 2 weeks followed by one week off in three week cycles, the dosage for the combination of neratinib and capecitabine will include lower starting doses of approximately capecitabine 1500 mg/m^2, namely 750 mg/m^2 per the phase 1/2 MTD.[29]
Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the starting capecitabine dose be rounded up to the nearest 500 mg or multiple of 150 mg for the BID dose. However, if initial capecitabine dosing is complex for a patient because of the need to use a complicated combination of 150 mg and 500 mg tablets and the provider wishes to use 500 mg tablets only, this is permitted. In addition, providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing and may round down (rather than up) if they prefer for the starting dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Of note, capecitabine is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Capecitabine tablets should be swallowed with water.

T-DM1 (Adapted from the investigator's brochure):

The pharmacokinetics of T-DM1 and its analytes have been evaluated in two Phase I studies (TDM3569g and BO24599), four phase II studies (TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976) and four phase III studies (TDM4370g/BO21977, TDM4997g/BO25734, TDM4788g/BO22589, and BO28408). The recommended dose of T-DM1 for breast cancer is 3.6 mg/kg given as an IV infusion every three weeks. the PK analysis from the phase 1 study (TDM3569g) following administration of 0.3 mg/kg to 4.8 mg/kg of T-DM1 every three weeks showed that at the dose of 3.6 mg/kg every three 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 doses ranging from 2.4-2.8 mg/kg every three weeks, T-DM1 exhibited linear pharmacokinetics. A weekly regimen has also been evaluated in TDM3569g, though we will not be administering a weekly dose in this protocol. There is no accumulation of T-DM1 when given every three weeks. Full dosing information for T-DM1 is available in the investigator's brochure.

T-DM1 when combined with neratinib. In the phase IB trial, NSABP FB-10 presented at the AACR meeting in 2017,[39] the doses of T-DM1 were kept standard (3.6 mg/kg) and neratinib was dose escalated from 120 mg to 240 mg in different dose escalation cohorts. Overall, no dose limiting toxicities (DLTs) occurred at 160 mg of neratinib and this was the dose selected for the expansion phase of this study. There were 3 DLTs at the 200-mg dose and 2 DLTs at the 240-mg dose of neratinib. In this protocol, 160 mg will also be the starting dose for the patients treated in Cohorts 4A-4C, along with standard dose T-DM1. For patients on Cohort 4C who have received prior T-DM1, if a prior dose reduction was required, they may use their prior tolerated dose as the starting dose on study or may begin at full dose- this will be up to the treating provider based on the degree of past side effects and tolerance.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria – Main Protocol (all Cohorts)

Eligible patients will be identified via their treating physician and will be recruited within the breast oncology programs at participating institutions. Participants must meet the following criteria on screening examination to be eligible to participate in the study:

4.1.1 Patients (men or women) must have histologically or cytologically confirmed invasive breast cancer, with metastatic disease. Patients without pathologic or cytologic confirmation of metastatic disease should have unequivocal evidence of metastasis by physical exam or radiologic study.

4.1.2 Invasive primary tumor or metastatic tissue confirmation of HER2-positive status, defined as presence of one or more of the following criteria:

Over-expression by immunohistochemistry (IHC) with score of 3+ (in > 30% of invasive tumor cells) AND/OR HER2 gene amplification (average of > 6 HER2 gene copies per nucleus or a FISH ratio [HER2 gene copies to chromosome 17 signals] of ≥ 2.0), according to guidelines and in keeping with past eligibility for ratio of ≥ 2.0 rather than the ratio of >2.2 required by new guidelines:

http://www.asco.org/quality-guidelines/recommendations-human-epidermal-growth-factor-receptor-2-testing-breast-cancer

Note: Patients with a negative or equivocal overall result (FISH ratio of < 2.0 or ≤ 6.0 *HER2* gene copies per nucleus) and IHC staining scores of 0, 1+, 2+ are not eligible for enrollment

4.1.3 No increase in corticosteroid dose in the week prior to baseline brain imaging

4.1.4 Age ≥ 18 years old

4.1.5 Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (Appendix A)

4.1.6 Patients must have normal organ and marrow function as described below:

- Absolute neutrophil count >_1,000/uL
- Platelets >_100,000/uL
- Total bilirubin ≤ 1.5 X upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤3 X institutional ULN without liver metastases, or ≤ 5X institutional ULN with liver metastases
- Creatinine ≤ 2.0 mg/dL or creatinine clearance ≥ 50 mL/min

4.1.7 Left ventricular ejection fraction ≥50%, as determined by RVG (MUGA) or echocardiogram within 60 days prior to initiation of protocol therapy

4.1.8 Prior therapy (see specifics by each cohort below)

- Prior trastuzumab is allowed for all cohorts
- Prior capecitabine is NOT allowed for participants enrolled to Cohorts 3A/3B ONLY
- Prior lapatinib is allowed for Cohorts 1, 2, and 3B, but NOT Cohort 3A.
- Prior T-DM1 is NOT allowed for Cohorts 4A and 4B but is required for Cohort 4C. Dose reductions on prior T-DM1 for Cohort 4C do not preclude enrollment on Cohort 4C. Patients on 4C may have progressed on prior T-DM1 in the CNS or non-CNS sites and had to have tolerated therapy without significant toxicity that would preclude retreatment.
- No prior therapy with neratinib is allowed on any cohort
- There is no limit to the number of previous lines of therapy (including chemotherapy, trastuzumab, and endocrine therapies). At least 2 weeks washout period post chemotherapy, any prior protocol therapy, lapatinib, other targeted or biologic or immunotherapy, or radiation therapy is required prior to study entry
- No washout is required for hormonal therapy, but concurrent hormonal therapy is not allowed for patients on study. The only exception to this is longstanding ovarian suppression in pre-menopausal patients, if this has been started ≥ 6 months prior to study enrollment. Other hormonal therapies are not allowed while patients are on study.

4.1.9 The effects of neratinib, capecitabine, and T-DM1 on the developing human fetus are not known. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.1.10 HIV-positive individuals on combination antiretroviral therapy are eligible for enrollment and will be monitored closely for potential pharmacokinetic interactions with neratinib.

4.1.11 Concomitant medications listed in Appendix J should be avoided (when possible) while on study.

4.1.12 Ability to understand and willingness to sign a written informed consent document

4.1.13 For Cohorts 1, 3A/3B, 4B and 4C patients must have new or progressive measurable CNS lesions, as assessed by the patient's treating physician. This includes patients who have progressed after at least one line of standard local treatment for CNS disease (WBRT, SRS, or surgical resection as below).

4.1.14 In Cohort 2, eligible patients will include those who have CNS disease that is amenable for surgery (typically < 3 brain metastases and with planned resection by neurosurgery). These patients may include those who have received or not received previous treatment(s) for their CNS.

4.1.15 Further eligibility details for patients with progressive disease (Cohorts 1, 3A/3B, 4A, 4B, 4C):

- Patients must have measurable CNS disease, defined as at least one parenchymal brain lesion that can be accurately measured in at least one dimension with longest dimension ≥10 mm by local radiology review. Note: measurable non-CNS disease is NOT required for study participation
- It is anticipated that some patients may have multiple progressive CNS lesions, one or several of which are treated with SRS or surgery with residual untreated lesions remaining. Such patients are eligible for enrollment on this study providing that at least one residual (i.e. non-SRS-treated or non-resected) lesion is measurable (**≥10 mm)**. The location of the measurable lesion should be documented in the patient chart and case report form.
- Patients who have had prior cranial surgery are eligible, provided that there is evidence of measurable residual or progressive lesions, and at least 2 weeks have passed since surgery. If a patient has surgical resection followed by WBRT, then there must be evidence of progressive CNS disease after the completion of WBRT.
- Except for those in Cohort 4A where prior local CNS therapy is not allowed, patients who have had prior WBRT and/or SRS and then whose prior treated lesions have progressed thereafter are also eligible for all other cohorts. In this case, lesions which have been treated with SRS may be considered as target lesions if there is unequivocal evidence, in the opinion of the treating physician, of progression.

4.1.16 Further eligibility details for patients with operable disease (Cohort 2):

- It is anticipated that that patients who have intracranial disease amenable to surgery will have measurable CNS disease prior to study entry and to resection. However, this is not an eligibility requirement. Measurable disease is also not required to continue on protocol subsequent to surgical resection.
- For patients who undergo surgery, postoperative whole brain radiation therapy will not be allowed while patients are on study (concurrent neratinib and radiation therapy has not been studied and toxicity of this is unknown). Patients will require discontinuation of neratinib if WBRT will be administered. However, if the treated provider feels that targeted radiosurgery (SRS, gamma knife, etc.) would be of benefit postoperatively, patients may proceed with this and then begin neratinib AFTER radiation completes

4.1.17 Further eligibility details for patients on Cohort 4A: All patients on Cohort 4A will *not* have received prior radiation or surgery to their brain. Prior systemic therapy aimed to treat disease in the brain is allowed (i.e. prior systemic standard therapy or protocol systemic therapy for brain mets)

Note: Laboratory tests required for eligibility must be completed within 4 weeks prior to study entry. Baseline measurements in the CNS must be documented from tests up to 21 days

prior to planned start of protocol therapy unless not covered by insurance. If insurance coverage is an issue, a case by case approval of testing beyond this window may be approved by the overall study PI. Other non-laboratory tests must be performed as indicated.

4.2 Exclusion Criteria – Main Protocol

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

4.2.1 Participants who have had chemotherapy or radiotherapy (including investigational agents) within 2 weeks prior to entering the study or those who have not recovered adequately from adverse events due to agents administered more than 4 weeks earlier (excluding alopecia). Washout from trastuzumab or hormonal therapy is not required.

4.2.2 Participants who are currently receiving any other investigational agents

4.2.3 History of severe allergic reactions or intolerability attributed to compounds of similar chemical or biologic composition to neratinib (all cohorts), capecitabine for Cohorts 3A/3B, and T-DM1 for Cohorts 4A-4C

4.2.4 Concurrent use of enzyme-inducing antiepileptic drugs (EIAEDs), including phenytoin, carbamazepine, oxcarbazepine, fosphenytoin, phenobarbital, pentobarbital, or primidone

4.2.5 Patients who are receiving any cancer-directed concurrent therapy, such as concurrent chemotherapy, radiotherapy, or hormonal therapy while on study. Concurrent treatment with bisphosphonates and denosumab is allowed for bony metastases but should be started before the first dose of neratinib.

4.2.6 Any prior treatment with capecitabine for patients enrolled to Cohorts 3A/3B, prior lapatinib for participants on Cohort 3A, and T-DM1 for Cohorts 4A-4B.

4.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

4.2.8 For Cohorts 4A, 4B, and 4C: Patients with myocardial infarction or cardiomyopathy onset within the last 6 months are excluded

4.2.9 Active hepatitis B or hepatitis C with abnormal liver function tests (Cohorts 4A-4C)

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: Patients with positive Hepatitis B or C serologies without known active disease are eligible if they meet all laboratory requirements in section 3.1.6. Patients with laboratory evidence of vaccination to Hepatitis B (e.g., positive antibodies) are also eligible.

4.2.10 Active liver disease from autoimmune disorders or sclerosing cholangitis

4.2.11 Lung disease from etiology other than metastatic breast cancer resulting in dyspnea at rest (4A-4C)

4.2.12 More than two seizures over the last 4 weeks prior to study entry

4.2.13 Patients with known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body. However, Head CT with contrast is allowed in place of MRI at baseline and throughout the study if MRI is contraindicated and a participant's CNS lesions are clearly measurable on the head CT.

4.2.14 Those with leptomeningeal metastases as the only site of CNS disease

4.2.15 Significant malabsorption syndrome or inability to tolerate oral medications

4.2.16 Any predisposing chronic condition resulting in baseline grade 2 or higher diarrhea

4.2.17 Inability to comply with study and/or follow-up procedures

4.2.18 Pregnant women are excluded from this study because neratinib (and other agents on study) is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with neratinib, breastfeeding should be discontinued if the mother is treated with neratinib. Negative urine pregnancy test is required for women of childbearing potential within 4 weeks of planned treatment start.

4.2.19 Individuals with a history of a different active malignancy are ineligible.

4.3 Inclusion Criteria for Continuing Therapy on the Extension Phase

Participants enrolled on Cohorts 1, 2 and 3 must meet the following criteria on screening examination to be eligible to participate in the study (note: Cohort 2 has slightly different criteria because patients will be adding capecitabine as described). There is no extension phase offered for patients treated on Cohorts 4A-4C:

4.3.1 Participants must have met all criteria to be enrolled on the main protocol for receipt of neratinib in Section 3.1. At the time of enrollment on the extension phase for Cohorts 1 and 3, patients must have experienced progression of non-CNS disease by RECIST 1.1 criteria.

4.3.2 Cohorts 1 and 3: Participants must have stable disease or be responders (PR or CR) to neratinib in the CNS at the time of non-CNS progression. Cohort 2: Participants must have progressive disease in CNS *or* non-CNS sites

4.3.3 ECOG performance status 0-2 (see Appendix A) (all cohorts)

4.3.4 Participants must have adequate organ and marrow function as defined below (all cohorts):

- Absolute neutrophil count > 1,000/μL
- Platelets > 100,000/μL
- Total bilirubin ≤ 1.5x ULN
- AST (SGOT)/ALT (SGPT) < 3.0 X institutional upper limit of normal OR ≤ 5X institutional upper limit of normal with liver metastases
- Creatinine ≤ 2 mg/dL or creatinine clearance ≥ 50 mL/min

4.3.5 The effects of trastuzumab, capecitabine, and neratinib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.3.6 Left ventricular ejection fraction ≥50%, as determined by RVG (MUGA) or echocardiogram within 60 days prior to initiation of extension phase therapy (all cohorts)

4.3.7 Ability to understand and the willingness to sign a written informed consent document (all cohorts)

4.4 Exclusion Criteria for Continuing Therapy on the Extension Phase

4.4.1 Exclusion criteria will include all criteria listed in Section 3.2 of the main protocol document

4.4.2 History of allergic reactions attributed to trastuzumab (Cohorts 1, 3) that were not treatable/preventable with pre-medications or desensitization protocols

4.5 Inclusion of Underrepresented Populations (all cohorts)

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

5. REGISTRATION PROCEDURES

5.1 Guidelines for Lead Institution and DF/HCC Institutions ONLY

All applicable institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Institutions that do not utilize OnCore will register eligible participants with the DF/HCC Office of Data Quality (ODQ) central registration system.

Registrations must occur prior to the initiation of protocol therapy. An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment and should begin treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled.

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

The ODQ registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the ODQ registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1) Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2) Complete the protocol-specific DF/HCC eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet all inclusion and exclusion criteria as described in the protocol and reflected on the eligibility checklist.**
3) Fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at [redacted]
4) The ODQ Registrar will (a) validate eligibility; (b) register the participant on the study.
5) An email confirmation of the registration will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration.
6) Patient can proceed with treatment.

Please contact the study coordinator and/or the ODQ registrar [redacted] with any questions regarding this process.

5.2 General Guidelines for TBCRC and Other Participating Institutions

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager or designee. All sites should call the Project Manager at [redacted] to verify slot availability. The required forms for registration are outlined below.

Participants MUST be registered with the Lead Institution (DFCI) prior to the start of protocol treatment. Following registration, participants should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration within allowed time period, the participant will become ineligible and will be cancelled from the study. The Project Manager should be notified of participant status changes as soon as possible. Any requests for eligibility exceptions and/or deviations must be approved by the DFCI IRB prior to execution.

5.2.1 Registration Process for TBCRC and Other Participating Institutions

To register a participant, the following documents should be completed by the research nurse or data manager and faxed to the lead institution's Project Manager or designee at [redacted] or emailed to [redacted]

The registration procedures are as follows:

1) All sites should call the Coordinating Center at [redacted] to notify of upcoming registration and slot availability.
2) Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
3) Complete the DF/HCC eligibility checklist using the eligibility assessments documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criteria as described in the protocol and reflected on the eligibility checklist.**
4) Fax the following documents to the Coordinating Center at [redacted]

- Completed Eligibility Checklist
- Copies of laboratory, imaging and pathology reports
- Patient and physician signed complete Consent Form
- HIPAA authorization form (if separate from the main consent form)
- Neurological Assessment Form

- MRI (or CT if applicable) brain report with evidence of measurable CNS disease

5) Once registration confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the Project Manager at [redacted] with any questions regarding this process.

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

Note: Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5.3 Data Collection

DFCI will collect, manage, and monitor data for this study. The DFCI electronic data collection system will be utilized. Please refer to Section 14, Data and Safety Monitoring, for further information on data submission requirements.

6. TREATMENT ADMINISTRATION

6.1 Treatment Overview

For Cohorts 1 and 2: These cohorts were an open-label, phase II study evaluating the administration of neratinib in patients with brain metastases from HER2-positive breast cancer. Treatment was administered on an outpatient basis. Target accrual was 45 patients with an estimated rate of accrual of 1-3 patients per month. Patients will be followed for up to two years after removal from study or until death, whichever occurs first. Patients will be asked if they may be contacted for future study in their consent forms so that additional analyses can be considered in the future. Expected toxicities and potential risks as well as dose modifications for neratinib and trastuzumab are described in *Section* 6. Treatment will include single-agent neratinib, administered orally at 240 mg once daily (six 40 mg tablets).

For patients on Cohort 2 who develop progression in their CNS or non-CNS sites, they will have the option to add capecitabine to their neratinib and would transition to q21 day cycles. In the optional extension phase for patients whose disease progresses outside the CNS in Cohort 1, treatment will continue on an every 21 day cycle and includes the addition of trastuzumab per one of the dosing schedules below. Neratinib dosing will be continuous during each cycle without treatment breaks.

For Cohorts 3A and 3B: These additional Cohorts were enrolled to evaluate the efficacy and toxicity of neratinib and capecitabine for patients with brain metastases from HER2-positive breast cancer. Treatments were administered on an outpatient basis. Target accrual was 35 patients for Cohort 3A and 25 patients for Cohort 3B. The estimated rate of accrual was 1-3 patients per month (combined for Cohort 3A/3B). Accrual to Cohorts 3A/3B began once Cohort 1 accrual was completed. The estimated date of accrual completion for Cohort 3A/3B was 40 months after these cohorts opened. Patients will be followed for up to two years after removal from study or until death, whichever occurs first. Patients will be asked if they may be contacted for future study in their consent forms so that additional analyses can be considered in the future. Expected toxicities and potential risks as well as dose modifications for neratinib and capecitabine are described in *Section* 6. Treatments include single-agent neratinib, administered orally at 240 mg once daily (six 40 mg tablets) and capecitabine, administered orally at approximately 750 mg/m^2 twice daily (1,500 mg/m^2 daily) for 14 days followed by 7 days off. Treatments may be taken together. For participants on this cohort, treatment consists of 21 day cycles. Neratinib dosing is continuous during each cycle without treatment breaks. In the optional extension phase for patients whose disease progresses outside the CNS, treatment will continue on an every 21 day cycle and includes the addition of trastuzumab per one of the dosing schedules below. Neratinib and capecitabine dosing will continue at the current dose levels and schedule.

For Cohorts 4A-4C: These Cohorts will be used to evaluate the efficacy and toxicity of neratinib in combination with T-DM1 for those with brain metastases from HER2-positive breast cancer. Treatments will be administered on an outpatient basis. Target accrual for Cohort 4A and 4B is 20 each and the target accrual for Cohort 4C is 23, as long as the first stage (at least one response out

of the first 9 patients) is passed. The estimated accrual across the three Cohorts will be 2-4 per month. The estimated date of accrual completion for Cohorts 4A-4C is 16-32 months after these Cohorts open. Patients will be followed for up to two years after removal from study or until death, whichever occurs first. Patients will be asked if they may be contacted for future study in their consent forms so that additional analyses can be considered in the future. Expected toxicities and potential risks as well as dose modifications for neratinib and T-DM1 are described in *Section* 6. Treatments include single-agent neratinib, administered orally at 160 mg once daily (four 40 mg tablets) and T-DM1, at a dose of 3.6 mg/kg intravenously every 21 days. For participants on these Cohorts, treatment consists of 21-day cycles. Neratinib dosing is continuous during each cycle without treatment breaks.

Treatment Description					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Neratinib (for Cohorts 1,2)	Take with food each morning┼	240 mg (six 40 mg tablets)	Orally	Days 1-28 (no breaks)	28 days
Neratinib (for Cohorts 3A/3B)	Take with food each morning┼	240 mg (six 40 mg tablets)	Orally	Days 1-21 (no breaks)	21 days
Neratinib (for Cohorts 4A-4C)	Take with food each morning┼	160 mg (four 40 mg tablets)	Orally	Days 1-21 (no breaks)	21 days
Trastuzumab (for extension phase only, Cohorts 1, 3A/3B)	Pre-medication according to institutional guidelines	8 mg/kg load,* followed by 6 mg/kg IV every 21 days OR 4 mg/kg load* followed by 2 mg/kg weekly	IV	Once every 21 days or once weekly	21 days
Capecitabine┼ (Cohorts 3A/3B and Cohort 2 for extension phase patients)	Take at the end of a meal (within 30 minutes). Take with glass of water. Can be taken with neratinib.	750 mg/m^2 twice daily (1,500 mg/m^2 daily)┼	Orally	Days 1-14 followed by 7 days of rest	21 days
T-DM1 (Cohorts 4A-4C) ¥	Pre-medications according to institutional guidelines	3.6 mg/kg every 21 days, administered over 90 minutes (+/- 15 minutes)	IV	Day 1 of each cycle	21 days

Treatment Description					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
		(1st infusion) and administered over 30 minutes (2nd infusion onward) (+/- 15 minutes)			

┼ *Please see recommendations about H2 blockers, PPI, antacids in Section 5.4.1 & Appendix J*
* *Loading dose not necessary if last treatment with trastuzumab was ≤ 4 weeks prior to enrollment on the extension phase*
┼ *Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the starting capecitabine dose be rounded up to the nearest 500 mg or multiple of 150 mg for the BID dose. However, if initial capecitabine dosing is complex for a patient because of the need to use a complicated combination of 150 mg and 500 mg tablets and the provider wishes to use 500 mg tablets only, this is permitted. In addition, providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing and may round down (rather than up) if they prefer for the starting dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Of note, capecitabine is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Capecitabine tablets should be swallowed with water.*
¥ For patients on Cohort 4C (prior T-DM1-treated) who required a dose reduction in the past during their prior course with T-DM1, they may start with their previously tolerated dose or they may start at the full dose of 3.6 mg/kg at the discretion of their treating provider (i.e. if a patient was dose reduced in the past to 3.0 mg/kg and enrolled on this study, his/her provider may start T-DM1 at 3.6 mg/kg or 3.0 mg/mg according to the degree of past toxicity concerns, reasons for dose reduction, etc.).

6.2 Study Evaluations

All required procedures and evaluations are detailed in the Study Calendar and Notes in *Section 11*.

6.3 Agent Administration and Dosing

6.3.1 Neratinib

Administration – Neratinib is administered orally once daily continuously for 3 or 4 weeks, depending on the Cohort (1 cycle=4 weeks for Cohorts 1 and 2; 1 cycle=3 weeks for Cohorts 3A/3B and 4A-4C). Patients are to fill out a pill diary for every cycle (Appendix B). For operative patients in Cohort 2, neratinib will be taken continuously for 7-21 days, up until the morning of surgery (cycle -1). Neratinib will be resumed within 10 days (+/- 3 days) postoperatively and will be delineated as cycle 1. If a provider wishes to delay re-initiation of therapy for a postoperative patient, he/she must speak with the lead PI to discuss the planned start date. Further, if SRS or similar targeted radiation is planned, patients should hold neratinib until this has been completed and can then re-start treatment

within 10 days of completing radiosurgery (+/- 3 days). Cycles are 28 days for all patients on Cohorts 1 and 2, regardless of whether patients undergo surgery and when they start/stop neratinib. For patients enrolled on the extension phase of the study for any Cohort, cycle length will be 21 days to accommodate dosing of trastuzumab (and capecitabine). For patients enrolled on Cohorts 3A/3B and 4A-4C, cycle length will be 21 days.

Dosing – 240 mg once daily (six 40 mg tablets) for all cohorts EXCEPT Cohorts 4A-4C where dosing will start at 160 mg once daily (four 40 mg tablets). Dosing is not based on weight-based criteria. Patients should take neratinib at the same time of day every day, in the morning, with food. Doses should not be retaken if skipped, missed, or vomited. Dose modifications are delineated below

Observation period – No observation period required. Patients will fill out a pill diary each cycle to assess adherence to therapy.

Vital Signs – Patients will be evaluated every 3 or 4 weeks depending on Cohort.

Infusion reactions – N/A

6.3.2 Capecitabine (Cohort 3)

Administration – Capecitabine is administered orally twice daily for 14 days followed by one week of rest for all participants on Cohorts 3A/3B. This should be taken after a meal, within 30 minutes after completion of the meal.

Dosing – 750 mg/m^2 twice daily ((1,500 mg/m^2 daily) for days 1-14 followed by 7 days of rest. Patients should take capecitabine after a meal and doses should be separated by approximately 12 hours. Doses should not be retaken if skipped, missed, or vomited. As above, since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the starting capecitabine dose be rounded up to the nearest 500 mg or multiple of 150 mg for the BID dose. However, if initial capecitabine dosing is complex for a patient because of the need to use a complicated combination of 150 mg and 500 mg tablets and the provider wishes to use 500 mg tablets only, this is permitted. In addition, providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing and may round down (rather than up) if they prefer for the starting dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Of note, capecitabine is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Capecitabine tablets should be swallowed with water.

For both capecitabine and neratinib, the dose is considered "missed" if not taken within approximately 2 hours of the usual administration time.

Observation period – No observation period required. Patients will fill out a pill diary each cycle to assess adherence to therapy.

Vital Signs – Patients will be evaluated every 3 or 4 weeks depending on Cohort.

Infusion reactions – N/A

6.3.3 T-DM1 (Cohorts 4A-4C)

Administration – T-DM1 is administered on Day 1, intravenously on day 1 of each 21-day cycle. The first T-DM1 dose will be administered over 90 minutes (+/- 15 minutes or per institutional policies) with pre-medications at the treating institution/physician's discretion. Infusions should be slowed or interrupted for patients experiencing infusion-related symptoms and patients should be observed for 30 minutes following the initial dose for fever, chills, or other infusion-related symptoms. If prior infusions were tolerated well, subsequent doses may be administered over 30 minutes without a minimum observation period after infusion. Administer T-DM1 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 and subsequent doses over 30 minutes (+/- 15 minutes or per institutional policies) if prior infusions were well tolerated. Flush IV line with saline after drug is administered. Do not administer with D_5W. Do not administer as an intravenous push or bolus.

Do not mix T-DM1, 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.

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

Dosing – 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.*

Observation Period – 30 minutes with first infusion, then per standard institutional guidelines.

Vital Signs – start of every cycle

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 T-DM1 is specified or expected. Patients who experience T-DM1 infusion-related temperature elevations of >38.5°C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen and/or H1 and H2 receptor antagonists (e.g., diphenhydramine or ranitidine) or by standard institutional protocols. 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 unless an allergy unit is available for administration under a standardized desensitization protocol (and should be approved by the PI on a case by case basis).

6.4 Concomitant Treatment and Supportive Care Guidelines

6.4.1 Cautioned Concurrent Medications

Neratinib:

- Because there is a potential for interaction of neratinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Patients should be cautioned to avoid any clear inhibitors or inducers of CYP3A4 (Appendix J) if possible, but these medications are not prohibited. Patients should also avoid St. John's Wort and grapefruit juice.
- Those patients on warfarin therapy should be monitored closely while on study (PT, PTT, INR), particularly those who are receiving neratinib in combination with capecitabine
- Those patients on digoxin should be monitored closely. Co-administration of neratinib and digoxin could result in increased digoxin levels and associated digoxin toxicity.
- Patients may not take concurrent EIAEDs, hormonal therapies, or any other cancer-directed therapies, except for subjects who enroll in the optional extension phase with administration of trastuzumab
- No concurrent radiation is allowed.
- Concurrent bisphosphonate and denosumab therapy is allowed but this treatment should have started prior to the first dose of neratinib.
- Concurrent steroids are allowed if dose has been stable or tapered for 1 week prior to baseline brain imaging. In addition, increases in steroid dosing after study entry are

allowed if clinically indicated. Note, although dexamethasone is a weak CYP3A4 inducer, concurrent therapy with neratinib is allowed if steroid therapy is clinically indicated.

- Interaction with Proton Pump Inhibitors (PPI) and other Acid-reducing Agents: The solubility of neratinib is pH dependent and treatments that alter the gastrointestinal pH such as PPIs, H2-receptor antagonists, and antacids may lower the solubility of neratinib. It has been observed that a single 240 mg dose of neratinib combined with lansoprazole may decrease neratinib AUC by up to 70% (PUMA-NER-101). It is unknown whether separating the PPI and neratinib reduces the interaction. If an H2-receptor antagonist such as ranitidine or famotidine is required, neratinib should be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist. If antacids are necessary, the antacid dose and neratinib dose should be separated by 2-4 hours whenever possible.

Capecitabine:

- Drugs Metabolized by Cytochrome P450 Enzymes: In vitro enzymatic studies with human liver microsomes indicated that capecitabine and 5'-DFUR had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1, suggesting a low likelihood of interactions with drugs metabolized by cytochrome P450 enzymes.
- Antacid: When Maalox®* (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine (1250 mg/m2, n=12 cancer patients), AUC and Cmax increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of capecitabine. May take maalox with caution. See Appendix J for more details.
- Capecitabine has a low potential for pharmacokinetic interactions related to plasma protein binding.
- CONTRAINDICATIONS: capecitabine is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.
- Capecitabine is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

T-DM1:

- DM1, the cytotoxic component of T-DM1, 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 T-DM1 should be avoided if possible due to the potential for an increase in DM1 exposure and toxicity

6.4.2 Supportive Medications

There are no required supportive medications with exception of diarrhea prophylaxis, which has evolved with each cohort enrolled to this study. For Cohorts 1-3, differing doses of loperamide were required to be initiated with the first dose of neratinib (Cohorts 1 and 2) and with the first doses of capecitabine and neratinib (Cohorts 3A/3B). For Cohorts 4A-4C, all patients will be asked to take colestipol 2g BID for 1 cycle along with loperamide (4 mg initial dose, then 4 mg approximately every 8 hours for days 1-14 of cycle 1, then 4 mg approximately every 12 hours for days 15-21 of cycle 1) [per personal communication from PUMA and based on results from PUMA-NER-6201]. If patients experience diarrhea, they may take increased anti-diarrheal remedies as directed *(Section 6.1.9 [Cohorts 1 and 2], Section 6.3 [Cohort 3]),*[77] *and Section 7.4.4 [Cohort 4].* If patients experience grade 1 diarrhea or less over the course of the first cycle of therapy, prophylactic anti-diarrheal may be stopped after the first cycle of therapy. Patients may refuse prophylaxis with cycle 1 if they have a clear clinical reason (i.e. suffer from chronic constipation, etc.). Section 6.3 and 6.4 has detailed instructions for patients on Cohorts 3A/3B and 4A/4C for management of their prophylaxis.

6.5 Optional Extension Phase – Neratinib in Combination with Trastuzumab (for Cohorts 1 and 3)

Subjects who obtain CNS response or disease stability with neratinib (Cohorts 1) or neratinib and capecitabine (Cohorts 3A/3B), yet subsequently develop disease progression exclusively outside of the CNS by RECIST 1.1, are eligible to enroll into the optional open-label extension of this protocol. In the extension phase, subjects will continue on oral neratinib (and capecitabine if on Cohort 3) in combination with trastuzumab. A separate informed consent document with information related to this combination must be reviewed and signed prior to initiation of the extension phase of treatment.

Upon enrollment to the extension phase, patients will continue to receive their current dose of neratinib (240 mg unless dose reductions have occurred), taken orally daily in addition to trastuzumab at a loading dose of 8 mg/kg followed by 6 mg/kg every 21 days or 4 mg/kg followed by 2 mg/kg weekly, intravenously. Capecitabine will also continue at current dosing for participants enrolled on Cohorts 3A/3B. Cycles in the extension phase will be 21 days in length for all Cohorts. Participants transitioning to the extension portion of the trial with progression to bones are allowed to initiate Bisphosphonate/denosumab supportive therapy.

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for trastuzumab and the combination of trastuzumab/neratinib and

trastuzumab/neratinib/capecitabine are described in *Section 6* (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy (with exception of bisphosphonate therapy).

Subjects on the extension study will be followed clinically on an every-3-week schedule, in order to accommodate trastuzumab dosing schedules (weekly or every-21 days). Radiographically, patients will be followed at 6 weeks once and then every 9 weeks thereafter (until discontinuation of combination due to disease progression [CNS or non-CNS] or tolerability issues). The subject will be similarly followed for safety and efficacy endpoints.

Optional Extension Phase for Cohort 2. Patients whose cancers progress in CNS and/or non-CNS sites will have the option to continue therapy with the addition of capecitabine to the current neratinib dose. Subjects on this extension study will be followed clinically on an every-3-week schedule, in order to accommodate capecitabine dosing schedules. Radiographically, patients will be followed at 6 weeks once and then every 9 weeks thereafter (until discontinuation of combination due to disease progression [CNS or non-CNS] or tolerability issues). The subject will be similarly followed for safety and efficacy endpoints. If additional progression is noted in the CNS or non-CNS sites after capecitabine is added, patients will come off study treatment.

Trastuzumab Administration for Extension phase (Cohorts 1 and 3):

- Patients will receive trastuzumab administered IV 4 mg/kg loading dose on Day 1, followed by 2 mg/kg weekly even if neratinib was held for any reason, or, they may receive trastuzumab administered IV 8 mg/kg loading dose on Day1, followed by 6 mg/kg every 3 weeks, even if neratinib was held for any reason. The choice of weekly versus Q3 weekly administration of trastuzumab is up to the choice of the treating physician. The loading dose will not be necessary if patients have received trastuzumab within 4 weeks of extension study entry.
- The initial loading dose of trastuzumab will be administered over approximately 90-minute period, followed by an approximate 60-minute post-infusion observation period. If this first dose is well tolerated, subsequent infusion periods may be shortened to approximately 30 minutes. If the initial or subsequent doses are not well tolerated, (e.g. the patient experiences fever and/or chills), subsequent infusions may be shortened only after a dose is well tolerated.
- Patients must remain under medical supervision for 1 hour following completion of the initial dose of trastuzumab. If no adverse events occur with the first infusion, the post infusion observation period for the second infusion may be shortened to 30 minutes and eliminated entirely with subsequent infusions.

- Minor schedule changes owing to observed holidays, inclement weather, etc. are permitted.
- Patients may interrupt therapy for protocol-directed reasons (i.e. toxicity) or for personal preferences (holidays, vacations, etc.). Treatment should resume according to protocol guidelines. Patients may not voluntarily (i.e. for vacations, holidays, etc.) omit trastuzumab for more than 1 every 3 weekly (6mg/kg) dose, or more than 2 consecutive weekly doses in a single cycle. If trastuzumab is omitted voluntarily due to the above, neratinib should be continued during that time, with the exception of protocol-directed reasons (i.e. toxicity). Each 3-week period will be considered one cycle.

6.5.1 General Concomitant Medication and Supportive Care Guidelines

- Because there is a potential for interaction of neratinib-trastuzumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.
- See *Appendix J* for a list of medications to be used with caution**.**

6.5.2 Antiemetics

Patients may be given antiemetics at the discretion of the treating physician. Because of the low emetogenic potential of neratinib, T-DM1, capecitabine, and trastuzumab, the following antiemetics are recommended if the patient experiences symptoms:

- Prochlorperazine 10 mg IV/PO x 1 PRN, and/or
- Lorazepam 1 mg IV/PO x 1 PRN, and/or
- Ondansetron 8 mg PO/IV x 1 PRN

6.5.3 Anticoagulants

Anticoagulation with heparin, heparin derivatives, and/or warfarin may be given at the discretion of the treating physician with careful monitoring.

6.5.4 Bisphosphonates and other supportive bone agents

Bisphosphonate and denosumab treatments when bone lesions are documented are allowed for the treatment of bone metastases. Oral bisphosphonate treatment allowed for patients with a low bone mineral density. Patients already receiving bisphosphonate or denosumab at the time of study entry can continue the treatment while on study. Patients with new bone metastases documented as part of study screening procedures may begin a bisphosphonate or denosumab after study registration, provided the first dose is given prior to the initiation of protocol-based therapy. Bisphosphonates/denosumab may not be started after the initiation of protocol-based therapy in Cohorts 1 or 2.

Patients with new bone metastases documented as part of non-CNC progression on trial may begin a bisphosphonate/denosumab at the time of enrollment to extension phase of the trial.

6.5.5 Growth Factors

Patients may receive erythropoietin or G-CSF while on study, at the discretion of the patients treating physician, when clinically indicated for hematologic toxicity. Prophylactic use of growth factors (prior to development of hematologic toxicity) is not necessary.

6.5.6 Diarrhea Management Guidelines –

See *Section 6.1.9.1* of the protocol for information on recommended medications for prevention and treatment of diarrhea.

6.6 Study Drug Availability

6.6.1 As part of the clinical trial, neratinib will be provided free of charge to study participants by Puma Biotechnology, Inc..

6.6.2 Patients and/or their insurance companies will be billed for the cost of trastuzumab and its administration, as it is considered standard of care for HER2-positive, metastatic breast cancer.

6.6.3 Neratinib must be prescribed by the study physician only; patients must also receive trastuzumab at the participating facility (extension cohorts).

6.6.4 Capecitabine and T-DM1 will be available by commercial supply and will be billed to insurance.

6.7 Discontinuation of Treatment

6.7.1 Duration of therapy will depend on individual response, evidence of disease progression and tolerance. The reasons for discontinuation of protocol treatment include:

- Evidence of disease progression during therapy at the discretion of the treating investigator.
- Non-compliance with the study protocol; including, but not limited to not attending the majority of scheduled visits. The Protocol Chair will determine when non-compliance should lead to removal from study. Note: The patients will still be included in the overall evaluation of response (intent-to-treat analysis).
- Unacceptable major toxicity/adverse event. Note: The patients will still be included in the overall evaluation of response (intent-to-treat analysis).
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment.

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

6.7.2 In the case of delays in reporting brain imaging results to/from the TIMC, patients may continue on therapy while awaiting central review IF disease progression on local review has not occurred. Progression in this case will be defined as the following:

- Progressive disease in the CNS, evidenced by an increase of greater than 20% in the sum of the longest diameters of target lesions AND an absolute increase in the size of ≥5 mm in at least one target lesion, taking as reference the smallest sum longest dimension recorded since the treatment started; or, the appearance of one or more new lesions ≥6 mm
- Progressive disease in extra-CNS sites by RECIST 1.1 criteria
- Note that for the purposes of calculation of response rate and time to progression, volumetric criteria will be used to assess CNS disease, as specified in the protocol. However, because volumetric analyses may not be conducted in real-time for clinical decision-making, the above criteria, based on longest dimension, will be used to determine whether a patient should continue on therapy.

If it is unclear whether radiographic changes are related to disease progression (for example, if changes could be due to radiation necrosis or infection), then additional imaging and other tests should be conducted as clinically indicated. If a patient fulfills criteria for disease progression as defined by increase in sum longest dimension of target lesions but confirmatory studies indicate that the findings are not due to progression, the patient may remain on study, provided that clear justification is documented in the patient record and in the case report form.

It is recognized that there may be infrequent situations where there is clinical uncertainty regarding CNS progression even in the setting of protocol-defined progression by volumetric measurements, particularly in the case of very low volume CNS disease. For example, in patients whose lesion has shrunk very substantially, a small apparent increase in size, of a range that could be due to slice variation or other factors, could lead to a central assessment of tumor progression. In these cases, patients may continue on protocol-based therapy if agreed upon by the study overall PI. If the next scan confirms continued progression, then the patient will be taken off treatment at that time and the date of progression will be back-dated to the date of the initial centrally-designated progression date. If the next scan does not confirm progression, the patient may remain on protocol therapy.

6.8 Criteria for Removal from Study

Treatment will be permanently discontinued if/when any of the criteria listed in *Section 5.7* apply. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. A copy of this form is in Appendix G. This form can also be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Rachel Freedman, MD, MPH at [redacted].

6.9 Withdrawal from Study

6.9.1 The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up.
- Study is terminated for any reason.

6.10 Duration of Follow Up

Participants will be followed approximately every 6 months for up to two years after discontinuation of therapy or until death, whichever occurs first. Participants who discontinue treatment for unacceptable adverse events will also be followed until resolution or stabilization of the adverse event.

7. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

7.1 Anticipated Toxicities for Neratinib

A list of the adverse events and potential risks associated with neratinib appears below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting. For toxicity management of diarrhea please refer to table 6.1.9.1.

7.1.1 Investigator Brochure Toxicity Table

[Adapted from 12SEP2012 Investigator's Brochure, version 1.0]

Table 70 Adverse Reactions Occurring in Subjects Receiving Neratinib (N = 512)

System Organ Class	All Causality Frequency	Preferred Term	All Grades N (%)	Grade 3 & 4 N (%)
Gastrointestinal disorders	Very Common	Diarrhoea	456 (89.1)	135 (26.4)
		Nausea	245 (47.9)	18 (3.5)
		Vomiting	179 (35.0)	24 (4.7)
		Abdominal pain (includes abdominal pain upper/lower)	155 (30.3)	9 (1.8)
General disorders and administration site conditions	Very Common	Fatigue	184 (35.9)	21 (4.1)
		Asthenia	80 (15.6)	8 (1.6)
Metabolism and Nutrition disorders	Very Common	Decreased appetite	164 (32.0)	17 (3.3)
		Dehydration	57 (11.1)	19 (3.7)
Skin and subcutaneous tissue disorders	Very Common	Rash (includes rash follicular/maculo-papular/generalized/ dermatitis acneiform/ pruritus)	163 (31.9)	3 (0.6)
Investigations	Very Common	Aspartate amino-transferase increased (AST)	53 (10.4)	12 (2.3)
		Alanine amino-transferase increased (ALT)	51 (10.0)	14 (2.7)
	Uncommon	Transaminases increased	4 (0.8)	2 (0.4)
Renal and urinary disorders	Uncommon	Renal failure (includes renal failure acute, acute prerenal failure)	3 (0.6)	2 (0.4)

7.1.2 Highlights From Reported Clinical Trial Toxicities

(for all mentioned toxicities, see Investigator Brochure Table above and below for further information)

- Gastrointestinal Symptoms: The most commonly reported treatment-related adverse events in previously conducted studies with neratinib were gastrointestinal disorders, and included diarrhea, nausea, abdominal pain, vomiting, and anorexia. Diarrhea has been considered manageable but can be severe and should be treated at the earliest occurrence. In most cases, the onset of diarrhea is within a few days to a week of therapy initiation, with tapering of symptoms over a few weeks. In some cases, treatment delay, anti-diarrhea therapy, and treatment cessation may be required. Methods for alleviation of diarrhea have been described previously and include anti-

diarrheal therapies such as loperamide (starting with 4 mg followed by 2 mg every 4 hours or after every loose stool (maximum 16 mg/day). Please see *Section 6.1.9.1* for further recommendations on prevention and treatment of diarrhea.[77] Close attention to hydration status is required.

- Increased Serum Creatinine or renal failure: Of all subjects who have taken neratinib, a few creatinine events and renal failure events have been reported.
- Transaminitis: Events have been reported with AST/ALT elevations in patients who took neratinib.
- Cytopenia: Myelosuppression, thrombocytopenia, and neutropenia have more recently been added to the list of potential adverse drug reactions for neratinib.
- Others: Asthenia, headache, pyrexia, fatigue, pain, weight loss, rash have also been reported in patients taking neratinib.(See *Section 6.1* for additional toxicity table, adapted from the Investigator's Brochure, September 2012)

7.1.3 Other Toxicity Information from Non-Clinical Studies

- Cardiovascular Effects: No QT prolongation or significant cardiovascular toxicities were observed in rats and dogs treated with neratinib in pre-clinical studies. No changes were seen on serial ECG monitoring and no changes in heart weight or microscopic heart findings were noted.
- Respiratory Effects: Neratinib had no effect on respiratory function (respiratory rate, tidal volume, minute volume) in rats.
- Ocular Effects: Concentrations of radio-labeled neratinib were higher and persisted longer in the skin and uveal tract of pigmented rats (vs. non-pigmented), suggesting an affinity for melanin-containing tissues. In a follow-up 4-week toxicity study in beagle dogs (who have pigmented eyes), no compound-related eye changes were observed. Furthermore, microscopic examinations of the eye did not reveal any abnormalities.

7.1.4 Safety Information from Similar Marketed Drugs:

- Other marketed drugs that inhibit the erbB family of tyrosine kinases may be demonstrative of potential toxicities with neratinib. These include agents such as erlotinib, gefitinib, lapatinib, and trastuzumab. These agents have been associated with gastrointestinal disorders (above), ventricular dysfunction and congestive heart failure (CHF), interstitial lung disease, and dermatologic toxicities.
- Ventricular Dysfunction and Congestive Heart Failure: Dyspnea, cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, and reduced ejection fraction (EF) have been reported in patients who receive trastuzumab. Lapatinib has been reported to also decrease EF and increase the QT interval. Previous results in patients who received neratinib have demonstrated no QT prolongation at the recommended dose of 240 mg once daily with food. The implications for reduced EF in patients who receive neratinib are uncertain and close monitoring of this is included for patients on study.

- Interstitial Lung Disease (ILD): ILD has been rarely reported with administration of lapatinib, gefitinib, and erlotinib and has been described as pneumonia, pneumonitis, or alveolitis. This has been described to have acute onset of dyspnea, sometimes associated with a cough and low-grade fever. Pulmonary complications have also been reported with trastuzumab and include pulmonary infiltrates, non-cardiogenic pulmonary edema, pleural effusions, and acute respiratory distress syndrome. Pneumonitis has also been reported in patients who received neratinib on study, although the implications in patients who receive this agent are not clear. Urgent evaluation of acute onset pulmonary symptoms is recommended for patients who are receiving neratinib.
- Dermatologic Toxicities: Rashes have been commonly reported with agents such as erlotinib and gefitinib and palmar-plantar erythrodysesthesia (hand-foot syndrome) have been reported with lapatinib. Grade 1-3 rashes have been reported in clinical studies with neratinib and subjects should be monitored for this.

7.1.5 Neratinib Management and Dose Modifications/Delays for Drug-Related Toxicities **FOR COHORTS 1 AND 2 ONLY**.

****For patients enrolled on COHORTS 3A/3B, see Section 6.3****
Patients will begin therapy at 240 mg once a day, orally. This will be administered as six 40 mg tablets. **At the time of therapy initiation, patients will begin primary prophylactic use of loperamide (2 mg) with each neratinib dose**. This prophylaxis will continue for the first cycle of therapy and can be stopped after cycle 1, as long as diarrhea is grade 1 or less. If patients do not tolerate prophylactic loperamide and have grade 1 or less diarrhea, loperamide can be stopped before the end of cycle 1 per the treating provider's discretion.

Toxicity Management Table <u>for Cohorts 1 and 2 only</u> [liver and cardiac toxicity management discussed below]

(Also see *Section 6.1.9.1 and FIGURE below with diarrhea treatment algorithm*)

Event (based on NCI CTC Version 4)	Recommended Action
Grade 1 (non-diarrhea)	Continue current dose level
Grade 2 (non-diarrhea)	Continue current dose level
Diarrhea – <u>grade 1</u> [i.e. increase of <4 stools per day over baseline or mild increase in ostomy output compared to baseline)	Begin dietary and pharmacologic interventions. Begin loperamide at 4 mg initial dose, followed by 2 mg every 4 hours or after every unformed stool – consider continuation of loperamide at this frequency until diarrhea-free for 12 hours. <u>Continue current dose level of neratinib</u>. If diarrhea worsens despite these measures, <u>see below (grade 2,3) for management.</u>
Diarrhea – <u>grade 2</u> [i.e. increase of 4-6 stools per day over baseline; IV fluids indicated <24 hours; moderate increase in ostomy output compared to baseline; not interfering with ADL	Same as grade 1 for dietary and pharmacologic interventions. If recovery to grade ≤1 or baseline <u>AND</u> duration of grade 1 diarrhea <5 days or grade 3 < 2 days, <u>continue neratinib at same dose</u> and resume

Event (based on NCI CTC Version 4)	Recommended Action
	prophylactic loperamide 2 mg with each subsequent study medication administration. If worsening to OR persisting and intolerable grade 2 symptoms >5 days despite optimal therapy or associated with fever, dehydration, Grade 3-4 neutropenia, hold study drug until recovery to grade ≤1 or baseline (see grade 3 diarrhea for dosing) If worsening to OR persisting grade 3 >2 days despite optimal therapy or associated with fever, dehydration, grade 3-4 neutropenia, hold study drug until recovery to grade ≤1 or baseline (see grade 3 diarrhea for dosing)
Diarrhea – grade 3 [i.e. increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; hospitalization; severe increase in ostomy output compare with baseline; not interfering with ADL; lasting > 2 days despite optimal medical therapy or associated with fever, dehydration, or grade 3-4 neutropenia; any grade 4 diarrhea]	Same as grade 1 for dietary and pharmacologic interventions. In addition, hold neratinib until recovery to grade ≤ 1 or baseline. If recovery occurs within 7 days of therapy hold, resume neratinib at same dose and continue prophylactic loperamide (2 mg with each dose). If recovery occurs > 7 days and < 21 days after treatment hold, reduce neratinib to next dosing level* and resume prophylactic loperamide 2 mg with each administration. All subsequent treatments will be administered at this lowered dose. If grade 3 diarrhea subsequently returns at next dose level, further reduce to next lower level* if recovery occurs > 7 days and < 21 days after treatment hold If recovery occurs > 21 days after treatment hold or if grade 3-4 diarrhea returns at lowest dosing level, therapy will be permanently discontinued.
Diarrhea – grade 4 (i.e. life threatening consequences)	Treatment with loperamide, as above, hold study medication, and follow guidelines for recovery for grade 3 symptoms above
Pneumonitis/Interstitial Lung Disease Grade 2 (symptomatic) or grade 3+	Symptomatic grade 2: Hold neratinib until resolution to ≤ grade 1 or baseline. If this resolves within 21 days of stopping drug, re-start at next lower dose level.* If ≥ grade 3 toxicity occurs, discontinue neratinib indefinitely.
Other grade 3 (including nausea/vomiting despite optimal medical therapy, and asthenia lasting >3 days or rash unless subjects are already receiving appropriate medical therapy)	Hold neratinib. Once toxicity recovers to grade ≤ 1 or baseline, reduce to next dosing level (if occurs within 21 days of stopping treatment).* Patients will permanently discontinue therapy if symptoms do not resolve at 21 days or if lowest dosing level already reached.
Grade 4 (hematologic or non-hematologic)	Hold neratinib. Investigator, sponsor, and treating provider review data and determine whether subject should continue on therapy with appropriate dose adjustments
Liver function abnormalities‡	See recommendations below
LVEF changes	See recommendations below

**** See Dose Reduction Table below***

Note on dosing: *If dose has been previously held for grade 2 toxicity and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce by 1 dose level. Once a dose of neratinib has been reduced for a subject, all subsequent doses should be administered at the lower dose, unless further dose reduction is necessary. In specific cases, dose re-escalation can be considered by the treating provider. If a patient recovers from a ≤ grade 3 nausea, diarrhea, or vomiting event, and if the event recovers to a grade 1 and remains there for 4 weeks following a dose reduction, it is acceptable to re-escalate dosing to the previous dosing level. However, only one dose re-escalation is advised and no doses should exceed 240 mg once daily.*

7.1.6 Guidelines for Management Drug Related Liver Toxicity for Cohorts 1 and 2 only

Changes in LFTs have been reported in subjects taking neratinib. Patients who experience grade 3 diarrhea or any signs/symptoms of hepatotoxicity such as worsening of fatigue, nausea/vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia should be evaluated for LFT changes, including bilirubin fractionation (indirect and direct bilirubin) and prothrombin time. Liver imaging should be considered for patients with signs or symptoms of worsening hepatotoxicity.

Event (based on NCI CTC 4.0) ǂ **For participants on Cohorts 1 and 2**	**Recommended management**
Grade 4 ALT/AST (>20x ULN), **or** Grade 4 Bili (>10x ULN) and direct bili ≥ 35% of total bili	Permanently discontinue neratinib; Evaluate for alternative causes. Report as SAE.
Grade 3 ALT/AST (5-20x ULN) **or** Grade 3 total bilirubin (>3-10x ULN)	Hold neratinib until recovery to ≤ grade 1 or baseline. Evaluate for alternative causes as appropriate. For subjects with ALT <grade 1 at baseline, resume neratinib at next lower dose level* if recovery to baseline occurs within 21 days. If grade 3 ALT or bilirubin occurs despite one dose reduction, permanently discontinue neratinib. Report as SAE.
ALT/AST > 3xULN **and** Total bilirubin >2x ULN **and** Alkaline Phosphatase > 2x ULN	Hold neratinib and contact the PI to discuss next steps, including evaluation for other causes and management of investigational product. This must be reported as an SAE.

** **See Dose Reduction Table below***
ǂ For patients who have known metastatic liver disease and previously documented ALT/AST elevations from disease, providers should use discretion when ALT/AST elevations persist with neratinib. If liver laboratory abnormalities worsen while on therapy, dose modifications or cessation of therapy should be considered, as above. If there are any questions on how to adjust dosing, please contact the PI.

7.1.7 Asymptomatic decrease in left ventricular ejection fraction (LVEF) percentage points from baseline* [Note: depressed EF has typically not been observed in previous neratinib studies]—this table should guide reductions for Cohorts 1 and 2 ONLY

For dose adjustments for participants on Cohort 3, please see separate table in 6.3.2)

Relationship of LVEF to radiology facility's lower limit of normal (LLN)	Decrease of <10 percentage points	Decrease of 10 to 15 percentage points	Decrease of ≥ 16 percentage points
Within normal limits	Continue therapy	Continue therapy	Continue therapy and repeat MUGA after 4 weeks
1-5 percentage points below LLN	Continue and repeat MUGA after 4 weeks	Hold and repeat MUGA after 4 weeks	Hold and repeat MUGA after 4 weeks
≥ 6 percentage points below the LLN	Continue and repeat MUGA after 4 weeks	Hold and repeat MUGA after 4 weeks	Hold and repeat MUGA after 4 weeks

If no recovery after 4 weeks of holding drug, patients will come off study unless in the opinion of the Principal Investigator and Puma Biotechnology, Inc., there is reason to believe that the patient is still experiencing clinical benefit.

Patients will stop receiving neratinib and be removed from study for the following reasons: grade 3 cardiac toxicity (symptomatic congestive heart failure) or LVEF < 40%

Note: Cardiac assessments will be billed to the patient's insurance company.

7.1.8 *Dose Reduction Table for Cohorts 1 and 2 ONLY

Dose Reduction	Neratinib dosing	Number of 40 mg tablets	Number of 240 mg tablets (if available)
Starting Dose	240 mg once daily	6	1
First dose reduction (-1)	200 mg once daily	5	n/a
Second dose reduction (-2)	160 mg once daily	4	n/a
Third dose reduction (-3)	120 mg once daily	3	n/a

7.1.9 Supportive Care Recommendations for Cohorts 1 and 2 ONLY

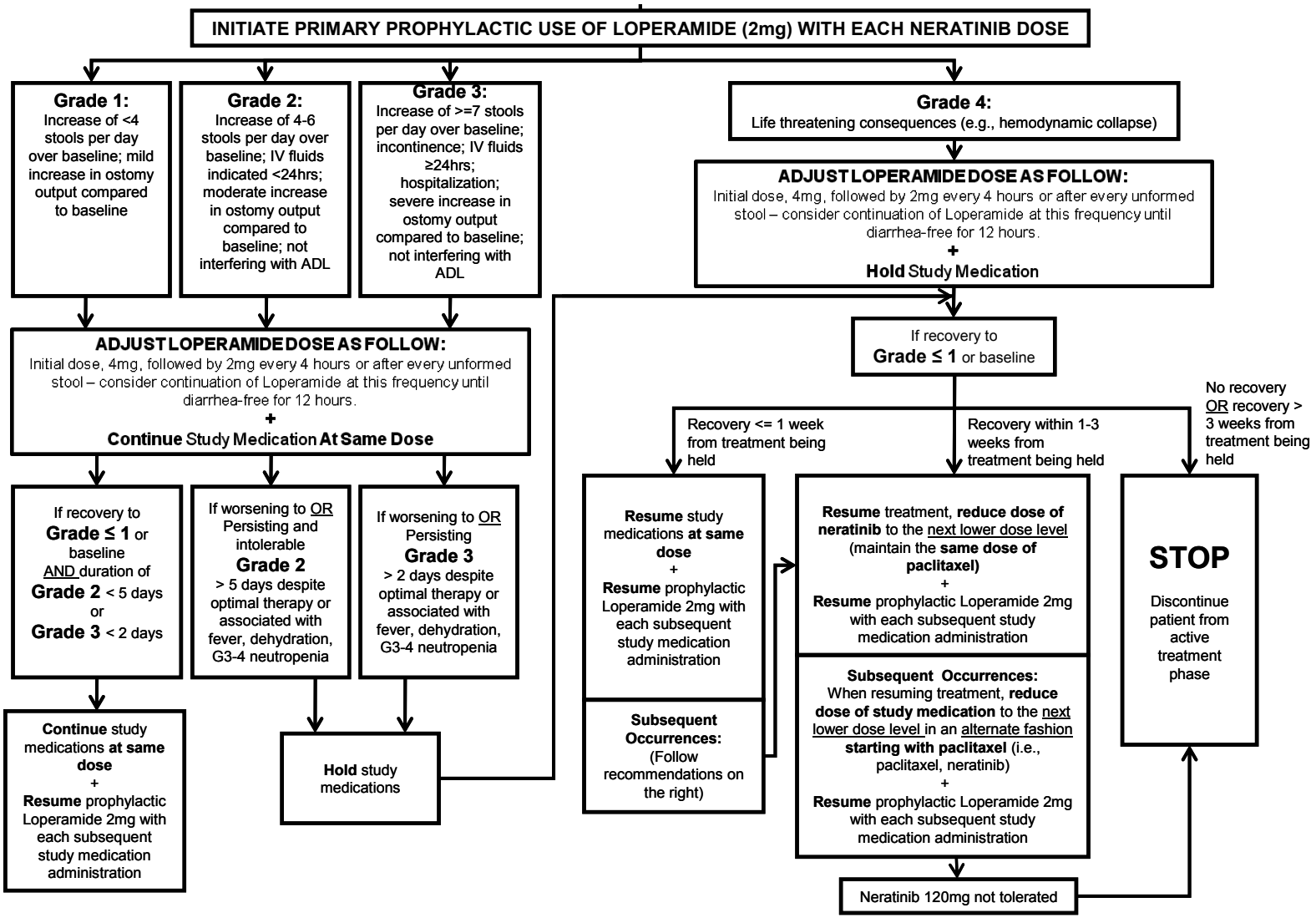
- **Diarrhea**: Previously observed diarrhea is usually not severe and is responsive to therapies such as loperamide. This diarrhea usually occurs within a few days to one week of therapy and often improves over the next few weeks. Diarrhea should be treated with prophylaxis and aggressively at the very first occurrence. Patients should have ready access to anti-diarrheal agents at home, starting on day 1 of treatment. Patients should be strongly encouraged to report any diarrhea to their participating site. In addition, all patients will receive a phone call from a member of the research staff at their participating center between days 3-6 (cycle 1) on therapy to ensure that diarrhea is under control. If diarrhea occurs, centers may consider asking patients to document a diary of their diarrhea episodes. Of note, an optional diary sheet for diarrhea episodes and management is provided in

Appendix M and may be used as appropriate and as desired by each treating provider/center.

For uncomplicated grade 1-2 diarrhea, dietary and pharmacologic treatments can begin. Patients should do the following: (1) avoid lactose-containing foods, (2) drink 8-10 glasses of clear liquid per day, (3) eat small and frequent meals, and (4) eat a low-fat diet with inclusion of rice, bananas, applesauce, etc. For pharmacologic intervention, patients should take loperamide 4 mg orally at the first onset of diarrhea. This can be repeated with 2 mg every 2-4 hours until resolution of diarrhea (diarrhea-free for 12 hours; *maximum dose of loperamide per day is 16 mg*). Providers may also instruct patients to follow previously described guidelines for treatment of diarrhea.[77] Other agents such as lomotil may be administered as well. For grade 3 or 4 diarrhea or diarrhea of any grade with dehydration, fevers, bleeding, neutropenia, providers should exclude infectious cases and should consider stool cultures.

For grade 3 or 4 or any grade with complicating features (dehydration, fever, and/or grade 3-4 neutropenia), infectious causes of diarrhea should be excluded and documented as appropriate. Stool cultures may be performed as a way of excluding infectious causes of diarrhea per the investigator's discretion. Results from the stool cultures should be documented on the CRF as applicable. The same dietary measures mentioned above should be advised. For pharmacological treatment, the standard dose of loperamide should be recommended, as above. In addition to loperamide and lomotil, providers may consider administration of octreotide (SANDOSTATIN®) [100–150 μg SC BID or IV (25–50 μg/h) if dehydration is severe, with dose escalation up to 500 μg TID] with use of intravenous fluids as appropriate. Providers may consider prophylactic antibiotics as needed (e.g., fluoroquinolones), especially if diarrhea is persistent beyond 24 h or there is fever or grade 3–4 neutropenia.

Figure. Summary of algorithm for diarrhea management in **Cohorts 1 and 2 as described above**



- **Rash**: Skin rashes should be treated in a similar fashion to rashes observed in patients receiving other erbB inhibitors and standard acne therapies can be prescribed, including topical and oral antibiotic therapies (minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone [short course]).
- **Nausea**: Routine premedication for nausea is not necessary. Patients who report nausea should be treated with standard anti-nausea/antiemetic therapy. If the patient vomits after taking the tablets, patients should not retake doses.
- **Myelosuppression**: Myelosuppression is an uncommon toxicity but has been reported in patients who receive neratinib. Growth factor support with pegfilgrastim or filgrastim is allowed for patients on study, if required. Per provider discretion, erythropoiesis-stimulating agents are also allowed on study but should be avoided unless provider deems this necessary.

7.1.10 Other Special Considerations

- For toxicities which are considered by the treating investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption.
- The treating investigator may reduce a subject's dose for a toxicity of any grade/duration where s/he believes it to be in the best interests of the subject.
- Any consideration to modification of the above dose modification guidelines should be discussed with the Protocol Chair for approval or disapproval in advance.

7.2 Anticipated Toxicities and Management for Trastuzumab (all cohorts except Cohorts 4A-4C, **extension phase only**)

7.2.1 There is no dose modification for trastuzumab.

Patients will continue to receive the dose of 2 mg/kg weekly or 6 mg/kg every 3 weeks, as long as they remain on study.

Patients will stop receiving trastuzumab and be removed from protocol for the following reasons:

- Grade 3 cardiac toxicity (symptomatic congestive heart failure)
- Ejection fraction less than 40%

7.2.2 Criteria for Evaluating Cardiac and Respiratory Events (for those receiving trastuzumab on extension phase of Cohorts 1-3)

<u>Cardiac Failure/Dysfunction</u>:

Reports of trastuzumab-related cardiotoxicity during pivotal trials of data collected from 7 phase II and III clinical trials for trastuzumab in patients with metastatic breast cancer are available. The analysis was performed by an independent Cardiac Review and Evaluation Committee. The severity of these events was categorized using the New York Heart Association function classification system. The incidence of class III or IV cardiac dysfunction was 2% for those receiving first-line trastuzumab, 4% for those receiving trastuzumab in the refractory setting, 2% for those receiving concurrent paclitaxel plus trastuzumab, 1% for those receiving paclitaxel alone, 16% for those receiving concurrent AC and trastuzumab, and 4% for those receiving AC alone. The incidence and severity of cardiac dysfunction was greatest among patients receiving concurrent AC and trastuzumab. The risk of cardiotoxicity was lower in those receiving concurrent paclitaxel and trastuzumab or paclitaxel alone, despite that most of these patients had prior anthracyclines. There is no known increased risk for cardiotoxicity when neratinib and trastuzumab are administered in combination.

Only subjects with a left ventricular ejection fraction (LVEF) ≥ 50% will be eligible for this study. An echocardiogram or MUGA/RVG should be performed every 12 weeks to assess the cardiac ejection fraction while receiving neratinib and trastuzumab. Any clinically significant cardiac adverse event should be treated according to current medical practice. Subjects with an NCI CTCAE Grade 3 or 4 left ventricular systolic dysfunction or interstitial pneumonitis must be withdrawn from study treatment but will still be followed for outcomes.

Treatment is based on measured ejection fraction as it relates to the radiology facility's lower limit of normal (LLN) and change in ejection fraction from baseline. Guidelines for performing MUGA scan and management of patients who have an asymptomatic decrease in LVEF from baseline are in the table below:

Asymptomatic decrease in LVEF percentage points from baseline			
Relationship of LVEF to the radiology facility's LLN	**Decrease of <10 percentage points**	**Decrease of 10 to 15 percentage points**	**Decrease of ≥ 16 percentage points**
Within normal limits	Continue	Continue	Hold treatments and repeat MUGA/Echo after 4 weeks
1 to 5 percentage points below LLN	Continue and repeat MUGA/echo after 4 weeks	Hold treatments and repeat MUGA/echo after 4 weeks	Hold treatments and repeat MUGA/Echo after 4 weeks
≥ 6 percentage points below the LLN	Continue and repeat MUGA/echo after 4 weeks	Hold treatments and repeat MUGA/echo after 4 weeks	Hold treatments and repeat MUGA/Echo after 4 weeks

- If a treatment "hold" is specified, both agents should be held until specified above
- If the subject is restarted on therapy, other therapies should be restarted at previous doses

- Neratinib and trastuzumab therapy must be permanently discontinued when two consecutive "hold" categories occur
- Cardiac assessments will be billed to the patient and/or her/his insurance company, as routine cardiac monitoring for patients receiving trastuzumab is considered standard practice.

Interstitial pneumonitis has been reported in rare patients to date in studies receiving trastuzumab. Patients with signs/symptoms that are suggestive of interstitial pneumonitis should stop trastuzumab pending investigation, diagnosis, and treatment. Patients with a confirmed diagnosis of grade 3 or 4 interstitial pneumonitis thought to be related to trastuzumab or neratinib, in the treating physician's opinion, must be withdrawn from the study.

7.2.3 Management of Acute Infusion Syndrome (for trastuzumab extension cohorts)

Infusion Reactions:
During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). Trastuzumab discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent trastuzumab infusion. These symptoms can be treated with an analgesic/antipyretic such as meperidine, or an antihistamine such as diphenhydramine.

Serious adverse reactions to trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress have been reported infrequently. In rare cases, these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids, and withdrawal of trastuzumab as indicated.

If patients develop an infusion reaction, patients should be treated according to the following guidelines, or according to institutional guidelines, according to the discretion of the study physician:

- Stop trastuzumab infusion and notify physician.
- Assess vital signs.
- Administer acetaminophen 650 mg PO.

- Consider administration of: meperidine (Demerol) 50 mg IM, diphenhydramine 50 mg IV, Ranitidine 50 mg IV or cimetidine 300 mg IV, and dexamethasone 10 mg IV
- **Or** famotidine 20 mg IV.
- If vital signs stable, resume trastuzumab infusion.
- Patients tend not to develop infusion syndromes with subsequent cycles. No standard premedication is required for future treatments if patients have developed an infusion syndrome. Patients may be given acetaminophen prior to treatments.

If grade 3 or 4 toxicity occurs during an infusion of trastuzumab, the infusion must be immediately stopped. The patient must be monitored for a minimum of 1 hour after the infusion is stopped. If an outpatient, the patient must be admitted to the hospital for monitoring if the toxicity does not resolve within 3 hours.

If a grade 3 or 4 toxicity occurs during the post-infusion observation period, the patient must be evaluated for a minimum of 1 hour from the time the toxicity was first noticed. If an outpatient, the patient must be admitted to the hospital for monitoring if the toxicity does not resolve within that hour.

7.2.4 Other Adverse Events and Potential Risks of trastuzumab:

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in the treatment group receiving trastuzumab and chemotherapy, especially in the trastuzumab and AC subgroup, compared with the treatment group receiving chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with trastuzumab.

Hematologic toxicity is infrequent following the administration of trastuzumab as a single agent, with an incidence of Grade III toxicities for WBC, platelets, and hemoglobin, all <1%. No Grade IV toxicities were observed.

Diarrhea: Of patients treated with trastuzumab as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving trastuzumab in combination with chemotherapy.

Please refer to the package insert for a comprehensive list of adverse events for trastuzumab.

7.3 Anticipated toxicities and management for capecitabine and neratinib for participants on **Cohorts 3A/3B***

7.3.1 Expected toxicities from FDA capecitabine prescribing information (Section 6.3.2 includes dose modification information):

- **Coagulopathy**: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. Patients taking coumarin derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR).
- **Diarrhea**: capecitabine can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. The median time to first occurrence of grade 2-4 diarrhea was 31 days (range from 1 to 322 days). For prophylaxis recommendations, dose reductions and guidance, please see below in dose modifications.
- Necrotizing enterocolitis (typhlitis) has been reported.
- **Geriatric Patients (gastrointestinal toxicity):** Patients =80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events. Among the 14 patients 80 years of age and greater treated with capecitabine, three (21.4%), three (21.4%) and one (7.1%) patients experienced reversible grade 3 or 4 diarrhea, nausea and vomiting, respectively. Among the 313 patients age 60 to 79 years old, the incidence of gastrointestinal toxicity was similar to that in the overall population.
- **Hand-and-Foot Syndrome**: Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) is characterized by the following: numbness, dysesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering and severe pain. For dose reductions, please see dose modification table below.
- **Cardiac**: There has been cardiotoxicity associated with fluorinated pyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease.
- **Hepatic Insufficiency**: Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when capecitabine is administered. The effect of severe hepatic dysfunction on the disposition of capecitabine is not known.
- **Hyperbilirubinemia**: Grade 3 or 4 hyperbilirubinemia occurred in 17% (n=97) of 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m2 daily for 2 weeks followed by a 1-week rest period. Of 339 patients who had hepatic metastases at baseline and 231 patients without hepatic metastases at baseline, grade 3 or

4 hyperbilirubinemia occurred in 21.2% and 10.4%, respectively. Seventy-four (76%) of the 97 patients with grade 3 or 4 hyperbilirubinemia also had concurrent elevations in alkaline phosphatase and/or hepatic transaminases; 6% of these were grade 3 or 4. Only 4 patients (4%) had elevated hepatic transaminases without a concurrent elevation in alkaline phosphatase. See dose modification table.

- **Hematologic**: In 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m2 administered daily for 2 weeks followed by a 1-week rest period, 4%, 2%, and 3% of patients had grade 3 or 4 neutropenia, thrombocytopenia and decreases in hemoglobin, respectively.
- **Carcinogenesis, Mutagenesis and Impairment of Fertility**: Long-term studies in animals to evaluate the carcinogenic potential of capecitabine have not been conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus test in vivo
- **Nausea and vomiting** has also been reported in patients taking capecitabine.
- **Stomatitis** has been reported in patients taking capecitabine
- **Pancreatitis** has been rarely reported for patients taking capecitabine and neratinib

Table. Toxicities with capecitabine monotherapy protocol. (from FDA brochure on capecitabine)

Table 16 Percent Incidence of Adverse Events Considered Remotel Possibly or Probably Related to Treatment in ≥5% of Patients Participating in the Single Arm Trial in Stage IV Breast Cancer

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
Body System/Adverse Event	Total %	Grade 3 %	Grade 4 %
GI			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal Pain	20	4	–
Constipation	15	1	–
Dyspepsia	8	–	–
Skin and Subcutaneous			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	–
Nail Disorder	7	–	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Pain in Limb	6	1	–
Neurological			
Paresthesia	21	1	–
Headache	9	1	–
Dizziness	8	–	–
Insomnia	8	–	–
Metabolism			
Anorexia	23	3	–
Dehydration	7	4	1
Eye			
Eye Irritation	15	–	–
Musculoskeletal			
Myalgia	9	–	–
Cardiac			
Edema	9	1	–
Blood			
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Anemia	72	3	1
Lymphopenia	94	44	15
Hepatobiliary			
Hyperbilirubinemia	22	9	2

– Not observed
NA = Not Applicable

7.3.2 Toxicity management for neratinib and capecitabine (use this section for all dose modifications and toxicity information for Cohorts 3A/3B and for those on Cohort 2 extension [capecitabine added to neratinib])

General Toxicities Requiring Dose Adjustment of Capecitabine [a] (When Administered in Combination with Neratinib)

****PLEASE REFERENCE THE TABLES BELOW FOR MANAGEMENT OF DIARRHEA, PULMONARY, HEMATOLOGIC, LIVER, PANCREATIC and LVEF TOXICITIES FOR COHORTS 3A AND 3B*****

****Note that if the treating providers feels strongly that the patient will benefit from starting one agent at a time for any therapy hold rather than together (to ensure good tolerance or to understand which drug is causing a specific toxicity), this is acceptable, but we ask study teams to contact the Overall PI / Study Chair, and start both drugs as close together as possible and at the suggested dose reductions. If it becomes *clear* that a toxicity is related to one agent and not another, providers have the ability to dose reduce the insulting agent ONLY. However, if providers are uncertain of which agent is causing the toxicity, please follow the dose modifications in the tables for both drugs. ****

Event [b]	Action
Grade 2 adverse reaction	
• 1st appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume both drugs at the starting dose level.
• 2nd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID).
• 3rd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).
• 4th appearance	• Discontinue **neratinib** and **capecitabine** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID).
• 2nd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).
• 3rd appearance	• Discontinue **neratinib** and **capecitabine** permanently.
Grade 4 adverse reaction	
• 1st appearance	• Discontinue **neratinib** and **capecitabine** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** and **capecitabine** until resolved to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).

[a] *Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose, per provider discretion on what will work best for each patient. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing, but all dosing adjustments should be documented in CRFs*

[b] Based on NCI CTCAE v.4.0.

Table. Gastrointestinal Toxicities Requiring Dose Adjustment of Neratinib & Capecitabine

****Note that if the treating providers feels strongly that the patient will benefit from starting one agent at a time for any therapy hold rather than together (to ensure good tolerance or to understand which drug is causing a specific toxicity), this is acceptable but we ask study teams to contact the Overall PI / Study Chair, and start both drugs as close together as possible and at the suggested dose reductions. If it becomes *clear* that a toxicity is related to one agent and not another, providers have the ability to dose reduce the insulting agent ONLY. However, if providers are uncertain of which agent is causing the toxicity, please follow the dose modifications in the tables for both drugs. ****

FOR COHORTS 3A AND 3B ONLY

Event [a]	Actions
Grade 1 Diarrhea: Increase of <4 stools per day over baseline; mild increase in output compared to baseline. OR **Grade 2 Diarrhea:** Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline. **Lasting <5 days**	• Adjust anti-diarrheal treatment per the guidelines for management of diarrhea at the first onset of diarrhea (refer to Section 6.3.3). • Continue **neratinib** and **capecitabine** at full doses. • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea (refer to Section 6.3.3). • Fluid intake of ~2 L/day should be maintained to avoid dehydration. • Once the event resolved to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration. • If provider feels a dose reduction is in the patient's best interest, please follow the dosing instructions for intolerable grade 2 diarrhea below. • If diarrhea is occurring because of noncompliance to prophylaxis or suboptimal prophylaxis, providers may adjust anti-diarrheal per guidelines (6.3.3) before dose reductions are made
Persisting and intolerable Grade 2 Diarrhea: lasting >5 days despite treatment with optimal medical therapy, or associated with fever, dehydration, or Grade 3-4 neutropenia. OR **Grade 3 Diarrhea:** despite treatment with optimal medical therapy, or associated with fever, dehydration, or Grade 3-4 neutropenia. OR **Any Grade 4 diarrhea:** Life-threatening consequences: urgent intervention indicated.	• Adjust anti-diarrheal treatment per the guidelines for management of diarrhea at the first onset of diarrhea (refer to Section 6.3.3). • Hold **neratinib** and **capecitabine** until recovery to Grade ≤1 or baseline. • Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea. • Fluid intake of ~2 L/day should be maintained by IV, if needed. • If recovery occurs: ○ ≤1 week after withholding treatment, resume same doses of **neratinib** and **capecitabine** unless provider feels strongly that a dose reduction is in the best interest of the patient. In that case, follow the reductions for 'recovery for within 1-3 weeks' in bullet below

Event [a]	Actions
	○ Within 1-3 weeks after withholding treatment, reduce **neratinib** dose to 160 mg and maintain the same dose of **capecitabine**. • If event occurs a second time and the **neratinib** dose has not already been decreased, reduce **neratinib** dose to 160 mg (maintain the same dose of **capecitabine**). If **neratinib** dose has already been reduced, then reduce the dose of **capecitabine** to 1100 mg/m^2 (550 mg/m^2 BID) [b] (maintain the same dose of **neratinib**). • If subsequent events occur, reduce the dose of **neratinib** or **capecitabine** to the next lower dose level in an alternate fashion (i.e., reduce **capecitabine** to 750 mg/m^2 (375 mg/m^2 BID) [b] if **neratinib** was previously reduced, or reduce **neratinib** to 120 mg if **capecitabine** was previously reduced). • Once the event resolved to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.

Abbreviations: L: liter.
[a] Based on NCI CTCAE v.4.0.
[b] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose, per provider discretion on what will work best for each patient. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing, but all dosing adjustments should be documented in CRFs.

Pulmonary Toxicity:

Guidelines for adjusting doses of **neratinib** in the event of pulmonary toxicities are shown below in the Table. Interstitial lung disease, which can sometimes be fatal, has been reported with other oral tyrosine kinase inhibitors that target HER1 ± HER2, including lapatinib, gefitinib and erlotinib. Rare cases of pneumonitis (0.6%) and lung infiltration (0.4%) have been reported in patients treated with **neratinib** monotherapy, and were considered drug-related.

- Patients receiving **neratinib** should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough and fever and treated appropriately.

Table. Pulmonary Toxicities Requiring Dose Adjustment of Neratinib

FOR COHORTS 3A AND 3B ONLY

Event [a]	Actions
Grade 2 Pneumonitis/Interstitial Lung Disease: Symptomatic; medical intervention indicated; limiting instrumental activities of daily living.	• Hold **neratinib** until recovery to Grade ≤1 or baseline. • Reduce **neratinib** to 160 mg or discontinue **neratinib** per Investigator's best medical judgment.
Grade ≥3 Pneumonitis/Interstitial Lung Disease: Severe symptoms; limiting self-care activities of daily living; oxygen indicated.	• Discontinue **neratinib** permanently.

[a] Based on NCI CTCAE v.4.0.

Hematologic Toxicity:

Patients with baseline neutrophil counts of <1.0 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not be treated with **capecitabine**. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 hematologic toxicity, treatment with **capecitabine** should be held.

Hematologic Abnormalities Requiring Dose Adjustment of Capecitabine (when administered in combination with Neratinib)
FOR COHORTS 3A AND 3B ONLY

Event (Based on NCI CTCAE v. 4.0)	Action
Grade 3: **Neutrophil:** <1000-500/mm^3 (<1-0.5 × 10^9/L), **Platelet:** <50,000-25,000/mm^3 (<50-25× 10^9/L) **Hemoglobin decreased**: <8-6.5 g/dL; <4.9-4 mmol/L; <80-65 g/L; transfusion indicated	• Neratinib should be continued at the same dose. • Hold capecitabine until event resolves or decreases to Grade 1 or Grade 2 • Reduce next capecitabine dose to 1110 mg/m^2 (550 mg/m^2 BID). • If the event recurs a 2nd time, hold **capecitabine** until event resolves or decreases to Grade 1 or Grade 2 • Reduce next **capecitabine** dose to 750 mg/m^2 (375 mg/m^2 BID) • If the event recurs/persists, discontinue **capecitabine** permanently.
Grade 4 **Neutrophil:** <500/mm^3 (<0.5 × 10^9/L), **Platelet:** <25,000/mm^3 (<25 × 10^9/L) **Hemoglobin decreased**: Life-threatening consequences; urgent intervention indicated	• Neratinib should be continued at the same dose. • Capecitabine should be discontinued permanently OR if the Investigator's deems it to be in the patient's best interest to continue, hold capecitabine until resolved to Grade ≤1 • If the Investigator's decides to resume capecitabine reduce the dose to 750 mg/m^2 (375 mg/m^2 BID)

Abbreviations: NCI CTCAE v. 4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Liver-Toxicity:
Guidelines for adjustment of **neratinib** and **capecitabine** in the event of liver toxicity are shown in below in the table. Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events. Patients who experience Grade ≥3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia should be evaluated for changes in liver function tests. Fractionated bilirubin and PT must also be collected during hepatotoxicity evaluation.

Table. Liver Function Test Abnormalities Requiring Dose Adjustment of Neratinib and Capecitabine **Note that if the treating providers feels strongly that the patient will benefit from starting one agent at a time for any therapy hold rather than together to ensure good tolerance or to understand which drug is causing a specific toxicity), this is acceptable but we ask study teams to contact the Overall PI / Study

Chair, and start both drugs as close together as possible and at the suggested dose reductions. If it becomes *clear* that a toxicity is related to one agent and not another, providers have the ability to dose reduce the insulting agent ONLY. However, if providers are uncertain of which agent is causing the toxicity, please follow the dose modifications in the tables for both drugs. **

FOR COHORTS 3A AND 3B ONLY

Event [a]	Actions
Grade 3 ALT (>5-20 x ULN) or Grade 3 bilirubin (>3-10 x ULN)	• Hold **neratinib** and **capecitabine** until recovery to Grade ≤1 for patients with ALT Grade ≤1 at baseline OR Grade ≤2 for patients with Grade 2 ALT at baseline. • Evaluate alternative causes. • For patients with ALT Grade ≤1 at baseline: resume at a reduced doses of **neratinib** 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID) [b] if recovery to Grade ≤1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite the above-mentioned dose reduction, permanently discontinue **neratinib** and **capecitabine**.
Grade 4 ALT (>20 x ULN) or Grade 4 Bilirubin (>10 x ULN)	• Permanently discontinue **neratinib** and **capecitabine** • Evaluate alternative causes
ALT >3 x ULN and Total bilirubin >2 x ULN and Alkaline phospatase <2 x ULN (potential Hy's law indicators of drug-induced liver damage)	• Hold **neratinib** and **capecitabine**. The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, the possibility of hepatic neoplasm (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, total bilirubin, direct bilirubin, PT and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, concomitant medications, recreational drug and supplement consumption, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the criteria mentioned above (i.e., ALT >3 x ULN associated with bilirubin >2 x ULN and alkaline phosphatase <2 x ULN), with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases, irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Such potential Hy's Law cases should be reported as SAEs. • **Contact the Sponsor immediately** to discuss next steps, including evaluation of alternative causes, and management of investigational product. These events must be reported as SAEs.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; SAE: serious adverse event; ULN: upper limit of normal.
NOTE: During evaluation of hepatotoxicity, bilirubin must be fractionated, PT must be measured, and liver imaging should be considered.
[a] *Based on NCI CTCAE v.4.0.*
[b] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

Pancreatic toxicity: Given rarity of pancreatitis reports (with neratinib and capecitabine), pancreatic enzymes do not need to be checked routinely for patients on study. It is recommended to check them only if clinical suspicion for pancreatitis exists and there should be a low threshold to check amylase/lipase in the setting of pain, nausea, vomiting and other signs of pancreatitis.

Guidelines for adjustment of neratinib and capecitabine in the event of pancreatic toxicity are shown in below in the table.

FOR COHORTS 3A AND 3B ONLY

Event (Based on NCI CTCAE v. 4.0)	Action
Grade 2 Pancreatitis: Enzyme elevation or radiologic findings OR **Grade 3 Pancreatitis:** Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	• Temporarily suspend (i.e., hold **neratinib** and **capecitabine** • Evaluate for any possible alternative causes • If no alternative cause for pancreatitis is identified, discontinue **neratinib** and **capecitabine** permanently. • If an alternative cause is identified, e.g., gallstones), or enzyme levels return to baseline within 3 weeks with clinical recovery, restart treatment with reduced doses of **neratinib** 160 mg and **capecitabine** 1100 mg/m^2 (550 mg/m^2 BID). • If event occurs a second time, discontinue **neratinib** and **capecitabine** permanently.
Grade 4 Pancreatitis: Life-threatening consequences; urgent intervention indicated	• Discontinue **neratinib** and **capecitabine** permanently.

NOTE: During enzyme evaluation for pancreatitis, amylase should be fractionated if possible (P-amylase, S-amylase).

Left Ventricular Ejection Fraction Toxicity (Cohorts 3A/3B):

Guidelines for adjustment of **neratinib** in the event of abnormalities in LVEF are shown below in the table. LVEF assessments will be performed according to the Schedule of Procedures in the study calendars in Section 11. It is strongly recommended to use the same method of cardiac evaluation (ECHO or MUGA) at each time point for each patient.

Table. Left Ventricular Ejection Fraction (LVEF) Results Requiring Dose Adjustment of Neratinib (Cohorts 3A/3B)

Event	Actions
Asymptomatic absolute decline of LVEF ≥15% from baseline OR absolute decline of LVEF ≥10% and below the lower limit of normal of 50%	A) If LVEF is below 40%: Hold **neratinib** and seek cardiology input OR continue **neratinib** with great caution. Initiate monthly monitoring of LVEF • If while monitoring monthly, LVEF remains <40%: reconsider **neratinib** only if appropriate and after cardiology consult. • If while monitoring monthly, LVEF increases to ≥40%: continue **neratinib**, monitor LVEF every 12 weeks and consider cardiac support with input from cardiologist. B) If LVEF is between 40% to 50%: continue **neratinib** with caution and surveillance. Initiate monthly monitoring of LVEF • If while monitoring monthly, LVEF falls to <40%: Follow bullet point A instructions described above. • If while monitoring monthly, LVEF remains ≥40%: continue **neratinib**, monitor LVEF every 12 weeks and consider cardiac support with input from cardiology.
Symptomatic cardiac failure	• **Neratinib** should be discontinued.

Abbreviations: LVEF: left ventricular ejection fraction.

If a patient has a second episode of asymptomatic decline in LVEF that meets either of the above criteria, permanently discontinue **neratinib**, repeat LVEF in 3-4 weeks and consider cardiology consult.

Note that, for AEs other than asymptomatic LVEF decline, if **neratinib** is held for >3 weeks, the patient should be withdrawn from treatment. In case of asymptomatic LVEF decline, patients may resume **neratinib** within 1 week after LVEF recovery is documented as above, even if the timeframe exceeds 3 weeks. If a site does not provide normal ranges for ECHO or MUGA, a LLN of 50% should be used.

7.4 Toxicity Management for Patients on Cohorts 4A-4C

*****COHORTS 4A-4C: TOXICITIES AND DOSE ADJUSTMENT FOR PATIENTS RECEIVING T-DM1 AND NERATINIB.*****

*****If providers are certain that a toxicity is related to one drug over another, contact the Protocol Chair if you wish to adjust the dose medication recommendations below******

7.4.1 For Cohorts 4A-4C ONLY: T-DM1 infusion reaction management

CTCAE v4.0 Adverse event	CTCAE c4.0 grade	Action to be taken	
		T-DM1	Neratinib
Immune System disorders			

Allergic reaction/infusion reaction to T-DM1 **for all infusion reactions, they should be treated per provider preferences and/or institutional guidelines for hypersensitivity with regard to use of steroids, diphenhydramine, etc.** See directly below for additional details on management.	Grade 1	Maintain dose, slow infusion, discretion of provider for treatment	Can continue therapy
	Grade 2	Decrease infusion rate by 50% or interrupt	Can continue therapy
	Grade 3	Hold until grade 1 or less: decrease infusion rate 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue	Can continue therapy
	Grade 4	Discontinue	Can continue therapy

****Infusion reactions/allergic reaction -** T-DM-1. Infusion reactions may occur with T-DM1, similar to those seen with trastuzumab. Rashes can also occur with neratinib. Management of reactions should be as follows (see table below for instructions as well):

• Grade 1 infusion reaction to T-DM1:
− Slow the infusion and assess the patient; management is at the investigator's discretion.

•Grade 2 infusion reaction to T-DM1:
− Decrease the infusion rate by 50% (or interrupt) and monitor closely for worsening condition.
− Administer appropriate therapy per investigator's discretion.
− Restart at **50%** infusion rate, may increase rate by 50% increments every 30 minutes as tolerated.
− When symptoms resolve to ≤ grade 1, infusion may be resumed later that day or on the next day with premedications.
− Premedications are recommended for all subsequent treatments.
− Infusions may be restarted at full rate at the next cycle with appropriate monitoring for all subsequent treatments.

• Grade 3 infusion reaction to T-DM1:
− If determined by the investigator to be **non-serious**, follow the instructions for grade 2 infusion reaction
− If determined by the investigator to be **serious**, immediately and permanently discontinue T-DM1.

7.4.2 For Cohorts 4A-4C Only: Myelosuppression, Cardiac, Pulmonary, and Diarrhea Management (FOR T-DM1 AND NERATINIB)

CTCAE v4.0 Adverse event	CTCAE v4.0 grade	Action to be taken	
		T-DM1	Neratinib
Blood and lymphatic system disorders			
Febrile neutropenia	Grade 3	Hold until ≤grade 1 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue	Hold until ≤grade 1 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue
	Grade 4	Hold until ≤grade 1 1st appearance: decrease one dose level or discontinue 2nd appearance: discontinue	Hold until clinically stable 1st appearance: decrease one dose level 2nd appearance: discontinue
Neutrophil count decreased	Grade 3	Hold until >/= 1000 mm3 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue	Hold until >/= 1000 mm3 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue
	Grade 4	Discontinue	Discontinue
Platelet count decreased	Grade 2,3	Hold until >/= 75,000/mm3 Hold until neratinib can be resumed, then maintain dose 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue	If felt to be related to T-DM1 alone, provider may continue dosing without change in neratinib dosing for all grades of platelet toxicity. If toxicity felt to be related to neratinib or if uncertain if related: Hold until >/= 75,000/mm3 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease dose level 4th appearance: discontinue
	Grade 4	Discontinue	Discontinue unless provider feels strongly that toxicity is related to T-DM1. In that case,
Cardiac Disorders (see additional text below)		**T-DM1**	**Neratinib**

CTCAE v4.0 Adverse event	CTCAE v4.0 grade	Action to be taken	
		T-DM1	Neratinib
Acute coronary syndrome Myocardial infarction	Grade 2	Hold both agents and conduct a cardiac evaluation. Based on this, continuation of study therapy is at the investigator's discretion	
	Grade 3, 4	Discontinue both agents	
Conduction disorder Supraventricular tachycardia and nodal arrhythmia Ventricular arrhythmia	Grade 2	Hold both agents until rhythm controlled; then resume and maintain doses	
	Grade 3, 4	Discontinue therapy of both agents	
LVEF assessments for asymptomatic patients	≥ 50%	Continue therapy with both agents	
	45–49%	Continue therapy and repeat echo/MUGA in 3 weeks	
	≤ 44%	Discontinue study therapy with both agents	
Pulmonary disorders			
Dyspnea	Grade 2	Hold both agents until </= grade 1 and CHF and interstitial pneumonitis have been ruled out. If caused by CHF or interstitial pulmonary toxicity, discontinue protocol therapy If caused by infection or asthmatic process, resume therapy when symptoms have resolved to </= grade 1.	
	Grade 3,4	Discontinue	
Pneumonitis/pulmonary infiltrates/other pulmonary events Hypoxia Pneumonitis Pulmonary fibrosis	Grade 2	Hold all study treatment until pneumonitis is evaluated. If infection is documented, treatment may be resumed when pulmonary AEs have resolved to </= grade 1 If non-infectious interstitial lung disease is confirmed, study treatment must be discontinued	
Gastrointestinal disorders- Diarrhea		**T-DM1**	**Neratinib**
Diarrhea (attributed to therapy; see mediation management below the table, Section 6.4.4)	Grade 1	Maintain dose without delay; adjust anti-diarrhea medications	
	Grade 2 and lasting more than 24 hours	Hold T-DM1 until neratinib can be resumed, then maintain dose. If neratinib cannot be re-initiated and is discontinued, can continue T-DM1	Hold until ≤grade 1; adjust anti-diarrhea medication; 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue
	Grade 3	Hold T-DM1 until neratinib can be resumed, then maintain dose. If neratinib cannot be re-initiated and is discontinued, can continue T-DM1	Hold until ≤grade 1; adjust anti-diarrhea medication; 1 appearance: decrease one dose level 2nd appearance: decrease one dose level

CTCAE v4.0 Adverse event	CTCAE v4.0 grade	Action to be taken	
		T-DM1	Neratinib
			3rd appearance: discontinue
	Grade 4	Can continue T-DM1 if felt to be related to neratinib; if uncertain if related to T-DM1, then dose reduce at the treating provider's discretion	Discontinue

FOR COHORTS 4A-4C ONLY

7.4.3 Cardiac left ventricular dysfunction

Symptomatic decrease in LVEF

• *Congestive heart failure (grade 3):*

Patients should be monitored for signs and symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema). If the patient develops any of these signs and symptoms, T-DM1 and neratinib must be held.

The investigator must confirm the diagnosis of CHF with either an echocardiogram or a MUGA scan. Once the diagnosis of CHF is confirmed, study therapy must be discontinued. Further therapy is at the investigator's discretion.

• *Severe refractory/poorly controlled CHF (grade 4):*

Discontinue study therapy.

Asymptomatic decrease in LVEF

Reminder: Study therapy must be discontinued for patients who have a symptomatic decrease in LVEF

• For asymptomatic patients, the decision to continue or stop study therapy is based on the value of the measured ejection fraction.

7.4.4 Diarrhea

Diarrhea is a commonly occurring toxicity with T-DM1 and neratinib combination therapy. Monotherapy with neratinib has a median time of 3 days to onset of diarrhea. With combination therapy, it is anticipated that diarrhea may occur earlier. For the majority of patients, diarrhea subsides after about first cycle. **Therefore, it is critical that prophylactic medications begin at the start of therapy and continue during C1.** Primary antidiarrheal prophylactic medication must begin with the first dose of neratinib. Patients must be instructed to have ready access to antidiarrheal agents (loperamide and colestipol) at home, starting on Day 1 of treatment as described below. Patients must also

be instructed regarding the importance of prompt reporting of diarrhea, use of antidiarrheal medications and non-pharmacologic interventions. Patients who have multiple loose bowel movements in a day or any worsening of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, or eosinophilia should be promptly evaluated for changes in liver function as appropriate. A diary describing patient-reported adherence to the mandatory colestipol and loperamide during cycle 1 and diarrhea experienced during cycle 1 will be collected on C2 D1 (Appendix Za). In addition, to understand the extent of diarrhea and use of diarrhea medications during subsequent cycles, patients will keep diaries documenting diarrhea and use of anti-diarrheal medications during cycle 2 and 3. These diaries will be collected on day 1 of cycle 3 and day 1 of cycle 4 respectively (Appendix Zb). These diaries will also include questions about missed doses of neratinib due to diarrhea (Appendices Za and Zb) and about skipped doses of anti-diarrheal medication due to constipation or due to other side effects (Appendix Za).

Management of Diarrhea and Dose Adjustment of Neratinib and T-DM1:

For new onset, uncomplicated Grade 1 or Grade 2 diarrhea

Dietetic measures

- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day.
- Eat frequent small meals.
- Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhea.

Pharmacological Treatment

- For patients not already taking loperamide, administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours.
- For patients with persistent Grade 1 diarrhea on loperamide, Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by the Sponsor).
- For Grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy), consider adding octreotide (short-acting) 150 µg SC three times daily (TID); or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscular (IM)

- Can also consider budesonide treatment (9 mg once daily) as per the discretion of the treating provider.

For Grade 3 or Grade 4 diarrhea with complicating features (dehydration, fever, and/or Grade 3-4 neutropenia)

Dietetic measures (same as above)

Pharmacological treatment

- For patients not already taking loperamide, administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day).
- For patients with persistent diarrhea on loperamide, Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by the Sponsor).
- Can also administer octreotide (100-150 µg SC BID or intravenously (IV) (25-50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID).
- Use IV fluids as appropriate.
- Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia.
- Can also consider budesonide treatment (9 mg once daily) as per the discretion of the treating provider.

Stool cultures should be done to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or 4 neutropenia) per the Investigator's discretion. Results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella,* and *Shigella* testing, when performed, should be reported using the appropriate CRF.

Patients with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction.

Other GI TOXICITY MANGEMENT FOR COHORTS 4A-4C ONLY

CTCAE v4.0 Adverse event	CTCAE v4.0 grade	Action to be taken	
		T-DM1	Neratinib
Gastrointestinal disorders			
Mucositis	Grade 2	Hold T-DM1 until neratinib can be resumed, 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue	Hold until grade 1 or less 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue
	Grade 3,4	Discontinue both agents	
Vomiting (despite anti-emetics	Grade 2	Hold T-DM1 until grade 1 or less 1st appearance: decrease one dose level 2nd appearance: decrease one dose level or discontinue 3rd appearance: discontinue	Hold until grade 1 or less 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue
	Grade 3,4	Discontinue both agents unless the provider feels strongly it is related to one agent over the other. In that case, can continue the non-offending agent unless symptom re-appears; then follow algorithm	
Hepatobiliary disorders	For any signs of liver disfunction > grade 2 AST/ALT or grade 2 or more bilirubin elevation felt to be non-disease related, discontinue study therapy and consider patient evaluation by a hepatologist. If there any signs of portal hypertension (e.g. ascites or varices) and cirrhosis-like pattern on CT scan of the liver, the possibility of Nodular Regenerative Hyperplasia (NRH) should be considered. See below "Investigations": ALT/SGTP, AST/SGOT, and bilirubin		
ALT increased (or AST) or bilirubin increased	Grade 2	Hold T-DM1until </= grade 1 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue	Hold until </= grade 1 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue
	Grade 3	Hold neratinib and T-DM1 until recovery to ≤ Grade 1. Evaluate alternative causes. Resume neratinib and T-DM1 at the next lower dose level if recovery to ≤ Grade 1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue both agents.	
	Grade 4	Permanently discontinue study therapy evaluate alternative causes Per CTCAE v4.0	

7.4.5 Liver dysfunction (Hy's Law)

Hy's Law is based on the observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. A diagnosis of potential drug-induced liver injury caused by a study drug can only be determined/inferred by excluding other potential causes of liver injury (e.g., other drugs or viral hepatitis) and by ruling out an obstructive cause for the elevated bilirubin (e.g., alkaline phosphatase should not be substantially elevated) (FDA 2009; Temple 2006).

Definition of cases potentially meeting Hy's Law criteria

Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

• *Patients with AST or ALT baseline values within the normal range* who subsequently present with AST or ALT ≥ 3 times the ULN concurrent with a total bilirubin ≥ 2 times the ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the ULN or not available.

• *Patients with pre-existing AST or ALT baseline values above the normal range* who subsequently present with AST or ALT ≥ 2 times the baseline values and ≥ 3 times the ULN, or ≥ 8 times the ULN (whichever is smaller) concurrent with a total bilirubin of ≥ 2 times the ULN and increased by one ULN over baseline or > 3 times the ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the ULN or not available.

Evaluation of potential Hy's Law cases

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. The possibility of progressive disease should be considered.

Potential Hy's Law cases should be reported as serious adverse events

FOR COHORTS 4A-4C ONLY

Skin and subcutaneous tissue disorders		T-DM1	Neratinib
Rash acneiform	Grade 2	Hold until grade 1 or less, then resume: 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue	1st appearance: hold until improvement then: maintain dose 2nd appearance: If recurrent or intolerable, hold until improving and decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue

Skin and subcutaneous tissue disorders		T-DM1	Neratinib
	Grade 3	Hold until grade 1 or less, then resume: 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue	Hold until grade 1 or less 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue
	Grade 4	Discontinue both agents	
Paronychia. See figure below	Grade 2	Hold until grade 1 or less, then resume: 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level 4th appearance: discontinue	1st appearance: continue without delay or hold until improvement and maintain dose 2nd appearance: if recurrent or intolerable, hold until improving and decrease one dose level 3rd appearance: maintain dose or decrease one dose level or discontinue if intolerable
	Grade 3	Hold until grade 1 or less, then resume: 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue	Hold until grade 2 or less 1st appearance: maintain dose 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level or discontinue, per provider discretion
	Grade 4	Discontinue both agents	

FOR COHORTS 4A-4C ONLY

7.4.6 Management of dermatologic toxicities

Management of paronychia and fissures in fingertips

Paronychia and fissures involving the fingertips have not been determined to be an effect of neratinib, but are an effect of similar drugs. Therefore, the following management instructions are provided:

- *Paronychia*

For treatment of paronychia, antiseptic bathes and topical corticosteroids are recommended. Other topical measures include use of silver nitrate applications. Topical or oral antibiotics should be considered if local infection is present. If no improvement is seen, a dermatology consultation is recommended. See Table above for dose modifications and delays for paronychia. (See Figure below)

- *Fissures in fingertips*

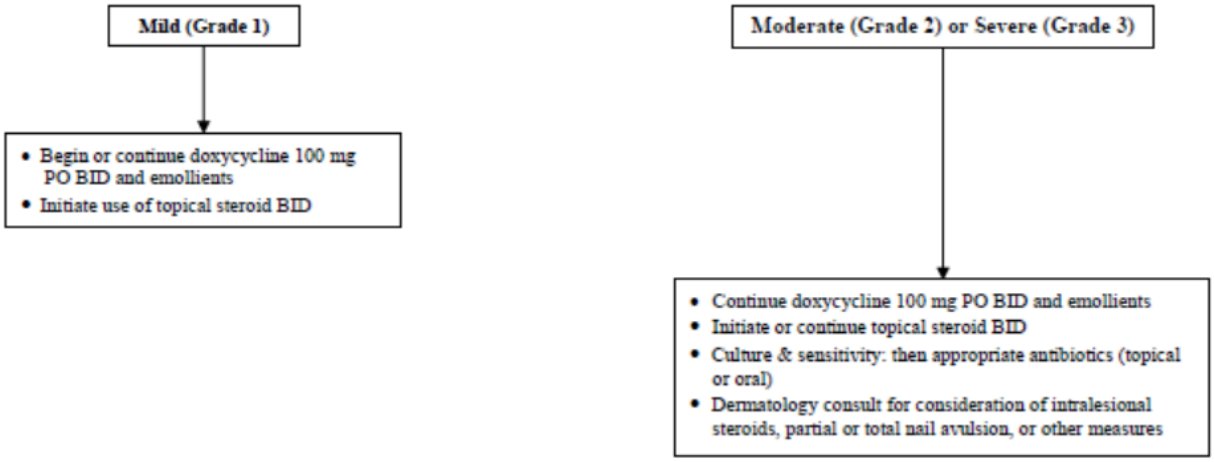
For fissures in the fingertips, an application of zinc oxide 30% (or higher) ointment may be used.

Management of rash acneiform

Rash is described in around 18% of patients treated with neratinib and 12% in patients treated with T-DM1. However, in FB-10 phase I trial, it was not described as a major adverse event. See table below for management and dose modifications for neratinib and T-DM1.

MANAGEMENT OF PARONYCHIA

Figure 3. Management of paronychia
NOTE: See Section 10.8.2 and Table 8 for neratinib dose modification instructions



Notes:
1. Dermatology consultation at the investigator's discretion unless noted otherwise.
2. Emollients (alcohol-free): Eucerin®, Cetaphil®, Aquaphor®, CeraVe®,or other similar product
3. Topical steroid: Hydrocortisone 2.5% cream or alclomethasone 0.05% cream.
4. Treatment with medication(s) referenced should be based on evaluation of the patient and the recommended uses and associated risks with the medication(s) as outlined in the associated prescribing information. (Oiski 2008)

FOR COHORTS 4A-4C ONLY

Management of peripheral neuropathy and any other adverse event

Nervous system disorders			
		T-DM1	Neratinib
Peripheral neuropathy	Grade 3	Hold until grade 2 or less, then: 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue	Hold until grade 2 or less, then continue without delay unless provider feels dose reduction necessary and reduce one dose level
	Grade 4	Discontinue both agents	
Other toxicities attributable to therapy	Grade 2	Hold until </= grade 1 then:	Hold until </= grade 1 then:

Nervous system disorders			
		T-DM1	Neratinib
(investigator must determine attribution of AE and only follow dose modifications for the causal agent)		1st appearance: maintain dose or decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level or discontinue	1st appearance: maintain dose or decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: decrease one dose level or discontinue
	Grade 3	Hold until </= grade 1 then: 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue	Hold until </= grade 1 then: 1st appearance: decrease one dose level 2nd appearance: decrease one dose level 3rd appearance: discontinue
	Grade 4	Discontinue	Discontinue

7.5 Concomitant treatment for patients – Cohorts 3A/3B

At screening, patients will be asked what medications they have taken during the last 30 days, which medications are ongoing at the time of screening, any medical conditions that require medication, and all prior cancer therapies. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

7.5.1 Required Concomitant Treatment – COHORTS 3A AND 3B ONLY

Loperamide Antidiarrheal Therapy

Diarrhea is the major dose-limiting toxicity of neratinib with onset typically occurring early in the course of treatment (during the first few weeks of treatment). Primary prophylactic use of antidiarrheal medication is **mandatory** for all enrolled patients and the prophylaxis has evolved with each cohort. Loperamide is the recommended standard therapy to treat diarrhea in this study and colestipol has been added for cycle 1 for those on Cohorts 4A-4C. Second-line antidiarrheal treatments and adjunctive therapies (i.e., octreotide [SANDOSTATIN®]) (or equivalent as approved by the Sponsor) are also recommended for use when appropriate.

A research nurse or provider must review with the patient the patient instructions (Appendix Q) for the management of diarrhea and the diaries (Appendix R) for the patient's daily recording of investigational product dose, any adverse reactions, number of stools, and use of loperamide and/or other antidiarrheals. Copies of the Patient Instructions and Patient Diary are to be handed to the patient before leaving the site with investigational product on or before Cycle 1/Day 1, with clear instructions to contact the medical team in

the event of *de novo* onset or persistent Grade ≥2 diarrhea to discuss the appropriate course of treatment.

Documentation of any occurrences of stools or diarrhea must be as precise as possible and captured in the Patient Diary. For AE recording, documentation of "Intermittent" events of diarrhea is limited to Grade 1. If events of Grade 1 diarrhea are separated by 3 days without any diarrhea, then each event must be documented as separate AEs with corresponding start and stop dates.

The entries on the Patient Diary should be reviewed together with the patient for the first 2 cycles. If the patient has experienced diarrhea since the last visit, details of the daily number of stools provided on the diary help to grade the diarrhea as precisely as possible (per NCI CTCAE v.4.0). Also, the daily dose of loperamide (or other antidiarrheals, if applicable) noted on the diary will be reviewed and recorded on the CRF.

Loperamide will be dispensed directly by the site on or before Cycle 1/Day 1 with neratinib. Colestipol will also be required for those on Cohorts 4A-4C. It is very important to initiate diarrhea prophylaxis concomitantly with the first dose of neratinib to minimize occurrence and severity of diarrhea.

****Prophylactic dosing instructions** (FOR COHORTS 3A, 3B ONLY)**

- Inform patients that they are likely to experience diarrhea while taking neratinib.
- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first dose of neratinib, followed by 2 mg (1 tablet/capsule) every 4 hours for the first 3 days. After the first 3 days, take loperamide 2 mg every 6 to 8 hours for 1 cycle of therapy. For patients with persistent Grade 1 diarrhea (<4 stools per day above baseline) on loperamide, Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by Sponsor).
- For Grade 2 diarrhea during Cycle 1 (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneous [SC] injection 3 times a day, or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg by intramuscular injection (equivalent medication may be used with approval of the Sponsor).
- The sites must contact the patient by phone daily for 24-72 hours after the first dose of neratinib-capecitabine to inquire about any diarrhea.
- If a patient has no diarrhea and wishes to stop prophylactic loperamide prior to the completion of 1 cycle, this must be discussed with the provider/research nurse and documented clearly in the chart.

(These phone calls are mandatory and must be recorded in the study chart together with response from the patient and action taken.)

- Instruct patients to promptly report diarrhea symptoms.
- Instruct patient to record the number of stools per day (see Patient Diary, Appendix R) and the dose of anti-diarrheal medication taken each day for the first 2 cycles.

For new onset uncomplicated Grade 1 or Grade 2 diarrhea- COHORTS 3A AND 3B ONLY

Dietetic measures

- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day.
- Eat frequent small meals.
- Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhea.

Pharmacological Treatment

- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours.
- For patients with persistent Grade 1 diarrhea on loperamide, Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by the Sponsor).
- For Grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy), consider adding octreotide (short-acting) 150 µg SC three times daily (TID); or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscular (IM) (equivalent medication may be used with approval of the Sponsor).

For Grade 3 or Grade 4 diarrhea with complicating features (dehydration, fever, and/or Grade 3-4 neutropenia) – COHORTS 3A AND 3B ONLY

Dietetic measures (same as above)

Pharmacological treatment

- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day).

- Administer octreotide (100-150 µg SC BID or intravenously (IV) (25-50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID).
- Use IV fluids as appropriate.
- Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia.

Stool cultures should be done to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or 4 neutropenia) per the Investigator's discretion. Results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella,* and *Shigella* testing, when performed, should be reported using the appropriate CRF.

Patients with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction.

7.6 Diarrhea prophylaxis for patients receiving neratinib and T-DM1 ON COHORTS 4A-4C:

Intensive primary prophylaxis

Recent preclinical studies suggest that multiple mechanisms may be involved in the pathogenesis of neratinib-induced diarrhea, including elements of secretory and inflammatory diarrhea (Puma biotechnology, on file). Interim analysis of CONTROL study reported a Cohort of patients testing budesonide, a locally acting corticosteroid used for inflammatory gastrointestinal conditions, had reduced grade 3 diarrhea by approximately 50% (to 16%) (Barcenas 2016). Budesonide has a high first-pass metabolism with minimal systemic absorption. It is therefore felt to cause fewer side effects than traditional glucocorticosteroids and to be generally well tolerated (O'Donnell 2010). However, in an updated presentation of the CONTROL trial at the San Antonio Breast Cancer Symposium in Dec 2017, the regimen with the lowest diarrhea rates during cycle 1 was the Cohort assigned to colestipol and loperamide, with grade 3-4 diarrhea events occurring in 10.8% of patients compared with >25% in the other Cohorts (who were randomized to other prophylaxis regimens). Further, the cost of colestipol is significantly lower than budesonide with excellent tolerance and this agent will be provided free-of-charge to patients on study during cycle 1. Loperamide costs will also be covered for Cycle 1 only. Patients should be counseled to call if they have >2 episodes of diarrhea after starting therapy.

Antidiarrheal medications (Imodium and colestipol) must begin with the first dose of neratinib and should continue throughout the first cycle unless patients have trouble tolerating these medications. In that case, providers have discretion to make changes in these medications. Beyond C1, ongoing prophylaxis is discretionary per the treating provider.

**** NOTE: During Cycle 1: Patients should take colestipol 2 gm twice daily for 21 days, with the first dose taken at least 4 hours before neratinib and loperamide prophylaxis, and the second dose to be taken at least **2 hours after neratinib** and loperamide prophylaxis****

• **Loperamide (Imodium®)**

- Loperamide is an over-the-counter medication frequently used to stop diarrhea. It is widely available for this use and costs will be covered by Puma for the first cycle of therapy for loperamide. This agent will be administered by pharmacies along with a patient's neratinib (and colestipol as per below)
- Patients must receive an initial dose of loperamide 4 mg (2 tablets) with the first dose of neratinib.
- Following the initial dose of loperamide patients should take loperamide 4 mg (2 tablets) approximately every 8 hours for through day 14 of cycle 1 (12 mg/day).
- During days 15-21, patients should take loperamide 4 mg (2 tablets) approximately every 12 hours. Prophylaxis may then stop. If a patient experiences significant constipation and no diarrhea, adjustments in prophylaxis may be made on a case by case basis with the treating provider.
- Diaries will be provided to document adherence to this agent during cycle 1 as described above and in the study calendar (Appendix Za)
- Adherence to this agent during cycle 1 will also be assessed by ythe Voils Measure as described above and in the study calendar (Appendix Zc)
- Use of this agent beyond cycle 1 will be assessed via diaries as described above and in the study calendar (Appendix Zb)

- **Colestipol (colestid)**

- Colestipol is a medication used to lower cholesterol and decrease diarrhea. It is widely available for this use and costs will be covered by Puma for the first cycle of therapy only so that these agents will be dispensed by research pharmacies for cycle 1 along with a patient's neratinib.
- Patients should take colestipol 2 g BID for cycle 1, then stop
- Diaries will be provided to document adherence to this agent during cycle 1 as described above and in the study calendar (Appendix Za)
- Adherence to this agent during cycle 1 will also be assessed by the Voils Measure as described above and in the study calendar (Appendix Zc)
- Use of this agent beyond cycle 1 will be assessed via diaries as described above and in the study calendar (Appendix Zb)

7.7 Dose reduction tables

7.7.1 Dose Reduction tables for Cohorts 3A/3B and Cohort 2 extension

Table. Dose Reduction Levels for Neratinib-Related Toxicity (for Cohorts 3A/3B)

Dose Level	Neratinib
Starting Dose	240 mg
-1	160 mg
-2	120 mg

Recommended dose reductions for the -1 and -2 dose levels of capecitabine in combination with neratinib are below in the table.

Table. Dose Reduction Levels for Capecitabine-Related Toxicity for Cohorts 3A and 3B (When Administered in Combination with Neratinib)

Dose Level	Capecitabine (administered in combination with neratinib)
Starting Dose	1500 mg/mg^2 (750 mg/m^2 BID) [a]
-1 [b]	1100 mg/m^2 (550 mg/m^2 BID)
-2 [b]	750 mg/m^2 (375 mg/m^2 BID)

Abbreviation: BID: twice daily

[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the starting capecitabine dose be rounded up to the nearest 500 mg or multiple of 150 mg for the BID dose. However, if initial capecitabine dosing is complex for a patient because of the need to use a complicated combination of 150 mg and 500 mg tablets and the provider wishes to use 500 mg tablets only, this is permitted. In addition, providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing and may round down (rather than up) if they prefer for the starting dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

[b] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) (to 75% [level -1] or 50% [level -2] of the starting dose) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing, but all dosing adjustments should be documented in CRFs.

If doses of investigational product are held on any cohort, study procedures for that cycle should also be delayed. This also applies to tumor assessments, which should continue to be done every 2-3 cycles per the study calendar. Missed dose(s) of investigational product (i.e., any dose that is not administered within the protocol-defined administration window) will not be made up. The dose adjustment guidelines represent the minimum set of measures that Investigators must follow. However, additional measures may be taken, as necessary, for certain patients per the Investigator's medical judgment. All dose modifications/adjustments should be documented in the patient's source file.

Once an investigational product dose has been reduced for a patient, all subsequent cycles must be administered at that dose, unless further dose reduction is required. Dose re-escalation is not permitted.

7.7.2 Dose Reduction tables for T-DM1 Cohorts 4A-4C

T-DM1	**Dose Level 0** ***Starting Dose***	**Dose Level −1**	**Dose Level −2**	**Dose Level −3**
T-DM1	3.6 mg/kg	3.0 mg/kg	2.4 mg/kg	Discontinue
Note: if patient is being treated on Cohort 4C and began with a dose reduction in T-DM1 because of prior toxicity on this agent, if further dose reductions are required while on study, reductions should be done in stepwise fashion (so that if patient started at 3.0 mg/kg and needed a dose reduction one level, they would go to 2.4 mg/kg and would then discontinue T-DM1 from there if additional reductions were required)				

Table. Dose Reduction Levels for Neratinib-Related Toxicity (for Cohorts 4A-4C)

Dose Level	**Neratinib**
Starting dose	160 mg
-1	120 mg
-2	80 mg

8. DRUG FORMULATION/STORAGE/SUPPLY

8.1 Neratinib and Capecitabine:

8.1.1 Neratinib is an investigational agent and will be supplied free-of-charge from Puma Biotechnology, Inc.

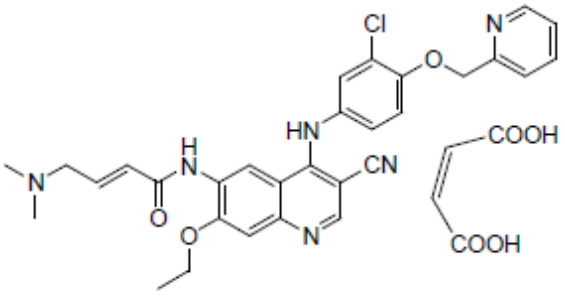
Capecitabine is approved by the FDA for use in metastatic breast cancer and will be billed to commercial insurance. Standard copayments will apply.

8.1.2 Neratinib: The CAS Indexed Name for Neratinib is 2-Butenaminde, N-[4-[[3-chloro-4-(2-pyridinylmethoxy)phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-,(2E)-,(2Z)-2-butenedioate (1:1).

Capecitabine: Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) in vivo. Bioactivation: Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxyesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-

fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.
The molecular structures are shown below and were adapted from the Investigator's Brochure (neratinib) and from the FDA (capecitabine):

Molecular structure of neratinib:



Molecular Structure and metabolic pathway of capecitabine:

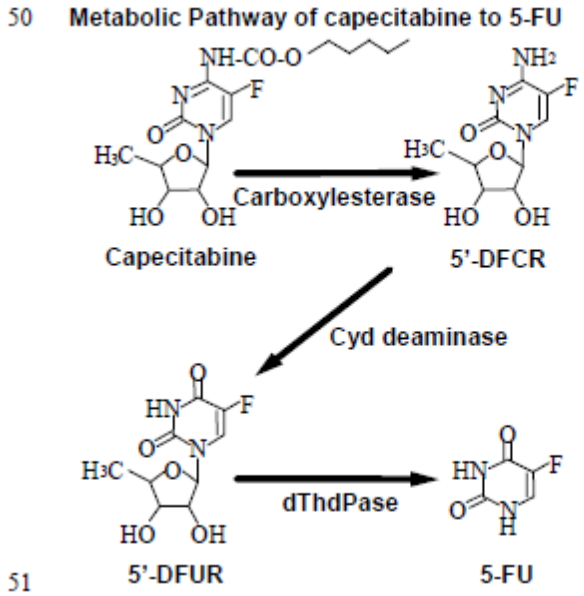


Table* Physical, Chemical, Pharmaceutical Properties of Neratinib and Capecitabine

	Neratinib	**Capecitabine**
Formula	$C_{30}H_{29}ClN_6O_3 \bullet C_4H_4O_4$	$C_{15}H_{22}FN_3O_6$
Molecular Weight	673.11	359.35

Appearance	Off-white to yellow powder	Capecitabine is a white to off-white crystalline powder
Solubility in water (room temperature)	0.4-0.5 mg/mL at pH 5.1	Aqueous solubility of 26 mg/mL at 20re)
Dosage form	tablets	tablets

*Adapted from the Investigator's Brochure

Table* Tablet Formulations for Neratinib

Drug Product
Active Ingredient
Neratinib maleate (10 mg, 40 mg, 80 mg as free base)
Inactive Ingredients
Mannitol
Crospovidone
Colloidal Silicon Dioxide
Microcrystalline Cellulose
Magnesium Stearate
#0 or #2 HPMC (Hypromellose) Capsule, Reddish-brown

*Adapted from the Investigator's Brochure

Table Tablet Formulations for Capecitabine

Drug Product
Active Ingredient
5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine (150 mg, 500 mg)
Inactive Ingredients
anhydrous lactose
croscarmellose sodium
hydroxypropyl methylcellulose
microcrystalline cellulose
magnesium stearate
purified water
The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

8.1.3 Pharmacokinetics

a. Highlights From Studies In Healthy Subjects (Neratinib)

Study 3144A1-107-US

The pharmacokinetic profile in 56 human subjects was studied in healthy subjects and conducted through Wyeth. Study 3144A1-107-US was a randomized, double-blind, placebo-controlled, inpatient, sequential group study of escalating oral doses of neratinib administered to healthy subjects after an overnight fast of 10 hours or greater. In cohorts of 8 subjects, 6 subjects received active drug in varying doses and 2 subjects received placebo. Subjects who received neratinib 240 mg doses received a second dose of treatment or placebo with a high-fat meal. Two additional cohorts of subjects were administered higher doses of neratinib (400 mg and 640 mg) with a high-fat meal. Blood

samples for determining the plasma pharmacokinetics (PK) of neratinib were obtained within 2 hours before agent administration and at selected time points up to 96 hours after agent administration.

Plasma samples were available from 42 subjects who received neratinib (120-800 mg) under fasting and fed conditions, over 5 dose-escalation cohorts, 1 crossover food-effect cohort (240 mg), and 2 parallel-treatment food-effect cohorts (400 mg and 630 mg doses).

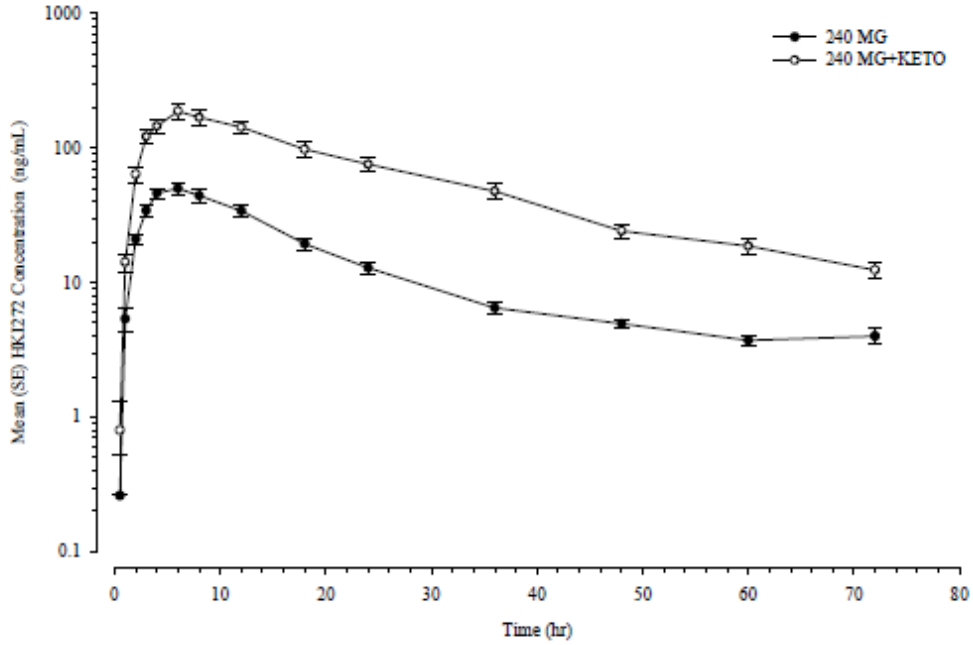
Following administration of neratinib 120 mg – 800 mg doses (at fasting conditions), the median time to maximum concentration (t_{max}) of neratinib was slow at 4 to 7 hours. Mean peak plasma concentration (C_{max}) after a single escalated dose under fasting conditions ranged from 27.3 ng/mL (120 mg dose) to 121 ng/mL (800 mg dose), and mean AUC (area under the concentration-versus-time curve) for neratinib (fasting) increased with increasing dose, however this did not occur in a linear manner. A plateau was reached at the 400-mg dose and higher doses did not increase the mean AUC. The volume of distribution for these subjects was large, ranging from 63 to 96 L/kg and the mean apparent oral clearance (Cl/F) ranged from 2.8 to 6.3 L/h/kg. After one dose, the mean elimination half-life ($t_{1/2}$) of neratinib ranged from 10-17 hours.

When a single dose of neratinib was administered to fed subjects (240 mg and 600 mg), neratinib exposure increased with increasing dose in a linear fashion. The mean plasma concentrations of neratinib over time in healthy subjects and fed conditions are adapted from the Investigator's brochure and are shown below:

Study 3144A1-106-US

This was an open-label, randomized, 2-period, sequential, drug-interaction study to evaluate the potential PK interaction between ketoconazole (multiple doses) and neratinib (single dose) in 24 healthy subjects. This study included 2 treatment periods separated by a 13-day washout between neratinib doses. In the first period, a single oral dose of neratinib (240 mg) was given on day 1. In the second period, subjects received ketoconazole 400 mg on days - 1-4 and a single dose of neratinib (240 mg) on day 1 only. All doses of both agents were preceded by a 10-hour fast, except for the ketoconazole given on day -1. Blood samples were collected on day 1 within 2 hours before agent administration and at selected time points up to 72 hours after agent administration in both periods. In this study, mean concentrations of neratinib were higher after treatment of concomitant ketoconazole compared with neratinib administered alone.

Figure 7-2: Mean Concentration-Versus-Time Profile of Neratinib in Plasma After a Single Oral Dose of Neratinib 240 mg Alone or in Combination With Ketoconazole in Healthy Subjects: Study 3144A1-106-US



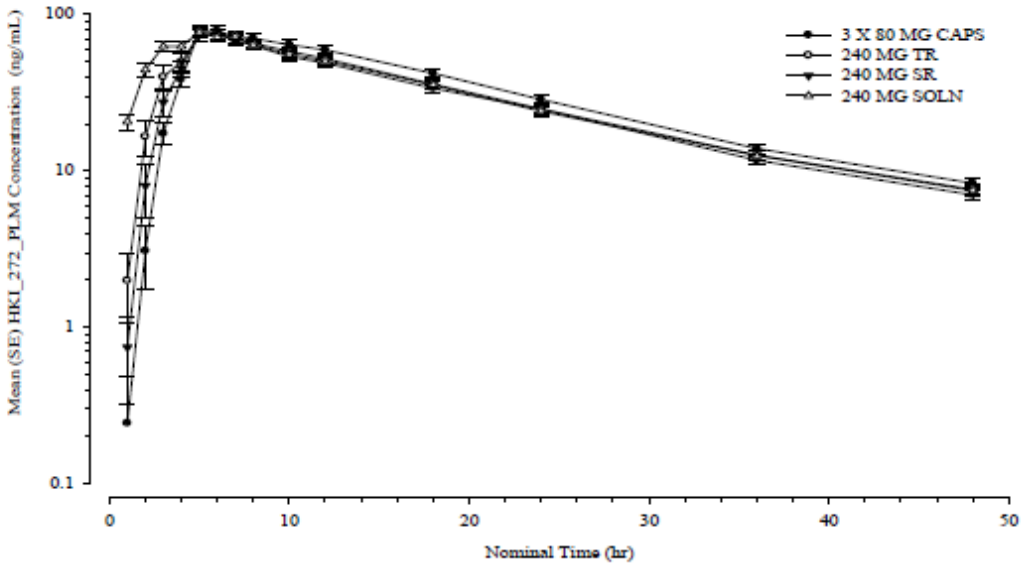
Analyses demonstrated that neratinib alone and with ketoconazole (fasting conditions) had mean C_{max} values of 55 ng/mL and 201 ng/mL, respectively, and mean values for AUC were 903 ng•h/nL and 4660 ng•h/mL, respectively. Exposure with treatment was associated with some inter-subject variability, with Coefficient of Variation (CV) values up to 58% for C_{max} and up to 53% for AUC. After administration of neratinib, median t_{max} was 6 hours between the two treatments. When neratinib was administered with ketoconazole, the Cl/F of neratinib decreased approximately 4-fold, from 346 to 87 L/h. The $t_{½}$ of neratinib increased from 12-18 hours when given with ketoconazole. The data demonstrated that neratinib exposure was increased when co-administered with ketoconazole compared with neratinib exposure when administered alone (3.2-fold for C_{max} and 4.8-fold for AUC).

Study 3144A1-1109-US

This study was a phase 1, open label, single-dose, 4-treatment. 3-period crossover, and balanced incomplete block design, inpatient or outpatient study with healthy subjects, to examine the comparative bioavailability of 2 new formulation tablets of neratinib 240 mg tablets with a reference capsule and an oral solution. Here, subjects were randomly assigned to receive 1 or 4 treatment sequences. Subjects assigned to each sequence received 3 of 4 formulations, according to the randomization sequence. The 4 formulations were as follows: (1) neratinib 1 x 240 mg slow release tablet (SR), (2) neratinib 1 x 240 mg target-release tablet (TR), (3) neratinib 3 x 80 mg capsules (CAPS),

and (4) neratinib 240 mg oral solution (SOLN). Each neratinib dose was separated by at least 14 days of washout and blood samples for pharmacokinetic analysis were drawn on day 1 within 2 hours before, and at selected time points up to 48 hours after receipt of neratinib. Mean plasma concentrations over time after single dose neratinib under fed conditions are shown below:

Figure 7-3: Mean Concentration-(Mean±SD) Versus-Time Profiles of Neratinib in Plasma Following Single Oral Dose of Neratinib 240-mg Capsule, Target Tablet, Slow-Release Tablet, and Solution in Healthy Subjects Under Fed Conditions: Study 3144A1-1109-US



Abbreviations: SR=neratinib 240-mg slow-release tablet; TR=neratinib 240-mg target-release tablet; CAPS=neratinib 240-mg capsules; SOLN=neratinib 240-mg solution

Mean plasma concentration-time profiles of neratinib were similar for all formulations. After a single dose of neratinib (240 mg) with food in these healthy subjects, C_{max} of neratinib was achieved in 5-6 hours, with a median t_{max} of 5 hours for SOLN and TR and 6 hours for the SR and CAPS. After oral administration of neratinib, C_{max} and AUC were 84 ng/mL and 1623 ng•h/mL for the CAPS, 81 ng/mL and 1432 ng•h/mL for the TR, 82 ng/mL and 1474 ng•h/mL for the SR, and 82 ng/mL and 1556 ng•h/mL for SOLN. Intersubject variability for C_{max} and AUC were small. The $t_{½}$ of neratinib of 13 hours was consistent among formulations and the mean clearance (CL_T) was approximately 2 L/h/kg. The 90% confidence intervals (CI) of the geometric mean ratio for Cmax, AUC_t (area under the concentration-time curve from time zero to the time of last quantifiable concentration), and AUC of neratinib all fell within 80% and 125%, indicating that all tested formulations were bioequivalent to the CAPS formulation.

Study 3144A1-105-US

This study was a randomized, single-dose, double blind protocol with respect to neratinib, crossover, placebo and open-label, moxifloxacin-controlled study of the effects of neratinib

on cardiac repolarization in healthy subjects. This study aimed to examine the effect on the QTc after administration of a single neratinib dose (240 mg).

For both the therapeutic and sub-therapeutic dose comparisons, the upper bounds of the 90% CI for the baseline-adjusted population QTc were <10 msec at all time points post-dose. In addition, the overall sensitivity of the study conditions was demonstrated with a statistically significant prolongation of QTc, with a mean increase of 6.5 msec at the moxifloxacin median t_{max} after moxifloxacin administration compared with that of placebo.

After a single dose of neratinib 240 mg administered with food, the mean C_{max} as 68 ng/mL (CV—40%) and mean AUC was 1236 ng•h/mL (CV—39%). These results were consistent with data previously reported for both healthy subjects and those with cancer. Under conditions of ketoconazole inhibition of neratinib metabolism, mean C_{max} (CV) of 163 ng/mL (46%) and mean AUC of 3801 ng•h/mL (49%) were 2.4- and 3-fold, respectively, higher than when single dose neratinib was given alone. These increased neratinib exposures represent a 2.2- and 4-fold increase from mean exposures at steady state observed in subjects with cancer after daily dosing of neratinib 240 mg with good (C_{max}, 73 ng/mL and AUC_{55} 939 ng•h/mL). Furthermore, 13 subjects in this study had a C_{max} > 219 ng/mL during the subtherapeutic dosing comparison, a 3-fold increase from the mean C_{max} observed in subjects in study 3144A1-102-US. The highest C_{max} reached in an individual subject n the subtherapeutic dose comparison sequence was 327 ng/mL. By comparison, the highest neratinib plasma concentration observed to date in any subject with cancer has been 247 ng/mL. The results are from an assessment of plasma concentration data for 241 patients who received neratinib in studies 3144A1-102-US, 3144A1-200-WW, and 3144A1-201-WW. On the basis of these studies, the neratinib plus ketoconazole treatment utilized is representative of subtherapeutic neratinib exposures under clinical conditions. The results of the QTc prolongation studies demonstrated no prolongation of QTc with neratinib at the recommended dose of 240 mg once daily when taken with food and under conditions of subtherapeutic plasma concentrations.

b. Studies In Patients With Cancer (Neratinib)

Study 3144A1-102-US

This was a phase 1, open-label, ascending single and multiple oral dose study of neratinib in patients with erbB1- or erbB2-overexpresing advanced tumor, as determined by IHC, and for whom no standard treatment was available. Neratinib 40 mg – 400 mg was administered with food as a single dose on day 1. After a one-week PK and observation period, neratinib was given as a continuous daily dose in 28-day cycles for 6 cycles. Blood samples and PKs were collected on day 1 at time zero, and at selected time points up to 48 hours after single-dose administration of neratinib. Samples were taken at day 14 (time

zero) and at selected time points up to 24 hours after daily oral administration of neratinib for 14 days.

The mean plasma concentrations of neratinib over time after single, ascending doses of neratinib on day 1 are shown below and the mean plasma concentrations over time of neratinib on day 21 (after once daily ascending doses of neratinib) are shown below:

Figure 7-4: Neratinib Mean (SE) Concentration-Versus-Time Profile in Plasma After Single Ascending Oral Doses of Neratinib in Subjects With Cancer on Day 1: Study 3144A1-102-US

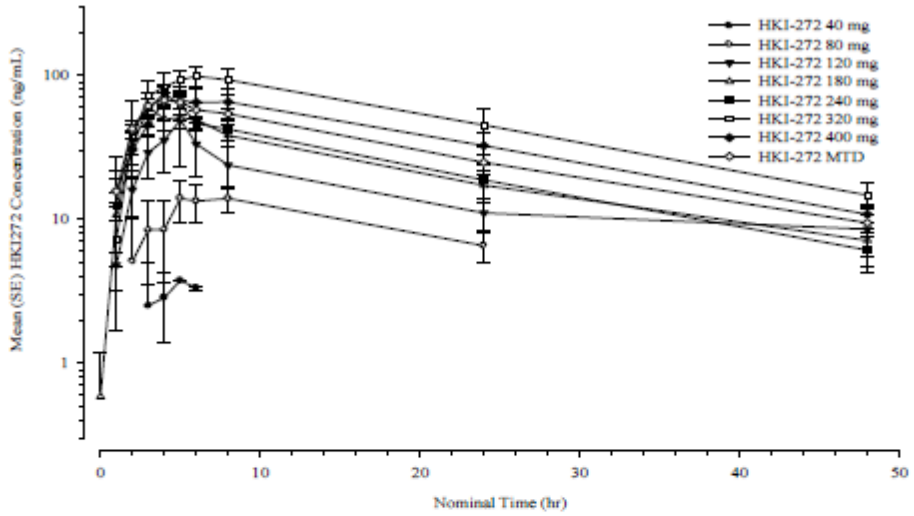
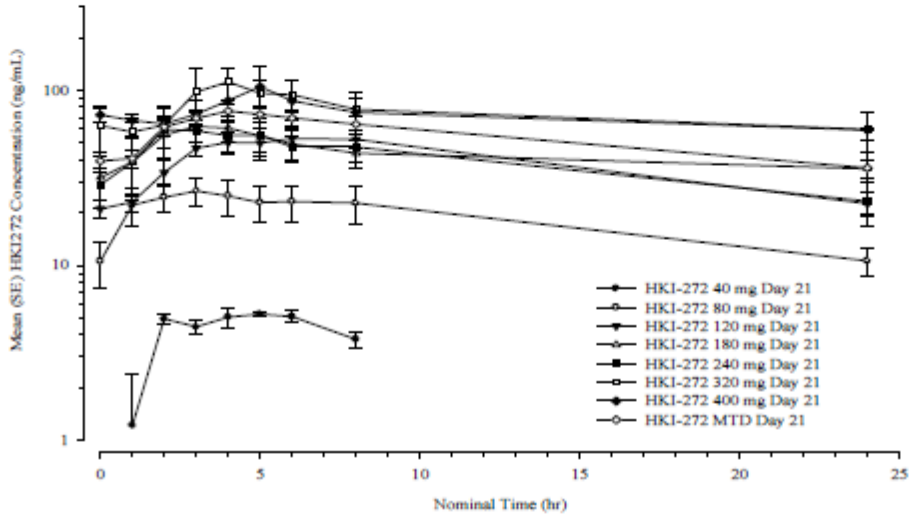


Figure 7-5: Neratinib Steady-State Mean (SE) Concentration-Versus-Time Profile in Plasma on Day 21 After Once-Daily Ascending Oral Doses of Neratinib in Subjects With Cancer: Study 3144A1-102-US



PK analyses indicated that after a single dose, absorption of neratinib was relatively slow, with a median t_{max} of 3-6.5 hours. Mean C_{max} on day 1 after a single dose ranged from 5 ng/mL (CV=44% with 40 mg dose) to 76.5 ng/mL (CV=52% with 400 mg dose). For these doses, the steady-state mean C_{max} on day 21 ranged from 5.8 ng/ML (CV=8%) to 105 ng/mL (CV=43%), respectively. After a single dose of neratinib on day 1, mean AUC ranged from 54.2 ng•h/mL (CV=37%, 40 mg dose) to 1833 ng•h/mL (CV=42%, 400 mg dose). On day 21, mean steady-state AUC vs. time curve (AUC_{55}) ranged from 76.0

ng•h/mL (40 mg dose) to 1704 ng•h/mL (400 mg dose) (CV=20%). Multiple-dose exposure curves were 1.17- to 2.66-fold higher than single-dose exposures (mean accumulation ration [R], AUC_{55}/AUC from 0 to 24 hours [$AUC_{0\text{-}24h}$]) at the doses of 40 mg to 400 mg. The mean accumulation ratio was 1.18 after administration of 240 mg neratinib and 1.24 after administration of 320 mg neratinib (maximum tolerated dose), indicating no major accumulation of neratinib after repeated, and continuous daily administration in subjects with cancer.

Trough concentrations of neratinib measured through cycle 6 did not show any significant changes with protracted treatment. The apparent steady-state volume of distribution (V_{55}/F) was large, with values ranging from 33-155 L/kg (CV 9% to 128%). Mean clearance (CL_T) ranged from 2.5 to 8 L/h/kg (CV=8% to 67%). Mean $t_{½}$ after single ascending doses on day 1 ranged from 8 to 17 hours (CV=8% to 65%). After single or multiple doses, neratinib C_{max} and AUC appeared to increase with increasing dose. However, statistical lack-of-fit tests for Cmax and ACU vs. dose indicated that the relationship between C_{max} and AUC vs. dose was not linear. Preliminary statistical analysis (a 1-factor ANOVA) to assess the effect of sex on PK-exposures suggested no statistically significant difference in C_{max} (p=.4 to .7) or AUC (p=.3 to .7) between men and women.

Study 3144A1-104-JA

This study was an open-label, phase 1, sequential group study in Japanese patients with metastatic or advanced stage cancer who had not responded to standard therapies and for which standard therapies were no longer available.

Blood samples for PK evaluation were obtained on days 1-3 after a single dose and on days 21 and 22 after 14 days of continuous dosing of neratinib. Preliminary PK results are presented for 21 subjects who received neratinib 80 mg (n=3), 160 mg (n=3), 240 mg (n=10; 3 in dose-finding phase and 7 at the recommended dose), or 320 mg (n=5). Preliminary PK analyses showed that neratinib absorption was moderately slow with a median t_{max} of 3-6 hours. Mean C_{max} on day 1 (after single dose) ranged from 33.3 ng/mL (80 mg dose) to 93.2 ng/mL (320 mg dose). For the same respective doses, the steady-state mean C_{max} on day 21 ranged from 41.9 ng/mL to 143 ng/mL.

After a single dose of neratinib on day 1, mean AUC ranged from 368 ng•h/mL (80 mg) to 2288 ng•h/mL (320 mg). ON day 21, for the same respective doses, mean AUC at stead-stage (AUC_{55}) ranged from 581 ng•h/mL to 2040 ng•h/mL. The exposure of neratinib after oral administration in these subjects with cancer increased with increasing dose and the mean accumulation ratio ranged from 1.19 to 2.03, indicating no major accumulation of drug after repeated daily dosing (in patients with cancer). Mean V_{55}/F was large with values ranging from 76 L/kg to 192 L/kg. Mean apparent oral clearance ranged from 2.5 to

12 L/h/kg. Mean $t_{½}$ after a single dose on day 1 ranged from 7 to 16 hours. After single and multiple doses of neratinib, no relevant differences were noted between Japanese and non-Japanese subjects in the PK profiles of neratinib.

c. Pharmacokinetics of Capecitabine

Pharmacokinetics in Colorectal Tumors and Adjacent Healthy Tissue: Following oral administration of capecitabine 7 days before surgery in patients with colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

Human Pharmacokinetics: The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m2/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¾ of an hour. The inter-patient variability in the Cmax and AUC of 5-FU was greater than 85%.

8.1.4 Form

Neratinib (40 mg tablets) will be supplied by Puma Biotechnology, Inc. and will be packaged into bottles for patient administration (28-day supply + 7 days to allow for +/- 3 days on each end of the cycle and 1 additional day). The color of the tablets is reddish-brown.

Capecitabine tablets are supplied as biconvex, oblong film-coated tablets. They are available as follows and will be supplied by commercial pharmacies: 150 mg (color: peach) and 500 mg tablets (color: peach) and packaged into bottles. Insurance companies will typically supply a 14-day supply (to be followed by 7 days of rest) at a time. Capecitabine should be taken with water within 30 minutes after a meal.

8.1.5 Storage and Stability

Neratinib tablets should be stored at 25° C (77° F) or lower but should not be frozen. Tablets will be stored by sites at room temperature in a controlled and locked storage area. Subjects will be instructed to store pills in a safe place at room temperature. Note: Brief excursions up to 30° (86°F) are allowed.

Capecitabine should be stored at 25°C (77° F); excursions permitted to 15° to 30°C (59° to 86°F); keep tightly closed. [See USP Controlled Room Temperature]

8.1.6 Handling

Neratinib and capecitabine tablets require no specific handling precautions. 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.

8.1.7 Availability

Neratinib is an investigational agent and will be supplied free-of-charge to the study team and patients from Puma Biotechnology Inc.

Capecitabine is a commercially available agent and will be billed to insurance as standard of care. Usual copays will apply.

8.1.8 Preparation

Neratinib will be pre-prepared and packaged by Puma Biotechnology Inc. and shipped directly to participating institution pharmacies. Drug orders will be placed by each participating center once Puma Biotechnology Inc. has received the site information required to ship drug to each site. Study drug will be distributed to each center. Once a patient meets criteria to continue therapy, he/she will receive study drug (after each study visit).

Capecitabine will be prepared and dispensed by commercial pharmacies.

8.1.9 Administration

Neratinib (Cohorts 1, 2) will be packaged in bottles containing a maximum of 210 tablets (40 mg) (This is equal to a 28-day supply + 7 days for allowed window of follow-up). Tablets will be self-administered orally by patients once daily as six 40 mg tablets (total 240 mg). Further doses will be determined at each cycle, depending on toxicities and need for dose adjustment. Labeling of the bottles containing tablets will be done in accordance with local procedures (as required by law). Patients will return any unused pills at next protocol visit.

For Cohorts 3A/3B, neratinib investigational product will be supplied as 40 mg film-coated tablets packaged in bottles with desiccant. Neratinib (240 mg initial dose; provided as six 40 mg tablets) will be self-administered orally by patients on a daily basis, starting with Cycle 1/Day 1. Neratinib should be taken with food, in the morning. Neratinib is to be

taken continuously in 21-day cycles, with no rest between cycles. It can be taken with capecitabine.

Capecitabine will be dispensed by commercial pharmacies as a 14-day supply (to allow for one week of rest) and will be refilled at each cycle. This will be supplied as 150 mg and/or 500 mg film-coated tablets packaged in bottles. Capecitabine (total dose of 1500 mg/m^2 daily, in 2 evenly divided doses of 750 mg/m^2) will be self-administered orally by patients, starting with Cycle 1/Day 1. Ideally, a combination of 500 mg and 150 mg tablets will be combined to sum the recommended starting dose. Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the starting capecitabine dose be rounded up to the nearest 500 mg or multiple of 150 mg for the BID dose. However, if initial capecitabine dosing is complex for a patient because of the need to use a complicated combination of 150 mg and 500 mg tablets and the provider wishes to use 500 mg tablets only, this is permitted. In addition, providers may use their discretion on rounding to a dose that will lessen the need for complicated dosing and may round down (rather than up) if they prefer for the starting dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing. Doses are to be taken daily on Days 1 to 14 of each 21-day cycle. Capecitabine should be taken with water within 30 minutes after a meal and can be taken with neratinib. During treatment with neratinib plus capecitabine, patients should be monitored for conditions that may require dose to be held or discontinued, as described in Section 6.3 Careful attention should be paid to the onset of diarrhea or hand-foot syndrome in particular, and early dose adjustment or prophylactic therapy should be implemented as described. Daily dosing of neratinib plus capecitabine should continue until a criterion for treatment withdrawal or study withdrawal is met.

8.1.10 Ordering

The investigator or those named as sub-investigators agree to supply study drug (neratinib) only to those subjects who are enrolled in the study. The investigator or designee will keep a current and accurate inventory of all clinical drug supplies provided by Puma Biotechnology, Inc. A new prescription will be provided to each patient for each cycle of therapy. The study site will maintain a dispensing log and compliance with the treatment regimen will be calculated at the site from this information at each visit.

Each participating center will order its own inventory of neratinib and submit the order form to the DFCI team. Once the coordinating center (DFCI) ascertains regulatory compliance for each participating site, it will send Puma Biotechnology, Inc. the order form and site information (including IRB approvals) required to ship the drug. Drug will be shipped directly to that participating site by Puma Biotechnology, Inc.

8.1.11 Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and dispensing of neratinib using the Institutional Drug Accountability Record Form or another comparable drug accountability form. It is recommended (but not required) to request that participants return to clinic for study visits with their unused commercial Capecitabine supply in order to facilitate with the drug adherence and accountability documentation. In cases when participant is unable to bring the unused commercial capecitabine supply – it would not be considered a violation.

8.1.12 Destruction and Return

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

8.2 Trastuzumab

8.2.1 Product description: Herceptin® Lyophilized Formulation

Trastuzumab will be supplied for use as a freeze-dried preparation at a nominal content of either 440 mg or 150 mg per vial for parenteral administration (may vary based upon commercial availability). The drug is formulated in histidine, trehalose, and polysorbate 20. Commercially available trastuzumab will be used as part of this study. Subject's insurance will be billed for trastuzumab.

8.2.2 Solution preparation:

Each 440-mg vial is reconstituted with 20 mL of Bacteriostatic Water for Injection (BWI), USP (containing 1.1% benzyl alcohol), which is supplied with each vial. The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. The reconstituted formulation (440 mg vial) is designed for multiple use. Unused drug may be stored for 28 days at 2ºC-8ºC (36ºF-46ºF).

Each 150-mg vial is reconstituted with 7.4 mL of Sterile Water for Injection (SWFI). The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 ml of 0.9% Sodium Chloride Injection, USP. Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no preservative. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2ºC-8ºC; discard any unused Herceptin after 24 hours.

Reconstituted Herceptin should be clear to slightly opalescent and colorless to pale yellow.

8.2.3 Storage requirements:

Vials of the lyophilized formulation of trastuzumab must be stored at 2ºC-8ºC to ensure optimal retention of physical and biochemical integrity. DO NOT FREEZE. Trastuzumab may be sensitive to shear-induced stress (e.g. agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of trastuzumab results in aggregation of the protein and may create cloudy solutions.

8.2.4 Availability

Trastuzumab is commercially available and will be ordered by each prescribing provider for the duration for the study. Neratinib is an investigational agent and will be supplied free-of-charge from Puma Biotechnology, Inc.

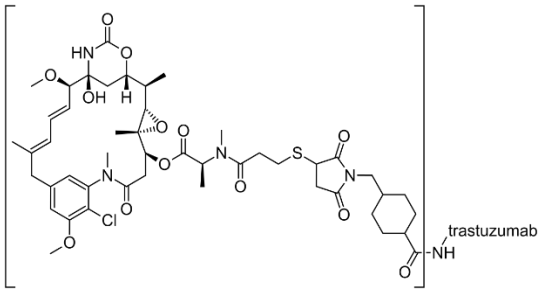
8.3 T-DM1

NOTE: The following adapted from the package insert. Commercial supplies of T-DM1 will be used for this study and current prescribing information should be used at all times.

T-DM1 is a HER2-targeted antibody and microtubule inhibitor drug conjugate currently indicated as a single agent for treatment of patients with HER2-positive, metastatic breast cancer who previously received a taxane and trastuzumab, separately or in combination.

8.3.1 T-DM1 structure

T-DM1 (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 antimicrotuble 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. Molecular structure of T-DM1:



8.3.2 Formulation

Lyophilized powder in single-use vials: 100 mg per vial or 160 mg per vial of ado-trastuzumab 120 emtansine.

8.3.3 Pharmacokinetics

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 t1/2) 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 t½ 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.

8.3.4 Storage and Stability

T-DM1 is supplied as:

Carton Contents	NDC
One 100 mg vial, single use vial	NDC 50242-088-01
One 160 mg vial, single use vial	NDC 50242-087-01

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.

Special Handling: Follow procedures for proper handling and disposal of anticancer drugs per one's institutional policies.

8.3.5 Preparation

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf)

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is KADCYLA (T-DM1) and not trastuzumab.

Administer KADCYLA as an intravenous infusion only with a 0.22 micron in-line non-protein adsorptive polyethersulfone (PES) filter. Do not administer as an intravenous push or bolus.

Do not mix KADCYLA, or administer as an infusion, with other medicinal products.

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

Reconstitution: Use aseptic technique for reconstitution and preparation of dosing solution. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the mg KADCYLA vial, or 8 mL of Sterile Water for Injection into the 160 mg KADCYLA vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do not shake. Inspect the reconstituted solution for particulates and discoloration.

The reconstituted solution should be clear to slightly opalescent and free of visible particulates. The color of the reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored.

The reconstituted lyophilized vials should be used immediately following reconstitution with Sterile Water for Injection. If not used immediately, the reconstituted KADCYLA vials can be stored for up to 4 hours in a refrigerator at 2ºC to 8ºC (36°F to 46°F); discard unused 107 KADCYLA after 4 hours. Do not freeze.

The reconstituted product contains no preservative and is intended for single-use only.

Dilution: To determine the correct dose (mg) of KADCYLA. Calculate the volume of the 20 mg/mL reconstituted KADCYLA solution needed. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Do

not use Dextrose (5%) solution. Gently invert the bag to mix the solution in order to avoid foaming. The diluted KADCYLA infusion solution should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up 117 to 4 hours prior to use. Do not freeze or shake.

8.3.6 Administration

T-DM1 is administrated 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 and subsequent doses over 30 minutes if prior infusions were well tolerated. Flush IV line with saline after drug is administered. Do not administer with D_5W. Do not administer as an intravenous push or bolus.

Do not mix T-DM1, 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.

8.3.7 Ordering of T-DM1

T-DM1 is commercially available for Cohorts 4A-4C. Given that Cohort 4C patients will have had prior T-DM1 exposure, treatment teams may wish to seek approval ahead of time so that coverage is known before enrollment. We will not be able to cover T-DM1 for any patient on study.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies (Cohort 1 enumeration and molecular studies; Cohort 3A/3B molecular studies only)

The primary aim of this correlative, exploratory analysis in Cohort 1 is to describe correlation of CTC number with OS in patients with progressive CNS disease. A second exploratory analysis (for Cohorts 1 and 3A/3B) will use FISH analyses to examine the levels of MET oncogene and HER2 co-amplification in CTCs at different time points during a patient's disease course (baseline and at progression). Third, for Cohorts 1 and 3A/3B, molecular studies with FISH for HER2 gene amplification will be performed to examine the relationship between the HER2 status of a patient's

primary breast cancer, metastatic lesions, and CTCs. Lastly, exploratory analyses will evaluate HER2-positive CTCs using FISH for EGFR gene amplification to examine the possible mechanisms of resistance driven by EGFR. An aliquot of CTCs may also be stored for future analyses. All patients on study will be included in the CTC correlative analyses and all tubes will be immediately shipped to and analyzed at Dana-Farber Cancer Institute. In addition, tubes for CTC collection will be shipped in advance to participating centers.

All collected samples in this trial will be of collection.

Planned Correlative Studies Using Circulating Tumor Cells (CTCs) in Cohorts 1 and 3A/3B

Test	Baseline	Progression/Off study
CTC for enumeration and for banking (for future MET amplification and other future molecular studies) [2 tubes]	X	X

9.2 CTC Enumeration (in collaboration with Drs. Krop, Ly) Cohort 1 only

We will collect 2 tubes for circulating tumor cells (CTCs) at baseline and then again at the time the patient comes off study (for progression, toxicity, etc.). These samples will be examined for both enumeration and for molecular HER2 studies or for future study as outlined. Briefly, 15 mls of whole blood (2 tubes) will be collected in CellSave tubes. ™ Samples can sit at room temperature for up to 72 hours but must be mixed immediately with fixative to help prevent clotting. CTCs will be analyzed using two potentially different methods:

9.2.1 Standard technique (CellSearch Epithelial Kit [CEK] for enumeration)

Here, CTCs will be collected using the well validated automated CellSearch™ processing technique (Veridex). In this CEK system, the captured cells are permeabilized and labeled with cytokeratin CD45 specific antibodies, and the nuclear stain '4-6-Diamidino-2-phenylindole (DAPI), and analyzed by semi-automated counting of appropriately labeled CTCs.[78] CTCs are defined as CD45 negative and positive for cytokeratin and DAPI. Stained cells are collected by the Veridex system in a "MagNest" cartridge. This cartridge is automatically scanned. Semi-automated counting is performed according to the manufacturer's instructions by a trained pathologist.

9.2.2 CellSearch Profile Kit Method (CPK)

Samples processed using the CPK method (per manufacturer's instructions) will be collected in a tube with dilution buffer (PBS, 0.5% BSA and 0.1% sodium azide) and immediately transferred to SuperFrost Plus slide as cytospin preparations using a ThermoFisher Cytospin 3. Centrifugation will be performed at 500g for 5 minutes with a cytology funnel, thin filter (Fisher). The cells on the resulting cytospin slide will be fixed with either: (1) methanol for immunofluorescence or immunohistochemistry or (2)

methanol:acetic acid (3:1) for FISH. Cells will be manually stained with cytokeratin phycoerythrin/DAPI/CD45-allophycocyanin (Dako) and then manually counted using a standard fluorescence microscope (Olympus). FISH will also be performed manually.

9.3 Other CTC studies

NOTE: Analysis of CTC by FISH for studies on HER2 Discordance, EGFR analysis, and co-amplification of MET and HER2 (in collaboration with Dr. Krop and Dr. Ly; for Cohorts 1 and 3A/3B).

The MET/CEP 7 and HER2/CEP17 bacterial artificial chromosome (BAC) probes will be obtained from Vysis Molecular (Abbot Park, Illinois). BAC MET (RP11-95I20) will be obtained from CHORI (Children's Hospital of Oakland Research Hospital). Labeling will be completed with the Nick Translation Kit (Vysis Molecular (Abbot Park, Illinois). One slide will be used for MET and another will be used for HER2. Slides will be maintained in a horizontal position throughout the entire hybridization and washing procedure. Briefly, cells are fixed with methanol-acetic acid (3:1), dehydrated in an alcohol series (50%, 75%, 90%, 100%) and air-dried. Five microliters of the probe mixture are applied, and the slides are covered with cover glass and sealed with rubber cement. Pre-hybridization is done with hybridization buffer without dextran sulfate for 1 hour at 37ºC. Denaturation is performed at 94ºC for 5 minutes. Hybridization is completed overnight at 37ºC. Following hybridization, slides are washed in 1x SSC 3 times for 10 minutes each at 37ºC (maintaining the horizontal position), briefly air dried, and counterstained with Vectashield/DAPI (Vector). Two-color FISH slides will be created for each MET and for each HER2 amplification analysis. Manual quantification of tumor cells will be performed by determining the total number of whole nuclei (DAPI-positive signals). A similar methodology will be used to test CTCs for EGFR amplification to explore potential mechanisms of resistance to therapy.

9.4 CNS Neratinib Concentrations and Other Potential CSF Studies (see Appendices K and L for instructions and shipping) (Cohort 2 only)

The primary aim of this correlative analysis is to examine concentrations of neratinib and its metabolites in intracranial specimens and CSF. Up to five patients with intracranial disease amenable to surgery (as determined by treatment team and neurosurgery before therapy initiation) will be enrolled on the intracranial drug testing component study (Cohort 2). These patients will also undergo CSF and plasma drug concentration testing at the time of surgery.

Surgical patients will be treated with 7-21 days of neratinib preoperatively to allow for neratinib to reach steady state to allow for no delay in surgical plan (note: neratinib steady state reached at 3-4 days). This treatment will be followed by immediate surgical resection (patients will take neratinib on morning of surgery). The date and time of the last neratinib dose administration (on the sample collection day) as well as the date and time of sample (i.e. intracranial specimens, CSF and plasma) collections will be recorded (see Appendix K for CSF and plasma collections and Appendix L for intracranial tumors). **Prior to the patient's scheduled craniotomy, the study**

team will discuss and confirm the plan of sample collection by phone to ensure successful collection. Depending on the type of surgery planned and location of tumor being removed, the neurosurgeon may have to perform a lumbar puncture under anesthesia prior to the start of surgery. This will require a separate clinical procedure consent obtained by the neurosurgeon. This is mentioned in the revised patient consent for the protocol. A discussion should occur 24-96 hours prior to craniotomy/tissue/CSF collection as a teleconference and will be coordinated by the treating center's clinical research coordinator. The discussion will include the overall study PI, the site PI, and the study coordinator and will need to be communicated and confirmed with the neurosurgeon performing the procedure. In addition to coordinating collection, coordination of sample shipment will be discussed. While awaiting shipment, samples should be frozen immediately at -80 °C as described below.

At surgery, 4 cc of CSF will be collected per instructions in Appendix K. The samples of CSF will be collected in pre-labeled tubes or containers. The CSF will be examined for neratinib and its metabolite analysis by validated LC/MS/MS assay (Appendix K). An additional 4 cc of CSF will be banked at Dana-Farber for future study.

At resection, 0.4 - 0.5 mL of tumor will be frozen immediately without any treatment applied to tissues (at -80° C) and will be transferred on dry ice to Dr. Agar (Brigham and Women's, see Appendix L). Another 0.4 – 0.5 mL of tumor will be banked for future research, unless insufficient tissue is available.

In addition, 3 mL of blood will be collected into a 5mL K3EDTA vacutainer tube for plasma concentrations of neratinib/metabolites testing at Covance.

Any excess tissue not needed for clinical reasons or neratinib analyses will be banked for future research.

****Plans for evaluation of intracranial tumor (Dr. Agar): Mass Spectrometry Imaging of Tumor Specimens to Evaluate BBB Drug Penetrance**

Specimens will be removed from the tumor as they would in a standard brain tumor resection. In this proposed study, the specific geometric coordinates, registered to preoperative MRI images, could also be recorded. Specimens will be analyzed via mass spectrometry imaging (MSI) and light microscopy, the gold standard for determining the presence of tumor. We intend to correlate the drug distribution in specimens with the presence or absence of vasculatureto assess penetrance of the blood-tumor barrier, and correlate to MRI contrast enhancement information at the voxel corresponding to the specific sampling location.

For sample preparation for MSI analyses, frozen specimens are minimally embedded at their base using O.C.T. (Sakura Finetek, Torrance, CA), sectioned at 10 μm using a Microm HM525 cryostat (Mikron Instruments Inc., San Marcos, CA), and thaw-mounted onto ITO coated glass slides and

kept at -20C^0.Matrix solution is 7mg/ml α-cyano-4-hydroxycinnamic acid (α-CHCA) or 30 mg/ml 2,5-dihydroxybenzoic acid (DHB), 50% ACN, 0.2%TFA. A matrix solution of 5 ml is prepared daily and sonicated for 30 minutes. The matrix is deposited using the ImagePrep (BrukerDaltonics, Billerica, MA) with the manufacturer's default method for approximately 85 thin layers of matrix deposition (1.5 hours). For optical images, a sister tissue section is fixed in -20^{0}C methanol, and stained with hematoxylin and eosin. The matrix coated section is placed in a desiccator for 20 minutes, and then imaged by MALDI mass spectrometry using the MALDI TOF-TOF UltrafleXtreme (BrukerDaltonics) and/or the MALDI Apex-qe 9.4 Tesla FTICR mass spectrometer (BrukerDaltonics).

The matrix-coated section is imaged by MALDI mass spectrometry by rastering the laser in a two-dimensional array across the surface of the tissue section, and with data acquisition in positive ion mode over the mass range of 200 – 2000 *m/z*at each pixel to include the *m/z* of interest. The spatial resolution is implied by the diameter of the laser focus and/or the raster movement spacing. The 1 kHz all-solid-state laser with smartbeam II technology can be focused to 10 µm, imposing this lower limit of spatial resolution.
Compound identification is verified on the basis of elemental composition and accurate mass, using the SmartFormula (BrukerDaltonicsInc, Billerica, MA) algorithm, which matches measured versus predicted isotopic patterns. Image reconstruction is performed using the FlexImaging 2.1 software (BrukerDaltonics, Billerica, MA). Neratinib has the chemical formula $C_{30}H_{29}Cl_1N_6O_3$ with a corresponding monoisotopic mass of 556.19895 Da.

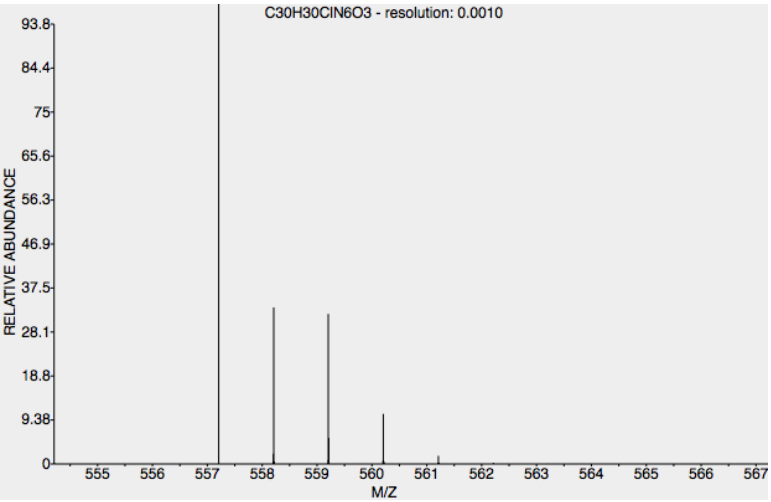


Figure. Simulated spectrum of [Neratinib + H]$^+$.

9.4.1 Blood sample and CSF processing instructions:

3 mL of blood will be collected into a 5mL K3EDTA vacutainer tube for plasma concentrations of neratinib/metabolites testing. Gently mix contents of the tube containing

the blood sample. Take care that blood does not come into further contact with the stopper. Immediately place vacutainer on ice. Centrifuge tube of blood within 2 hours of collection at 1,000 x g for 10 minutes in a refrigerated (4ºC) centrifuge. Label the 2.0 mL cryovial with appropriate specimen labels (at least 2 hours prior to freezing). Collect the plasma using disposable pipettes. Transfer the plasma into the labeled 2.0 mL cryovials for each sample taken, and store in an upright position. Freeze samples in an upright position in a -70°C monitored freezer in their respective labeled cryovial storage box. Samples must be frozen for at least 24 hours prior to shipment to Covance at:

Covance Bioanalytical Services, LLC
8211 SciCor Drive
Suite B
Indianapolis, IN 46214

Lastly, CSF taken at surgery will be sent to Covance for neratinib and its metabolite concentration analysis. As above, other potential CSF analyses may also include CTC enumeration and HER2 testing in the CSF, although further CSF studies will be elaborated upon in a study amendment as appropriate. Samples of blood and CSF should be sent directly to Covance for testing 24-72 hours after collection whenever possible but samples can be frozen at -70°C until shipments are ready. **Prior to shipping any samples, please confirm that samples are OK to ship with CRC at Dana-Farber Cancer Institute.**

For collection/shipping instructions for tumor specimens, see Appendix L

9.5 Neurocognitive Testing for Patients with CNS Disease (Cohort 1 only) (Appendix O)

Within this trial, we will include a brief battery of neurocognitive testing for Cohort 1 at multiple time points: at baseline, cycle 2 day 1 (coinciding with the first scheduled imaging of the brain), cycle 3 day 1, and at the time of patient going off study (either due to disease progression, toxicity, or other cause). Patients who progress prior to cycle 2 or 3 initiation will use their most recent testing as their "off study" testing (and will thus have fewer total time points of testing completed). It is recognized that in some cases patients will not be able to complete neurocognitive testing at the time of disease progression because of a poor performance status, emotional distress, and worsening physical or neurological symptoms. In these cases, incomplete neurocognitive exam will not be considered a protocol violation. Reasons for incomplete testing should be documented clearly. The testing will include the following: Hopkins Verbal Learning Test-Revised (HVLT-R) to assess learning and memory, and Trail Making Test Parts A and B and Controlled Oral Word Association (COWA) to assess executive function and visual motor scanning speed. In addition to

these tests, patients will complete other questionnaires assessing depression and quality of life. These will include: Hospital Anxiety and Depression Scale (HADS) and the EORTC QLQ30/BN20. It is expected that this testing should take approximately 40-45 minutes and can be administered by a trained study coordinator under the auspices of the study neuropsychologist. Tests will be scored and interpreted centrally by the study neuropsychologist (Dr. Wefel) and data from the neurocognitive testing will be also stored centrally by Dr. Wefel until the completion of the study. See Appendix O for further details regarding test battery and study coordinator training.

****Management of Elevated HADS score****

The HADS, described above, gauges depression and anxiety. Participants scoring 15 or for the total score are considered to be experiencing significant distress. When surveys are received, the HADS will be scored within one week of receipt. If a participant scores 15 or above on the total scale, study oncologist will be alerted by one of the investigators to make aware of the finding and handle further patient care as appropriate. This will be discussed in the patient informed consent document.

9.6 Patient reported outcomes, diarrhea questionnaires, evaluation of adherence to diarrhea prophylaxis

Patients will be approached in clinic on their study visits to complete the necessary questionnaires on Day 1 of cycles 1-4 and one time by phone during cycle 1, as outlined in the study calendar (Cohorts 4A-4C only). See Appendix Za.

9.7 Archival Sample Collections (Cohorts 3A/3B only)

Archived primary tumor biopsies or surgical specimens or metastatic specimens will be requested for future research so that PIK3CA, PTEN analyses and other genomic tests can be done in participants receiving treatment on study. These analyses will be exploratory in nature and may be combined with results from specimens on other protocols for CNS-directed treatments.

9.8 CSF collections for those undergoing clinical lumbar punctures (Cohorts 4A-4C only)

For any patient on these cohorts, undergoing lumbar puncture, we will ask permission to obtain fluid for circulating tumor DNA examination. We aim to collect 5-10 specimens for this and if clinical lumbar punctures are not occurring frequently, we will amend the protocol to include formal testing of this with participants.

9.8.1 CSF Processing Protocol for ctDNA

Note: All liquid transfers should be performed in a sterile laminar flow hood.

1. Process samples within 2 hours of collection.

CSF Pre-processing

1. Transfer CSF to a 15mL Falcon tube
2. Spin 15mL tubes containing CSF at 1900g for 10 minutes at room temperature with the brake reduced to 6

a. A small pellet may be visible after the spin

3. Carefully remove tubes from centrifuge and transfer CSF to well-labeled cryotube(s)
4. Make note of the draw type (ventricular shunt, lumbar puncture, peri-operative, etc.) and collection tube type

Store tube(s) at -80°C until submission

9.8.2 Specimen Handling and Processing for CSF on Cohorts 4A-4C

The following methods will be used to collect and process the specimens:
Following collection of the specimen, samples will be snap-frozen. This sample handling is optimal for obtaining high quality tumor sample for whole exome sequencing. Specific instructions are listed in Appendix V. All samples will be anonymized by assigning a unique sample ID number prior to use.

9.8.3 CSF Specimen Shipping

Sites should ship CSF Specimens frozen on dry ice to the Clinical Research Coordinator at the address below, Monday through Thursday. Samples collected on Fridays should be stored in the freezer until the following Monday or next available business day:

Brigham and Women's Hospital
DFCI Breast Tissue/Blood Bank
[redacted]

Email [redacted] with the sample information and tracking information the day before shipping specimens.

Coded laboratory specimens will be stored in the Tumor Bank of the DFCI. These specimens will become the property of DFCI. Patients will be informed that their specimens may be used for research by investigators at DF/HCC and other approved collaborators. Shared specimens will be identified with a sample ID number; all patient identifying material will be removed.

9.9 Blood collection for Cohorts 4A-4C Only

9.9.1 Mandatory Research blood draw for ctDNA

At baseline, C2 D1, and at end of treatment, 1 tube of whole blood will be collected in a 10 ml Streck tube for ctDNA analysis. If sample collection is missed for any reason at baseline or at the time of progression, then the sample should be drawn at a future appointment.

Processing: Label appropriately. Draw venous blood into Streck tubes at time-points listed in the table above and in the protocol. Fill the tube completely. Immediately mix by gentle inversion 8 to 10 times. DO NOT FREEZE OR REFRIGERATE TUBES. This will result in a breakdown of cfDNA. Tubes must be shipped within 24 hours of blood draw. Streck tubes may be shipped overnight **Monday through Thursday (not on Fridays or the day before a holiday)** at ambient temperature to DFCI at the address below.

Shipping:
Brigham and Women's Hospital
DFCI Breast Tissue/Blood Bank
[redacted]

Email [redacted] with the sample information and tracking information the day before shipping specimens.

9.9.2 Optional Blood (for plasma/germline DNA)

Collected at baseline or may be collected at any subsequent time point if not collected at baseline.

Ten mL blood will be drawn into EDTA containing test tube, and whole blood will be aliquoted into cryovials. Five mL blood will be drawn into blue topped tube. Plasma will be separated from the cellular component by centrifugation at 2600rpm for 15 minutes and aliquoted into cryovials.

All cryovials will be catalogued, frozen at -80 degrees C and stored in DF/HCC Clinical Trials Core laboratory for future assays.

Shipping:
Brigham and Women's Hospital
DFCI Breast Tissue/Blood Bank
[redacted]

Email [redacted] with the sample information and tracking information the day before shipping specimens.

10. SPECIMEN BANKING

10.1 Cohort 1

Specimen banking for Cohort 1 is completed and was collected at baseline and at progression.

10.2 Cohort 2 and 3 and Cohorts 4A-4C

Optional blood will be collected at baseline and will be banked for future potential plasma/germline DNA examination. Any additional leftover study blood and tissue samples will also be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. Any samples will only be released for use in future studies after approval by the Principal Investigator and other regulatory bodies, as appropriate.

Ten mL blood will be drawn into EDTA containing test tube, and whole blood will be aliquoted into cryovials.

Five mL blood will be drawn into blue topped tube. Plasma will be separated from the cellular component by centrifugation and aliquoted into cryovials.

All cryovials will be catalogued, frozen at -80 degrees C and stored in DF/HCC Clinical Trials Core laboratory for future assays. Please refer to **Appendix T** for shipping guidelines.

If the blood collection is missed at baseline, it may be collected at any time point while on study. The banked samples will be used to analyze DNA, RNA and protein in future studies.

10.3 Cohorts 3A-3B and Cohorts 4A-4C

Blood will be collected at baseline, cycle 2 day 1, and at end of treatment for the analysis of ctDNA and to be processed and then banked in the DF/HCC Clinical Trials Core laboratory for future research purposes.

One 10 ml of whole blood will be collected in Streck Tubes. The blood sample will be collected and processed at baseline and time of progression for evaluation of ctDNA. Tubes are provided by the Sponsor as needed.

If the blood collection is missed at baseline or at the time of progression, then the blood will be collected at a future appointment.

Please refer to **Appendix U** for specimen collection and shipping guidelines.

11. FUTURE RESEARCH

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

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

12. STUDY CALENDARS

Screening laboratory studies and physical examinations (including neurological examination) are to be conducted within 4 weeks prior to start of protocol therapy. Screening scans (other than brain imaging must also be done ≤4 weeks prior to the start of therapy. MUGA or echo must be done within 60 days prior to the start of therapy. Baseline brain MRIs (or CT head with contrast if MRI contraindicated) preferred to be done within 14 days, but can be up to 21 days prior to start of protocol therapy unless insurance will not cover repeat testing. If this is the case, please discuss this with the PI so a decision can be made on whether to proceed. Baseline bone scan is not required but should be performed if clinically indicated. In the event that a patient's conditions is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Subjects who discontinue study therapy but have responsive or stable disease will be followed approximately every 3-6 months for progression and overall survival. Minor deviations in scheduling of procedures (i.e. cycle 1 procedures, +/- 3 days; from cycle 2 forward treatment schedule, -3 days to +7 days; from Cycle 3 forward, +/- 7 days) are allowed to accommodate for vacation, holidays, or patient convenience.

All assessments must be performed prior to administration of any study medication.

Note: If patients opt to receive trastuzumab after non-CNS progression while on neratinib, please see the Extension Study Calendar for further required testing and information.

12.1 Study Calendar for Cohorts 1 and 2 (Neratinib Only)[S]

Evaluation	Baseline	Cycle -1 Day 1 (Cohort 2 only)	Cycle 1 Day 1	Cycle 1 Day 3-6 (in person or by phone)	Cycle 1, Day 7-21 (Cohort 2 only)	Cycle 2, Day1	Day1 of Each Cycle, (Cycle 2 forward)	Every 2 Cycles (during Days 22-26)	Cycle 3, Day 1	Every 3 Cycles	End of Therapy[N]	Follow-Up [I, T]
Informed consent	X											
Inclusion/exclusion criteria	X											
Patient Education for Diarrhea [R]	X	X [O]	X [O]									
Demographics	X											
Medical/surgical history [P]	X											
Concomitant medications	X	X	X			X	X					
Baseline Symptoms (CTCAE 4.0)	X											
Height	X											
Vital Signs (Weight and Blood Pressure)	X		X			X	X					
Karnofsky **AND** ECOG Performance Status (see Appendix A)	X [A]	X [A]	X [A]			X [A]	X [A]				X[A]	
Physical examination	X	X [J]	X [J]			X	X				X	X
Neurological examination [A]	X	X [J]	X [J]			X	X				X	X
Urine Pregnancy test [B]	X											
12-lead EKG	X											
Urinalysis [C]	X											
Adverse event evaluation (including diarrhea)		X		X		X	X				X	X

Evaluation	Baseline	Cycle -1 Day 1 (Cohort 2 only)	Cycle 1 Day 1	Cycle 1 Day 3-6 (in person or by phone)	Cycle 1, Day 7-21 (Cohort 2 only)	Cycle 2, Day1	Day1 of Each Cycle, (Cycle 2 forward)	Every 2 Cycles (during Days 22-26)	Cycle 3, Day 1	Every 3 Cycles	End of Therapy[N]	Follow-Up [I, T]
CBC, including differential and platelets	X	X [J]	X [J]			X	X					X
Serum chemistries [D]	X	X [J]	X [J]			X	X					X
Coag, Studies (PT, PTT, INR)	X											
CTC collection [E]	X		X *(only if not collected at baseline)*								X	X *(only if not collected at time off study)*
Optional Blood (for plasma/germline DNA) [F]	X *(may be collected at any subsequent time point if not collected at baseline)*											
Phone call to assess for diarrhea (at least once during cycle -1 [Cohort 2] **and** cycle 1, days 2-6) [all Cohorts]		X		X								
Collect and Review pill diary (Appendix B)						X	X					
MUGA or echocardiogram [G]	X									X		
Brain MRI (Appendix F)	X [Q]							X [L]				

Evaluation	Baseline	Cycle -1 Day 1 (Cohort 2 only)	Cycle 1 Day 1	Cycle 1 Day 3-6 (in person or by phone)	Cycle 1, Day 7-21 (Cohort 2 only)	Cycle 2, Day1	Day1 of Each Cycle, (Cycle 2 forward)	Every 2 Cycles (during Days 22-26)	Cycle 3, Day 1	Every 3 Cycles	End of Therapy[N]	Follow-Up [I, T]
Non-CNS Tumor Evaluation (MRI or CT and clinical assessment of visible of palpable lesions) [H]	X							X [H]				
Bone scan	X [K]							X [K]				
Neurocognitive testing [M] (Appendix O) **Cohort 1 Only**	X [M]		X [M]			X [M]			X [M]		X [M]	
Questionnaires (HADs and EORTC QLQ30/BN20) **Cohort 1 Only**	X		X			X			X		X	
Neratinib Dispensation		X	X			X	X					
Craniotomy specimen collection, blood draw and CSF collection for neratinib concentration in selected patients (if operable) *Additional tissue and CSF to be banked as described in Section 8.4					X							

A. Neurologic examination worksheet (Appendix E) to be completed at baseline and at each study visit. Karnofsky and ECOG performance status listed on worksheets.
B. In women of childbearing potential only and completed within 4 weeks of therapy initiation. Can be repeated as indicated during study enrollment.
C. Urine dipstick and send for microscopic analysis (+/- urine culture) if abnormal. Should be tested within 4 weeks of trial enrollment

D. To include Na, K, HCO3, Cl, Albumin, Total Protein, BUN, Cr, glucose, AST, ALT, alkaline phosphatase, total bilirubin, LDH, Magnesium, Calcium, phosphorous
E. For Cohort 1 and 2 patients. A total of 15 ml of blood will be collected in two CellSave™ tubes at each of the indicated time points. Samples will be processed immediately (within 72 hours) and transferred to SuperFrost Plus slide as cytospin preparation. Additional slides will be banked at -20 degrees C for future processing. See *section 8* for collection details and Appendix H for processing and shipping instructions.
F. Banking: Ten mL blood will be drawn into EDTA containing test tube, and whole blood will be aliquoted into cryovials. Five mL blood will be drawn into blue topped tube. Plasma will be separated from the cellular component by centrifugation and aliquoted into cryovials. All cryovials will be catalogued, frozen at -80 degrees C and stored in DF/HCC Clinical Trials Core laboratory for future assays. If this is not collected at baseline, it may be collected at any time point while on study.
G. Evaluation of LVEF to occur at baseline (within 60 days of enrollment) and every 3 cycles (+/- 14 days). After completion of 12 cycles ECHOS to decrease to every 4 cycles (16 weeks). When possible, the same modality (e.g. MUGA or ECHO) should be performed for consistency in measurements. Of note, insurance companies now prefer echocardiogram in most cases.
H. Patients in Cohorts 1-2 should have imaging of the Chest-Abdomen-Pelvis at baseline. After completion of 12 cycles, scans can decrease in frequency to every 3 cycles. If there are no pelvic lesions or abnormalities identified, future non-CNS imaging may include chest and abdomen only, as appropriate. For alternative imaging options (non-CT), please see *Section 12.6.* For patients in Cohort 2: if baseline non-CNS images were completed ≤ 4 weeks of re-initiating neratinib on cycle 1, these images will not require repeating prior to cycle 1. If non-CNS imaging was done > 4 weeks since baseline, these images will be repeated on C1D1 (+/- 3 days). Non-CNS imaging will continue for all cohorts every 2 cycles (Days 22-28 of C2, C4, C6, etc. Day 28 imaging allowed for non-CNS testing because central review is not required.)
I. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (14-42 days) after the decision to discontinue treatment. Follow-up will also continue by phone or in person every 3-6 months to assess for progression and survival information.
J. Required only if > 1 week has passed since baseline examinations
K. Bone scan not required for study but may be done at baseline and every 2 cycles, if clinically indicated
L. If there is evidence of progression on brain MRI (or CT head if MRI contraindicated), patients will be taken off study and will proceed to further CNS-directed therapy per provider's discretion. **All other patients will have MRI brain (or CT head if MRI contraindicated) completed at C2, C4, C6, etc. during days 22-26**. Upload of brain imaging to TIMC by day 26 of the re-staging cycle will allow central review to occur prior to start of next cycle. Cohort 2 will have baseline brain imaging [i.e. cycle -1, preoperatively]. Postoperatively, patients will have brain imaging repeated on C1D1 (+/- 3 days). The Cycle 1 images for Cohort 2 will be reviewed by TIMC but patients may start neratinib on cycle 1 prior to central review confirmation (If delays in TIMC read or upload of images occurs, please refer to Section 12.7.5 for details on evaluation of disease)
M. Neurocognitive testing (Appendix O) will be assessed for patients in Cohorts 1 only. This will occur on C1 D1 (<u>only</u> if not done at baseline), C2 D1, C3D1, and at progression. Neurocognitive testing at D1 of cycles 2 and 3 may occur +/- 7 days from D1 with each cycle. If patients come off study prior to C3 D1 testing, then C3D1 testing may serve as testing upon discontinuation of therapy (due to clinical deterioration or documented disease progression, unless patient is too sick to undergo testing). <u>In addition, end of study testing will not be performed in patients who progress and go off study <8 weeks from previous testing at beginning of cycle 3. If patients are unable to complete testing at the time of progression, reasons for not performing testing should be documented.</u>
N. Patients who enroll into the optional extension of this protocol with trastuzumab should be followed according to the Extension Study Calendar

O. Only if not done at Baseline and/or C1 D-1(Cohort 2). See R below. All patients should start prophylactic loperamide 2 mg with initiation of therapy on study. This should continue for the first cycle of therapy only, as long as diarrhea is grade 1 or less at the end of cycle 1 without recent worsening of symptoms. Providers may discontinue prophylaxis early at their discretion.
P. Must include: Cancer history (tumor histology, stage at diagnosis, previous treatments [chemotherapy, hormonal therapy, surgery, radiation in the adjuvant and metastatic settings])
Q. Prefer to be within 14 days, but can be up to 21 days prior to start of treatment.
R. Instruct all patients to have loperamide (Imodium) at home and ready for use. Patients should begin taking loperamide 2 mg with each neratinib dose, starting Cycle 1, Day 1 (or cycle -1, Day 1 for surgical patients). In the case of diarrhea, see toxicity management instructions. Instruct patients to call with ANY onset of diarrhea.
S. Cycle length = 28 days
T. Patients who enroll into the optional extension of this protocol with trastuzumab (Cohort 1) or capecitabine (Cohort 2) should be followed according to the corresponding study procedures listed in the calendar below (Section 11.3)

12.2 Study Calendar for Cohorts 3A/3B

Screening laboratory studies and physical examinations (including neurological examination) are to be conducted within 4 weeks prior initiation of treatment. Screening scans (other than brain MRIs [or head CT with contrast if MRI contraindicated]) must also be done ≤4 weeks prior to the start of therapy. MUGA or echo must be done within 60 days prior to the start of extension phase therapy. Baseline brain MRIs preferred to be done within 14 days, but can be up to 21 days prior to start of protocol therapy. Subjects who discontinue therapy will be followed approximately every 3-6 months for progression and overall survival. Minor deviations in scheduling of procedures are allowed to accommodate for vacation, holidays, or patient convenience, as previously stated.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Note: If patients opt to receive trastuzumab after non-CNS progression while on neratinib and capecitabine, please see the Extension Study Calendar above for further required testing and information.

12.2.1 Study Calendar for Cohort 3[I]

Evaluation	Baseline	Cycle 1 D1	Cycle 1 D2, D3, D4	D1 of every cycle, (Cycle 2 forward)	Cycles 2, 4, 6, D17-19	Every 3 cycles C9, C12, C15, etc.; D17-19	Every 4 cycles (+/- 14 days)	Discontinue Therapy [F]	Follow-up [F]
Informed consent	X								
Inclusion/exclusion criteria	X								
Concomitant medications	X	X		X				X	
Baseline Symptoms (CTCAE 4.0)	X								
ECOG and Karnofsky Performance Status (see Appendix A)	X	X		X				X	X
Vital signs (weight and Blood Pressure)	X	X		X				X	X
Physical examination	X	X		X				X	X
Diarrhea evaluation by phone once daily [M]			X						
Review and sign diarrhea instruction sheet (appendix Q).		X							
Give patient diary (appendix R)		X		X					
Neurological examination [A]	X	X		X				X	X
Adverse event evaluation (including diarrhea)				X				X	X
CBC, including differential and platelets	X	X [L]		X					X
Serum chemistries [C]	X			X					X
CTC collection [J]	X	X *(only if not collected at baseline)*						X	X *(only if not collected at time off study)*
Urine Pregnancy test [B]	X								
Collect and review pill diary (Appendix R for Cohort 3)				X					
MUGA or echocardiogram [D]	X						X		
Brain MRI (Appendix F) [H]	X				X [I]	X [I]			

Evaluation	Baseline	Cycle 1 D1	Cycle 1 D2, D3, D4	D1 of every cycle, (Cycle 2 forward)	Cycles 2, 4, 6, D17-19	Every 3 cycles C9, C12, C15, etc.; D17-19	Every 4 cycles (+/- 14 days)	Discontinue Therapy [F]	Follow-up [F]
Non-CNS Tumor Evaluation (MRI or CT and clinical assessment of visible of palpable lesions) [E, H]	X				X [I]	X [I]			
Bone scan [G]	X [G]				X [G]				
Neratinib Dispensation (research), Capecitabine dispensation (commercial pharmacy)		X		X					
Optional Blood (for plasma/germline DNA) [K]	X *(may be collected at any subsequent time point if not collected at baseline)*								
Mandatory Research blood draw for ctDNA [N]	X *(may be collected at any subsequent time point if not collected at baseline)*							X	X *(only if not collected at time off study)*
Archival tissue collection [O]	X								

A. Neurologic examination worksheet (Appendix E) to be completed at baseline and at each study visit.
B. In women of childbearing potential only and completed within 4 weeks of extension therapy initiation. Can be repeated as indicated during study enrollment.
C. To include Na, K, HCO3, Cl, Albumin, Total Protein, BUN, Creatinine, glucose, AST, ALT, Alk. Phos., Total Bilirubin, LDH, Magnesium, Calcium, Phosphorous
D. Evaluation of LVEF to occur at baseline and every 4 cycles (± 14 days). After completion of 16 cycles, ECHOS to decrease to every 5 cycles (15 weeks). When possible, the same modality (e.g. MUGA or ECHO) should be performed for consistency in measurements.
E. Patients should have imaging of the Chest-Abdomen-Pelvis at baseline. If there are no pelvic lesions or abnormalities identified, future non-CNS imaging may include chest and abdomen only, as appropriate. For alternative imaging options, please see *Section 12.6*
F. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (14-42 days) after the decision to discontinue treatment. Follow-up will also continue for 2 years by phone or in person every 3-6 months to assess for progression and survival information.
G. Bone scan not required for study but may be done at baseline and then coincide with other restaging scans, if clinically indicated.

H. Upon enrollment Cohort 3, the initial brain MRI (or CT head if MRI contraindicated) and body imaging will be completed after approximately 6 weeks of therapy with the combination (C2, Days 17-19 or 48-96 hours) prior to next cycle to allow for central review prior to next cycle). If progression is not observed after 3 re-staging evaluations (i.e. ≈18 weeks), further staging will be completed every 9 weeks (i.e. Days 17-19 of C9, C12, C15, etc.).
I. For Cohort 3A and 3B patients: A total of 15 ml of blood will be collected in two CellSave™ tubes at each of the indicated time points. Samples will be processed immediately (within 72 hours) and transferred to SuperFrost Plus slide as cytospin preparation. Additional slides will be banked at -20 degrees C for future processing. See *section 8* for collection details and Appendix H for processing and shipping instructions.
J. Banking: Ten mL blood will be drawn into EDTA containing test tube, and whole blood will be aliquoted into cryovials. Five mL blood will be drawn into blue topped tube. Plasma will be separated from the cellular component by centrifugation and aliquoted into cryovials. All cryovials will be catalogued, frozen at -80 degrees C and stored in DF/HCC Clinical Trials Core laboratory for future assays. If this is not collected at baseline, it may be collected at any time point while on study.
K. Required only if > 1 week has passed since baseline examinations
L. If cycle 1, Days 2-4 fall on a weekend, phone calls should be done on the next possible work days (i.e. should be done on Monday and Tuesday instead of a Saturday and Sunday)
M. At baseline and at end of treatment, 1 tube of whole blood will be collected in a 10 ml Streck tube for ctDNA analysis. If sample collection is missed for any reason at baseline or at the time of progression, then the sample should be drawn at a future appointment.
N. Archival blocks of available tumor tissue (both primary and metastatic) should be collected but will not hold up enrollment/registration. This material should be provided preferably as paraffin blocks, if not, at least ten 5micron sections on charged or coated slides and ten 5-7 micron sections on regular non-coated slides (total of 20 slides from primary and metastatic sites). In cases where there is limited tissue availability such that provision of the archival samples will risk using up the tissue reserve, archival tissue collection is not required; however, the PI should be notified of such cases and the reason for lack of tissue submission should be documented. See Specimen Requisition in Appendix S for shipping instructions. Although requested at baseline, tissue collections can occur at any point while a patient is on study.

12.3 STUDY CALENDAR FOR EXTENSION PORTION OF THE STUDY

Screening laboratory studies and physical examinations (including neurological examination) are to be conducted within 4 weeks prior to start of the extension phase of the protocol. Screening scans (other than brain MRIs [or head CT with contrast if MRI contraindicated]) must also be done ≤4 weeks prior to the start of therapy. MUGA or echo must be done within 60 days prior to the start of extension phase therapy. Baseline brain MRIs must be done within 4 weeks of start of protocol therapy. Subjects who discontinue study extension therapy will be followed approximately every 3-6 months for progression and overall survival. Minor deviations in scheduling of procedures are allowed to accommodate for vacation, holidays, or patient convenience, as previously stated.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

12.3.1 Study Calendar for Extension Phase of Study [J] (Cohorts 1-3 for patients who extend therapy with trastuzumab)

Evaluation	Baseline	Cycle 1 D1	D1 of every cycle, (Cycle 2 forward)	Cycle 2, D17-19	Every 3 cycles C5, C8, C11, etc.; D17-19	Every 4 cycles (+/- 14 days)	Discontinue Therapy [F]	Follow-up [F]
Informed consent	X							
Inclusion/exclusion criteria	X							
Concomitant medications	X	X	X				X	
Baseline Symptoms (CTCAE 4.0)	X							
ECOG and Karnofsky Performance Status (see Appendix A)	X	X	X				X	X
Vital signs (weight and Blood Pressure)	X	X	X				X	X
Physical examination	X	X	X				X	X
Neurological examination [A]	X	X	X				X	X
Adverse event evaluation (including diarrhea)			X				X	X
CBC, including differential and platelets	X		X					X
Urine Pregnancy test [B]	X							
Serum chemistries [C]	X		X					X
Collect and review pill diary (Appendix B)			X					
MUGA or echocardiogram [D]	X					X		
Brain MRI (Appendix F)	X			X [I]	X [I]			
Non-CNS Tumor Evaluation (MRI or CT and clinical assessment of visible of palpable lesions) [E]	X			X [I]	X [I]			
Bone scan [G]	X [G]			X [G]				
Neratinib Dispensation (Cohort 1,2)		X	X					
Trastuzumab administration [H] (Cohorts 1 and 3 only; Cohort 2		X (and every						

Evaluation	Baseline	Cycle 1 D1	D1 of every cycle, (Cycle 2 forward)	Cycle 2, D17-19	Every 3 cycles C5, C8, C11, etc.; D17-19	Every 4 cycles (+/- 14 days)	Discontinue Therapy [F]	Follow-up [F]
will not receive trastuzumab but will receive capecitabine)		7or 21 days)						
Neratinib Dispensation (research), Capecitabine dispensation (commercial pharmacy) for Cohort 2[K] and for Cohort 3A/3B		X	X					
Review and sign diarrhea instruction sheet (appendix Q) – COHORT 2 ONLY		X						

A. Neurologic examination worksheet (Appendix E) to be completed at baseline and at each study visit.
B. In women of childbearing potential only and completed within 4 weeks of extension therapy initiation. Can be repeated as indicated during study enrollment.
C. To include Na, K, HCO3, Cl, Albumin, Total Protein, BUN, Creatinine, glucose, AST, ALT, Alk. Phos., Total Bilirubin, LDH, Magnesium, Calcium, Phosphorous
D. Evaluation of LVEF to occur at baseline and every 4 cycles (± 14 days). When possible, the same modality (e.g. MUGA or ECHO) should be performed for consistency in measurements. After completion of 12 cycles (including treatment cycles for Cohort 1 or 2), or 16 cycles (including treatment cycles for Cohort3), ECHOs / MUGAs can decrease in frequency to every 5 cycles (15 weeks). That is, 48 weeks after initial study dose, ECHOs / MUGAs can decrease in frequency.
E. Patients should have imaging of the Chest-Abdomen-Pelvis at baseline. If there are no pelvic lesions or abnormalities identified, future non-CNS imaging may include chest and abdomen only, as appropriate. For alternative imaging options, please see *Section 12.6*
F. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (14-42 days) after the decision to discontinue treatment. Follow-up will also continue for 2 years by phone or in person every 3-6 months to assess for progression and survival information.
G. Bone scan not required for study but may be done at baseline and then coincide with other restaging scans, if clinically indicated.
H. Cohorts 1 and 3: Trastuzumab to be administered as a 8 mg/kg loading dose followed by 6 mg/kg every 21 days or as 4 mg/kg loading dose followed by 2 mg/kg weekly (per provider choice). If trastuzumab was administered ≤ 4 weeks prior to extension study entry, no loading dose is required. Study visits will transition to every 21 days during the extension phase.
I. Upon enrollment to the extension phase, the initial brain MRI (or head CT with contrast if MRI contraindicated) and body imaging will be completed after approximately 6 weeks of therapy with the combination (C2, Days 17-19 to allow for central review prior to next cycle). If progression is not observed, further staging will be completed every 9 weeks (i.e. Days 17-19 of C5, C8, C11, etc.).
O. Cycle length = 21 days
J. Cohort 2 extension will be addition of capecitabine to neratinib and not trastuzumab

12.4 Study Calendar for Cohorts 4A-4C[A]

Screening laboratory studies and physical examinations (including general impression worksheet) are to be conducted within 4 weeks prior initiation of treatment. Screening scans (other than brain MRIs [or head CT with contrast if MRI contraindicated]) must also be done ≤4 weeks prior to the start of therapy. Baseline brain MRIs preferred to be done within 14 days, but can be up to 21 days prior to start of protocol therapy. If insurance coverage is an issue, a case by case approval of testing beyond this window may be approved by the Protocol Chair. Subjects who discontinue therapy will be followed approximately every 6 months for progression and overall survival. Minor deviations in scheduling of procedures are allowed to accommodate for vacation, holidays, or patient convenience, as previously stated.

All assessments must be performed prior to administration of any study medication.

Evaluation	Baseline	Cycle 1 D1	Cycle 1 D10	Cycle 2 Onward				Discontinue Therapy [L]	Follow-up [L]
				D1 of every cycle	Cycles 2, 4, 6 D17-19	Every 3 cycles (C9, C12, C15, etc.) D17-19	Every 4 cycles (+/- 14 days)		
ECOG Performance Status (see Appendix A), Vital signs (weight and blood pressure), Concomitant medications	X	X		X				X	
Physical examination	X	X [K]		X				X	
EKG	X								
General Impression Worksheet [A]	X	X *(only if not collected at baseline)*		X				X	
CBC/diff, platelets, Serum chemistries [B]	X	X [K]		X					
Hepatitis panel including Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis C antibody	X								
Urine Pregnancy test [C]	X								
MUGA or echocardiogram [D]	X						X		
Brain MRI (Appendix F) [E]	X				X	X			
Non-CNS Tumor Evaluation [F]	X				X	X			
Bone scan [G]	X				X	X			
Diarrhea evaluation by phone [H]		X							
Mandatory Research blood draw for ctDNA (See Section 9.9.1)	X	X *(only if not collected at time baseline)*		X C2D1 only				X	X *(only if not collecte at time off study)*
Optional Blood (for plasma/germline DNA) (See Section 9.9.2) [I]	X								
Adverse event evaluation (clinician-assessed CTCAE)				X				X	
Optional research CSF collection [J]		Anytime while on study treatment							
PRO-CTCAE (patient-reported GI symptoms) (Appendix W)[71], [M]		X	X *(by phone)*	X (C2, C3, C4 only)					
Modified STIDAT measure [5] (Appendix X		X		X (C2, C3, C4 only)					
PROMIS measure[4] (Appendix Y)		X							

Evaluation	Baseline	Cycle 1 D1	Cycle 1 D10	Cycle 2 Onward				Discontinue Therapy [L]	Follow-up [L]
				D1 of every cycle	Cycles 2, 4, 6 D17-19	Every 3 cycles (C9, C12, C15, etc.) D17-19	Every 4 cycles (+/- 14 days)		
Diarrhea medication and diarrhea diary (Appendix Za and Zb)		X							
Patient diary for neratinib (Appendix C)		X		X					
Voils adherence measure (Appendix Zc)				C2D1 only					
Survival and Progression information									X

A. General impression worksheet (Appendix D) to be completed at baseline or C1D1 and at each study visit.
B. To include Na, K, HCO3, Cl, Albumin, Total Protein, BUN, Creatinine, glucose, AST, ALT, Alk. Phos., Total Bilirubin, LDH, Magnesium, Calcium, Phosphorous
C. In women of childbearing potential only.
D. Evaluation of LVEF to occur at baseline and every 4 cycles (± 14 days). After completion of 16 cycles, ECHO/MUGA to decrease to every 5 cycles (15 weeks). When possible, the same modality (e.g. MUGA or ECHO) should be performed for consistency in measurements.
E. The initial brain MRI (or CT head if MRI contraindicated) and body imaging will be completed after 2 cycles of therapy with the combination (C2, Days 17-19 or 48-96 hours) prior to next cycle to allow for central review prior to next cycle). If progression is not observed after 3 re-staging evaluations (i.e. ≈18 weeks), further staging will be completed every 3 cycles (i.e. Days 17-19 of C9, C12, C15, etc.).
F. MRI or CT and clinical assessment of visible or palpable lesions. Patients should have imaging of the Chest-Abdomen-Pelvis at baseline and whenever brain imaging is completed. For alternative imaging options, please see *Section 12.6*
G. Bone scan not required for study but may be done at baseline and then coincide with other restaging scans, if clinically indicated.
H. Phone call once by research staff (nurse or CRC), one time, 2-4 days after treatment start. If cycle 1, Days 2-4 fall on a long weekend, the phone call should be done on the next possible business day.
I. May be collected at any subsequent time point if not collected at baseline. See Section 9.9.2.
J. For anyone undergoing clinically indicted lumbar puncture. See Section 9.8.
K. Required only if > 1 week has passed since baseline examinations
L. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (14-42 days) after the decision to discontinue treatment. Follow-up will also continue for 2 years by phone or in person every 3-6 months to assess for progression and survival information.
M. PRO-CTCAE for GI symptoms will be done phone day 10 (+/- 4 days) of cycle 1 by CRC or nurse.

13. MEASUREMENT OF EFFECT

Response in the CNS and response in non-CNS sites will be evaluated and recorded separately in this trial. Response and progression in the CNS will **NOT** be evaluated using RECIST 1.1, but rather will be evaluated in this study using composite criteria (Cohorts 1,3) and using RANO-BM criteria (Cohorts 4A-4C), further defined below.

Response and progression in non-CNS sites for all Cohorts will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.[79]

For the purposes of this study, participants on Cohorts 1 and 2 should be re-evaluated for response every 2 cycles (or 8 weeks). For participants on Cohorts 3A/3B and Cohorts 4A-4C, participants will be evaluated for response every 2 cycles (or 6 weeks). If patients have not progressed by their third re-staging evaluation (i.e. ≈18 weeks), staging interval will change to every 3 cycles (or 9 weeks). In addition to a baseline scan, confirmatory scans should also be obtained every 8 weeks (Cohorts 1 and 2) and every 6 or 9 weeks (Cohorts 3A/3B and 4A-4C) following initial documentation of objective response (and not less than 4 weeks following initial documentation of objective response unless clinically necessary). Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

13.1 Definitions

13.1.1 Evaluable for toxicity

All participants who receive at least one dose of neratinib (Cohorts 1 and 2), at least one dose of neratinib and/or capecitabine (Cohorts 3A/3B), and at least one dose of neratinib and/or T-DM1 (Cohorts 4A-4C) will be evaluable for toxicity from the time of their first treatment. Those patients who enroll on study but never receive study treatment will not be evaluable for toxicity analyses.

13.1.2 Evaluable for objective response

Participants who have measurable disease present at baseline and have received at least one dose of study drug will be considered evaluable for response (all Cohorts, except Cohort 2 where measurable disease is not required), even if there are major protocol violations/deviations. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression, clinical progression, or die prior to the end of cycle 1 will also be considered evaluable.) In the case of a screening failure (i.e. if there is a patient who was deemed eligible per local read (lesion 10 mm or greater) but later, on central read, is found to be 9 mm), additional subjects may be enrolled to reach the targeted accrual number and the subject who failed

screening will be replaced. In addition, patients (except Cohort 2) found on auditing or review not to have measurable CNS disease at baseline will be replaced.

13.2 Response Categories

Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

13.3 Analysis of the Response Rate

All of the participants who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Participants in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9, and sometimes category 3, will be protocol specific.

13.4 All conclusions should be based on all eligible participants

Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

13.5 Disease Parameters

13.5.1 Measurable disease in the CNS

Measurable lesions are defined as those that can be accurately measured in at least one dimension, with longest diameter >10 mm on T1-weighted, gadolinium-enhanced MRI images or head CT with contrast.

13.5.2 Measurable disease in non-CNS sites

Tumor lesions:
Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

- 20mm by chest X-ray.

Malignant lymph nodes:
To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

13.5.3 Non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10mm or pathological lymph nodes with ≥ll to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

13.5.4 Special considerations regarding lesions measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

13.6 Specifications by methods of measurements

13.6.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

13.6.2 Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Guidelines have defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans) and is required for evaluation of brain lesions (unless contraindicated). IV/oral contrast are required for CT scans.

MRI Brain: Imaging with MRI brain is required for all patients on study to evaluate brain lesions. MRI images will include T1-weighted images with and without gadolinium contrast, T2-weighted images, and FLAIR (fluid-attenuated inversion recovery) images. If MRI is strongly contraindicated, head CT (with contrast) can be used for CNS tumor assessments

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

FDG PET and PET/CT: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET (one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD

- At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments[79] and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces

additional data which may bias an investigator if it is not routinely or serially performed.

In this study, PET and PET-CT studies will serve as an acceptable alternative to CT or MRI to evaluate non-CNS lesions if patients have a contraindication to these imaging modalities (i.e. severe contrast allergy or moderate renal dysfunction that makes MRI or CT undesirable). The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response.[80] Whole-body acquisition is important since this allows for samples of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

- Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. Ideally, if PET-CT is used for baseline measurements, this would continue throughout the study for re-assessment.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: tumor markers alone (CA 27.29, CA 15-3, CEA) cannot be used to assess objective tumor response.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any

effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

13.7 Response Criteria

13.7.1 Target lesions

All measurable lesions up to a maximum of 5 lesions in the CNS and a maximum of 5 non-CNS lesions (with maximum of two lesions per non-CNS organ), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). For non-CNS sites, the sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response in non-CNS sites. For CNS lesions, target lesions will be analyzed according to central volumetric review.

13.7.2 Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

13.7.3 Evaluation of Target Lesions in the CNS (by Composite Criteria – primary endpoint for Cohorts 1 and 3A/3B; secondary endpoint for Cohorts 4A-4C)[24]

CNS Complete Response (CR): All of the following must be satisfied:

- Complete resolution of all measurable (≥1cm diameter) and non-measurable brain metastases
- No new CNS lesions (new lesion defined as ≥6 mm)
- Stable or decreasing steroid dose
- Stable/improved neurological signs or symptoms (according to the question on neurological worksheets, “are the patient’s tumor-related neurological signs and symptoms worsening, stable, or improved?”)
- No progression of systemic (non-CNS) disease as assessed by RECIST

CNS Partial Response (PR): All of the following must be satisfied:

- ≥50% reduction in the volumetric sum of all measurable (≥ 1 cm diameter) brain metastases compared to baseline
- No progression of non-measurable lesions
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- Stable/improved neurological signs or symptoms (according to the question on neurological worksheets, "are the patient's tumor-related neurological signs and symptoms worsening, stable, or improved?")
- No progression of systemic (non-CNS) disease as assessed by RECIST

CNS Stable Disease (SD): All of the following must be satisfied:

- <50% reduction in the volumetric sum of all measurable (≥ 1 cm diameter) brain metastases compared to baseline, and not fulfilling the criteria for progressive disease
- No progression of non-measurable lesions
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- Stable/improved neurological signs or symptoms (according to the question on neurological worksheets, "are the patient's tumor-related neurological signs and symptoms worsening, stable, or improved?")
- No progression of systemic (non-CNS) disease as assessed by RECIST

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

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

- ≥40% increase in the volumetric sum of all measurable lesions as compared to the smallest volume since protocol-based therapy was initiated, OR
- Progression of non-measurable lesions*, OR
- New lesions (new lesion defined as ≥6 mm), OR

- Increasing steroid requirement (except for transient increase lasting ≤ 14 days). Note: As CNS progression is an eligibility requirement, increasing steroid dose within 4 weeks after study entry will not necessarily constitute disease progression, OR
- New/progression tumor-related neurologic signs and symptoms (NSS) except for transient worsening lasting ≤14 days. (As CNS progression is an eligibility requirement, worsening of NSS within 4 weeks after study entry will not necessarily constitute disease progression), OR
- Progression of systemic (non-CNS) disease as assessed by RECIST

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

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

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

Table. Summary of Composite Criteria for CNS Response

	Complete Response	Partial Response	Stable Disease	Progressive Disease
Qualifying Criteria	All	All	All	Any
Brain lesions (volumetric MRI)				
Target	CR	≥ 50% volume decrease	< 50% volume decrease	≥ 40% volume increase
Non-target	None/CR	None/no progression		Progression
New	None			Yes
Steroids	Stable or decreasing			Increasing dose
Neurological signs/symptoms	Stable or improving			New or worsening
Systemic disease (RECIST)	No progression			Progression

13.7.4 Evaluation per RANO-BM[1] (primary endpoint for Cohorts 4A-4B and secondary endpoint for Cohorts 3A-3B)

Antitumor Effect –RANO-BM****

Tumor response and progression for CNS disease will be assessed centrally by the DF/HCC Tumor Imaging Metrics Core according to RANO-BM criteria. Please refer to the full publication for additional details.

Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria

a. Definitions

- Definition of Measurable Disease: Measurable disease is defined as a contrast enhancing lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm, visible on two or more axial slices that are preferably ≤ 5 mm apart with 0-mm skip (and ideally ≤ 1.5 mm apart with 0-mm skip). In addition, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. In the event the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least two times the slice thickness. If there are interslice gaps, this also needs to be considered in determining the minimum size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring ≥ 10 mm in longest diameter and ≥ 5 mm in the perpendicular plane. The cystic or surgical cavity should not be measured in determining response (Figure 1 in the original publication).
- Definition of Non-measurable Disease: All other lesions, including lesions with longest dimension < 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

b. Specifications of Methods of Measurement

- Method of Assessment: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. It is important to use imaging techniques that are consistent across all imaging time points in order to ensure that the assessment of interval appearance or disappearance of lesions or of change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging (for example, Appendix A of the original publication) is particularly important when evaluating lesions < 10 mm in LD and/or small changes in lesion size.
- Imaging Modality: Gadolinium-enhanced MRI is the best currently available, sensitive, and reproducible method to measure CNS lesions selected for response assessment.

Suggested brain MRI specifications are detailed in Appendix A of the original publication. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD). All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'.

c. Definition of Best Overall CNS Response

Best overall CNS response represents a composite of radiographic CNS target and non-target response (see definitions above), corticosteroid use, and clinical status. In non-randomized trials where CNS response is the primary endpoint, confirmation of PR or CR at least 4 weeks later is required to deem either one the best overall response. At each protocol-specified time point, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 1 shows the additional corticosteroid and clinical status requirements to deem a PR or CR.

d. Evaluation of Target Lesions

- **Complete response (CR):** Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.
- **Partial response (PR):** At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- **Progressive disease (PD):** At least a 20% increase in the sum LD of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the elative increase of 20%, at least one lesion must increase by an absolute value of ≥ 5 mm to be considered progression.
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD while on study.

e. Evaluation of Non-Target Lesions

Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.

- **CR:** Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

- **Non-CR/Non-PD:** Persistence of one or more non-target CNS lesion(s).
- **PD:** Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

Special Notes on the Assessment of Target and Non-Target CNS Lesions:

a) *Target lesions that become too small to measure:* While on study, all CNS target lesions should have their actual measurement recorded, even when very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) that the radiologist does not feel comfortable assigning an exact measure, a default value of 5 mm should be recorded on the case report form.

b) *Lesions that coalesce on treatment*: As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum LD of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum LD for the 'coalesced' lesion.

c) *Definition of new lesion(s):* The finding of a new CNS lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with ≤ 1.5 mm slice thickness, then the new lesion should also be visible in axial, coronal, and sagittal reconstructions of ≤ 1.5 mm projections. If a new lesion is equivocal, for example because of its small size (i.e., ≤ 5 mm), continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

d) *Definition of Unequivocal Progression of Non-Target Lesion(s):* When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease alone, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.

e) *Guidance in the Case of Uncertain Attribution of Radiographic Findings and/or Equivocal Cases:* If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is required to distinguish true progression versus treatment effect as standard MRI alone is not sufficient. Per protocol, the scan should be repeated at the next protocol scheduled evaluation or sooner, and generally within ~6 weeks. An investigator may choose a shorter time interval in the case of progressive symptoms or other clinically concerning findings. If there is continued increase in enhancement concerning for tumor growth, then this may be consistent with radiographic progression and the patient should be taken off study. If the lesion is stable or decreased in size, then this may be consistent with treatment effect and the patient may remain on study. For patients with equivocal results even on the next restaging scan, the scan may be repeated again at a subsequent protocol scheduled evaluation or sooner although surgery and/or use of an advanced imaging modality are strongly encouraged. Regardless of the additional testing obtained, if subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised. Patients may also have an equivocal finding on a scan (for example, a small lesion that is not clearly new). It is permissible to continue treatment until the next protocol scheduled evaluation. If the subsequent evaluation demonstrates that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Notes Regarding Corticosteroid Use and Clinical Deterioration:

a) An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression.

b) The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Summary of the Proposed RANO Response Criteria for CNS Metastases

Criterion	CR	PR	SD	PD
Target lesions	None	≥30% decrease in sum LD relative to baseline	<30% decrease relative to baseline but<20% increase in sum LD relative to nadir	≥20% increase in sum LD relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA+
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any+

Abbreviations: CNS = central nervous system; CR = complete response; LD= longest dimension; NA = not applicable; PD = progressive disease; PR= partial response; RANO= Response Assessment in Neuro-Oncology; SD = stable disease.

*Progression occurs when this criterion is met.
**New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy based approaches, new lesions alone to do not define progression (See "Guidance in the Case of New Lesion(s) while on Immunotherapy").
+Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Antitumor Effect – non-CNS disease

Response and progression in extracranial sites of metastases will be evaluated in this study using the international criteria proposed by the RECIST 1.1 criteria[79]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Definition of Measurable Disease: Measurable disease is defined as a contrast enhancing lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm, visible on two or more axial slices that are preferably </= 5 mm apart with 0-mm skip (and ideally </= 1.5 mm apart with 0-mm skip). In addition, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. In the event the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least two times the slice thickness. If there are interslice gaps, this also needs to be considered in determining the minimum size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring >/= 10 mm in longest diameter and >/=5 mm in the perpendicular plane. The cystic or surgical cavity should not be measured in determining response.

Definition of Non-measurable Disease: All other lesions, including lesions with longest dimension < 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

Specifications of Methods of Measurement

Method of Assessment: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. It is important to use imaging techniques that are consistent across all imaging timepoints in order to ensure that the assessment of interval appearance or disappearance of lesions or of change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging is particularly important when evaluating lesions < 10 mm in LD and/or small changes in lesion size.

Imaging Modality: Gadolinium-enhanced MRI is the best currently available, sensitive, and reproducible method to measure CNS lesions selected for response assessment. Suggested brain MRI specifications are detailed in Appendix A of the original publication. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD). All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or ‘unequivocal progression’.

Definition of Best Overall CNS Response

Best overall CNS response represents a composite of radiographic CNS target and non-target response (see definitions above), corticosteroid use, and clinical status. In non-randomized trials where CNS response is the primary endpoint, confirmation of PR or CR at least 4 weeks later is required to deem either one the best overall response. At each protocol-specified timepoint, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 1 shows the additional corticosteroid and clinical status requirements to deem a PR or CR.

Evaluation of Target Lesions

- **Complete response (CR):** Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.
- **Partial response (PR):** At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- **Progressive disease (PD):** At least a 20% increase in the sum LD of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm to be considered progression.
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD while on study.

Evaluation of Non-Target Lesions

Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

- **CR:** Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
- **Non-CR/Non-PD:** Persistence of one or more non-target CNS lesion(s).
- **PD:** Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions.

Special Notes on the Assessment of Target and Non-Target CNS Lesions:

a) *Target lesions that become too small to measure:* While on study, all CNS target lesions should have their actual measurement recorded, even when very small (*e.g.*, 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is

sufficiently small (but still present) that the radiologist does not feel comfortable assigning an exact measure, a default value of 5 mm should be recorded on the case report form.

b) *Lesions that coalesce on treatment:* As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum LD of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum LD for the 'coalesced' lesion.

c) *Definition of new lesion(s):* The finding of a new CNS lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with </= 1.5 mm slice thickness, then the new lesion should also be visible in axial, coronal, and sagittal reconstructions of </= 1.5 mm projections. If a new lesion is equivocal, for example because of its small size (*i.e.*, </= 5 mm), continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion.

d) Definition of Unequivocal Progression of Non-Target Lesion(s): When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease alone, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. *When the patient has only non-measurable disease,* there must be an overall level of substantial worsening to merit discontinuation of therapy.

Guidance in the Case of Uncertain Attribution of Radiographic Findings and/or Equivocal Cases: The RANO-BM group acknowledges that in the case of patients followed after SRS or during immunotherapy-based approaches, there may be radiographic evidence of enlargement of target and non-target lesions which may not necessarily represent tumor progression. If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is required to distinguish true progression versus treatment effect as standard MRI alone is not sufficient. The methods used to distinguish between the two entities should be specified prospectively in the clinical protocol. Patients may be continued on protocol therapy pending further investigation with one or more of the following options: (1) Repeat the scan at the next protocol scheduled evaluation or sooner, and generally within ~6 weeks. An investigator may choose a shorter time interval in the case of progressive symptoms or other clinically concerning findings. If there is continued increase in enhancement concerning for tumor growth, then this may be consistent with radiographic progression and the patient should be taken off study. If the lesion is stable or decreased in size, then this may be consistent with treatment effect

and the patient may remain on study. For patients with equivocal results even on the next restaging scan, the scan may be repeated again at a subsequent protocol scheduled evaluation or sooner although surgery and/or use of an advanced imaging modality (in the case of SRS) are strongly encouraged. (2) Surgical pathology obtained via biopsy or resection. (3) For SRS treated lesions, an advanced imaging modality such as perfusion MR imaging, MR spectroscopy, or 18FLT or 18FDG positron emission tomography (PET) may be used as additional evidence of tumor progression or treatment effect/radionecrosis. Upon review of the literature and extensive discussions by the Working Group, we were not able to conclude that any one modality or approach can be recommended across all patients to distinguish between radiation necrosis versus true progression, as the literature is not sufficiently robust, and recommend clinical judgment and involvement of a multidisciplinary team. We recognize this is less than satisfactory and agree that developing more sensitive and specific methods for distinguishing between treatment effect and tumor progression are needed.

Regardless of the additional testing obtained, if subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised. Patients may also have an equivocal finding on a scan (for example, a small lesion that is not clearly new). It is permissible to continue treatment until the next protocol scheduled evaluation. If the subsequent evaluation demonstrates that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Notes Regarding Corticosteroid Use and Clinical Deterioration:
a) An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression.

b) The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a significant decline in performance status be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose

DEFINING RESPONSE IN NON-CNS SITES (note: This will occur centrally by TIMC at Dana-Farber /Harvard Cancer Center Sites for Cohorts 3A/3B and Cohorts 4A-4C only and will otherwise be done by local read for all cohorts for sites outside DF/HCC)

13.7.5 Evaluation of Target non-CNS Lesions:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- **Partial Response (PR)**: At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the unequivocal appearance of one or more new lesions is also considered progression.)
- Stable Disease (SD) ((non-CR, non-PD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
- Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data are missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data are available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease.

13.7.6 Delays in central review (all Cohorts)

In the case of delays in uploading/reporting brain imaging results to/from the TIMC (or for delays in reads for non-CNS lesions in Cohorts 3A/3B), patients may continue on therapy while awaiting central review IF disease progression on local review has not occurred. Progression in this case will be defined as the following:

- progressive disease in the CNS, evidenced by an increase of greater than 20% in the sum of the longest diameters of target lesions AND an absolute increase in the size of ≥5 mm in at least one target lesion, taking as reference the smallest sum longest dimension recorded since the treatment started; or, the appearance of one or more new lesions ≥6 mm
- progressive disease in extra-CNS sites by RECIST 1.1 criteria
- Note that for the purposes of calculation of response rate and time to progression, volumetric criteria will be used to assess CNS disease, as specified in the protocol. However, because volumetric analyses may not be conducted in real-time for clinical decision-making, the above criteria, based on longest dimension, will be used to determine whether a patient should continue on therapy.
- If it is unclear whether radiographic changes are related to disease progression (for example, if changes could be due to radiation necrosis or infection), then additional imaging and other tests should be conducted as clinically indicated. If a patient fulfills criteria for disease progression as defined by increase in sum longest dimension of target lesions but confirmatory studies indicate that the findings are not due to progression, the patient may remain on study, provided that clear justification is documented in the patient record and in the case report form.

13.7.7 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
CR	CR	No	CR

PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

For Patients with *Non-Measurable* Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	NonCR/non-PD
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

13.7.8 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13.7.9 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression, second cancer, or death, whichever occurs first. Included in the definition of progression for PFS are: objective progression of CNS lesions on imaging, neurologic deterioration leading to study discontinuation, global deterioration of health status requiring discontinuation of treatment, objective progression of non-CNS lesions, and death. If a patient discontinues study treatment because of toxicity, that will not be counted toward the PFS rate. For neurologic symptoms, the default will be to assume that worsening of neurologic symptoms requiring discontinuation of treatment is related to progressive disease. All such events will be adjudicated according to the Neurological Examination Worksheet (see Appendix E), supplemented by referral to the medical record, as appropriate.

13.7.10 Response Review

All brain MRI scans (or CT head with contrast if MRI contraindicated) will be reviewed centrally by the DF/HCC Tumor Imaging Metrics Core (TIMC). CNS response will be assessed centrally using the criteria outlined. MRI imaging should occur as delineated above during approximately 48-96 hours prior to the start of the next cycle for all Cohorts in order to allow sufficient time for central review prior to next cycle initiation. For example, for a patient completing cycle 2 who is undergoing re-staging, brain imaging should occur 2-3 days prior to initiation of cycle 3 for all Cohorts (days 17-19 on Cohorts 3A/3B and extension phase where cycle length is 21 days AND days 24-26 for Cohorts 1,2 where cycle length is 28 days). Please see Appendix F for details on imaging requirements and image transfer. Non-CNS scans will be evaluated and recorded in the study-specific case report forms (CRFs) by individual site personnel. However, for Cohorts 3A/3B, non-CNS scans will also be read centrally for DF/HCC patients only. Centralized measurements of non-CNS sites will not be performed as part of this study for all participants on Cohorts 1,2 and for non-DF/HCC sites for Cohorts 3A/3B and Cohorts 4A-4C.

13.7.11 Other Response parameters

Neurological Signs and Symptoms (NSS)
Tumor-associated NSS will be recorded on Appendix E at each study visit for Cohorts 1-3 ONLY. Improvement or worsening of non-tumor associated NSS, will not constitute a change in NSS.

Appendix E contains a global question for the treating investigator, asking whether a patient's neurological status is improved, stable, or worse. The response to this question

will be used in the response criteria as specified in *Section 12.7.3* and will also be analyzed in relation to the itemized portion of the NSS worksheet, in order to further evaluate the utility of the worksheet in evaluating NSS longitudinally over time.

For this analysis, we will describe the correlation between response to the global definition and improvement in the itemized portion, defined as follows:
Improvement of NSS will be defined if all of the following are satisfied:

- Decrease by 1 or more grades from baseline of any tumor-related NSS, with confirmation at least 4 weeks (1 cycle) later
- No development or worsening in any tumor related NSS during this interval
- Stable or decreasing steroids during this interval

For analysis, we will use the form most closely aligned with the time of staging, unless clear clinical progression is documented before the next staging scans are completed.

General Impression Worksheet (Appendix D) – **Cohort 4 only-**
This should be filled out by the provider at each study visit on day 1 of each cycle. For analysis, we will use the form most closely aligned with the time of staging, unless clear clinical progression is documented before the next staging scans are completed

14. Adverse Event Reporting Requirements

14.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

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

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

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

In the event of an adverse event, the first concern will be for the safety of the participant. Investigators are required to report to the Principal Investigator, the TBCRC, and ANY serious treatment-related, emergent, adverse event as soon as possible.

14.2 Definitions

14.2.1 Adverse Event (AE)

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

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

14.2.2 Serious Adverse Event (SAE)

A serious adverse event is any sign, symptom or medical condition that emerges during neratinib treatment or during a post-treatment follow-up period that (1) was not present at the start of neratinib treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of neratinib treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria below:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

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

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures

- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

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

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk. Refer to *Section 6.1* for a listing of expected adverse events associated with neratinib.
- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

14.2.3 Attribution

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

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is probably related to the study treatment.
- Possible – The AE is possibly related to the study treatment.
- Unlikely - The AE is unlikely related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

14.3 Reporting Procedures

14.3.1 General

All adverse events will be captured on the appropriate CRFs. Reporting participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate CRFs.

The descriptions and grading scales found in the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting.

The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.

14.3.2 Reporting Requirements

Each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described in Section 13.4.

14.3.3 Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 30 days or five half-lives after the treatment periods, whichever is longer. The status of the mother and child (if applicable) should be reported to Puma Biotechnology, Inc. after delivery.

14.4 Reporting to the Overall PI, IRB, TBCRC, Puma Biotechnology, Inc., and the FDA

14.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of treatment, during treatment, or within 30 days of the last dose, regardless of causality to study drug, will be reported to the DF/HCC Principal Investigator (*Section 14.4.2*). Events that meet reporting criteria should also be reported to the IRB (*Sections 14.4.3 and 14.4.4*), the TBCRC (*Section 14.4.5*), Puma Biotechnology, Inc. (*Section 14.4.6*), and the FDA (*Section 14.4.7*). This includes events meeting the criteria outlined in *Section 14.2.2*, as well as the following:

- Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

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

14.4.2 Reporting to the DF/HCC Principal Investigator

All serious adverse events must be reported to the DFCI investigator within 24 hours of the event. Notification of this serious adverse event must be sent to [redacted] Events should be reported using a MedWatch form (3500A) as available on the FDA website (see link below). Report serious adverse events by email to:

[redacted]

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

14.4.3 Reporting to Institutional Review Board

DF/HCC institutions must report all SAEs directly to the DFCI IRB using the DFCI IRB-serious advent reporting form found on the Oncology Protocol System website in addition to notifying the PI. All other participating institutions' SAE report notifications will be reviewed by the lead institution to determine if the event(s) meets DFCI IRB SAE reporting requirements. If the event does meet the DFCI IRB reporting requirements, the study coordinator or designee will submit the event information to the DFCI IRB using the DFCI IRB IND Safety Reporting Form.

For non-DF/HCC institutions, all adverse events and serious adverse events will be reported to the participating center's IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

14.4.4 Reporting to the IRB for non-DF/HCC Institutions

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

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

Overall Principal Investigator

[redacted]

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

14.4.5 Reporting to TBCRC

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

14.4.6 Prompt Reporting of SAEs to Puma Biotechnology, Inc.

All serious adverse events, in addition to being reported to the participating sites' IRB of record and to the PI, must be reported by e-mail by the Coordinating Center (DFCI) to Puma Biotechnology Inc. Drug Safety within 24 business hours via the form provided in Appendix I. E-mail this form to:

Puma Biotechnology, Inc Drug Safety at: **PumaSAE@parexel.com**

The Lead Site (DFCI) Team is responsible for SAE reporting to Puma Biotechnology, Inc. and FDA.

The SAE report should comprise a full written summary, detailing the relevant aspects of the adverse event in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Puma Biotechnology, Inc. Drug Safety within 24 hours at the fax number or phone number listed above.

Instances of death or congenital abnormality, if brought to the attention of the investigator, AT ANY TIME, after cessation of study medication and linked by the investigator to a previous clinical trial, should be reported immediately.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate SAE and AE reports. However, there may be instances were Puma Biotechnology, Inc. will request copies of medical records for certain cases. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to Puma Biotechnology, Inc.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and the individual signs/symptoms.

14.4.7 Food and Drug Administration (FDA)

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

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

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

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

14.5 Non-Serious Adverse Event Reporting

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

14.6 Reporting to Hospital Risk Management

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

14.7 Monitoring of Adverse Events and Period of Observation

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

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

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

15. DATA AND SAFETY MONITORINIG (See Appendix N for further information)

15.1 Data Management and Reporting

The ODQ at Dana-Farber will collect, manage, and monitor data for this study for this study. Please refer to Appendix N for more information concerning the completion and submission scheduled for the eCRFs to ODQ and the monitoring/auditing plan.

15.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with ODQ
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration

Cognitive testing forms and demographic sheet (Cohort 1 only)	Within 10 days of each testing session (baseline, cycle 3 day 1, progression). To be submitted separately to Dr. Wefel at MD Anderson.
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

15.3 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; 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. For a more detailed description of the Data and Safety Monitoring Plan, please see Appendix N.

15.4 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. See Appendix N for more detailed information on Monitoring.

16. REGULATORY CONSIDERATIONS

16.1 Protocol Review and Amendments

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

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

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

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

16.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant must be obtained before the participant is involved in any study-related procedure. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved.

The investigator will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained. **Please note: to**

adhere to DFCI policies only physicians are allowed to consent patients to trials with more than minimal risk to patient.

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

16.3 Research Ethics and Practice

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

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

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

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

17. MULTI-CENTER GUIDELINES

17.1 Study Documentation

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

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

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

The requirements for data management, submissions, and monitoring are outlined below.

17.2 Records Retention

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

17.3 Publication Plan

Upon completion of protocol accrual, the results of the primary and secondary endpoints will be submitted for poster presentations at the American Society of Clinical Oncology annual meeting or the San Antonio Breast Cancer Symposium, depending on the timing of availability of results. Final results will be submitted for publication in a peer reviewed scientific journal within 2 years of the date of completion and will be available to the public at that time. This manuscript will contain the full report of results from all study endpoints and exploratory endpoints. The principal investigator will have access to all study data, will lead the data analysis, and will to hold primary responsibility for publication and poster presentation of all study results. Puma Biotechnology, Inc. collaborators and the TBCRC investigators will be provided all manuscripts and abstracts prior to submission to review data and provide comments. Final approval of all submitted work will be made by the principal investigator. In addition, it is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation.

18. STATISTICAL CONSIDERATIONS

18.1 Study Design and Endpoints

This is a series of open-label, single-arm phase 2 trials for patients with HER2-postive metastatic breast cancer and measurable CNS disease. Neratinib, an agent with promising clinical activity in patients with HER2-positive cancers, will be given at a starting dose of 240 mg orally daily without breaks. Cycle duration will be 4 weeks for Cohorts 1 and 2 and 3 weeks for Cohorts 3 and 4.

Patients in Cohort 1 will be evaluated on day 1 of each cycle for toxicity and will be re-staged every 2 cycles (8 weeks) with MRI of the brain (or CT head with contrast if MRI contraindicated) as well as non-CNS imaging (with CT or MRI) to evaluate non-CNS response. Patients will remain on study until progression, unacceptable toxicity, or withdrawal of consent. If patients are found to have non-CNS progression, an option to receive concurrent trastuzumab and neratinib will be offered. Additional correlative studies will also be included.

For Cohorts 3A and 3B, neratinib and capecitabine will be administered at a starting dose of 240 mg once daily and 750 mg/m2 twice daily over the course of a 21-day cycle. Neratinib will be administered without treatment breaks and capecitabine will be administered for days 1-14 followed by 7 days of rest. These Cohorts will be analyzed separately from one another and separately from Cohorts 1 and 2 and will have a primary endpoint of objective response rate by composite criteria. Patients will be evaluated on day 1 of each cycle for toxicity and will be re-staged every 2 cycles (6 weeks) with MRI of the brain (or CT head with contrast if MRI contraindicated) as well as non-CNS imaging (with CT or MRI) to evaluate non-CNS response. Once three staging evaluations have passed (i.e. 18 weeks on study), patients will transition to re-staging every 3 cycles (9 weeks). Patients will remain on study treatments until progression, unacceptable toxicity, or withdrawal of consent. Additional correlative studies will also be included. Of note, Cohorts 3A/3B will not include participants crossing over from neratinib alone but will enroll patients separately, once Cohort 1 has completed accrual.

For Cohorts 4A, 4B, 4C, neratinib and T-DM1 will be administered at starting doses of 160 mg once daily orally and 3.6 mg/kg IV every 21 days, respectively. Neratinib will be administered without treatment breaks. Each Cohort 4 sub-group (A, B, C) will be analyzed separately from one another and separately from Cohorts 1-3 with a primary endpoint of CNS response by RANO-BM criteria. Patients will be evaluated on day 1 of each cycle for toxicity and will be re-staged every 2 cycles (6 weeks) with imaging of the brain and chest/abdomen/pelvis. Once three staging evaluations have passed (i.e. 18 weeks on study), patients will transition to re-staging every 3 cycles (9 weeks). Patients will remain on study treatments until progression, unacceptable toxicity, or withdrawal of consent. Additional correlative studies will also be included.

The study population for Cohorts 1, 3A/3B, 4B/4C will include patients with HER2-positive, metastatic breast cancer with CNS involvement, who have progressed after at least one line of standard treatment for CNS disease (i.e. WBRT, SRS, or surgical resection). Treatment options for such patients are limited and there are no FDA-approved systemic therapies for this indication. The largest prospective trial in such a setting is the phase II study of lapatinib monotherapy, in which the CNS objective response rate was 6%.[24] These results demonstrate proof-of-principle that small molecule inhibitors targeting HER2 have the potential for CNS efficacy. At the same time, there is substantial room for improvement. Our planned correlative analyses will also allow further understanding of potential predictors of treatment benefit, concentrations of neratinib in the CNS, and overall survival for patients with metastatic CNS disease.

18.2 Primary Endpoint

The primary efficacy parameter is the objective response rate (CR+PR) in the CNS for patients in Cohort 1, 3A, and 3B (using composite criteria) and 4A, 4B, and 4C (using RANO-BM criteria). Each cohort will be analyzed separately and independently.[24] Measurements of CNS lesions will be performed centrally by the Harvard Tumor Imaging Metrics Core (TIMC). For the composite criteria, an objective PR will be defined as ≥50% reduction in sum volume of CNS target lesions, without evidence of new lesions, systemic disease progression, worsening neurological symptoms, or increase in corticosteroid dose. For the RANO-BM criteria, an objective PR will be defined as the following: ≥30% decrease in the sum of longest diameters of CNS disease for ≥4 weeks with no new lesions, stable/improved clinical condition, and stable/decreased corticosteroid dose. A 95% confidence interval will be calculated around the rate of ORR in the CNS.

We have previously reported a CNS objective response rate of 6% (exact 95% CI 3.6% to 10.2%) with single-agent lapatinib, and 20% with the combination of lapatinib and capecitabine in the extension phase of the study, and have based our sample size calculations for Cohort 1 on these findings.[24]

COHORT 1 will have a two-stage design with an estimated total accrual of 40 patients. In the first stage, 18 patients will be enrolled. If none of the 18 patients has a response in the CNS, the trial will end accrual early. If at least 1 of the 18 patients has a response, another 22 patients will be entered on study (for a total of 40). At the time of Cohort 1, previous data demonstrated comparable responses in lapatinib-treated and lapatinib-naïve patients, so both types of patients were analyzed together in Cohort 1. All patients who receive one dose of study drug will be evaluable and included in analyses. If eligible and consented patients drop-out before initiation of protocol therapy, they will not be included in analyses. If patients fail screening or are registered but never start protocol therapy, they will be replaced to meet initial accrual goals.

With this design, if at least 5 of these 40 patients achieve a CNS response, the drug will be deemed worthy of future study. This two-stage design has 92% power to detect a response of at least 20% against the null of 6% while maintaining a one-sided type I error rate of 9%. The observed ORR of 12.5% would exceed the upper confidence limit of Lin and colleagues' multicenter study with lapatinib (ORR 6%, 95% CI 3.6% to 10.2%).[24] If the true ORR (in the brain, without prior progression in non-CNS site) is 6%, then the probability of stopping accrual early is 33%. If the true ORR is 15%, then the probability of stopping early is 5% and if the true ORR is 20%, the probability of stopping early is 2%. If the true ORR is 6%, 15%, or 20%, then the probability of deciding neratinib is worthy of further research is 9%, 72%, and 92%, respectively.

We realize this trial is designed with a relatively low probability of stopping early if the true response rate is as low as 6%, but this patient group has limited treatment options. Nearly all patients will have had prior chemotherapy for metastases, and most of them will have had prior radiotherapy for brain metastases. Most patients will have had prior trastuzumab as well. In this difficult clinical situation, we have chosen to allow a higher threshold in the first stage to declare the drug unworthy of further study.

COHORT 3A

For Cohort 3A, a two-stage design will also be utilized with an estimated total accrual of 35 patients. In the first stage, 19 patients will be enrolled. If at least 5 of the 19 patients have a response in the CNS, then another 16 patients will be enrolled (for total of 35). Because previous data have demonstrated lower responses in patients with prior lapatinib, participants with prior lapatinib use (and/or capecitabine use) willbe excluded from this Cohort. All patients who receive one dose of study drug will be evaluable and included in analyses. If eligible and consented patients drop-out before initiation of protocol therapy, they will not be included in analyses.

With this design, if at least 9 of the 35 (26%) are observed to have an objective response in brain, then the combination of neratinib and capecitabine will be considered worthy of further research. If the true response rate of the combination is 15%, there will be an 86% chance of stopping accrual early, and only a 5% chance of declaring the combination worthy of further research. If the true response rate of the combination is 35%, there will be a 15% chance of stopping accrual early, and an 80% chance of declaring the combination worthy of further research. This was designed so that we would be able to comfortably assess whether the CNS ORR of the combination (capecitabine and neratinib) is more promising as a combination than capecitabine alone. Estimating the historical ORR with capecitabine alone is somewhat challenging because of the lack of robust trials examining monotherapy in the CNS. However, from what has been reported, capecitabine alone was associated with a 14% ORR in non-CNS sites in Geyer et al's trial of capecitabine vs. capecitabine-lapatinib[81] and an 18% CNS ORR when given with temozolomide in a small study performed at MD Anderson.[35] Although the Geyer paper did not assess CNS response as a primary

endpoint, one would assume that the CNS ORR would not exceed the observed ORR in non-CNS sites. In addition, given that the combination of lapatinib and capecitabine was associated with a CNS ORR of 20% in patients who had progressed on lapatinib monotherapy,[24] the alternative hypothesis of reaching a CNS ORR of 35% was selected so that the current combination would have to demonstrate promising efficacy that exceeds that reported with capecitabine and lapatinib in order to move on for further study (as compared to historical ORR for the capecitabine-lapatinib combination).

COHORT 3B

In this two-stage Cohort, 15 patients will be entered in the first stage. If at least 2 of them have an objective response (PR or CR) in brain, then another 10 patients will be entered (for a total of 25). If at least 3 of the 25 (12%) are observed to have an objective response in brain, then the combination of neratinib and capecitabine will be considered worthy of further research. If the true response rate of the combination is 5%, there will be an 83% chance of stopping accrual early, and only a 9% chance of declaring the combination worthy of further research. If the true response rate of the combination is 20%, there will be a 17% chance of stopping accrual early, and an 81% chance of declaring the combination worthy of further research.

COHORTS 4A, 4B, and 4C (up to 24 in Cohort 4C):

The primary efficacy endpoint is ORR using the RANO-BM criteria. The only available data on T-DM1 CNS response using the RANO-BM criteria come from the Bartsch et al study,[10] in which 3 of 10 patients had a PR (observed 30%, 80% CI of 12% to 55%).

Cohorts 4A and 4B can have had prior chemotherapy, but not prior T-DM1. Cohort 4A will not have prior CNS radiation or surgery; Cohort 4B will have had some CNS progression after prior WBRT, craniotomy, and/or prior SRS. The accrual goal for each of these Cohorts is 20 patients. Cohort 4A and 4B efficacy results will be analyzed separately and not combined.

In each Cohort, if at least 10 of the 20 patients have a CNS response, the combination will be deemed worthy of future study. This design has power of 80% for a true ORR of 57% and will have a one-sided type I error rate of 5% for a true ORR of 30%.

Cohort 4C subjects are required to have progressed on T-DM1 (although the progression may have been in either non-CNS metastatic sites or CNS metastatic sites or both). So we assume the response rate will be lower than in Cohorts 4A and 4B. In Cohort 1 of this protocol, 5% of the 40 patients treated with neratinib alone had a CNS response using the RANO-BM criteria, so 5% serves as the null hypothesis. This Cohort will have a two-stage design with up to a total accrual of 24 patients. In the first stage, 10 patients will be enrolled. If none of the 10 has a CNS response using the RANO-BM criteria, then accrual will end early. If at least 1 of the 10 has a CNS response

using the RANO-BM criteria, then another 14 patients will be entered on this Cohort (for a total of 24). If at least 3 of the 24 have a CNS response, then the combination will be considered worthy of future study in patients who have progressed on T-DM1. With this design, if the true RANO-BM response rate in this group is 5%, then there will be a 60% chance of stopping accrual at 10 patients and there will be only a 10% chance of deeming the combination to be worthy of future study (i.e., a one-sided type I error rate of 10%). If the true RANO-BM response rate is 24% then there will be a 6% chance of stopping accrual at 10 patients and a 91% chance of deeming the combination worthy of further study in this subset.

18.3 Sample Size/Accrual Rate

The total planned sample size for Cohort 1 is 40 patients. Cohort 2 will include up to 5 patients. Cohorts 3A and 3B were to enroll up to 60 additional patients. It was estimated that accrual to these two Cohorts would be 1-3 patients per month in total. These cohorts have closed to enrollment.

Cohorts 4A and 4B are planned to accrue 20 patients each. If the first stage is passed for Cohort 4C (with 1 responder in the first 9 enrolled), the second stage will open (n=14) for a total maximum sample size of 24, so these three cohorts are expected to accrue a total of 50-64 patients. The estimated accrual rate for Cohorts 4A-4C will be 2-4 per month. The estimated duration of accrual for Cohorts 4A-4C is 13-32 months after these cohorts open. Patients on all cohorts will be followed for up to two years after removal from study or until death, whichever occurs first.

18.4 Stratification Factors

Although we will not stratify patients at enrollment, we will repeat ORR calculations in various subgroups as secondary/explanatory endpoints, i.e. lapatinib-naïve and lapatinib-treated

18.5 Analysis of Secondary (and Clinical Exploratory) Endpoints

Secondary endpoints for Cohorts 1, 3A/3B, and 4A/B/C will include PFS, OS, CNS response by Macdonald criteria[2], first site disease progression, , safety and tolerability of therapy, and ORR in the CNS for lapatinib-treated and naïve patients (For Cohort 2, we will calculate PFS). All patients who receive at least one cycle of therapy with neratinib, capecitabine, or T-DM1 will be considered evaluable for secondary endpoint analysis. All patients will have central review of brain imaging at TIMC.

- PFS and OS will be estimated by Kaplan Meier Methods and 95% confidence curves will be estimated. Median PFS and OS will be calculated.
- First site of disease progression and safety and tolerability will be tabulated.
- Safety and tolerability of therapy (to be tabulated by frequency)
- CNS ORR (as defined by Macdonald)[2] (Cohort 1 only) will be calculated (with a 95% CI)

- ORR in the CNS for lapatinib-naïve patients vs. those in lapatinib-treated patients (to be calculated as above, with 95% CI provided) (for Cohort 1 only)
- PFS will be calculated in patients who underwent craniotomy (Cohort 2, n ≤ 5)

18.6 Analysis of Exploratory Endpoints

18.6.1 CTC Correlative Studies (Cohorts 1 and 2 only)

The CTC analysis for participants on Cohort 1 will combine samples from patients who are enrolled on one of two protocols for patients with metastatic breast cancer to the CNS: (1) proposed neratinib trial (Cohorts 1 and 2, n=45) and (2) current trial at Dana-Farber which administers carboplatin and bevacizumab (n=40) (with trastuzumab if HER2-positive). Assuming neither protocol closes early, there will be ≈80 patient samples included for analysis. Based upon prior data, the observed median survival in patients with refractory brain metastases was 6.4 months, and about 55% survived past 6 months.[24] We will test whether the percent of patients living past 6 months (after study entry) in the group with < 5 CTC/7.5 mL of whole blood is significantly greater than the percent of patients living past 6 months in the group with ≥5 CTC/7.5 mL (one-sided Fisher exact test). The threshold of 5 CTC/7.5 mL was chosen because of previously reported data demonstrating differing prognoses for patients with more than or less than 5 CTC/7.5 mL whole blood.[40] In our study, if 40 of 80 patients have <5 CTC/7.5 mL, there will be 0.80 power to declare the group with low CTC count to have better survival if the true probability of surviving past 6 months is 70% in that group and 40% in the group with ≥ 5 CTC/7.5 mL. Because this is an exploratory analysis, there will be no adjustment for doing 2 comparisons, one based on baseline CTC and one based on cycle 1 CTC.

All other tubes will be processed in the laboratory of Dr. Ian Krop for FISH analysis and other molecular analyses. For patients with HER2-positive breast cancer, FISH for HER2, centromere 17, and MET will be performed. These remaining correlative CTC studies are exploratory and will be hypothesis-generating only (Cohorts 1 and 3)

18.6.2 Neratinib concentrations (Cohort 2 only)

In exploratory analyses, concentrations of neratinib and its metabolites will be performed by Covance using CSF and plasma specimens. Craniotomy specimens will be tested for neratinib concentrations by Dr. Nathalie Agar at Brigham and Women's. The relationship between neratinib's brain tumor (and/or CSF) concentration and plasma concentration will be tabulated by calculating concentration ratios. These analyses will be purely exploratory as these assays have been developed primarily for this protocol. If further CSF is required for technical reasons or if the investigators feel that additional samples would aid analyses, permission for further CSF collection may be requested in a forthcoming addendum.

18.6.3 Neurocognitive Function Correlatives (Cohort 1 only)

We will compare baseline and follow up cognitive testing performance among patients in Cohort 1 (some of whom have had WBRT, SRS, surgery, or a combination of therapies). The results of this analysis will be exploratory since we do not know the number of patients who will be enrolled who have had WBRT alone, SRS alone, or both treatment modalities. We will compare changes in scores over time among patients who achieve a complete or partial response or prolonged stable disease (>4 months) in the central nervous system to those who progress at or before the week 8 testing.

18.6.4 Endpoints for Those on Optional Extension Study (all Cohorts)

Patients who opt to receive concurrent therapy when their disease progresses outside of the CNS will be followed for toxicity, CNS and non-CNS response, site of first progression, and OS. The number of patients expected to enroll on this phase is small and all analyses will be exploratory only.

18.6.5 ctDNA

We will explore mutational changes using ctDNA within blood for all patients at baseline, C2 and progression to understand the change in mutational load and type of mutations seen over time. Given the lack of data on ctDNA evolution for patients with CNS disease, we will report all outcomes descriptively, including changes seen in patients over time and compared to patients treated in other Cohorts (within 4A-4C) who have different treatment exposures. We will explore these results for patients with and without extracranial disease. All of this will provide important, preliminary data to support future study.

18.6.6 Diarrhea, adherence to anti-diarrheal medications, and patient-reported outcomes (Cohorts 4A-4C)

PROs related to diarrhea will be reported as exploratory endpoints in patients participating in Cohorts 4A-C. Scores on the PRO-CTCAE questions collected day 1 of cycles 1-4 and day 10 of cycle 1 will be reported over time using descriptive statistics. Similarly, scores on the STIDAT[5] and PROMIS[4] questionnaires collected day 1 of cycles 1-4 will be reported over time using descriptive statistics. In addition, we will tabulate differences between severity of diarrhea and other gastrointestinal symptoms as reported on the PRO-CTCAE questions and clinician-assessed diarrhea and other gastrointestinal toxicities using standard CTCAE grading. Diarrhea as documented by patient diaries will also be summarized for each severity category of the PRO-CTCAE and the clinician severity category. We will describe adherence to recommended anti-diarrheal prophylaxis during cycle 1 by describing patient diary submissions and results of the Voils Extent of Non-adherence questionnaire. The association between adherence and diarrhea severity will be evaluated on an exploratory basis. Patient-reported skipped doses of neratinib due to

gastrointestinal toxicity and skipped doses of anti-diarrheal medication due to constipation or other side effects will be evaluated on an exploratory basis. Use of anti-diarrheal therapy during cycles 2 and 3 will be described based on patient diary submissions. Given the small numbers and the exploratory nature of the PRO evaluations in this study, we do not aim to assess an *a prior*i hypothesis regarding diarrhea, but rather to simply describe the patient experience.

18. REFERENCES

1. Macdonald DR, Cascino TL, Schold SC, Jr., et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-80, 1990
2. Rabindran SK, Discafani CM, Rosfjord EC, et al: Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res 64:3958-65, 2004
3. Yarden Y: The EGFR family and its ligands in human cancer. signalling mechanisms and therapeutic opportunities. Eur J Cancer 37 Suppl 4:S3-8, 2001
4. Gschwind A, Fischer OM, Ullrich A: The discovery of receptor tyrosine kinases: targets for cancer therapy. Nat Rev Cancer 4:361-70, 2004
5. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-82, 1987
6. Lin NU, Winer EP: Brain metastases: the HER2 paradigm. Clin Cancer Res 13:1648-55, 2007
7. Eichler AF, Kuter I, Ryan P, et al: Survival in patients with brain metastases from breast cancer: the importance of HER-2 status. Cancer 112:2359-67, 2008
8. Gori S, Rimondini S, De Angelis V, et al: Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: incidence, survival, and risk factors. Oncologist 12:766-73, 2007
9. Lin NU, Carey LA, Liu MC, et al: Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 26:1993-9, 2008
10. Lin NU, Dieras V, Paul D, et al: Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 15:1452-9, 2009
11. Wong KK, Fracasso PM, Bukowski RM, et al: A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. Clin Cancer Res 15:2552-8, 2009
12. Burstein HJ, Sun Y, Dirix LY, et al: Neratinib, an Irreversible ErbB Receptor Tyrosine Kinase Inhibitor, in Patients With Advanced ErbB2-Positive Breast Cancer. J Clin Oncol
13. Awada A, Dirix L, Beck HL, et al: Safety and Efficacy of Neratinib (HKI-272) in Combination with Vinorelbine in ErbB2+ Metastatic Breast Cancer. Presented at the San Antonio Breast Cancer Symposium, December 2009. .
14. Chow L, Gupta S, Hershman D, et al: Safety and Efficacy of Neratinib (HKI-272) in Combination with Paclitaxel in ErbB2+ Metastatic Breast Cancer. Presented at the San Antonio Breast Cancer Symposium, December 2009.
15. Saura C, Martin M, Moroose R, et al: Safety of Neratinib (HKI-272) in Combination with Capecitabine in Patients with Solid Tumors: A Phase 1/2 Study. Presented at the San Antonio Breast Cancer Symposium, December 2009.
16. Kuhn JG, Robbins H, Mehta M, et al: Tumor Sequestration of Lapatinib (NABTC 04-01). Neuro Oncol 10(5):783 (Abstract ET-05). 2008
17. Polli JW, Humphreys JE, Harmon KA, et al: The role of efflux and uptake transporters in [N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine (GW572016, lapatinib) disposition and drug interactions. Drug Metab Dispos 36:695-701, 2008

18. Blum JL, Jones SE, Buzdar AU, et al: Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17:485-93, 1999

19. O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20:2812-23, 2002

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

21. Rivera E, Meyers C, Groves M, et al: Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. Cancer 107:1348-54, 2006

22. Burstein HJ, Storniolo AM, Franco S, et al: A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. Ann Oncol 19:1068-74, 2008

23. Cristofanilli M, Budd GT, Ellis MJ, et al: Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 351:781-91, 2004

24. Liu MC, Shields PG, Warren RD, et al: Circulating tumor cells: a useful predictor of treatment efficacy in metastatic breast cancer. J Clin Oncol 27:5153-9, 2009

25. Bianco AR, Shin I, Ritter C, et al: Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors. Oncogene 22:2812-2822, 2005

26. Gomez H, Doval DC, Chavez MA, et al: Biomarker results from a phase II randomized study of lapatinib as first-line treatment for patients with ErbB2 FISH-amplified advanced or metastatic breast cancer. Presented at the San Antonio Breast Cancer Symposium, abstract 1071, 2005., 2005

27. Jo M, Stolz DB, Esplen JE, et al: Cross-talk between epidermal growth factor receptor and c-Met signal pathways in transformed cells. J Biol Chem 275:8806-11, 2000

28. Agarwal S, Zerillo C, Kolmakova J, et al: Association of constitutively activated hepatocyte growth factor receptor (Met) with resistance to a dual EGFR/Her2 inhibitor in non-small-cell lung cancer cells. Br J Cancer 100:941-9, 2009

29. McCune BK, Earp HS: The epidermal growth factor receptor tyrosine kinase in liver epithelial cells. The effect of ligand-dependent changes in cellular location. J Biol Chem 264:15501-7, 1989

30. Alroy I, Yarden Y: The ErbB signaling network in embryogenesis and oncogenesis: signal diversification through combinatorial ligand-receptor interactions. FEBS Lett 410:83-6, 1997

31. Burgering BM, Coffer PJ: Protein kinase B (c-Akt) in phosphatidylinositol-3-OH kinase signal transduction. Nature 376:599-602, 1995

32. Liu W, Li J, Roth RA: Heregulin regulation of Akt/protein kinase B in breast cancer cells. Biochem Biophys Res Commun 261:897-903, 1999

33. Muthuswamy SK, Gilman M, Brugge JS: Controlled dimerization of ErbB receptors provides evidence for differential signaling by homo- and heterodimers. Mol Cell Biol 19:6845-57, 1999

34. Chan TO, Rittenhouse SE, Tsichlis PN: AKT/PKB and other D3 phosphoinositide-regulated kinases: kinase activation by phosphoinositide-dependent phosphorylation. Annu Rev Biochem 68:965-1014, 1999

35. Klijn JG, Berns PM, Schmitz PI, et al: The clinical significance of epidermal growth factor receptor (EGF-R) in human breast cancer: a review on 5232 patients. Endocr Rev 13:3-17, 1992

36. Tsutsui S, Ohno S, Murakami S, et al: Prognostic value of epidermal growth factor receptor (EGFR) and its relationship to the estrogen receptor status in 1029 patients with breast cancer. Breast Cancer Res Treat 71:67-75, 2002

37. Ferrero JM, Ramaioli A, Largillier R, et al: Epidermal growth factor receptor expression in 780 breast cancer patients: a reappraisal of the prognostic value based on an eight-year median follow-up. Ann Oncol 12:841-6, 2001

38. Rampaul RS, Pinder S, Wencyk P, et al: EGFR expression in operable breast cancer: is it of prognostic significance? . Clin Breast Cancer 10:2578, 2008

39. Knowlden JM, Hutcheson IR, Jones HE, et al: Elevated levels of epidermal growth factor receptor/c-erbB2 heterodimers mediate an autocrine growth regulatory pathway in tamoxifen-resistant MCF-7 cells. Endocrinology 144:1032-44, 2003

40. Martin LA, Farmer I, Johnston SR, et al: Enhanced estrogen receptor (ER) alpha, ERBB2, and MAPK signal transduction pathways operate during the adaptation of MCF-7 cells to long term estrogen deprivation. J Biol Chem 278:30458-68, 2003

41. Mueller KL, Hunter LA, Ethier SP, et al: Met and c-Src cooperate to compensate for loss of epidermal growth factor receptor kinase activity in breast cancer cells. Cancer Res 68:3314-22, 2008

42. Aoyama H, Tago M, Kato N, et al: Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 68:1388-95, 2007

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

44. Welzel G, Fleckenstein K, Mai SK, et al: Acute neurocognitive impairment during cranial radiation therapy in patients with intracranial tumors. Strahlenther Onkol 184:647-54, 2008

45. Welzel G, Fleckenstein K, Schaefer J, et al: Memory function before and after whole brain radiotherapy in patients with and without brain metastases. Int J Radiat Oncol Biol Phys 72:1311-8, 2008

46. Burstein HJ, Y S, AR T, et al: Neratinib (HKI-272), an irreversible pan erbB receptor tyrosine kinase inhibitor: phase 2 results in patients with advanced HER2+ breast cancer; Presented at the San Antonio Breast Cancer Symposium, December 12, 2008. Breast Cancer Res Treat, 2008

47. Swaby R, Blackwell KL, Jiang Z, et al: Neratinib in combination with trastuzumab for the treatment fo advanced breast cancer: A phase I/II study. J Clin Oncol, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 27:1004

48. Benson AB, 3rd, Ajani JA, Catalano RB, et al: Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 22:2918-26, 2004

49. Riethdorf S, Fritsche H, Muller V, et al: Detection of circulating tumor cells in peripheral blood of patients with metastatic breast cancer: a validation study of the CellSearch system. Clin Cancer Res 13:920-8, 2007

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

51. Shankar LK, Hoffman JM, Bacharach S, et al: Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med 47:1059-66, 2006

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

19. APPENDICES

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	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.

APPENDIX B: NERATINIB PILL DIARY (COHORTS 1 AND 2 ONLY)

Name_____Subject # _____ Dose _____ Cycle _____

Day	Date (DD-MM-YY)	Time Taken	No. of neratinib capsules taken
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			

*Please take your neratinib capsules at the same time every day in the morning with food. Please do not make up any missed doses (or vomited doses). Please contact your study team with any questions.

Subject Signature _____ Date _____

Reviewed by _____Date _____
(Study staff)

No. of capsules returned _____

APPENDIX C: NERATINIB PILL DIARY (COHORT 4)

Participant Initials _____ Participant ID # _____ Dose _____ Cycle _____

Day	Date	Time Taken	Number of Neratinib Pills Taken	Comments
Ex	**12/28/17**	**9 am**	**6**	**Vomited hour later**
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

*Please take your neratinib capsules at the same time every day in the morning with food. Please do not make up any missed doses (or vomited doses). Your medication should be stored in the containers given to you by the clinic staff or pharmacist. The medication should be stored at room temperature (i.e. not more than 25◦C or 77◦ F) and should be kept away from pets and children. Please contact your study team with any questions.

Participant Signature _____ Date _____

FOR STUDY TEAM USE ONLY

Reviewed by _____ Date _____

No. of pills dispensed _____ No. of pills returned _____

No. of pills that should have been taken _____

Discrepancy Notes:
_____

APPENDIX D: GENERAL IMPRESSION WORKSHEET [COHORT 4 ONLY]

(to be completed at baseline and at the end of each 3-week cycle)

Patient_____Examiner_____Date_____

In the opinion of the treating physician, overall, has the patient had clinical deterioration since baseline?

( ) YES

( ) NO

In the opinion of the treating physician, overall, has the patient had clinical deterioration since his/her last visit

( ) YES

( ) NO

Is the patient currently taking corticosteroids?

( ) YES

( ) NO

If yes, please list name of medication and dose (e.g. decadron, 4 mg QD):
_____

Please indicate the patient's ECOG Performance Status (see Appendix A for definitions): _____

Please indicate the patient's Karnofsky Perfomance Status (see Appendix A for definitions): _____

APPENDIX E: NEUROLOGICAL EXAMINATION WORKSHEET

[FOR COHORTS 1-3 ONLY. PLEASE USE APPENDIX D FOR COHORT 4]

(to be completed at baseline and at the end of each 3-week cycle)

(pg. 1 of 2)

PLEASE NOTE IF SIGNS/SYMPTOMS ARE THOUGHT RELATED OR NOT RELATED TO PATIENT's BRAIN METASTASES

Patient_____ Examiner_____Date_____

Level of consciousness (check one)
___Normal
___Somnolence or sedation not interfering with function
___Somnolence or sedation interfering with function, but not interfering with ADLs
___Obtundation or stupor; difficult to arouse; interfering with ADLs
___Coma

Neurological Symptoms (check if present, and specify CTCAE grade)
*if asymptomatic, check here _____

Headache	___present, specify grade____
Dizziness/lightheadedness	___present, specify grade____
Vertigo	___present, specify grade____
Nausea/vomiting	___present, specify grade____
Visual problems	___present, specify grade____
Seizure	___present, specify grade____
Other	___absent ___present, specify_____grade_____

Cranial nerves II-XII+
___Normal
___present, not interfering w/ADLs
___present, interfering w/ADLs
___life-threatening, disabling

+If abnormal, please specify which cranial nerve(s) affected_____

Language
Dysphasia or aphasia ___absent
___awareness of receptive or expressive aphasia, not impairing ability to communicate
___receptive or expressive dysphasia, impairing ability to communicate
___inability to communicate

Sensation**
___normal
___loss of deep tendon reflexes or paresthesia, but not interfering with function
___objective sensory loss or paresthesia interfering with function, but not with ADLs
___Sensory loss or paresthesia interfering with ADLs
___Permanent sensory loss that interferes with function

***If abnormal, please specify location/distribution*_____

NEUROLOGICAL EXAMINATION WORKSHEET

(pg. 2 of 2)

Patient_____ Examiner_____ Date_____

Strength*

R upper extremity	__Normal	___Abnormal; please specify_____
L upper extremity	__Normal	___Abnormal; please specify_____
R lower extremity	__Normal	___Abnormal; please specify_____
L lower extremity	__Normal	___Abnormal; please specify_____

**If abnormal, please specify muscle group and grade according to the scale below: (e.g. biceps, grade 2)*

grade 1 = asymptomatic with weakness on physical exam
grade 2 = symptomatic and interfering w/function, but not interfering with ADLs
grade 3 = symptomatic and interfering with activities of daily living
grade 4 = bedridden or disabling

Ataxia***

R upper extremity (finger-to-nose testing)	___Normal	___Abnormal, specify grade ___
L upper extremity (finger-to-nose testing)	___Normal	___Abnormal, specify grade ___
Gait	___Normal	___Abnormal, specify grade ___
Balance (Romberg)	___Normal	___Abnormal, specify grade ___

***If any of above abnormal, please assign grade using the following criteria

grade 1 = asymptomatic but abnormal on physical exam, and not interfering with function
grade 2 = mild symptoms interfering with function, but not interfering with ADLs
grade 3 = moderate symptoms interfering with ADLs
grade 4 =bedridden or disabling

In the opinion of the treating physician, overall, are the patient's *tumor-related* neurological signs and symptoms worsening, stable, or improved (please check one)?

___ Worsening
___ Stable
___Improved

Is the patient currently taking corticosteroids?

___Yes
___ No

If yes, please list name of medication and dose (e.g. decadron, 4 mg QD)_____

Please indicate the patient's ECOG Performance Status (see Appendix A for definitions): ____

Please indicate the patient's Karnofsky Perfomance Status (see Appendix A for definitions): _____

APPENDIX F: MRI BRAIN SPECIFICATIONS [ALL COHORTS]

MRI brain scans will be done at each participating center. Scans will be completed at baseline and every 2 cycles (days 22-26 during C2,C4,C6, etc.) while patients remain on study (all Cohorts). With this, TIMC will have sufficient time to review scans centrally and report results to the participating site. Brain MRI should have 5 mm or less slice thickness for axial post-contrast images using T1 or SPGR sequence.

MRI Brain scans will include the following:

- T1-weighted images with and without gadolinium contrast
- T2-weighted images
- FLAIR (fluid-attenuated inversion recovery)

Data Transfer:

- Images from DF/HCC sites are uploaded directly to TIMC.

Non-DF/HCC sites:

Each site will be given access to TIMC to order MRI reviews for their patients. Please refer to the TIMC manual, appendix P for detailed instructions.

New User Registration:

Please email the TIMC help desk [redacted] and provide the following information:

- Full name
- Home institution
- Study role
- [redacted]Include the [redacted]

Email [redacted] and [redacted] to notify of completed scan, include tracking number and ship priority overnight to ensure timely review.

Images from non-DF/HCC sites should be sent by FedEx Overnight Priority to:

[redacted]

Please refer to the Tumor Imaging Metrics Core Manual for further reference and instructions.

APPENDIX G: OFF-TREATMENT & OFF STUDY FORM

INSTRUCTIONS: To be completed when a subject completes protocol treatment and/or when the subject comes off-study. Please fill out all the information requested below and email to the ODQ registrars at [redacted]

STUDY SUBJECT INFORMATION

Subject Name (Last, First) _____

Hospital I.D. #

Protocol Number or Name
****

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

Reason

***If Reason 4* – Specify Toxicity** _____ **Phase I DLT Y/N** _____

***If Reason 7* – Date of Death** _____

***If Reason 9* – Other (please describe)** _____

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

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

Reason

***If Reason 4* – Specify Toxicity** _____ **Phase I DLT Y/N** _____

***If Reason 7* – Date of Death** _____

***If Reason 9* – Other (please describe)** _____

Completed By **Phone#** **Date**

Definitions for the Treatment Ended/Off Study Form

d. DATE TREATMENT ENDED e.	This is when protocol treatment for a subject (i.e. chemotherapy, radiation, surgery etc) is stopped due to the various reasons listed below (1-10). The date treatment ended is linked to Chemo-order entry as applicable. Therefore, it is critical that as subjects complete protocol therapy that this is documented in the ODQ registration system.
OFF STUDY	*This is when the subject will no longer be followed on the protocol due to the reasons listed below (1-10). Subjects can come off treatment before they come off study if they are still being followed on protocol or, they may come off treatment at the same time. This often is protocol dependent.*
1. Subject Canceled	This is selected only when a subject never starts protocol treatment (i.e. chemotherapy, radiation, surgery etc). This should be selected for *both* off treatment and off study if the subject never started treatment.
2. Subject Ineligible-	**This is selected when a subject has already begun treatment (i.e. chemotherapy, radiation, surgery etc) and has been deemed ineligible. Some protocols require follow-up for ineligible subjects so the subject may continue on follow-up. This may be selected for off treatment or off study**. **NOTE:** The subject will be taken *Off Treatment* **AND** taken *Off Study* when selecting this number, unless 'Yes' is selected for Follow-up.
3. Subject Completed Protocol Requirements	**This is selected when a subject has finished the protocol requirements. (may mean treatment is finished or follow-up is finished). This may be selected for off treatment or off study.**
4. Unacceptable Toxicity	This is selected when a subject experiences toxicity that either the subject or physician find unacceptable. Please specify the toxicity and if a Phase I trial select Yes or No to indicate if the toxicity is a protocol DLT. This may be selected for off treatment or off study.
5. Progressive disease/Relapsed	This is selected when a subject's disease worsens and meets the criteria in the protocol for progression; i.e. the tumor is measured and evaluated according to the tumor evaluation criteria written in the protocol (RECIST, WHO, etc) and it is deemed "progressive" (the tumor has grown larger or the disease has spread to other parts of the body). This may be selected for off treatment or off study.

6. Subject Withdrawal of Consent and Follow-up	**This is selected when a subject, at any time during the study, decides to no longer participate in either the treatment portion of the protocol or the follow-up portion. Subject must be off treatment and off study.**
7. Subject Died-	If the subject dies while still receiving protocol treatment this option can be chosen for off treatment. If the subject has completed treatment but is in follow-up then this reason can be chosen for off-study but should not be selected for off-treatment. Please indicate the date of death when selecting this number. **NOTE:** The subject will be taken *Off Treatment* **AND** taken *Off Study* when selecting this number. **For DFCI only**: PI or study staff designee must notify the Medical Record Department/Health Information Services, [redacted]
8. Lost to Follow-up	This is selected when the subject cannot be located during the treatment or follow-up portion of the protocol and all communication is lost. Subject must be off treatment and off protocol.
9. Other	This is selected when the reason for stopping protocol treatment does not meet any of the other reasons listed on this form. A description of the reason MUST be written in. This may be selected for off treatment or off study.
10. Subject Withdrawal of Consent but Agrees to be Followed	This is selected when a subject, at any time during the study, decides to no longer participate in the treatment portion of the protocol *BUT* agrees to participate in the follow-up portion. Used for off treatment only.
11. Subject unable to proceed to treatment	This is selected when a subject meets eligibility requirements, is registered, and has study specific procedures performed but is unable to proceed to the study treatment (for example: transplant). This could be due to progression prior to the study intervention, subject no longer medically fit to receive transplant, donor unavailable, or in the case of vaccine studies, vaccine cannot be made. This should be selected for both off treatment and off study.

APPENDIX H: CTC REQUISITION FORM [COHORTS 1-3 ONLY]

Circulating Tumor Cell/ Circulating Endothelial Cell Studies

Study Case Number _____
Sample Identifier/Number_____
Hospital/Institution Name_____
Collection Date_____Collection Time _____(both required)

Time Point collected (circle one): Pre-treatment _____ Progression_____ Other_____

_____, M.D.
FIRST AND LAST NAME of submitting physician
ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)

Submitted for:
- ☐ **Circulating tumor cell (CTC) enumeration**
- ☐ **Additional sample (for cytospin/banking for future molecular studies for MET, HER, etc).**

SAMPLE COLLECTION:
1. Ensure that peripheral blood collection occurs prior to administration of intravenous therapy.
2. If the patient is being treated with radiation or had a recent CT scan, it is recommended to wait at least 3 days after administration before drawing a blood sample.
3. The blood sample must be collected in a CellSave preservative tube. Label the tube with the sample identifier/number, protocol number, and submitting investigator and date of collection.
4. Collect 8 ml (minimum of 5 ml) per tube of blood for best results. Gently invert the tube 4 times to prevent clotting immediately after filling the tube.

SAMPLE STORAGE AND TRANSPORT:
1. The blood sample can be transported and stored at room temperature (15-30C) until processing. Do NOT refrigerate or freeze the sample.
2. Samples must be processed within 72 hours of collection, but best results are obtained if the sample is processed as soon as possible.
3. Do not submit clotted samples.
4. Samples should be hand delivered or shipped by same day courier or overnight parcel directly to:

[redacted]

Samples will then be hand delivered to [redacted]

5. Email notification should be sent to [redacted] to alert her to expect the shipment.

For Lab Use Only:

Date Received	
Date Processed	
Lab Personnel Initials	
Comments	

APPENDIX I: SERIOUS ADVERSE EVENT REPORTING TO PUMA

All Serious Adverse Events will be reported to Puma Biotechnology, Inc. by the DFCI study team.

SAE reports will be e-mailed to [redacted]

APPENDIX J: MEDICATIONS TO USE WITH CAUTION WHILE ON NERATINIB

List of Cytochrome P450 Inhibitors and Inducers (updated list also available at http://medicine.iupui.edu/clinpharm/ddis/table.aspx)

Special considerations for H2 antagonists, Proton pump inhibitors, and antacids:

It is unknown whether separating PPIs and neratinib reduces the interaction. If an H2-receptor antagonist such as ranitidine or famotidine is required, neratinib should be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist. If antacids are necessary, the antacid dose and neratinib dose should be separated by 2-4 hours whenever possible. Use of these agents are allowed but should be done with caution and with limited use.

INHIBITORS

Norfloxacin (3A4)
Ritonavir (3A4)
Clarithromycin (3A4)
Erythromycin (3A4)
Fluconazole (3A4)
Fluvoxamine (3A4)
Grapefruit juice (3A4)
Grapefruit-containing products (3A4)
Indinavir (3A4)
Itraconazole (3A4)
Ketoconazole (3A4)
Mibefradil (3A4)
Miconazole (3A4)
Nefazodone (3A4)
Nelfinavir (3A4)
Saquinavir (3A4)
Troleandomycin (3A4)
Voriconazole (3A4)
Amiodarone
Cannabinoids
Fluoxetine
Lopinavir
Metronidazole
Quinine
Sertraline
Zafirlukast

INDUCERS

Barbiturates
Rifampin (3A4)
St. John's wort (3A4)
Troglitazone
Cotrimoxazole
Efavirenz
Mexiletine
Ethosuximide
Rifabutin (3A4)
Troglitazone
St. John's wort (3A4)
Rifampin (3A4)
Oral contraceptives Rifabutin (3A4)
Nevirapine
Metyrapone
Methadone

In boldface are identified strong CYP3A4 inducers/inhibitors.
From: Tatro BO. *Drug Interaction Facts 2003: The Authority on Drug Interaction;*.2003.

In addition, for those on Cohorts 4A-4C with T-DM1, DM1, the cytotoxic component of T-DM1, 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 T-DM1 should be avoided if possible due to the potential for an increase in DM1 exposure and toxicity

APPENDIX K: SPECIMEN REQUISITION FORM FOR NERATINIB AND METABOLITE CONCENTRATIONS (PLASMA AND CSF ONLY; COHORT 2 ONLY)

Study Case Number _____
Sample Identifier/Number_____
Hospital/Institution Name_____
Collection Date_____Collection Time _____(both required)
Specimen Type (CSF, plasma) _____
Date/Time of last dose of neratinib _____(required)

Time Point collected (circle one): Pre-treatment Pre-cycle (no. cycle) Progression Other_____

Protocol Name: A Phase II Trial of HKI-272 (Neratinib) for Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast cancer and Brain Metastases

Protocol Number: _____

FIRST AND LAST NAME of submitting physician _____

ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)

SPECIMEN COLLECTION:
(A) CSF

- 4 cc of fluid will be required for analysis (but any fluid obtained should be sent, even if volume is less). Collect in pre-labeled tubes or regular CSF containers routinely used for lumbar punctures. Once collected, fluid should be immediately frozen (within 15 minutes if possible) and shipped on dry ice as above.

(B) Blood samples:

- 3 mL of blood will be collected into a 5mL K3EDTA vacutainer tube for neratinib/metabolites PK sampling.

STORAGE AND TRANSPORT:
Blood sample processing instructions:

- Gently mix contents of the tube containing the blood sample.
- Take care that blood does not come into further contact with the stopper.
- Immediately place vacutainer on ice.
- Centrifuge tube of blood within 2 hours of collection at 1,000 x g for 10 minutes in a refrigerated (4°C) centrifuge.
- Label a 2.0 mL cryovials with appropriate specimen labels (at least 2 hours prior to freezing).
- Collect the plasma using disposable pipettes.
- Transfer the plasma into the labeled 2.0mL cryovials for each sample taken, and store in an upright position.
- Freeze samples in an upright position in a -70°C monitored freezer in their respective labeled cryovial storage box. Samples must be frozen for at least 24 hours prior to shipment.
- Email notification should be sent to [redacted] to alert them to expect the shipment

APPENDIX L: SPECIMEN REQUISITION FORM FOR NERATINIB AND METABOLITE CONCENTRATIONS (INTRACRANIAL SPECIMENS ONLY-COHORT 2 ONLY)

Study Case Number _____
Sample Identifier/Number_____
Hospital/Institution Name_____
Collection Date_____Collection Time _____(both required)
Specimen Type: intracranial tumor
Date/Time of last dose of neratinib _____(required)

Time Point collected (circle one): Pre-treatment Pre-cycle (no. cycle) Progression Other_____

Protocol Name: A Phase II Trial of HKI-272 (Neratinib) for Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast cancer and Brain Metastases

Protocol Number: _____

FIRST AND LAST NAME of submitting physician _____

ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)

SPECIMEN COLLECTION:

STORAGE AND TRANSPORT:

- At resection, 0.4 – 0.5 ml of tumor should be collected.
- Flash freeze samples at -80 degrees Celsius
- Email notification should be sent to [redacted] to alert of expected shipment

Ship/hand deliver samples as directed to:

[redacted]

The study team will then deliver samples to [redacted]

APPENDIX M: OPTIONAL DIARRHEA MANAGEMENT SHEET (Cohorts 1 and 2)

(Maximum dose of Imodium = 16 mg per day)

Date / Time	Medication	Description
1.	Imodium 2 tablets	
2.	Imodium 1 tablet	
3.	Lomotil 2 tablets	
4.	Imodium 1 tablet	
5.	Imodium 1 tablet	
6.	Lomotil 2 tablets	
7.	Imodium 1 tablet	
8.	Imodium 1 tablet	
9.	Lomotil 2 tablets	
10.	Imodium 1 tablet	
11.	Imodium 1 tablet	
12.	Lomotil 2 tablets	
13.	Imodium 1 tablet	
14.	Imodium 1 tablet	

Please call your participating center if you have more than four loose stools over your normal amount for a day.* Keep a log for everyday that you have diarrhea symptoms.

Date / Time	Medication	Description
1.	Imodium 2 tablets	
2.	Imodium 1 tablet	
3.	Lomotil 2 tablets	
4.	Imodium 1 tablet	
5.	Imodium 1 tablet	
6.	Lomotil 2 tablets	
7.	Imodium 1 tablet	
8.	Imodium 1 tablet	
9.	Lomotil 2 tablets	
10.	Imodium 1 tablet	
11.	Imodium 1 tablet	
12.	Lomotil 2 tablets	
13.	Imodium 1 tablet	
14.	Imodium 1 tablet	

APPENDIX N: DSMP

DFCI IRB Protocol #: 11-344
TBCRC 022

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

Table of Contents

1.0 INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Components

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

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

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

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

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

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

Coordinating Center: In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. Multi-Center Guidelines). In addition to

the Lead Institution, the Office of Data Quality (QDQ) provides support services to assist the Protocol Chair.

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

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

2.0 GENERAL ROLES AND RESPONSIBILITIES

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

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Rachel Freedman, M.D. will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

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

- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials).
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center (Lead Institution)

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

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

In addition to the Lead Institution, the DF/HCC Office of Data Quality provides the following support services to assist the Protocol Chair:

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

2.3 Participating Institution

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

The general responsibilities for each Participating Institution are as follows:

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

3.0 PROTOCOL DEVELOPMENT

3.1 Activation of a Protocol

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

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

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify, qualify and initiate Participating Institutions and obtain accrual commitments.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

3.2 Coordinating Center Support Function

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

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

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

4.0 PROTOCOL MANAGEMENT

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

4.1 Protocol Distribution

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

4.2 Protocol Revisions and Closures

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

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

Revisions for life-threatening Causes: Participating Institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to

protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

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

4.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent from participating institutions. As best a possible, the template should be followed with the specifications outlined in the DF/HCC guidance document on Model Consent Language.

Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Lead Site for their revision prior to submission to the participating site's IRB.

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

4.4 IRB Documentation

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

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

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

4.5 IRB Re-Approval

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

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

4.6 Participant Confidentiality and Authorization Statement

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

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

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

4.7 Participant Registration

Please refer to protocol *S*ection 4.2 for detailed instructions on participant registration requirements.

4.8 DF/HCC Multi-center Protocol Case Number

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

4.9 DF/HCC Multi-center Protocol Registration Policy

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

4.9.2 **Eligibility Exceptions:** The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. In addition, the Cancer Therapy Evaluation Program (CTEP) specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements. The DF/HCC ODQ requires each institution to fully comply with this requirement.

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

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

4.10 Schedule of Data Submission

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

4.10.1 Eligibility Checklist

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

Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)
1) Parameters for eligibility
2) Parameters for exclusion
3) Parameters for stratifications

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

- Lab tests required for eligibility must be completed within 14 days prior to study enrollment by the ODQ.
- For protocols requiring measurable disease, lab baseline measurements must be completed within 14 days prior to study enrollment by the ODQ. Examples: flow cytometry, HLA typing, fluid cytology, tumor markers and hormones (CEA, CA-27-29, CA-125).
- Non-lab tests required for eligibility must be performed within 30 days prior to study entry. Example: radiological scans

- For bone marrow transplant (BMT) protocols and non-protocol treatment plans, eligibility tests must be completed within 42 days prior to enrollment by the ODQ. The extended period of time is allowed to facilitate insurance approval while ensuring participant safety.

4.10.2 On-study Form(s)

Purpose - documents the following items:

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

4.10.3 Baseline Assessment Form(s)

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

4.10.4 Treatment Form(s)

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

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

4.10.5 Adverse Event Report Form(s)

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

4.10.6 Response Assessment Form(s)

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

4.10.7 Off Treatment and Off Study Form(s)

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

4.10.8 Follow up / Survival Form

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

4.10.9 Data Form Review

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

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

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

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

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

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

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

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

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

4.10.10 Missing and Deficient Memorandum

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

Incomplete or Questionable Data

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

Missing Forms

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

5.0 REQUISITIONING INVESTIGATIONAL DRUG

Participating sites will order their own agent through the coordinating center (DFCI). Puma Biotechnology, Inc. will then provide the investigational agent, as specified in the protocol, *Section 7.1.10*.

Because neratinib is investigational, sites must ensure that the pharmacy will be able to receive and store the agent. The local IRB should be kept informed of who will supply the agent (i.e., Puma Biotechnology, Inc.) so that any regulatory responsibilities can be met in a timely fashion.

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

6.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

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

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

6.1 Serious Adverse Events

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

6.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol Section 14.

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

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

6.3 Guidelines for Processing IND Safety Reports

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

7.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all Institutions Participating in the DF/HCC Multi-center Protocol.

7.1 Definitions

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

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

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

7.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations.
The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

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

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

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

8.0 MONITORING: QUALITY CONTROL

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

8.1 Ongoing Monitoring of Protocol Compliance

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

The DF/HCC Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data Safety Monitoring Committee (DSMC). Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion. As this is a multicenter study, the following approach will be used to ensure proper data and safety monitoring:

Site Qualification
Once the protocol is IRB approved at the DF/HCC, a Site Selection and Feasibility Questionnaire and the IRB-approved protocol will be sent to the Site Principal Investigator at each Participating Site. The questionnaire will ask the Site PI to consider DF/HCC policies regarding informed consent, serious adverse event reporting and documentation, and pharmacy guidelines in their decision to participate. The questionnaire will also require site consideration of IRB procedures, subject enrollment, appropriateness of the Participating Site for carrying out the proposed protocol, plans for data submission and monitoring, and the identification of staff availability and credentials. The Participating Site will be instructed to return the completed questionnaire to DFCI Clinical Research Specialist as soon as possible.

The Principal Investigator will review the Site Selection and Feasibility Questionnaire and determine whether or not the site is qualified to participate. Sites determined to be qualified to participate will be invited to submit the protocol to their institutional IRB for review.

Required Regulatory Documentation
Before the study can be initiated at any site, the following documentation must be provided to the Dana-Farber Cancer Institute:

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- IRB FWA number

- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification and institution lab normal values
- Protocol acceptance signature page
- Executed clinical research contract

Once above listed documents are received, an amendment to add the participating institution will be submitted to the DF/HCC IRB. Site Initiation Teleconference will be scheduled upon receipt or the IRB approval.

All Participating Institutions will be instructed to maintain and update all essential regulatory documents. The Coordinating Center will be responsible for maintaining the Trial Master File which will include copies of all regulatory documentation for the Coordinating Center and each individual Participating Center. Record of all approvals and licensure expirations will be maintained and requested as needed from each Participating Institution.

Training, Delegation of Responsibility, and Oversight

A Site Initiation Teleconference will be scheduled with each Participating Institution prior to site approval for patient enrollment. This training must occur prior to enrollment of any participants at the Participating Site.

Participating Institutions will be required to complete a Delegation of Responsibility Log. A copy of this document will be retained in the Trial Master File. Participating Institutions will be instructed to inform the Coordinating Center immediately should there be a change in study personnel. Modifications to the Delegation of Responsibility Log and FDA 1572 form will be expected.

Monthly teleconferences will be held following study start-up, and thereafter at a frequency dependent on study accrual, and will include the principal investigators from each participating site (or a designated co-investigator if a PI is unavailable), as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. Subject accrual, toxicity assessments, protocol adherence, data entry, validity, integrity, and completeness, and management issues will be discussed at the meetings.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to the oversight IRB, the Scientific Progress Review Committee (SPRC) or the Dana-Farber Cancer Institute Data Safety Monitoring Committee (DSMC).

Verification of Participant Consent to Participate and Participant Eligibility

Please refer to Protocol Section 4.2 for detailed list and instructions on patient registration. To confirm subject eligibility to participate in the trial, the Coordinating Center will carefully review

the Eligibility Checklist, supporting source documentation and Consent From signed by the participant and their treating oncologist. Please note:

- ***Only physicians are allowed to consent subjects to participate in the trial. Consent forms signed by any other consenting individuals will not be accepted and registration will be denied.***
- ***A participant cannot initiate study treatment until an email Confirmation of Registration is received form the Coordinating Center.***

Each consent form will be reviewed to ensure 1) it is the most appropriate and current version, 2) that the participant information is included on all pages and that all pages of the consent have been submitted, 3) that the participant has signed the consent form, 4) that a physician has reviewed and signed the consent form on the same day/time as the participant, and that 5) all appropriate items have been completed.

Adverse Even Reporting
Please refer to protocol section 13 for detailed SAE reporting requirements.

Drug Accountability
Each participant will receive a Drug Diary and will be instructed on taking the study treatment. Participants must be instructed to return the signed Drug Diary at the end of each treatment cycle along with any unused medication. The study coordinator will completed a pill count, document number of returned tablets and submit the unused study medication to the Institutional Pharmacy for destruction per institutional policy. Participating pharmacies will be required to submit Drug Accountability Logs at the time of monitoring documenting receipt and shipments of drug supply, dispensing/ordering of supply, and destruction of unused study medication and/or damaged or expired drug.

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

All data submitted to the DF/HCC ODQ will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and if applicable ODQ Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution's Coordinators, the Principal Investigators, and the Protocol Chair. Once a first patient is enrolled at each site, that patient will be monitored. There will be quarterly monitoring, and each site will be monitored at least once a year. . Participating sites will be asked to provide the lead institution with all source documents used for verification of eCRF data. A site monitoring report will be issued to the participating site to allow for ease of corrective action planning.

8.2 Evaluation of Participating Institution Performance

8.2.1 Eligibility Checklist:

Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC ODQ prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC ODQ Protocol Registrar before the participant can be registered on a protocol. The DF/HCC ODQ cannot make exceptions to the eligibility requirements.

8.2.2 Accrual of Eligible Participants:

Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. The minimum accrual requirement for this study is 2 subjects annually. If sites do not meet this requirement the Overall PI will discuss the utility of continuing enrollment with the study site and will proceed accordingly.

9.0 AUDITING: QUALITY ASSURANCE

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

9.1 DF/HCC Sponsored Trials

Any site that accrues at least 3 subjects will be eligible for an audit. Five of the participating sites will be audited at a minimum. Approximately 3-4 subjects would be audited at the site over a 2 day period. If violations which impact subject safety or the integrity of the study are found, more subject records may be audited.

9.2 Participating Institution

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

9.3 Coordinating Center (Lead Institution or designee)

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

9.4 Sub-Standard Performance

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

9.4.1 Corrective Actions

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

APPENDIX O: NEUROCOGNITIVE TESTING – COHORT 1 ONLY

CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

STEP 1 – EXAMINER CERTIFICATION

The healthcare professional (e.g., psychologist, physician, nurse) who is responsible for test administration in this study must be certified by Dr. Wefel prior to administering the neurocognitive tests.

Prior to registering and/or testing a patient, potential examiners must:

(1) Contact [redacted] to obtain copies of the HVLT-R, TMT, COWA, Neurocognitive Test Completion Page, Demographics Page and Training Video Study ID password to complete the training and certification process. All other materials (Training Video Post Test and the Certification Worksheet) are at the end of this Appendix
(2) Read Sections 8.5, 11.1 and 17.6.3 of the protocol
(3) Read Appendix O (Certification and Administration Procedures for the Neurocognitive Test Battery)
[redacted] Go to the following web site to view the training video with the Study ID password provided by [redacted]
(5) Watch the training video
(6) Complete the Training Video Post Test (available at the end of Appendix O)
(7) Complete a "practice" assessment with the test forms provided by Dr. Wefel
(8) Complete the Certification Worksheet (Appendix O)
(9) All materials (i.e., Training Video Post Test, completed practice tests and Neurocognitive Test Completion Page, certification worksheet) must be faxed to Dr. Wefel, who will review them and correct any procedural errors with the trainee.
(10) If the trainee demonstrates competency, he/she will be notified of the certification approval to administer the tests to study subjects as part of TBCRC 022. A certification approval notice will be sent to DF/HCC Office of Data Quality (ODQ) for the registration process and to ensure that only TBCRC 022-approved examiners are testing subjects on protocol TBCRC 022.
(11) Once certified, Dr. Wefel will mail test packets to the site for use with patients on TBCRC 022.
(12) Within 10-days of testing, please submit copies of all neurocognitive test and summary forms for each study patient y[redacted] for centralized review.

STEP 2 – ALTERNATE TEST FORMS

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. The alternate forms have already been inserted into the packets you receive. Please administer the tests using the packets labeled for each time point (Baseline, Cycle 2 Day 1, Cycle 3 Day 1 and End of Therapy).

STEP 3 — TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

Additional comments:

1. Testing must be completed in one session. The total time for the neurocognitive assessment is approximately 25-30 minutes. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Part A (Trials 1, 2, 3); Trail Making Test Part A; Trail Making Test Part B; COWA; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with the HADS and EORTC QLQ30/BN20.
4. Submit all test and scoring forms (HVLT-R, TMT, COWA, Neurocognitive Test Completion Page, and Demographics Page [at baseline only]) to [redacted] for centralized scoring and review. Please keep all original test forms in the patients' study file.
5. In the event that a patient cannot complete a given test, please indicate the reason code on the Neurocognitive Test Completion Page.
6. Patients should not be given copies of their tests to avoid learning the material between test administrations.
7. Before dismissing the patient, thank the patient for his/her cooperation.

TEST ADMINISTRATION INSTRUCTIONS AND PROCEDURES

STANDARDIZED ADMINISTRATION

The neurocognitive test battery should be administered according to the assessment schedule in the protocol and prior to patients receiving information about the status of their disease. Testing must be completed in one session.

The standardized test instructions, which are printed on all test forms, must be read verbatim to every patient at every study visit. Full instructions, including all practice items, must be given by the test administrator at each assessment even if the patient is familiar with testing.

The HVLT-R and COWA test forms should be held by the test administrator so that the patient cannot see what you are writing. You may wish to use a clipboard as your writing surface. Please print legibly. Use a stopwatch to time the COWA and the Trail Making Test.

TESTING ENVIRONMENT

Testing is to be conducted in a quiet distraction free environment (for example, a clinic examining room).

Only the patient and the certified test administrator should be in the room during the testing. No other family members, friends or patients should be in the room during testing.

ESTABLISHING RAPPORT AND PROVIDING FEEDBACK TO THE PATIENT

The certified test administrator should be thoroughly familiar with the tests prior to their administration so that s/he can attend to establishing a comfortable working relationship with the patient. Please have all test administration supplies ready in advance (test forms, black pen, stopwatch, and clipboard).

Please introduce yourself to the patient and answer questions the patient may have about testing. Patients may ask, “What will I be doing today? How long will it take?” You may provide a general response such as, “We will spend about 25 minutes going through several measures that will help us to understand your cognitive function.”

Patients may ask, “How did I do?” You may respond with encouraging statements such as, “You worked very hard today. Thank you”, or, “These can be challenging tests – thank you for giving your full effort.” Do not try to provide specific information about patient performance such as, “You answered 10 out 12 correctly” or “You did better/worse than last time”. At the completion of testing please thank the patient for his/her cooperation.

Patients should not be given answers to the tests or copies of their tests to avoid learning the material between test administrations.

1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and three alternate forms:
Part A - Free Recall: Complete the three learning trials first
Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWA as well as the EORTC QLQ3/BN20 and HADS symptom self-report measures
Part C - Delayed Recognition: Complete immediately after Delayed Recall

Part A – Free Recall

Trial 1

Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"*

- Read the words at the rate of one word every 2 seconds.

Examiner: "OK. Now tell me as many of those words as you can remember."

- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Trial 2

Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

Trial 3

Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.

- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you *complete* 'Part A – Free Recall' (for example, 10:00 am) on the designated space on the HVLT-R form.

2. TRAIL MAKING TEST [Timed Test]

Part A – Sample: The Sample for Part A must be completed/attempted by each patient and every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a black pen and say:

Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3), *3 to 4* (point to 4), *and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.
The following explanations of mistakes serve as illustrations:

- ***"This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on he copy. Then say:
Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:
Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"

- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 3 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Test Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Test Data Sheet in minutes and seconds. Then say, **"*That's fine. Now we'll try another one.*"**

Part B – Sample: The Sample for Part B must be completed/attempted by each patient and every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:
Examiner*: "On this page (*point*) are some numbers and letters. Begin at number 1 (*point to 1*) and draw a line from 1 to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the end (*point to the circle marked END*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.
The following explanations of mistakes serve as illustrations:

- ***"You started with the wrong circle. This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 (*point*) to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, until you reach the circle marked END (*point*)"***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner*: "Now you try it. Remember, begin at number 1 (*point to 1*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, in order, until you reach the circle marked END (*point*). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Test Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:

After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the circle marked END (*point*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (*point to B*), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred - do NOT start from the beginning
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- Collect the worksheet and record the time to completion on the Trail Making Test Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Test Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- At the top of both Sample forms and both Test forms please write: patient initials, TBCRC protocol case number, date of testing and time point of testing

3. CONTROLLED ORAL WORD ASSOCIATION (COWA) [Timed Test]

This test has three parts (i.e., three letters) and two alternate forms.

Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' and 'Eating.'*

"For example, if I say 's,' you could say 'son', 'sit,' 'shoe,' or 'slow.' Can you think of other words beginning with the letter 's'?"

Wait for the patient to give a word. If it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the Test Completion Page.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner*: "That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."*

"You will have a minute for each letter. The first letter is '___'" (see COWA test sheet).

Allow exactly one minute for each letter

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording Responses:

- The record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. Record all patient responses verbatim. If his/her

speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.

- Incorrect responses should be struck through with a line and then initial and date in the margin next to the error.
- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.
- Responses should be legible – please line out and re-write any illegible responses in the margin next to the original word.
- Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you. <u>All duplicate entries that have been provided by the patient based on their alternative meanings must be marked "OK", initialed and dated.</u>
- If the test is discontinued or omitted, please indicate the reason on the Test Completion Page

4. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

- ***DO NOT READ THE WORD LIST AGAIN*.**
- Record the time on the clock that you *start* 'Part B – Delayed Recall' (for example, 10:20 am) on the designated space on the HVLT-R form.
- Administer 'Part B – Delayed Recall' after completing all Trail Making Tests and the COWAT. There should be at least 20 minutes between 'Part A' and 'Part B' of the HVLT-R. If the time is too short, allow the patients to complete a questionnaire.

Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember.*"

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, record the number of words that were correctly recalled on the summary form.

Part C – Delayed Recognition

Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"*

- Read the words from the top of the columns down.
- Check either the "**Y**" (Yes) or "**N**" (No) box next to each word to indicate the patient's response.
- Guessing is allowed – patients must offer a response to every item.
- If the test is discontinued or omitted, please indicate the reason on the Test Completion Page.

TBCRC 022 – TRAINING VIDEO POST TEST

Test Administrator Name: _____

Site Name/ Number: _____

Email: _____ Tel #: _____

1. On Free Recall (Part A) of the Hopkins Verbal Learning Test – Revised, words are read at a rate of:
    a. 1 word every 1 second
    b. 1 word every 2 seconds
    c. 2 words every 1 second
    d. 2 words every 2 seconds

2. On the Hopkins Verbal Learning Test – Revised, the length of the delay interval between Free Recall (Part A) and Delayed Recall (Part B) is approximately:
    a. 10 minutes
    b. 15 minutes
    c. 20 minutes
    d. 30 minutes

3. True or False: After the delay interval on the Hopkins Verbal Learning Test – Revised, you read the word list again before administering the Delayed Recall (Part B).

4. On the Trail Making Test, the maximum time allowed for Parts A and B, respectively, is:
    a. Part A= 3 minutes, Part B= 5 minutes
    b. Part A= 3 minutes, Part B= 3 minutes
    c. Part A= 5 minutes, Part B= 5 minutes
    d. Part A= 5 minutes, Part B= 3 minutes

5. True or False: If the patient makes an error on the Trail Making Test, you stop timing and correct their error. You then resume timing when they restart the test.

6. True or False: If the patient makes an error on the Trail Making Test, you stop them and have them begin at the beginning again.

7. How long are patients given for each letter on the Controlled Oral Word Association test:
    a. 2 minutes
    b. 1 ½ minutes
    c. 30 seconds
    d. 1 minute

8. True or False: You use a stopwatch to time the Trail Making Test and the Controlled Oral Word Association?

TEST ADMINISTRATOR CERTIFICATION WORKSHEET FOR TBCRC 022 – Cohort 1 only

This worksheet must be completed and signed by the person requesting certification and submitted to Dr. Wefel as described in this Appendix (N). The person requesting certification may not test a patient on TBCRC 022 until this certification request has been approved by Dr. Wefel.

_____ (Y/N)) 1. Have you reviewed Sections 8.5, 11.1 and 17.6.3 of the Protocol?

_____ (Y/N) 2. Have you read Appendix O of the Protocol?

_____ (Y/N) 3. Have you watched the Training Video?

_____ (Y/N) 4. Have you completed and submitted the Training Video Post Test?

_____ (Y/N) 5. Have you completed and submitted a practice assessment with the Neurocognitive Test Completion Page on a non-patient volunteer?

PLEASE PRINT IN CAPITAL LETTERS:
Name of test administrator:
Site Name/Number:
Telephone number of test administrator: _____
Fax number of test administrator: _____
E-mail address of test administrator: _____

_____ _____
Signature of test administrator Date

Once you have completed this form, please submit with all other training materials to:

[redacted]

For [redacted]

The above individual has been certified to administer the neurocognitive tests for TBCRC 022.

Signature: _____ Date of Approval: _____

APPENDIX P: TUMOR IMAGING METRICS CORE (TIMC) USER MANUAL [ALL COHORTS]

TUMOR IMAGING METRICS CORE

Welcome to the TIMC

The TIMC provides standardized measurement of imaging scans for oncology clinical trials. TIMC's web-based system ensures easy ordering and access with exceptionally fast turnaround. Tumor response assessment criteria include RECIST, RECIST 1.1, Cheson, irRC, SUV, and 3D volume.

Getting Started

This document provides step-by-step instructions to help you use the TIMC website. Topics covered include:

- New User Registration
- Patient Registration
- Scan Assessment Requests
- Patient Registration and Order Entry Information
- Results Reporting

Please contact the TIMC help desk at timc@nmr.mgh.harvard.edu for any questions or concerns that are not addressed below.

New User Registration:

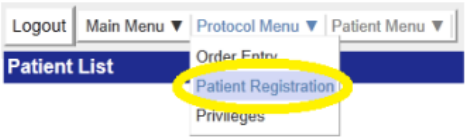
1. Please email the TIMC help desk at timc@nmr.mgh.harvard.edu and provide the following information:
   - Full name
   - Partners/DFCI or CareWeb username
   - Home institution
   - Study role
   - Disease group affiliation
   - The disease group program manager and/or study PI must be Cc on the email.
2. After account set-up, please go to www.tumormetrics.org and click **Client Login** or go to www.timclogin.org to directly access the login page.
3. Login with your Partners/DFCI or CareWeb username and password.

1

Note: Passwords are authenticated through the hospitals' password authorization system. Your TIMC login information will be automatically updated when you change your Partners/DFCI or CareWeb password.

Patient Registration:

1. After login, click on the link for the appropriate protocol number.
2. Select **Patient Registration** from the **Protocol Menu** pull-down.



3. Click **Add New Record** to register a new patient.

ID	• ID refers to the patient's DFCI ID. • DF/HCC QACT assigns a DFCI ID to each patient enrolled in a DF/HCC cancer center protocol.
First Name	• Enter the patient's full first name. Please confirm spelling.
Last Name	• Enter the patient's last name. Please confirm spelling.
Mid	• Mid refers to the first initial of the patient's middle name
Initials	• Initials will get auto-populated with the patient's initials.
DOB	• Date of birth using the format MM/DD/YYYY
Institution	• Institution where the patient is receiving treatment

2

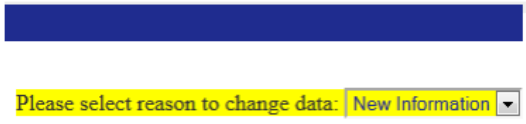
Inst. MRN	• Medical record number for the home institution
Date Registered	• Date registered will get auto-populated with today's date. • This is the date that the patient was registered with TIMC.
Date Off Protocol	• Leave Date off Protocol field blank at this time. • Date off Protocol will get auto-populated with the date of response assessment progression. • Please manually fill in Date Off Protocol if the patient comes off study for another reason (i.e., toxicity, *etc*).
Prim. Disease	• Select Patient's primary disease from pull-down. • Please email timc@nmr.mgh.harvard.edu if the patient's primary disease is not included in the list.
Failed Screening	• Failed Screening should be checked if the patient does not meet enrollment criteria per imaging assessment.

4. Click **OK**.

Making Changes:

TIMC website has an audit trail which requires users to enter a reason for the change before they can edit.

1. **Please select the reason to change the data** from the pull-down highlighted in yellow near the top right hand side of the browser window.

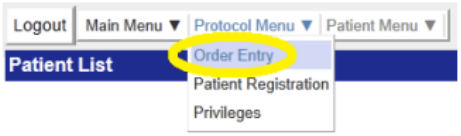


2. Click **Edit** to make changes to data entry.

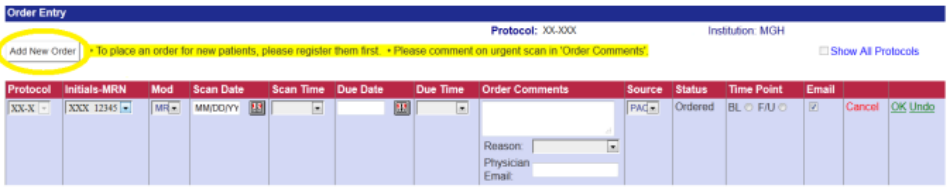
Scan Assessment Requests:

1. Click on the appropriate protocol number.
2. Select **Order Entry** from the **Protocol Menu** pull-down.

3



3. Click **Add New Order**.



Protocol	• ID refers to the patient's DFCI ID. • DF/HCC QACT assigns a DFCI ID to each patient enrolled in a DF/HCC cancer center protocol.
Initials-MRN	• Select the patient from the **Initials-MRN** pull-down. • Only registered patients will appear in this list.
Mod	• Select the scan modality from the pull-down (i.e., CT, MR, PT).
Scan Date	• Enter date as MM/DD/YY or click the calendar button to select the scan date.
Scan Time	• Round time to the nearest 30 minutes..
Due Date	• Enter date as MM/DD/YY or click the calendar button to select the scan date.
Due Time	• Round time to the nearest 30 minutes.
Order Comments	• Enter information about the scan (i.e., scans to include in the assessment, lesion(s) of interest, *etc*).
Reason	• Select a reason for urgent request from the **Reason** pull-down. • This field is required for urgent scans.

4

Physician Email	• Enter the treating physician's email address • This field is required for urgent scans
Source	**PACS** • Select **PACS** if the scans took place at DFCI, BWH, BIDMC, or MGH or were uploaded into the hospital PACS system. • TIMC can directly pull scans from DFCI, BWH, and MGH PACS. • BIDMC Imaging Archive Department pushes the scans to TIMC. • TIMC may not be able to provide results within a short timeframe due to BIDMC workflow. **CD** • Select CD if the scan is from an outside institution and needs to be uploaded manually. • CD can be dropped off at the TIMC location or uploaded to hospital PACS system by trial staff.
Status	This field is not editable and refers to the scan assessment status. • Ordered = Scan request has been made by trial staff • Inquiry = Inquiry initiated by TIMC; email response required by trial staff. • Processed = TIMC has started scan analysis. • Complete = Preliminary results are complete but scan has not been reviewed by a radiologist. • Final = Radiologist has reviewed and approved the scan assessment.
Time Point	• Choose baseline (BL) or follow-up (F/U).
Email	• Check the **Email** box if you would like to be notified by email when the scan assessment has been completed.

4. Click **OK**

   Note: The online system has an audit trail. To change data, please select the reason to change the data from the pull-down highlighted in yellow near the top right hand side of the browser window. Once a reason has been selected, click on 'Edit' to edit the patient information.

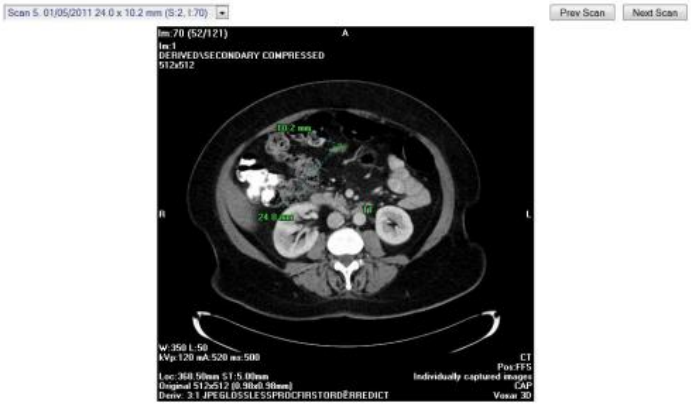
Please select reason to change data: New Information

Results Reporting:

- Click on the appropriate protocol.
- From the **Patient List** page, click on the appropriate patient link.
- Compare image captures across time points by clicking the lesion location link (left box).
- View annotated images for a specific scan date by clicking on the measurement link (right box).

#	Location	Target	Baseline
			07/22/10
1	Left Anterior Peritoneal Mass	Y	51.3 x 20.5 mm (S:2, I:37)
2	Left Pelvic Nodule	Y	10.3 x 6.9 mm (S:2, I:65)
3	Multiple Peritoneal Nodules / Carcinomatosis	N	NM (S:2, I:39)
4	Multiple Retroperitoneal Nodes	N	NM (S:2, I:40)
5	Multiple Pelvic Nodes & Nodules	N	NM (S:2, I:56)
	RECIST		61.6
	% change from Baseline:		0
	% change from Nadir:		0
	Scan used for Nadir:		
	% change from Prior:		0
	Response:		**BL**

- Click the **Next Lesion** button located near the top right hand side of the screen to view the image capture for the next lesion or select the lesion of interest from the **Select Lesion** pull-down located under the patient information.
- Click the **Next Scan** button located to the right hand side of the image capture (on the right) to go to the next scan or select the desired scan date from the pull-downs located above the image captures.

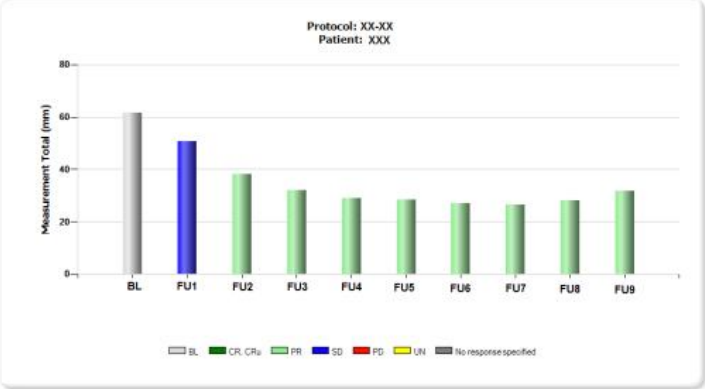


- Select **Patient Summary** from the **Patient Menu** pull-down to go back to the longitudinal measurement table.

6

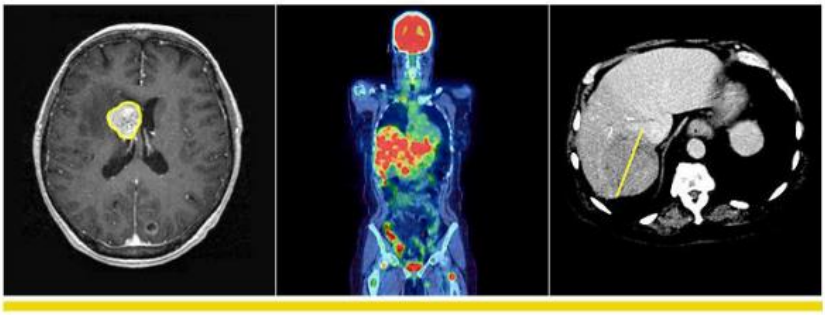
Longitudinal Graphs

- Click the graph button to view graphs. This button is located near the bottom left hand side of the screen.
- Compare time point and individual lesion measurement data to baseline, nadir (scan with the lowest measurement total), and prior scans.



For additional information about our services, please visit www.tumormetrics.org.

Thank you!



7

APPENDIX Q: (COHORT 2 EXTENSION AND COHORT 3) PATIENT INSTRUCTIONS FOR THE MANAGEMENT OF DIARRHEA IN NERATINIB STUDY

Please review these instructions with your study doctor/team. Once all of your questions are answered, make sure you are given a copy of these instructions to take home.

Diarrhea is the most common side effect you may have while participating in this study. Diarrhea usually starts within a few hours to a few days of the first dose of study drug. In order to reduce or even prevent diarrhea as far as possible, you will be supplied with an anti-diarrheal medicine called loperamide to take at the start of the study. **Primary prophylactic use of antidiarrheal medication is mandatory for all enrolled subjects.** Loperamide will be dispensed directly by your study doctor/team on day 1 with the instruction to initiate treatment with loperamide at the same time as you take your first dose of neratinib.

Start taking the anti-diarrheal medication immediately with the first dose of neratinib as directed by your study doctor/team.

Your study doctor/team will call you 24, 48 and 72 hours after your first dose of study drug to find out if you are experiencing diarrhea and to provide further treatment instructions and advice if necessary. You will also have an easy to follow flow-chart to help you each day in the management of diarrhea if it is present.

If you are having new-onset diarrhea, persistent diarrhea or diarrhea with increase of 7 or more stools per day over usual, call your study doctor/team at phone number _____ to let them know so they can work with you to control the diarrhea. If you are dizzy or weak because of diarrhea, go to the study doctor's office or go to the hospital immediately.

Please record the number of stools and any anti-diarrheal treatment during the first two cycles along with the daily dose of study medication in your diary and return the completed diary at the next scheduled visit.

Information to provide when talking to your doctor

When talking to the study doctor/team I will provide as much of the information below as possible, in order to help my study doctor/team to assess my diarrhea and decide on the best treatment:

- Number of stools per day as compared to my normal bowel habits
- Presence of diarrhea during the night
- Presence of fever, dizziness, abdominal pain/cramping, or weakness

- What the stool looks like, that is, watery stools, blood, or mucus
- When I took my last study drug
- Any other information that could explain my diarrhea (food, recent travel, contact with other people with diarrhea).

Medications to treat diarrhea
My study doctor/team will provide me with loperamide on day 1 with the instruction to start treatment with loperamide along with the first dose of neratinib. I need to take the medications as directed by my study doctor/team.

✓ Loperamide:
- I will take 2 tablets/capsules (4 mg) with the first dose of neratinib
- After the first dose, I will take 1 tablet/capsule (2 mg) every 4 hours for the first three days (not to exceed a total of 8 tablets/day; if I get constipated, I should contact my study doctor/team who will instruct me on how often and how much loperamide to take but I should not stop taking loperamide).
- After the first three days, I will take 1 tablet (2 mg) every 6 to 8 hours until the next scheduled clinic visit.
- If I continue to have diarrhea while taking loperamide, I should contact my study doctor/team for additional anti-diarrheal medication.
- If I have diarrhea with increase of up to 6 stools per day over usual any time after the first 28 days of study medication and I am not taking any anti-diarrheal medication, I will take 2 tablets/capsules (4 mg) immediately after the first loose stool and then 1 tablet (2 mg) every 4 hours or after each loose stool to a maximum dose of 8 tablets/capsules (16 mg) in any 24 hour period until I haven't had any loose stool for at least 12 hours.

□ Other medication (Study doctor/team to write in name of medication and instructions): _____

_____

_____

In case of more severe diarrhea and any diarrhea associated with fever, pain, infection, or dehydration, I may receive IV fluids, antibiotics and/or other medications.

Changes to my diet to treat diarrhea
If I have diarrhea, I will:

- Stop all lactose-containing products (milk, yogurt, cheese, etc)
- Drink 8 to 10 large glasses of clear liquids per day
- Eat frequent small meals
- Eat low fat foods such as the BRAT diet that includes **b**ananas, **r**ice, **a**pplesauce, and/or **t**oast:

- The BRAT diet is a bland diet that is low in fat and fiber and will not irritate the stomach;
- Bananas are high in potassium and can cause constipation which can help alleviate the diarrhea
- Other similar foods are crackers, cooked cereals and pasta
- This diet is not complete in nutrients and should only be taken for a short period of time and only upon the doctor's advice

My study doctor/team may have other suggestions for me. (Study doctor/team to write in any suggestions). _____

_____

_____

_____

_____

_____

_____

Study Medication adjustments

If I am experiencing loose stools or diarrhea and cannot reach my study doctor/team immediately, I will start taking anti-diarrheal medication per the instructions above until further advice is given by my study doctor/team. If I have more than 4-6 stools per day compared to normal despite taking anti-diarrheal medication for 24 hours, I will stop taking the study medication and wait for further instructions from my study doctor/team.

Please make sure you have reviewed this information and have received the following medications:

□ Neratinib Tablets

□ Loperamide

APPENDIX R: DIARY OF STUDY MEDICATION AND ANTI-DIARRHEALS [COHORT 2 EXTENSION AND COHORT 3 ONLY]

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol #: 11-344
Your MD _____ Phone _____
Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug A: Neratinib
How Much: Your Neratinib dose is _____
How Often: You will take each dose once a day with food.
When: You should take your dose in the morning.

Study Drug B: Capecitabine
How Much: Your Capecitabine dose is _____
How Often: You will take each dose twice a day - morning and evening.
When: You should take your doses 12 hours apart after a meal, within 30 minutes of finishing it.

SPECIAL INSTRUCTIONS:
(i) Avoid St. John's Wort and grape juice, take Maalox with caution;
(ii) Kepp your medications at room temperature;
(iii) Skipped, missed or vomited doses should not be made up. Do not take your dose if you have forgotten to take it for more than 2 hours from youe usual time.
(iv) please keep drugs in their original containers.
(v) Bring any unused study drug, all empty containers, and diary to the next clinic visit.
(vi) Notify your research nurse before starting any new medication

DOSING LOG

Cycle: ___

For each dose take:
pills/capsules/tablets of drug A (Neratinib)
pills/capsules/tablets of drug B (Capecitabine)

Please indicate the date, amount taken and any comments.

	Date	Amount Taken		Comments
		Neratinib	Capecitabine	
Ex:	6/1/2009	6	2	vomited hour later
Day 1	am			
	pm	do not take		
Day 2	am			
	pm	do not take		
Day 3	am			
	pm	do not take		
Day 4	am			
	pm	do not take		
Day 5	am			
	pm	do not take		
Day 6	am			
	pm	do not take		
Day 7	am			
	pm	do not take		
Day 8	am			
	pm	do not take		
Day 9	am			
	pm	do not take		
Day 10	am			
	pm	do not take		
Day 11	am			
	pm	do not take		
Day 12	am			
	pm	do not take		
Day 13	am			
	pm	do not take		
Day 14	am			
	pm	do not take		

	Date	Amount Taken	Comments
		Neratinib	
Ex:	6/1/2009	6	vomited hour later
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			

Symptom	Start Date	End Date	Severity

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

APPENDIX S: SPECIMEN REQUISITION FORM FOR ARCHIVAL TISSUE SPECIMENS (COHORT 3 ONLY)

ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)

Study Case Number _____

Study Identifier/Number_____

Hospital/Institution Name_____

Collection Date_____

Number of Slides or Blocks sent (specify) _____

Biopsy/Surgical site _____

Tissue Derived from (circle one):

Primary **Metastases**

Protocol Name: A Phase II Trial of HKI-272 (Neratinib) and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast cancer and Brain Metastases

Protocol Number: DFCI 11-344/TBCRC022

FIRST AND LAST NAME of submitting physician _____

SPECIMEN COLLECTION:

- For each site (primary and metastatic), please send the following:
- Paraffin block containing tumor tissue OR
- At least ten 5micron sections on charged or coated slides and ten 5-7micron sections on regular non-coated slides (total of 20 slides)

STORAGE AND TRANSPORT:
Please send the archival samples ambient to the address below, with an email notification to [redacted]

[redacted]

APPENDIX T: Frozen banking sample submission form [ALL COHORTS EXCEPT COHORT 1]

Protocol Number: DFCI 11-344/TBCRC 022

Patient ID	Timepoint	Date	# Whole Blood Cryovials	# Plasma Cryovials

Date of Shipment: _____

Site Name: _____

Site Contact Name: _____

Site Contact Phone Number: (_____)_____

Site Contact E-Mail: _____

Comments:_____

_____

_____

SAMPLE STORAGE AND TRANSPORT:

1. Frozen blood samples must be shipped on dry ice.
2. Samples should be shipped Priority Overnight directly to:

Brigham and Women's Hospital
DFCI Breast Tissue/Blood Bank
[redacted]

3. Email notification should be sent to [redacted] to alert DFCI staff of the expected shipment.

APPENDIX U: Blood circulating tumor DNA (ctDNA) REQUISITION FORM FOR COHORTS 3 AND 4 ONLY)

Protocol number: DFCI 11-344/TBCRC 022
Case Number / Participant Study ID:_____
Hospital/Institution Name_____
Collection Date_____Collection Time _____(both required**)**
Time Point collected (circle one): Pre-treatment _____ Progression_____ Other_____
_____, M.D.
FIRST AND LAST NAME of Submitting Physician
_____
First and Last Name of Person Shipping the tube

ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)

Submitted for:
☐ **ctDNA processing and banking**

SAMPLE COLLECTION:

1. It is preferred that the baseline blood collection occurs prior to administration of therapy, but if the sample is missed it can be collected at a later date.
2. If the patient is being treated with radiation or had a recent CT scan, it is recommended to wait at least 3 days after administration before drawing a blood sample.
3. The blood sample must be collected in a 10 mL Streck tube. Label the tube with the participant study identifier, protocol number, and submitting investigator name and date of collection.
4. Fill the Streck tube completely and immediately mix by gentle inversion 8 to 10 times.

SAMPLE STORAGE AND TRANSPORT:

1. The blood sample can be transported and stored at room temperature (6-37 ºC) until processing. Do NOT refrigerate or freeze the sample.
2. Samples must be processed within 14 days of collection, but best results are obtained if the sample is processed as soon as possible.
3. Do not submit clotted samples.
4. Ship within **24 hours of collection at ambient temperature.** Samples should be hand delivered or shipped by same day courier or overnight parcel directly to:

Brigham and Women's Hospital
DFCI Breast Tissue/Blood Bank
[redacted]

[redacted] alert DFCI staff of the expected shipment.

TUBE PRECAUTIONS:

- If samples cannot be shipped within 24 hours of collection, contact DFCI staff. DO NOT FREEZE OR REFRIGERATE TUBES as this could result in ctDNA breakage.
- Do not use tubes after expiration date.
- Fill the tube completely; overfilling or under filling of tubes will result in an incorrect blood-to-additive ratio and may lead to incorrect analytic results.

APPENDIX V: CSF REQUISITION FORM (COHORT 4)

Protocol Number: DFCI 11-344/TBCRC 022

Patient ID	Timepoint	Date	# Cryotubes

Date of Shipment: _____

Site Name: _____ Site Contact Name: _____

Site Contact Phone Number: (_____)_____ Site Contact E-Mail: _____

Comments:_____

_____

SAMPLE STORAGE AND TRANSPORT:

1. Sites should ship CSF Specimens frozen on dry ice, Monday through Thursday. Samples collected on Fridays should be stored in the freezer until the following Monday or next available business day:
2. Samples should be shipped Priority Overnight directly to:

Brigham and Women's Hospital
DFCI Breast Tissue/Blood Bank
[redacted]

3. [redacted] with the sample information and tracking information the day before shipping specimens.

APPENDIX W: Gastrointestinal PRO-CTCAE

(also available on the NCI website https://healthcaredelivery.cancer.gov/pro-ctcae/)
(If patients do not speak or read English, an interpreter or family member can assist the patient in filling this out)

Participant #:_____ Cycle:_____ Date:_____

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days.

In the the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?	None □	Mild □	Moderate □	Severe □	Very severe □
In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?	Not at all □	A little bit □	Somewhat □	Quite a bit □	Very much □
In the last 7 days, how OFTEN did you have NAUSEA?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?	None □	Mild □	Moderate □	Severe □	Very severe □
In the last 7 days, how OFTEN did you have VOMITING?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?	None □	Mild □	Moderate □	Severe □	Very severe □
In the last 7 days, how OFTEN did you have HEARTBURN?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?	None □	Mild □	Moderate □	Severe □	Very severe □
In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)?	Yes □	No □			
In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, what was the SEVERITY of your BLOATING	None □	Mild □	Moderate □	Severe □	Very severe □

OF THE ABDOMEN (BELLY) at its WORST?					
In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?	None □	Mild □	Moderate □	Severe □	Very severe □
In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?	None □	Mild □	Moderate □	Severe □	Very severe □
In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?	Not at all □	A little bit □	Somewhat □	Quite a bit □	Very much □
In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?	Not at all □	A little bit □	Somewhat □	Quite a bit □	Very much □
In the last 7 days, how OFTEN did you have HICCUPS?	Never □	Rarely □	Occasionally □	Frequently □	Almost constantly □
In the last 7 days, what was the SEVERITY of your HICCUPS at their WORST?	None □	Mild □	Moderate □	Severe □	Very severe □

APPENDIX X: Modified STIDAT (Day 1 of Cycles 1-4 ONLY)

If patients do not speak or read English, an interpreter or family member can assist the patient in filling this out.

Participant #:_____ Cycle:_____ Date:_____

Onset and Duration

1. In the past 7 days, did you experience any diarrhea? (If no, skip to question 3). □ Yes □ No

   a. If yes, how would you rate your diarrhea at its worst?

   □ Minimal diarrhea □ Moderate diarrhea □ Severe diarrhea

Stool Frequency

2. On average, how many times did you have diarrhea per day in the last 7 days? _____per day

3. On average, how many times did you pass normal stool per day in the last 7 days? _____per day

Diarrhea-Associated Symptoms

4. In the last 7 days, have you felt like you suddenly had to pass a stool? □ Yes □ No

5. In the last 7 days, did you have any abdominal discomfort? □ Yes □ No

6. In the last 7 days, were there times when you did not make it to the bathroom for a bowel movement? □ Yes □ No

Self-Treatment of Diarrhea

7. This question pertains to medications that you may have used in the last 7 days to help treat or prevent diarrhea. Please complete the following table.

Medication	Did you use this medication	Amount used in total	Did it help your diarrhea?
Imodium (loperamide)	□ Yes □ No		□ Yes □ No □ No I didn't have any diarrhea in the past 7 days
Lomotil (diphenoxylate)	□ Yes □ No		□ Yes □ No □ No I didn't have any diarrhea in the past 7 days
Octreotide	□ Yes □ No		□ Yes □ No □ No I didn't have any diarrhea in the past 7 days
Colestipol	□ Yes □ No		□ Yes □ No □ No I didn't have any diarrhea in the past 7 days
Budesonide	□ Yes □ No		□ Yes □ No □ No I didn't have any diarrhea in the past 7 days
Other:_____	□ Yes □ No		□ Yes □ No □ No I didn't have any diarrhea in the past 7 days

Impact on Quality of Qualify of Life

8. Rank how much your bowel habits in the last 7 days have affected your ability to perform work or daily activities of living

0 1 2 3 4 5 6 7 8 9 10

No impact Extreme impact

9. Rank how much your bowel habits in the last 7 days affected your energy level.

0 1 2 3 4 5 6 7 8 9 10

No impact Extreme impact

10. Rank how much your bowel haits in the last 7 days affected your mood.

0 1 2 3 4 5 6 7 8 9 10

No impact Extreme impact

11. Rank how much yoru diarrhea has affected your family life.

0 1 2 3 4 5 6 7 8 9 10

No impact Extreme impact

12. Rank how much your diarrhea has affected your social life.

0 1 2 3 4 5 6 7 8 9 10

No impact Extreme impact

APPENDIX Y: PROMIS Scale v1.0 – Gastrointestinal Diarrhea 6a

If patients do not speak or read English, an interpreter or family member can assist the patient in filling this out

Participant #: _____ Cycle: _____ Date: _____

Please respond to each question or statement by marking one box.

In the past 7 days:

How many days did you have loose or watery stools?

□ No days → if no days, go to #4

□ 1 day

□ 2 days

□ 3-5 days

□ 6-7 days

How much did having loose or watery stool interfere with your day-to-activities?

□ Not at all

□ A little bit

□ Somewhat

□ Quite a bit

□ Very much

How much did having loose or watery stool bother you?

□ Not at all

□ A little bit

□ Somewhat

□ Quite a bit

□ Very much

How often did you feel like you needed to empty your bowels right away or else you would have an accident?

□ Never → if never, you are finished

□ One time during the past 7 days

□ 2-6 times during the past 7 days

□ Often once a day

□ More than once a day

How much did the feeling you needed to empty your bowels right away interfere with your day-to-activities?

□ Not at all

□ A little bit

□ Somewhat

□ Quite a bit

□ Very much

How much did feeling you needed to empty your bowels right away bother you?

□ Not at all

□ A little bit

□ Somewhat

□ Quite a bit

□ Very much

APPENDIX Za: Anti-Diarrheal Medication and Diarrhea Diary Cycle 1 (Cohorts 4A-C)

Participant Initials: _____ Participant Number: _____

Day Number	Date	Imodium 2 mg tablets. Prescribed dose: 4 mg (2 tablets)			Colestipol 1 gm tablets Prescribed dose: 2 gm (2 tablets)			# of episodes of diarrhea during day	Additional anti-diarrheal medications taken		
		Dose #	Time taken	# of pills taken	Dose #	Time taken	# of pills taken		Medication name/dose	Time taken	# of pills (or injections) taken
1		Initial dose			Dose 1						
		Dose 1			Dose 2						
		Dose 2									
		Dose 3									
2		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
3		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
4		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
5		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
6		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
7		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
8		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
9		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
10		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
11		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									

Day Number	Date	Imodium 2 mg tablets. Prescribed dose: 4 mg (2 tablets)			Colestipol 1 gm tablets Prescribed dose: 2 gm (2 tablets)			# of episodes of diarrhea during day	Additional anti-diarrheal medications taken		
		Dose #	Time taken	# of pills taken	Dose #	Time taken	# of pills taken		Medication name/dose	Time taken	# of pills (or injections) taken
12		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
13		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
14		Dose 1			Dose 1						
		Dose 2			Dose 2						
		Dose 3									
15		Dose 1			Dose 1						
		Dose 2			Dose 2						
16		Dose 1			Dose 1						
		Dose 2			Dose 2						
17		Dose 1			Dose 1						
		Dose 2			Dose 2						
18		Dose 1			Dose 1						
		Dose 2			Dose 2						
19		Dose 1			Dose 1						
		Dose 2			Dose 2						
20		Dose 1			Dose 1						
		Dose 2			Dose 2						
21		Dose 1			Dose 1						
		Dose 2			Dose 2						

During this cycle, did you skip any doses of colestipol or loperamide due to constipation?

□ Yes □ No

During this cycle, did you skip any doses of colesiptol or loperamide due to other side effects?

□ Yes □ No

If yes, please list the reason here:_____

During this cycle, did you skip any doses of neratinib due to diarrhea?

□ Yes □ No

During cycle 1, please take your colestipol twice a day for 21 days.

During cycle 1, please take your loperamide (Imodium) at the time of your initial dose of neratinib and then 3 times a day for 14 days. After that, please take loperamide twice a day for 7 days.

If you experience diarrhea despite these medications, please take additional medications as directed by your provider.

Subject Signature _____ Date _____

Reviewed by _____Date _____
(Study staff)

No. of Imodium tablets returned _____

No. of Colestipol tablets returned_____

APPENDIX Zb: Anti-Diarrheal Medication and Diarrhea Diary for Cycles 2 - 3(Cohorts 4A-c)

Cycle: __ Participant Initials: _____ Participant Number: _____

Day Number	Date	# of episodes of diarrhea during day	Anti-diarrheal medications taken		
			Medication name/dose	Time taken	# of pills (or injections)
1					
2					
3					
4					
5					
6					

Day Number	Date	# of episodes of diarrhea during day	Anti-diarrheal medications taken		
			Medication name/dose	Time taken	# of pills (or injections)
7					
8					
9					
10					
11					
12					

Day Number	Date	# of episodes of diarrhea during day	Anti-diarrheal medications taken		
			Medication name/dose	Time taken	# of pills (or injections)
13					
14					
15					
16					
17					

Day Number	Date	# of episodes of diarrhea during day	Anti-diarrheal medications taken		
			Medication name/dose	Time taken	# of pills (or injections)
18					
19					
20					
21					

During this cycle, did you skip any doses of neratinib due to diarrhea?

□ Yes □ No

Call your study team if you have diarrhea.

Subject Signature _____ Date _____

Reviewed by _____Date _____

APPENDIX Zc: Adherence Measure

Participant Initials: _____ Participant #: _____ Date: _____

In order for anti-diarrheal medication to work best, people should take it according to the doctor's instructions. For one reason or another, people can't or don't always take all of their pills as prescribed. We want to know how often you have missed your anti-diarrheal medication. Please rate your agreement with the following statements.

On how many days over the past 7 days did you miss at least one dose of your loperamide?

Over the past 7 days…	Never	Rarely	Sometimes	Often	Always
I took all doses of my loperamide	□	□	□	□	□
I missed or skipped at least one dose of my loperamide	□	□	□	□	□
I was not able to take all of my loperamide	□	□	□	□	□

On how many days over the past 7 days did you miss at least one dose of your colestipol?

Over the past 7 days…	Never	Rarely	Sometimes	Often	Always
I took all doses of my colestipol	□	□	□	□	□
I missed or skipped at least one dose of my colestipol	□	□	□	□	□
I was not able to take all of my colestipol	□	□	□	□	□